

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

FORM 10-K

(Mark One)

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

For the fiscal year ended

December 31, 2021

OR

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

For the transition period from _____ to _____

Commission file number 001-34375

PLUS THERAPEUTICS, INC.

(previously known as Cytori Therapeutics, Inc.)
(Exact name of Registrant as Specified in Its Charter)

DELAWARE
(State or Other Jurisdiction of
Incorporation or Organization)
4200 MARATHON BLVD. SUITE 200, AUSTIN,TX
(Address of principal executive offices)

33-0827593
(I.R.S. Employer
Identification No.)

78756
(Zip Code)

Registrant's telephone number, including area code: (737) 255-7194

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value \$0.001 per share	PSTV	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 Section 15(d) of the Exchange Act. Yes No

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See 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
Non-Accelerated Filer
Emerging growth company

Accelerated Filer
Smaller reporting company

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

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

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

The aggregate market value of the common stock of the registrant held by non-affiliates of the registrant on June 30, 2021, the last business day of the registrant's most recently completed second fiscal quarter, was \$30.8 million based on the closing sales price of the registrant's common stock on June 30, 2021 as reported on the Nasdaq Capital Market, of \$2.56 per share.

As of February 18, 2022, there were 22,175,025 shares of the registrant's common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the registrant's definitive proxy statement for its 2022 Annual Meeting of Stockholders, which will be filed with the United States Securities and Exchange Commission within 120 days of December 31, 2021, are incorporated by reference into Part III of this Annual Report on Form 10-K.

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CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This report contains certain statements that may be deemed "forward-looking statements" within the meaning of U.S. securities laws. All statements, other than statements of historical fact, that address activities, events or developments that we intend, expect, project, believe or anticipate and similar expressions or future conditional verbs such as will, should, would, could or may occur in the future are forward-looking statements. Such statements are based upon certain assumptions and assessments made by our management in light of their experience and their perception of historical trends, current conditions, expected future developments and other factors they believe to be appropriate.

These statements include, without limitation, statements about our anticipated expenditures, including research and development, and general and administrative expenses; the Company's strategic collaborations and license agreements, intellectual property, FDA approvals and interactions and government regulation; the potential size of the market for our product candidates; our research and development efforts; results from our pre-clinical and clinical studies and the implications of such results regarding the efficacy or safety of our product candidates; the safety profile, pathways, and efficacy of our product candidates and formulations; anticipated advantages of our product candidates over other products available in the market and being developed; the populations that will most benefit from our product candidates and indications that will be pursued with each product candidate; anticipated progress in our current and future clinical trials; plans and strategies to create novel technologies; our IP strategy; competition; future development and/or expansion of our product candidates and therapies in our markets; sources of competition for any of our product candidates; our pipeline; our ability to generate product or development revenue and the sources of such revenue; our ability to effectively manage our gross profit margins; our ability to obtain and maintain regulatory approvals; expectations as to our future performance; portions of the "Liquidity and Capital Resources" section of this report, including our potential need for additional financing and the availability thereof; our ability to continue as a going concern; our ability to remain listed on the Nasdaq Capital Market; our ability to repay or refinance some or all of our outstanding indebtedness and our ability to raise capital in the future; our ability to transfer the drug product manufacture to a contract drug manufacturing organization; and the potential enhancement of our cash position through development, marketing, and licensing arrangements. The forward-looking statements included in this report are also subject to a number of additional material risks and uncertainties, including but not limited to the risks described under the "Risk Factor Summary" below.

We encourage you to read the risks described under "Risk Factor Summary" and elsewhere in this report carefully. We caution you not to place undue reliance on the forward-looking statements contained in this report. These statements, like all statements in this report, speak only as of the date of this report (unless an earlier date is indicated) and we undertake no obligation to update or revise the statements except as required by law. Such forward-looking statements are not guarantees of future performance.

RISK FACTOR SUMMARY

Below is a summary of the principal factors that may affect our business, financial condition, and results of operations. This summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factor summary, and other risks that we face, can be found below under the heading "Risk Factors" and should be carefully considered, together with other information in this Form 10-K and our other filings with the SEC.

Risks Related to Our Financial Position and Capital Requirements

- We have incurred losses since inception and expect to incur significant net losses in the foreseeable future and therefore may never become profitable and our operating results have been and will likely continue to be volatile.
- We will need substantial additional funding to develop our product candidates and conduct our future operations and to repay our outstanding debt obligations. If we are unable to obtain the funds necessary to do so, we may be required to delay, scale back or eliminate our product development activities or may be unable to continue our business operations.
- The disruption and volatility in the global capital markets may negatively impact our ability to obtain additional debt financings and modify our existing debt facilities and may increase the risk of non-compliance with covenants under our existing loan agreement.
- Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.

Risks Related to Our Business and Industry

- Our future success is in large part dependent upon our ability to successfully develop our nanomedicine platform and commercialize 186RNL and 188RNL-BAM and any failure to do so could significantly harm our business and prospects.
- If we are unable to successfully partner with other companies to commercialize our product candidates, our business could materially suffer.
- Our current business strategy is high-risk and may not be successful.
- If our competitors market or develop products that are marketed more effectively, approved more quickly than our product candidates, or demonstrated to be safer or more effective than our product candidates, our commercial opportunities could be reduced or eliminated.
- Product development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.
- Pre-clinical studies and preliminary and interim data from clinical trials of our product candidates are not necessarily predictive of the results or success of ongoing or future clinical trials of our product candidates.
- Because we have limited resources, we may decide to pursue a particular product candidate and fail to advance product candidates that later demonstrate a greater chance of clinical and commercial success.
- Clinical trial results may fail to support approval of our product candidates.
- If third parties we engage are not able to successfully perform due to the impact of the COVID-19 pandemic or otherwise, we may not be able to successfully complete clinical development, obtain regulatory approval or commercialize our product candidates and our business could be substantially harmed.
- We may have difficulty enrolling, or fail to enroll patients in our clinical trials, which could delay or prevent clinical trials of our drug candidates.
- Our success depends in substantial part on our ability to obtain regulatory approvals for our 186RNL and 188RNL-BAM product candidates. However, we cannot be certain that we will receive regulatory approval for these product candidates or our other product candidates.
- If a particular product candidate causes significant adverse events, then we may be unable to receive regulatory approval or market acceptance for such product candidate.
- If our product candidates and technologies receive regulatory approval but do not achieve broad market acceptance, especially by physicians, the revenue that we generate will be limited.
- All potential applications of our product candidates are investigational, which subjects us to development and marketing risks.
- If we or any party to a key collaboration, licensing, development, acquisition, or similar arrangement fails to perform material obligations, or commit a breach, under such arrangement, or any arrangement is terminated for any reason, there could be an adverse effect on our business.
- We and our product candidates are subject to extensive regulation, and the requirements to obtain regulatory approvals in the United States and other jurisdictions can be costly, time-consuming, and unpredictable. If we or our partners are unable to obtain timely regulatory approval for our product candidates, our business may be substantially harmed.
- We will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant expense, and if we or our collaborators fail to comply with such requirements, regulatory agencies may take action against us or them, which could significantly harm our business.

- Changing, new and/or emerging government regulations, including healthcare legislative reform measures, may adversely affect us.
- Adequate coverage and reimbursement from third party payors may not be available for our products and we may be unable to successfully contract for coverage from pharmacy benefit managers and other organizations; conversely, to secure coverage from these organizations, we may be required to pay rebates or other discounts or other restrictions to reimbursement, either of which could diminish our sales or adversely affect our ability to sell our products profitably.
- Some intellectual property that we have in-licensed have been discovered through government funded programs and thus may be subject to federal regulations such as "march-in" rights, certain reporting requirements and a preference for U.S.-based companies. Compliance with such regulations may limit our exclusive rights, and limit our ability to contract with non-U.S. manufacturers.
- Orphan drug designation may not ensure that we will enjoy market exclusivity in a particular market, and if we fail to obtain or maintain orphan drug designation or other regulatory exclusivity for some of our product candidates, our competitive position could be harmed.
- If we experience an interruption in supply from a material sole source supplier, our business may be harmed.
- We may engage in strategic transactions that could impact our liquidity, increase our expenses, and present significant distractions to our management.
- We must maintain quality controls and compliance with manufacturing standards.
- If we are unable to identify, hire and/or retain key personnel, or if any of our personnel were to test positive for COVID-19, we may not be able to sustain or grow our business.
- We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability if our insurance coverage for those claims is inadequate.
- A failure to adequately protect private health information could result in severe harm to our reputation and subject us to significant liabilities, each of which could have a material adverse effect on our business.
- We and our collaborators must comply with environmental laws and regulations, including those pertaining to use of hazardous and biological materials in our business, and failure to comply with these laws and regulations could expose us to significant liabilities.

Risks Relating to Our Intellectual Property

- Our success depends in part on our ability to protect our intellectual property.
- We may not be able to protect our trade secrets.
- We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.
- We may incur substantial costs as a result of litigation or other proceedings relating to patent and other intellectual property rights, and we may be unable to protect our rights to our product candidates and technology.
- If we are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in that litigation would have a material adverse effect on our business.

Risks Relating to the Securities Markets and an Investment in Our Common Stock

- Our stockholders may experience substantial dilution in the value of their investment if we issue additional shares of our capital stock, including in connection with the sale of our common stock by Canaccord.
- Future sales of our common stock may depress our share price.
- The market price of our common stock may be volatile and fluctuate significantly, which could result in substantial losses for stockholders.
- We may be or become the target of securities litigation, which is costly and time-consuming to defend.
- We may issue debt and equity securities or securities convertible into equity securities, any of which may be senior to our common stock as to distributions and in liquidation, which could negatively affect the value of our common stock.
- We could be delisted from the Nasdaq, which would seriously harm the liquidity of our stock and our ability to raise capital.
- Our charter documents contain anti-takeover provisions.
- We presently do not intend to pay cash dividends on our common stock.
- If securities and/or industry analysts fail to continue publishing research about our business, if they change their recommendations adversely, or if our results of operations do not meet their expectations, our stock price and trading volume could decline.

General Risk Factors

- The COVID-19 pandemic could adversely affect our business, results of operations, and financial condition.
- We may face business disruption and related risks resulting from the COVID-19 pandemic and the invocation of the Defense Production Act, either of which could have a material adverse effect on our business.
- Increased information technology security threats and more sophisticated and targeted computer crime could pose a risk to our systems, networks, and products.

PART I

Item 1. Business

References to "Plus," the "Company," "we," "us" and "our" refer to Plus Therapeutics, Inc. and its consolidated subsidiaries. References to "Notes" refer to the Notes to Consolidated Financial Statements included herein (refer to Item 8).

General

Plus Therapeutics, Inc. is a U.S. pharmaceutical company developing innovative, targeted radiotherapeutics for adults and children with rare and difficult-to-treat cancers. Our novel radioactive drug formulations and therapeutic candidates are designed to deliver safe and effective doses of radiation to tumors. To achieve this, we have developed innovative approaches to drug formulation, including encapsulating radionuclides such as Rhenium isotopes with nanoliposomes and microspheres. Our formulations are intended to achieve elevated patient absorbed radiation doses and extended retention times such that the clearance of the isotope occurs after significant radiation decay, which will contribute and provide less normal tissue/organ exposure and improved safety margins.

Traditional approaches to radiation therapy for cancer such as external beam radiation have many disadvantages including continuous treatment for 4-6 weeks (which is onerous for patients), that the radiation damages healthy cells and tissue, and that the amount of radiation delivered is very limited and, therefore, is frequently inadequate to fully destroy the cancer.

Our targeted radiotherapeutic platform and unique investigational drugs have the potential to overcome these disadvantages by directing higher, more powerful radiation doses at the tumor—and only the tumor—potentially in a single treatment. By minimizing radiation exposure to healthy tissues while simultaneously maximizing efficacy, we hope to reduce the toxicity of radiation for patients, improving their quality and life expectancy. Our radiotherapeutic platform, combined with advances in surgery, nuclear medicine, interventional radiology, and radiation oncology, affords us the opportunity to target a broad variety of cancer types.

Our lead radiotherapeutic candidate, Rhenium-186 NanoLiposome ("¹⁸⁶RNL") is designed specifically to target central nervous system (CNS) cancers including recurrent glioblastoma, leptomeningeal metastases, and pediatric brain cancers by direct localized delivery utilizing approved standard-of-care tissue access such as with conduction enhanced delivery ("CED") and intraventricular brain catheters (Ommaya reservoir). Our recently acquired radiotherapeutic candidate, Rhenium-188 NanoLiposome Biodegradable Alginate Microsphere ("¹⁸⁸RNL-BAM") is designed to treat many solid organ cancers including primary and secondary liver cancers.

Our headquarters and manufacturing facilities are located in Texas and are in proximity to world-class cancer institutions and researchers. Our dedicated team of engineers, physicians, scientists, and other professionals are committed to advancing our targeted radiotherapeutic technology for the benefit of cancer patients and healthcare providers worldwide and our current pipeline is focused on treating rare and difficult-to-treat cancers with significant unmet medical needs.

Pipeline

Our most advanced investigational drug, ¹⁸⁶RNL, is a patented radiotherapy potentially useful for patients with central nervous system (CNS) and other cancers. Preclinical study data describing the use of ¹⁸⁶RNL for several cancer targets have been published in peer-reviewed journals. Besides glioblastoma, leptomeningeal metastases, and pediatric brain cancer, ¹⁸⁶RNL has been reported to have potential applications for head and neck cancer, ovarian cancer, breast cancer and peritoneal metastases.

The ¹⁸⁶RNL technology was part of a licensed radiotherapeutic portfolio that we acquired from NanoTx, Corp. ("NanoTx") on May 7, 2020. The licensed radiotherapeutic has been evaluated in preclinical studies for several cancer targets and we have an active \$3.0 million award from U.S. National Institutes of Health/National Cancer Institute which will provide financial support for the continued clinical development of ¹⁸⁶RNL for recurrent glioblastoma through the completion of a Phase 2 clinical trial including enrollment of up to 55 patients. Thus far, 23 patients have been treated in the Phase 1 clinical trial and the Phase 2 clinical trial has not yet been initiated.

We are currently conducting the ReSPECT-GBM and ReSPECT-LM clinical trials for recurrent glioblastoma ("GBM") and leptomeningeal metastases ("LM"), respectively. In addition, we anticipate seeking FDA IND approval for the ReSPECT-PBC clinical trial for pediatric brain cancer ("PBC") in late 2022 or early 2023.

¹⁸⁶RNL versus External Beam Radiation Therapy

¹⁸⁶RNL is a novel injectable radiotherapy designed to deliver targeted, high dose radiation directly into glioblastoma tumors in a safe, effective, and convenient manner that may ultimately prolong patient survival. ¹⁸⁶RNL is composed of the radionuclide Rhenium-186 and a nanoliposomal carrier, and is infused in a highly targeted fashion, directly into the tumor via precision brain mapping and CED. Potential benefits of ¹⁸⁶RNL compared to standard external beam radiotherapy or EBRT include:

- The 186RNL radiation dose delivered to patients may be up to 20 times greater than what is possible with commonly used external beam radiation therapy (“EBRT”).
- 186RNL can be visualized in real-time during administration, possibly giving clinicians better control of radiation dosing and distribution.
- 186RNL potentially more effectively treats a bulk tumor and microscopic disease that has already invaded healthy tissue.
- 186RNL is infused directly into the targeted tumor, bypassing the blood brain barrier, which reduces radiation exposure to healthy cells, in contrast to EBRT which passes through normal tissue to reach the tumor, continuing its path through the tumor, hence being less targeted and selective.
- 186RNL is given during a single, short, in-patient hospital visit, and is available in all hospitals with nuclear medicine and neurosurgery, while EBRT requires out-patient visits 5 days a week for approximately 4-6 weeks.

ReSPECT-GBM Trial for Recurrent GBM

Glioblastoma is the most common, complex, and aggressive primary brain cancer in adults. Annually in the U.S., there are 12,900 GBM cases diagnosed and approximately 10,000 patients succumb to the disease each year. The average life expectancy with primary glioblastoma is less than 24 months, with a one-year survival rate of 40.8% and a five-year survival rate of only 6.8%. GBM often causes and presents with headaches, seizures, vision changes and other significant neurological complications. Despite the best available medical treatments to eliminate the initial brain tumor, some microscopic disease frequently remains, with tumor regrowth within months. Approximately 90% or more of patients with primary GBM experience tumor recurrence. Complete surgical removal of GBM is not typically possible and GBM is often resistant or quickly develops resistance to most available therapies. Even today, the treatment of GBM remains a significant challenge and it has been nearly a decade since the FDA approved a new therapy for this disease.

For recurrent GBM, there are few currently approved treatments that in the aggregate, provide only marginal survival benefit. Furthermore, these therapies are associated with significant side effects, which limit dosing and prolonged use.

While EBRT has been shown to be safe and effective in many malignancies including glioblastoma, the maximum possible administered dose is limited by toxicity to the normal tissues surrounding the malignancy. In contrast, targeted radiopharmaceuticals that precisely deliver radiation in the form of beta particles such as Iodine-131 for thyroid cancer, are known to be very safe and effective and minimize exposure to normal cells and tissues.

Interim results from our ongoing Phase 1/2a ReSPECT-GBM trial (ClinicalTrials.gov NCT01906385), suggest beta particle energy from our lead investigational drug 186RNL may also have utility in treating GBM and other malignancies. More specifically, the preliminary data from our Phase 1/2a ReSPECT-GBM trial indicates that radiation, in the form of high energy beta particles or electrons, can be effective against GBM. Thus far, we have been able to deliver up to 740 Gy of absorbed radiation to tumor issue without significant or dose limiting toxicities. In comparison, current EBRT protocols for recurrent glioblastoma typically recommend a total maximum dose of about 35 Gy.

In September 2020, the U.S. Food and Drug Administration (“FDA”) granted both Orphan Drug designation and Fast Track designations to 186RNL for the treatment of patients with GBM.

186RNL is presently under clinical investigation in a multicenter, sequential cohort, open-label, volume and dose escalation study of the safety, tolerability, and distribution of 186RNL given by CED to patients with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment (NCT01906385). The study uses a modified Fibonacci dose escalation, followed by a planned expansion at the maximum tolerated dose (MTD) / maximum feasible dose (MFD) to determine efficacy. The trial is funded through Phase 2 in large part by a NIH/NCI grant. The planned enrollment in the NIH/NCI grant is 21 patients in the dose-escalation part of the study and 34 patients in the expansion cohort. The study is in its 8th dosing administration cohort and is under development and internal review to potentially advance to a Phase 2 or registration trial.

At the Society for Neuro-Oncology Annual Meeting in November 2021, we presented patient data which at that time included the results for 22 patients treated in the ReSPECT-GBM trial. The trial, thus far, has shown that CED in recurrent GBM patients is feasible. Median absorbed dose to the tumor volume across all subjects in the first eight cohorts (n=22) was 267.5 Gy (range 8.9-740). In a subset of patients in whom tumor coverage was greater than or equal to 75%, the median absorbed dose was 405 Gy (range 146-593). By contrast, the median absorbed doses to the whole brain and the total body across all subjects were 0.55 Gy (range 0.001-2.728) and 0.09 Gy (range 0.001-0.182), respectively. Small doses, as delivered to the body, are typically well-tolerated. Based on observed and reported patient protocol activity and all available adverse event (AE) data, 186RNL has been well-tolerated. No AEs with an outcome of death or study drug-related serious AEs have been reported. Furthermore, no patient was discontinued

from the study because of an AE. All AEs have been mild or moderate (Grade 1 or 2) in intensity, except for one case of Grade 3 vasogenic edema, which was considered by the investigator to be unrelated to the study drug. AEs considered by the investigator to be at least possibly related to ¹⁸⁶RNL have included Grade 1 to 2 skin and soft tissue infection, intermittent cephalgia, neck and jaw pain, nausea with or without vomiting, constipation, increased lethargy, difficulty walking (gait disturbance), worsening double vision, and dysuria. Scalp discomfort and tenderness related to the surgical procedure has also been reported.

In the 22 subjects with recurrent GBM receiving a single administration of ¹⁸⁶RNL, the mean & median overall survival ("OS") for all 22 patients as of November 2021 was 48.1 & 33.1 weeks, respectively, with 7 patients alive. In a subset of 13 patients receiving a presumed therapeutic absorbed radiation dose to the tumor (>100 Gy), the mean & median OS was 64.8 & 47.1 weeks, respectively, with 7 of 13 patients alive. In contrast, in 9 patients receiving a presumed sub-therapeutic absorbed radiation dose to the tumor (<100 Gy), the mean and median OS was 23.9 & 22.3 weeks, respectively. A Kaplan-Meier curve comparing patients with presumed therapeutic vs. sub-therapeutic radiation dose to the tumor showed a statistically significant difference between the groups ($p=.0002$). It is hypothesized that targeted infusion of ¹⁸⁶RNL into the tumor by CED, which allows us to bypass the blood-brain barrier and normal brain and external tissues, significantly spares normal tissues from radiation exposure and potential toxicity and concentrates radiation to the tumor and surrounding region of interest.

ReSPECT-LM Clinical Trial for Leptomeningeal Metastases

LM is a rare complication of cancer in which the disease spreads to the membranes (meninges) surrounding the brain and spinal cord. The incidence of LM is growing and occurs in approximately 5% of people with late-stage cancer, or 110,000 people in the U.S. each year. It is highly lethal with an average 1-year survival of just 7%. LM occurs with cancers that are most likely to spread to the central nervous system. The most common cancers to spread to the leptomeninges are breast cancer, lung cancer, melanoma and gastrointestinal cancers---though most solid tumors have the potential for LM spread.

The ReSPECT-LM Phase 1 clinical trial (ClinicalTrials.gov NCT05034497) is predicated in part upon preclinical studies in which tolerance to doses of ¹⁸⁶RNL as high as 1,075 Gy was shown in animal models with LM without significant observed toxicity. Furthermore, treatment led to marked reduction in tumor burden in both C6 and MDA-231 LM models.

In October 2021, the FDA announced clearance of our Investigational New Drug ("IND") application for ¹⁸⁶RNL for the treatment of LM. Subsequently, in November 2021, the FDA granted a Fast Track designation for ¹⁸⁶RNL for the treatment of leptomeningeal metastases. The Company initiated the trial and began screening patients for the ReSPECT-LM Phase 1 clinical trial in Q4 2021.

The ReSPECT-LM multi-center, sequential cohort, open-label, dose escalation study is evaluating the safety, tolerability, and distribution of ¹⁸⁶RNL via intrathecal infusion to the ventricle of patients with LM after standard surgical, radiation, and/or chemotherapy treatment. The primary endpoint of the study is the incidence and severity of adverse events and dose limiting toxicities.

ReSPECT-PBC Clinical Trial for Pediatric Brain Cancer

In August 2021, we announced plans for treating pediatric brain cancer at the 2021 American Association of Neurological Surgeons (AANS) Annual Scientific Meeting. In July 2021, we reported that we had received FDA feedback pertaining to a pre-IND meeting briefing package in which the FDA stated that we are not required to perform any additional preclinical or toxicology studies.

Currently, the Company plans to investigate the use of ¹⁸⁶RNL in 2 pediatric brain cancers. High-grade glioma ("HGG") is a rare, fast-growing CNS tumor that forms in glial cells of the brain and spinal cord. It can be found almost anywhere within the CNS, but is most commonly within the supratentorium in children ages 15-19. HGG tumors in children act differently from those in adults, causing headaches, seizures, and difficulty achieving developmental milestones depending on the tumor location. Approximately 360-400 children are diagnosed with HGG annually in North America and the 5-year survival rate is approximately 20%. In contrast, ependymoma is a rare, slow- or fast-growing (depending on the grade) primary CNS tumor that forms in ependymal cells in the brain and spinal cord—and may spread throughout the CNS, though infrequently. All ependymomas can recur, but patients are often tumor-free for years before testing shows tumor regrowth, either at the initial tumor site or elsewhere within the CNS. Symptoms depend on tumor location and size, usually including irritability, sleeplessness, vomiting, nausea, back pain, arm/leg weakness, and headaches.

Approximately 250 children are diagnosed with ependymoma annually in the U.S. while 71% of children with Grade II and 57% with Grade III survive 5 years from diagnosis.

Based on the aggregate preclinical and clinical work completed to date in adult recurrent glioblastoma, we hypothesize that ¹⁸⁶RNL may offer potential clinical benefit for PBCs, such as high-grade glioma and ependymoma. We intend to submit an IND application to the FDA for ¹⁸⁶RNL for the treatment of PBC (high-grade glioma and ependymoma) in late 2022 or early 2023.

Rhenium-188 NanoLiposome Biodegradable Alginate Microsphere Technology

In January 2022, we announced that we licensed Biodegradable Alginate Microsphere (“BAM”) patents and technology from The University of Texas Health Science Center at San Antonio (“UT Health Science Center at San Antonio”) to expand our tumor targeting capabilities and precision radiotherapeutics pipeline. We intend to combine our Rhenium NanoLiposome technology with the BAM technology to create a novel radioembolization technology. Initially, we intend to utilize the Rhenium-188 isotope, ¹⁸⁸RNL-BAM for the intra-arterial embolization and local delivery of a high dose of targeted radiation for a variety of solid organ cancers such as hepatocellular cancer, hepatic metastases, pancreatic cancer and many others.

Preclinical data from an *ex vivo* embolization experiment in which Tc-BAM was intra-arterially delivered to a bovine kidney perfusion model was presented at the recent 2021 Society of Interventional Radiology (“SIR”) Annual Scientific Meeting. The study concluded that the technology required for radiolabeling BAM could successfully deliver, embolize and retain radiation in the target organ. ¹⁸⁸RNL-BAM is a preclinical investigational drug we intend to further develop and move into clinical trials. Specifically, in 2022, we intend to transfer the ¹⁸⁸RNL-BAM technology from UT Health Science Center at San Antonio, fabricate and scale the drug product, and complete certain preclinical studies to support a future FDA IND submission. Our likely initial clinical target is liver cancer which is the 6th most common and 3rd deadliest cancer worldwide. It is a rare disease with increasing U.S. annual incidence (42,000) and deaths (30,000).

Licensing

On December 31, 2021, we entered into a Patent and Technology License Agreement (the “UTHSA License Agreement”) with UT Health Science Center at San Antonio, pursuant to which UT Health Science Center at San Antonio granted us an irrevocable, perpetual, exclusive, fully paid-up license, with the right to sublicense and to make, develop, commercialize and otherwise exploit certain patents, know-how and technology related to the development of BAM containing nanoliposomes loaded with imaging and/or therapeutic payloads. Therapeutic payloads may include radiotherapeutics, chemotherapeutics, or thermotherapeutics.

The BAM technology is delivered into the vascular system via standard interventional vascular catheters that are placed precisely in the vessels feeding tumors. Once injected, BAM blocks all blood flow to the tumors and simultaneously delivers very high doses of cytotoxic compounds including radiation for an extended time. Many days later, the BAM are physiologically metabolized and excreted from the body.

The Company currently anticipates that it will initially focus on developing ¹⁸⁸RNL-BAM as a next-generation radioembolization therapy for liver cancer, in which BAM blocks the hepatic artery segments that supply blood to the malignant tumor while also providing ¹⁸⁸RNL radiotherapy directly to the tumor and surrounding tissue. According to the American Cancer Society, liver cancer is a rare disease with an increasing annual incidence and 5-year overall survival of only 20%. Per internal Company estimates, the global opportunity for localized embolization, chemoembolization, and radioembolization therapies for primary (hepatocellular carcinoma) and secondary (typically metastatic colorectal cancer, for example) liver cancer is \$1.3 billion.

The financial terms of the exclusive license agreement are primarily success-based with milestone and royalty payments contingent on achieving key clinical, regulatory and sales milestones.

The initial inventions and work behind the licensed patents and technologies were developed and led by William Phillips MD, Professor of Nuclear Medicine and team at UT Health Science Center at San Antonio. The ¹⁸⁸RNL-BAM technology incorporates Rhenium-188, or ¹⁸⁸Re, a unique isotope for radiotherapeutic embolization owing to its emission of a high energy electron (beta particle), half-life and a path length. ¹⁸⁸Re also emits gamma energy that permits high quality, real-time imaging of the BAM construct delivery localization and confirmation. BAMs are not permanent and are anticipated to degrade over time, allowing restoration of blood flow, decreasing radiation resistance, and allowing for safer physiological clearance of ¹⁸⁸Re through the kidneys, which may minimize bone marrow toxicity.

The transaction terms included an upfront payment in cash. Furthermore, we may pay development and sales milestone payments and a tiered single-digit royalty on U.S. and European sales. In addition, we may be obligated to pay an annual maintenance fee starting 2024.

On March 29, 2020, we entered into a Patent and Know-How License Agreement (the “NanoTx License Agreement”) with NanoTx, pursuant to which NanoTx granted us an irrevocable, perpetual, exclusive, fully paid-up license, with the right to sublicense and to make, develop, commercialize and otherwise exploit certain patents, know-how and technology related to the development of radiolabeled nanoliposomes.

The transaction terms included an upfront payment of \$400,000 in cash and \$300,000 in our voting stock (the “Equity Compensation”). Furthermore, we may pay up to \$136.5 million in development and sales milestone payments and a tiered single-digit royalty on U.S. and European sales.

The licensed drug portfolio is anchored around nanoliposome-encapsulated radionuclides for several cancer targets. The lead drug asset is ¹⁸⁶RNL, initially being developed for recurrent GBM. ¹⁸⁶RNL is infused directly into the brain tumor via precision brain mapping and CED catheters to administer very high therapeutic doses of radiation to patients whose cancer has recurred following initial surgical resection and treatment with chemotherapy and radiation.

The licensed radiolabeled nanoliposome platform was developed by a multi-institutional consortium based in Texas at the Mays Cancer Center / UT Health Science Center at San Antonio MD Anderson Cancer Center led by Dr. Andrew Brenner, MD, PhD, who is the Koltz Chair in Neuro-Oncology Research and Co-Leader of the Experimental and Developmental Therapeutics Program. The technology was previously owned by NanoTx and funded by both the National Institutes of Health/National Cancer Institute (NIH/NCI) and the Cancer Prevention and Research Institute of Texas (CPRIT). There is an active \$3M award from NIH/NCI which will financially support the continued clinical development of ¹⁸⁶RNL for recurrent glioblastoma.

Manufacturing

We have a dedicated nanoparticle research & development facility located in San Antonio, Texas. The facility and processes are designed to comply with current good manufacturing practices (“cGMP”) per FDA and EMA regulations for the manufacture of drug candidates for clinical trials, research, and development. As described below, upon completion of the research and development phase of a drug candidate, certain parts of the manufacturing processes for such candidate may be transferred to contract manufacturers to support clinical trials and commercial release. Upon approval of our drug candidates, our manufacturing capabilities will include validated manufacturing processes for the drug product as well as a quality assurance product release process with the ability to ultimately scale-up the process to meet increasing market demands. We believe our strategic investments in our analytical, development and manufacturing capabilities, including personnel with expertise from drug discovery through drug development, will allow us to advance our product candidates more quickly. Expertise gained in manufacturing our drug products may be applied to other formulations in the future, further leveraging our capabilities. Our San Antonio facility enables us to develop drug substances, and drug products, in a cost-effective manner while retaining control over the intellectual property, process and timing of development activities. The use of a qualified Contract Drug Manufacturing Organization (“CDMO”) will be utilized to perform various manufacturing processes as we deem appropriate to meet our operational objectives. In addition, we have entered into master services agreements (“MSAs”) with third parties, including Piramal Pharma Solutions, Inc. (“Piramal”), ABX Advanced Biochemical Compounds GmbH, IsoTherapeutics Group, LLC, and Radiomedix, Inc. in connection with the development, manufacture, and supply of our ¹⁸⁶RNL drug product.

Competition

We will compete primarily on the basis of the safety and efficacy of our therapies across a broad range of clinical indications to address significant unmet medical and market needs, supported by our brand name, pricing, products, published clinical data, regulatory approvals, and reimbursement. We believe that our continued success depends on our ability to:

- develop and innovate our product and technology platforms;
- initiate new and advance existing clinical development programs;
- secure and maintain regulatory agency approvals;
- build and expand our commercial footprint;
- produce high quality products per our specifications and in line with customer expectations;
- achieve improved economies of scale;
- generate and protect intellectual property;
- hire and retain key talent; and
- successfully execute acquisition, licensing, and partnership activities.

Competition for ¹⁸⁶RNL may come from a single or combination therapy in the future.

Recurrent Glioblastoma

Bayer, VBL Therapeutics, Kintara Therapeutics, Istari Oncology, Medicenna, MediciNova, Chimerix, PharmAbcine, VBI Vaccines, Ziopharm Oncology, Bristol Myers Squibb, ImmunoCellular, Novartis, EnGeneIC, Berg, Bexion, and others have reported drug development programs at various clinical stages for recurrent glioblastoma and Plus Therapeutics continues to monitor their progress.

Leptomeningeal Metastases

AngioChem, Merck, Bristol Myers Squibb, Roche, Y-mAbs, Kazia, AstraZeneca, Pfizer, and others have reported drug development programs at various clinical stages for leptomeningeal metastases and Plus Therapeutics continues to monitor their progress.

Pediatric Brain Cancer

AstraZeneca, Bristol Myers Squibb, Chimerix, Celgene, Eli Lilly, Nektar Therapeutics, Istari Oncology, Novartis, NovoCure, Takeda, Y-mAbs, Cellectar, and others have reported drug development programs at various clinical stages for pediatric brain cancer and Plus Therapeutics continues to monitor their progress.

Competition for ¹⁸⁸RNL-BAM may come from a single or combination therapy in the future.

Liver Cancer

Boston Scientific, SIR-TEX, Terumo, ABK Biomedical, and others have reported radioembolization therapy product development programs for liver cancer and Plus Therapeutics continues to monitor their progress.

Intellectual Property

Our success depends in large part on our ability to protect our proprietary technology, and to operate without infringing on the proprietary rights of third parties. We rely on a combination of patent, trade secret, copyright and trademark laws, as well as confidentiality agreements, licensing agreements and other agreements, to establish and protect our proprietary rights. Our success also depends, in part, on our ability to avoid infringing patents issued to others.

We license the proprietary formulation and proprietary methods of manufacture of the nanoliposome-encapsulated radionucleotides. ¹⁸⁶RNL and ¹⁸⁸RNL are covered by U.S. Patent No. 7,718,160, (the “¹⁶⁰ Patent”) which will expire in December 2026. Patent term extension, codified in 35 U.S.C. §156, provides a means of recapturing time lost during the regulatory approval process. Based upon this regulation, we will apply for patent term extension for the ‘¹⁶⁰ Patent for the time equal to the regulatory review period for ¹⁸⁶RNL. This has the potential to extend patent coverage for this product for at least another 5 years. The ‘¹⁶⁰ Patent covers the method of manufacture of ¹⁸⁶RNL and product-by-process claims. The patent family also contains granted patents in Canada (Patent No. 2,490,959), Europe (Patent No. EP1536843), and Australia (Patent No. 2003241598), which are expected to expire in May 2023. We are not aware of any valid patent claims that would be infringed by ¹⁸⁶RNL or ¹⁸⁸RNL.

¹⁸⁸RNL is also covered by U.S. Patent Appl. No. 17/611,929 titled Radiotherapeutic Microspheres. This application was filed on November 17, 2021, and is expected to expire on May 21, 2040, not including any patent term adjustment or patent term extension. The patent family also contains applications in Israel (IL288275), China (CN202080037924), Saudi Arabia (SA521430917), Korea (KR102021704215), Europe (EP2020809701), Australia (AU2020280044), Malaysia (MYPI2021006914), Singapore (SG11202112919), Brazil (BR112021023449), New Zealand (NZ782354), and Canada (CA3140856).

¹⁸⁸RNL is also covered by U.S. Patent Appl. No. 63/157,546 titled Loading Alginate Microspheres. This application was filed March 5, 2021.

We also own PCT Application No. PCT/US2021/059969, titled Radiolabeled Liposomes and Methods of Use Thereof, which is directed to methods of treating cancer comprising administering ¹⁸⁶Re and ¹⁸⁸Re nanoliposomes via convection-enhanced delivery. This application was filed on November 18, 2021, and is expected to expire in November 2041, not including any patent term adjustment or patent term extension.

We also own U.S. Patent Appl. No. 63/302,953, titled Radiolabeled Liposomes and Methods for Treating Leptomeningeal Metastases, which is directed to methods of treating cancer comprising administering ¹⁸⁶Re and/or ¹⁸⁸Re nanoliposomes via an intraventricular reservoir. This application was filed on January 25, 2022, and is expected to expire in January 2043, not including any patent term adjustment or patent term extension.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources. Our nanoparticle oncology drug candidates

must receive regulatory approvals from the EMA and the FDA and from other government authorities prior to sale of the product candidates in their respective jurisdictions.

FDA Approval Process

In the United States, pharmaceutical products are subject to extensive regulation by the FDA. Manufacturers of pharmaceutical products may also be subject to state and local regulation. The Federal Food, Drug, and Cosmetic Act, or the FDC Act, and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. Failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as the imposition by the FDA or an institutional review board, or IRB, of a clinical hold, FDA refusal to approve pending new drug applications, or NDAs, or supplements, withdrawal of approval, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties, and criminal investigation, penalties, or prosecution.

Product development for a new product or certain changes to an approved product in the United States typically involves:

- Completion of preclinical laboratory studies, formulation studies, and animal studies, some in compliance with the FDA's Good Laboratory Practices, or GLP, regulations, and the Animal Welfare Act administered and enforced by the United States Department of Agriculture;
- Submission to the FDA of an investigational new drug application, or IND, to support human clinical testing, which must become effective before clinical testing may commence;
- Approval by an IRB before each trial may be initiated at each clinical site;
- Performance of adequate and well-controlled clinical trials under protocols submitted to the FDA and reviewed and approved by each IRB, conducted in accordance with federal regulations and current Good Clinical Practices, or GCP, to establish the safety and effectiveness of the drug for each indication for which FDA approval is sought;
- Submission of an NDA to the FDA;
- Satisfactory completion of an FDA Advisory Committee review, if applicable;
- Satisfactory completion of an FDA inspection of the manufacturing facilities at which the product candidate is produced to assess compliance with current good manufacturing practices, or cGMP, and to assure that the facilities, methods and controls are adequate; and
- FDA review and approval of the NDA.

Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity, and novelty of the product or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation, and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product candidate. The conduct of some preclinical tests must comply with federal regulations and requirements, including as applicable, GLP and the Animal Welfare Act. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls, and a proposed clinical trial protocol. Additional preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin.

Clinical trials involve the administration of the investigational drug product to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND. Foreign studies conducted under an IND generally must meet the same requirements that apply to studies being conducted in the United States. The informed written consent of each study patient must be obtained before the patient may begin participation in the clinical trial. The study protocol, study plan, and informed consent forms for each clinical trial must be reviewed and approved by an IRB for each clinical site, and the study must be conducted under the auspices of an IRB for each trial site. Investigators and IRBs must also comply with FDA regulations and guidelines, including those regarding oversight of study patient informed consent, complying with the study protocol and investigational plan, adequately monitoring the clinical trial, and timely reporting of adverse events.

Clinical trials to support drug products for marketing approval are typically conducted in three sequential phases, but the phases may overlap. Phase 1 involves the initial introduction of the drug product into healthy human subjects or patients. In Phase 1 trials, the product is tested to assess safety, metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence on effectiveness. Phase 2 usually involves trials in a limited patient population to determine the effectiveness of the drug for a particular indication, dosage tolerance, and optimal dosage, and to identify common adverse effects and safety risks. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit the FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the product. In most cases, the FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug product. A single Phase 3 trial with other confirmatory evidence may be sufficient in certain instances.

The decision to suspend or terminate development of a product candidate may be made by either a health authority body, such as the FDA, by an IRB, or by a company for various reasons and during any phase of clinical trials. The FDA may order the temporary or permanent discontinuation of a clinical trial at any time or impose other sanctions if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. In most cases, in addition to sponsor oversight clinical trials are also overseen by an independent data safety monitoring board, or DSMB, which is a separate, independent group of qualified experts organized by the trial sponsor to evaluate at designated points in time whether or not a trial may move forward and/or should be modified. These decisions are based on unblinded access to data from the ongoing trial and generally involve determinations regarding the benefit-risk ratio for study patients and the scientific integrity and validity of the clinical trial.

In addition, the manufacturer of an investigational drug in a Phase 2 or Phase 3 clinical trial for a serious or life-threatening disease is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for expanded access to such investigational drug.

After completion of the required clinical testing, a drug product application is prepared and submitted to the FDA to request marketing approval for the product candidate in specific indications. FDA approval of the drug product is required before marketing of the product may begin in the United States. The drug product must include all relevant results of preclinical, clinical, and other testing and a compilation of data relating to the product candidate's pharmacology, chemistry, manufacture, and controls, including negative or ambiguous results as well as positive findings. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the product candidate to the satisfaction of the FDA. The cost of preparing and submitting a drug product application is substantial. Under the Prescription Drug User Fee Act, or PDUFA, the submission of most drug product applications is subject to a substantial application user fee, and the applicant under an approved drug product is also subject to an annual program fee for each prescription product, subject to certain limited deferrals, waivers and reductions that may be available. These fees are typically increased annually. The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. The FDA may refuse to accept for filing any NDA that it deems incomplete or not properly reviewable at the time of submission, in which case the NDA will have to be updated and resubmitted. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. The FDA's PDUFA review goal is to review 90% of priority applications within six months of filing and 90% of standard applications within 10 months of filing. Priority review may be granted to an application for a product candidate that the FDA determines has the potential to treat a serious or life-threatening condition and, if approved, would be a significant improvement in safety or effectiveness compared to available therapies. The review process for both standard and priority review may be extended by the FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission.

The FDA may also refer applications for drug candidates that present difficult questions of safety or efficacy, to an advisory committee—typically a panel that includes clinicians and other experts—for review, evaluation, and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations carefully when making decisions. Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will inspect the facility or the facilities at which the drug product is manufactured. The FDA will not approve the product unless compliance with cGMP is satisfactory and the NDA contains data that provide substantial evidence that the drug candidate is safe and effective in the intended indication.

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing, or information, in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA may issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Notwithstanding the submission of any requested

additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval and deny approval of a resubmitted NDA.

An approval letter authorizes commercial marketing of the drug candidate with specific prescribing information for specific indications. As a condition of approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug candidate outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the product. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the product's safety or efficacy.

Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing. For example, quality control and manufacturing procedures must conform, on an ongoing basis, to cGMP requirements, and the FDA periodically inspects manufacturing facilities to assess compliance with cGMP. Accordingly, manufacturers must continue to spend time, money and effort to maintain cGMP compliance. Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing an NDA.

Expedited Programs

In the United States, a product may be granted Fast Track designation if it is intended for the treatment of a serious or life-threatening condition and demonstrates the potential to address unmet medical needs for such condition. With Fast Track designation, the sponsor may be eligible for more frequent opportunities to obtain the FDA's feedback, and the FDA may initiate review of sections of an NDA before the application is complete. This rolling review is available if the applicant provides and the FDA approves a schedule for the remaining information. Even if a product receives Fast Track designation, the designation can be rescinded and provides no assurance that a product will be reviewed or approved more expeditiously than would otherwise have been the case, or that the product will be approved at all.

The FDA may designate a product candidate as a breakthrough therapy if it finds that the product candidate is intended, alone or in combination with one or more other product candidates or approved products, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. For product candidates designated as breakthrough therapies, more frequent interaction and communication between the FDA and the sponsor can help to identify the most efficient path for clinical development. Product candidates designated as breakthrough therapies by the FDA may also be eligible for 6 month priority review. The receipt of a breakthrough therapy designation for a product candidate may not result in a faster development process, review or approval compared to product candidates considered for approval under conventional FDA procedures and, in any event, does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the product candidates no longer meet the conditions for designation.

Accelerated approval under FDA regulations allows a product designed to treat a serious or life-threatening disease or condition that provides a meaningful therapeutic advantage over available therapies to be approved on the basis of either an intermediate clinical endpoint or a surrogate endpoint that is reasonably likely to predict clinical benefit. Approvals of this kind typically include requirements for confirmatory clinical trials to be conducted with due diligence to validate the surrogate endpoint or otherwise confirm clinical benefit and for all promotional materials to be submitted to the FDA for review prior to dissemination.

The FDA may grant priority review to a product candidate, which sets the target date for FDA action on the application at six months from FDA filing, or eight months from the sponsor's submission. Priority Review may be granted where a product is intended to treat a serious or life-threatening disease or condition and, if approved, has the potential to provide a safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in safety or efficacy compared to available therapy. If criteria are not met for Priority Review, the standard FDA review period is ten months from FDA filing or 12 months from sponsor submission. Priority Review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drug candidate products intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making a product available in the United States for such disease or condition will be recovered from sales of the product in the United States.

After the FDA grants orphan drug designation, the generic identity of the drug product and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. However, orphan drug designation does entitle a party to financial incentives, such as opportunities for grant funding towards clinical trial costs, tax credits for certain research and user fee waivers under certain circumstances. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to seven years of market exclusivity, which means the FDA may not approve any other application for a biologic for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity. The FDA can revoke a product's orphan drug exclusivity under certain circumstances, including when the product sponsor is unable to assure the availability of sufficient quantities of the product to meet patient needs. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same biologic for a different disease or condition.

Rare Pediatric Disease Priority Review Voucher Program

Under the Rare Pediatric Disease Priority Review Voucher program, the FDA may grant Rare Pediatric Disease designation for serious and life-threatening diseases that primarily affect children ages 18 years or younger and fewer than 200,000 individuals in the United States. The FDA may award a priority review voucher to the sponsor of an approved marketing application for a product that treats or prevents a Rare Pediatric Disease. The voucher entitles the sponsor to priority review of one subsequent marketing application.

A voucher may be awarded only for an application that:

- is a human drug application for the prevention or treatment of a Rare Pediatric Disease and does not contain an active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application;
- FDA deems eligible for priority review;
- is an original NDA or BLA;
- relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population;
- does not seek approval for an adult indication in the original rare pediatric disease product application; and
- is approved after September 30, 2016.

Before NDA or IND approval, the FDA may designate a product in development as a product for a rare pediatric disease, but such designation is not required to receive a voucher.

To receive a rare pediatric disease priority review voucher, a sponsor must notify the FDA, upon submission of the NDA or IND, of its intent to request a voucher. If the FDA determines that the NDA or IND is a rare pediatric disease product application, and if the NDA or IND is approved, the FDA will award the sponsor of the NDA or IND a voucher upon approval of the NDA or IND. The FDA may revoke a rare pediatric disease priority review voucher if the product for which it was awarded is not marketed in the U.S. within 1 year of the product's approval.

The voucher, which is transferable to another sponsor, may be submitted with a subsequent application and entitles the holder to priority review of the application. The sponsor submitting the priority review voucher must notify the FDA of its intent to submit the voucher with the application at least 90 days prior to submission of the application and must pay a priority review user fee in addition to any other required user fee. The FDA must take action on an application under priority review within six months of receipt of the application.

The Rare Pediatric Disease Priority Review Voucher program was renewed as part of the 2021 Coronavirus Response and Relief Supplemental Consolidated Appropriations Act, allowing a product that is designated as a product for a rare pediatric disease prior to September 30, 2024 to be eligible to receive a rare pediatric disease priority review voucher upon approval of a qualifying NDA after September 30, 2024. After September 30, 2026, the FDA may not award any rare pediatric disease priority review vouchers.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of the FDA-regulated products are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed in certain circumstances for up to two years after the date of

completion of the trial. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

Pediatric Information

Under the Pediatric Research Equity Act, or PREA, certain NDAs must include an assessment, generally based on clinical trial data, of the safety and effectiveness of the product candidate in relevant pediatric populations. The FDA may waive or defer the requirement for a pediatric assessment, either at a company's request or by its own initiative, including waivers for certain products not likely to be used in a substantial number of pediatric patients. Products with orphan drug designation are exempt from these requirements for orphan-designated indications with no formal waiver process required. Any original NDA submitted on or after August 18, 2020 for a new active ingredient must contain reports on molecularly targeted pediatric cancer investigations, unless the requirement is waived or deferred, if the drug that is the subject of the application is intended for the treatment of an adult cancer and is directed at a molecular target that the FDA has determined is substantially relevant to the growth or progression of a pediatric cancer. This requirement applies even if the adult cancer indication does not occur in the pediatric population, and even if the drug is for an adult indication for which orphan designation has been granted.

Under the Pediatric Research Equity Act, or PREA, certain NDAs must include an assessment, generally based on clinical trial data, of the safety and effectiveness of the product candidate in relevant pediatric populations. The FDA may waive or defer the requirement for a pediatric assessment, either at a company's request or by its own initiative, including waivers for certain products not likely to be used in a substantial number of pediatric patients. Products with orphan drug designation are exempt from these requirements for orphan-designated indications with no formal waiver process required. Any original NDA submitted on or after August 18, 2020 for a new active ingredient must contain reports on molecularly targeted pediatric cancer investigations, unless the requirement is waived or deferred, if the drug that is the subject of the application is intended for the treatment of an adult cancer and is directed at a molecular target that the FDA has determined is substantially relevant to the growth or progression of a pediatric cancer. This requirement applies even if the adult cancer indication does not occur in the pediatric population, and even if the drug is for an adult indication for which orphan designation has been granted.

Patent Term Restoration

After approval, owners of relevant drug patents may apply for up to a five-year patent extension as compensation for patent term lost during product development and the FDA regulatory review process. The allowable patent term extension is calculated as one half of the drug's testing phase—the time between the effective date of an IND and NDA submission—and all of the review phase—the time between NDA submission and approval, up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years. Only one patent applicable to an approved product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The United States Patent and Trademark Office, or USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

For patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the USPTO must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which an NDA has not been submitted.

Market Exclusivity

In the United States and elsewhere, certain regulatory exclusivities and patent rights can provide an approved drug product with protection from certain competitors' products for a period of time and within a certain scope. In the United States, those protections include regulatory exclusivity under the Hatch-Waxman Act, which provides periods of exclusivity for a branded drug product that would serve as an RLD for a generic drug applicant filing an ANDA under section 505(j) of the FD&C Act or as a listed drug for an applicant filing an NDA under section 505(b)(2) of the FD&C Act. If such a product is a "new chemical entity" ("NCE") generally meaning that the active moiety has never before been approved in any drug, there is a period of five years from the product's approval during which the FDA may not accept for filing any ANDA or 505(b)(2) application for a drug with the same active moiety. An ANDA or 505(b)(2) application may be submitted after four years, however, if the sponsor of the application makes a Paragraph IV certification (as described above). Such a product that is not an NCE may qualify for a three-year period of exclusivity if its NDA contains new clinical data (other than bioavailability studies), derived from studies conducted by or for the sponsor, that were necessary for approval. In this instance, the three-year exclusivity period does not preclude filing or review of an ANDA or 505(b)(2) application; rather, the FDA is precluded from granting final approval to the ANDA or 505(b)(2) application until three years after approval of the RLD. This three-year exclusivity applies only to the conditions of approval that required submission of the clinical data.

Post-Approval Regulation

Once approved, drug products are subject to continuing extensive regulation by the FDA. If ongoing regulatory requirements are not met, or if safety problems occur after a product reaches market, the FDA may take actions to change the conditions under which the product is marketed, such as requiring labeling modifications, restricting distribution, or even withdrawing approval. In addition to FDA regulation, our business is also subject to extensive federal, state, local and foreign regulation.

Good Manufacturing Practices. Companies engaged in manufacturing drug products or their components must comply with applicable cGMP requirements, which include requirements regarding organization and training of personnel, building and facilities, equipment, control of components and drug product containers, closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls and records and reports. The FDA inspects equipment, facilities and manufacturing processes before approval and conducts periodic re-inspections after approval. If, after receiving approval, a company makes a material change in manufacturing equipment, location, or process (all of which are, to some degree, incorporated in the NDA), additional regulatory review and approval may be required. Failure to comply with applicable cGMP requirements or the conditions of the product's approval may lead the FDA to take enforcement actions, such as issuing a warning letter, or to seek sanctions, including fines, civil penalties, injunctions, suspension of manufacturing operations, imposition of operating restrictions, withdrawal of FDA approval, seizure or recall of products, and criminal prosecution. Although we periodically monitor FDA compliance of the third parties on which we rely for manufacturing our product candidates, we cannot be certain that our present or future third-party manufacturers will consistently comply with cGMP or other applicable FDA regulatory requirements.

Sales and Marketing. Once a product is approved, the advertising, promotion and marketing of the product will be subject to close regulation, including with regard to promotion to healthcare practitioners, direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities and promotional activities involving the internet. In addition to FDA restrictions on marketing of pharmaceutical products, state and federal fraud and abuse laws have been applied to restrict certain marketing practices in the pharmaceutical industry. Failure to comply with applicable requirements in this area may subject a company to adverse publicity, investigations and enforcement action by the FDA, the Department of Justice, the Office of the Inspector General of the Department of Health and Human Services, and/or state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products.

Other Requirements. Companies that manufacture or distribute drug products pursuant to approved NDAs must meet numerous other regulatory requirements, including adverse event reporting, submission of periodic reports, and record-keeping obligations.

Other U.S. Healthcare Laws and Compliance Requirements

In the United States, our activities are potentially subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services (e.g., the Office of Inspector General), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, sales, marketing and scientific/educational grant programs must comply with the anti-fraud and abuse provisions of the Social Security Act, the false claims laws, the privacy provisions of the Health Insurance Portability and Accountability Act, or HIPAA, and similar state laws, each as amended.

The federal Anti-Kickback Statute prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term remuneration has been interpreted broadly to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. The exceptions and safe harbors are drawn narrowly and practices that involve remuneration that may be alleged to be intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. Our practices may not in all cases meet all of the criteria for protection under a statutory exception or regulatory safe harbor.

Additionally, the intent standard under the Anti-Kickback Statute was amended by the Affordable Care Act, or ACA, to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in

order to have committed a violation. In addition, the ACA codified case law 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 federal False Claims Act (discussed below).

The civil monetary penalties statute imposes penalties against any person or entity who, among other things, is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The federal False Claims Act prohibits, among other things, any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to, or approval by, the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes “any request or demand” for money or property presented to the U.S. government. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies’ marketing of the product for unapproved, and thus generally non-reimbursable, uses.

HIPAA created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device, a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. We may be subject to data privacy and security regulations by both the federal government and the states in which we conduct our business. HIPAA, and its implementing regulations, imposes requirements relating to the privacy, security and transmission of individually identifiable health information. In addition, state laws govern 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.

Additionally, the federal Physician Payments Sunshine Act within the ACA, and its implementing regulations, require that certain manufacturers of drugs, devices, biological and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program (with certain exceptions) to report information related to certain payments or other transfers of value made or distributed to physicians and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members. The reported data are posted in searchable form on a public website on an annual basis. Failure to submit required information may result in civil monetary penalties. Effective January 1, 2022, we are required to report on transfers of value to physician assistants, nurse practitioners or clinical nurse specialists, certified registered nurse anesthetists, and certified nurse-midwives.

In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of drug and biological products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Several states have enacted legislation requiring pharmaceutical and biotechnology companies to establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical and biotechnology companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

If our operations are found to be in violation of any of the federal and state healthcare laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including without limitation, civil, criminal and/or administrative penalties, damages, fines, disgorgement, exclusion from participation in government programs, such as Medicare and Medicaid, injunctions, private “qui tam” actions brought by individual whistleblowers in the name of the government, or refusal to allow us to enter into government contracts, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend, in part, on the extent to which third-party payors provide coverage, and establish adequate reimbursement levels for such products. In the United States, third-party payors include federal and state healthcare programs, private managed care providers, health insurers and other organizations. The process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the price of a product or for establishing the reimbursement rate that such a payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the FDA-approved products for a particular indication. Third-party payors are increasingly challenging the price, examining the medical necessity and reviewing the cost-effectiveness of medical products, therapies and services, in addition to questioning their safety and efficacy. We may need to conduct expensive pharmaco-economic studies in order to demonstrate the medical necessity and cost-effectiveness of our product candidates, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage for the product. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

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

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

Healthcare Reform

The ACA has substantially changed some aspects of healthcare financing and delivery by both governmental and private insurers. The ACA has affected existing government healthcare programs and resulted in the development of new programs.

Among the ACA provisions of importance to the pharmaceutical and biotechnology industries, in addition to those otherwise described above, are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain specified branded prescription drugs and biologic agents apportioned among these entities according to their market share in some government healthcare programs, that began in 2011;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, retroactive to January 1, 2010, to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively and capped the total rebate amount for innovator drugs at 100% of the Average Manufacturer Price, or AMP (which cap is now set to be removed effective January 1, 2024, which could increase our rebate liability particularly as we could be subject to an additional rebate in the amount that our AMP has exceeded the pace of inflation, if any);
- a Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals beginning in 2014 and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the 340B drug discount program; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

The Tax Cuts and Jobs Act was signed into law in December 2017, which eliminated certain requirements of the ACA, including the individual mandate. We cannot predict whether these challenges will continue or whether other proposals will be made or adopted, or what impact these efforts may have on us. It is possible that the ACA, as currently enacted or may be amended in the future, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, and new payment methodologies and in additional downward pressure on coverage and payment and the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products. We cannot be sure whether additional legislative changes will be enacted in the United States or outside of the United States, or whether regulatory changes, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be.

Other legislative changes relating to reimbursement have been adopted in the U.S. since the ACA was enacted. For example, on August 2, 2011, the Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals for spending reductions. The Joint Select Committee did not achieve a targeted deficit reduction, which triggered the legislation's automatic reductions. In concert with subsequent legislation, this has resulted in aggregate reductions to Medicare payments to providers of, on average, 2% per fiscal year through 2030 (with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic). The law provides for 1% Medicare sequestration in the second quarter of 2022 and allows the full 2% sequestration thereafter until 2030. To offset the temporary suspension during the COVID-19 pandemic, in 2030, the sequestration will be 2.25% for the first half of the year, and 3% in the second half of the year. As long as these cuts remain in effect, they could adversely impact payment for any products we may commercialize in the future. We expect that additional federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, and in turn could significantly reduce the projected value of certain development projects and reduce our profitability.

Additional legislative changes, regulatory changes, or guidance could be adopted, which may impact the marketing approvals and reimbursement for our product candidates. For example, there has been increasing legislative, regulatory, and enforcement interest in the United States with respect to drug pricing practices. There have been several Congressional inquiries and proposed and enacted federal and state legislation and regulatory initiatives designed to, among other things, bring more transparency to product pricing, evaluate the relationship between pricing and manufacturer patient programs, and reform government healthcare program reimbursement methodologies for drug products. If healthcare policies or reforms intended to curb healthcare costs are adopted or if we experience negative publicity with respect to pricing of our products or the pricing of pharmaceutical drugs generally, the prices that we charge for any approved products may be limited, our commercial opportunity may be limited and/or our revenues from sales of our products may be negatively impacted. CMS issued a final regulation, which became effective on April 1, 2016, to implement the changes to the Medicaid Drug Rebate Program under the ACA. On December 31, 2020, CMS issued a final regulation that modified prior Medicaid Drug Rebate program regulations to permit reporting multiple best price figures with regard to value-based purchasing arrangements (beginning in 2022); provide definitions for "line extension," "new formulation," and related terms, with the practical effect of expanding the scope of drugs considered to be line extensions that are subject to an alternative rebate formula (beginning in 2022); and revise best price and average manufacturer price exclusions of manufacturer-sponsored patient benefit programs, specifically regarding applicability of such exclusions in the context of pharmacy benefit manager "accumulator" programs (beginning in 2023).

Federal law also requires that a company that participates in the Medicaid Drug Rebate Program report average sales price information each quarter to CMS for certain categories of drugs that are paid under the Medicare Part B program. For calendar quarters beginning January 1, 2022, manufacturers are required to report the average sales price for certain drugs under the Medicare program regardless of whether they participate in the Medicaid Drug Rebate Program. Manufacturers calculate average sales price based on a statutorily defined formula as well as regulations and interpretations of the statute by CMS. CMS uses these submissions to determine payment rates for drugs under Medicare Part B. Starting in 2023, manufacturers must pay refunds to Medicare for single source drugs or biologicals, or biosimilar biological products, reimbursed under Medicare Part B and packaged in single-dose containers or single-use packages, for units of discarded drug reimbursed by Medicare Part B in excess of 10 percent of total allowed.

charges under Medicare Part B for that drug. Manufacturers that fail to pay refunds could be subject to civil monetary penalties of 125 percent of the refund amount.

Statutory or regulatory changes or CMS guidance could affect the pricing calculations for our approved products, and could negatively impact our results of operations. For example, Congress could enact a Medicare Part B inflation rebate, under which manufacturers would owe additional rebates if the average sales price of a drug were to increase faster than the pace of inflation. In addition, Congress could enact a drug price negotiation program under which the prices for certain high Medicare spend single source drugs would be capped by reference to the non-federal average manufacturer price. This or any other legislative change could impact the market conditions for our products. We further expect continued scrutiny on government price reporting and pricing more generally from Congress, agencies, and other bodies.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Additional Regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

Europe / Rest of World Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our product candidates. Whether or not we obtain FDA approval of a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the EU, for example, a clinical trial application must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the clinical trial application is approved in accordance with a country's requirements, clinical trial development may proceed.

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

To obtain regulatory approval of an investigational drug product under EU regulatory systems, we must submit a marketing authorization application. The application used to file the drug product in the United States is similar to that required in the EU, with the exception of, among other things, country-specific document requirements.

For other countries outside of the EU, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

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

Employees and Human Capital

As of December 31, 2021, we had 14 full-time employees. Of these full-time employees, seven were engaged in research and development, and seven were engaged in management, finance and administration. From time to time, we also employ independent contractors to support our operations. Our employees are not represented by any collective bargaining agreements and we have never experienced an organized work stoppage.

Diversity and Inclusion

We are committed to our continued efforts to increase diversity and foster an inclusive work environment. We recruit the best qualified employees regardless of gender, ethnicity, or other protected traits and it is our policy to fully comply with all laws (domestic and foreign) applicable to discrimination in the workplace. Our diversity, equity and inclusion principles are also reflected in our employee training and policies. We continue to enhance our diversity, equity and inclusion policies which are guided by our executive leadership team.

Workforce Health and Safety

In response to the COVID-19 pandemic, we instituted a remote work protocol to help ensure the safety of our employees, our community, and to adhere to federal, state, and local requirements and the Center for Disease Control (CDC) recommendations of social distancing and limited public exposure in connection with the COVID-19 pandemic. We did not implement any furlough, layoff, or salary reductions during this time. We continue to evaluate our ability to operate in light of recent resurgences of COVID-19 and the advisability of continuing operations based on federal, state and local guidance, evolving data concerning the pandemic and the best interests of our employees, third parties with whom we collaborate, and our stockholders.

Compensation and Benefits

We believe that we must offer and maintain market competitive compensation and benefit programs for our employees in order to attract and retain qualified personnel. In addition to cash compensation, we provide equity compensation, a company-matched 401(k) Plan, healthcare and insurance benefits, health savings and flexible spending accounts, paid time off, family leave, and employee assistance programs.

Corporate Information

We were initially formed as a California general partnership in July 1996 and incorporated in the State of Delaware in May 1997. We were formerly known as Cytori Therapeutics, Inc., before that as MacroPore Biosurgery, Inc. and before that as MacroPore, Inc. On July 20, 2019 we changed our name from Cytori Therapeutics, Inc. to Plus Therapeutics, Inc. Our corporate offices are located at 4200 Marathon Blvd., Suite 200, Austin, TX. Our telephone number is (737) 255-7194. We maintain a website at www.plustherapeutics.com.

Item 1A. Risk Factors

The risk factors described below, as well as statements described elsewhere in this Annual Report on Form 10-K, including our audited Consolidated Financial Statements and the related notes and "Management's Discussion and Analysis of Financial Conditions and Results of Operations", or in other SEC filings, describe risks that could materially and adversely affect our business, financial condition, and results of operations, which could also cause the trading price of our equity securities to decline. These risks are not the only risks that we face. Our business, financial condition and results of operations could also be affected by additional factors that are not presently known to us or that we currently consider to be immaterial to our operations.

Risks Related to our Financial Position and Capital Requirements

We have incurred losses since inception, we expect to incur significant net losses in the foreseeable future and we may never become profitable and our operating results have been and will likely continue to be volatile.

We generated negative cash flows from operations and have incurred net operating losses each year since we started business. For the year ended December 31, 2021, we incurred net losses of \$13.4 million and our net cash used in operating activities was \$10.3 million. As of December 31, 2021, our accumulated deficit was \$446.9 million. We expect to continue to incur net losses and negative cash flow from operating activities for at least the next twelve months. As our focus on development of nanomedicine and the development of therapeutic applications has increased, losses have resulted primarily from expenses associated with research and development and clinical trial-related activities, as well as general and administrative expenses. While we have implemented and continue to implement cost reduction measures where possible, we nonetheless expect to continue operating in a loss position on a

consolidated basis and expect that recurring operating expenses will be at higher levels for the year ended December 31, 2022 as we perform clinical trial and other development activities for our nanomedicine product candidates.

Our ability to generate sufficient revenue from any of our products, product candidates or technologies to achieve profitability will depend on a number of factors including, but not limited to:

- our ability to manufacture, test and validate our product candidates in compliance with applicable laws and as required for submission to applicable regulatory bodies, including manufacturing, testing and validation of our RNL candidates;
- our or our partners' ability to successfully complete clinical trials of our product candidates;
- our ability to obtain necessary regulatory approvals for our product candidates;
- our or our partners' ability to negotiate and receive favorable reimbursement for our product candidates, including for our product candidates that have been granted or may be granted orphan drug status or otherwise command currently anticipated pricing levels;
- our ability to negotiate favorable arrangements with third parties to help finance the development of, and market and distribute, our products and product candidates; and
- the degree to which our approved products are accepted in the marketplace.

Because of the numerous risks and uncertainties associated with our commercialization and product development efforts, we are unable to predict the extent of our future losses or when or if we will become profitable and it is possible we will never become profitable. If we do not generate significant sales from any of our product candidates that receive regulatory approval, there would be a material adverse effect on our business, results of operations, financial condition and prospects, which in turn could result in our inability to continue operations.

Our prospects must be evaluated in light of the risks and difficulties frequently encountered by emerging companies and particularly by such companies in rapidly evolving and technologically advanced biotech, pharmaceutical and medical device fields. Our visibility as to our future operating results and our clinical development timeline may be further limited by the impact of the ongoing COVID-19 pandemic. In addition, our budgeted expense levels are based in part on our expectations concerning future research and development activities. We may be unable to reduce our expenditures in a timely manner to compensate for any unexpected events. Accordingly, unexpected events could have an immediate and material impact on our business and financial condition. From time to time, we have tried to update our investors' expectations as to our operating results. If we revise any timelines we may give with respect to our clinical trials, it could materially harm our reputation and the market's perception of us and could cause our stock price to decline.

We will need substantial additional funding to develop our product candidates and conduct our future operations and to repay our outstanding debt obligations. If we are unable to obtain the funds necessary to do so, we may be required to delay, scale back or eliminate our product development activities or may be unable to continue our business operations.

We have had, and we will continue to have, an ongoing need to raise additional cash from outside sources to continue funding our operations, including our continuing substantial research and development expenses and potential commercialization activities. We do not currently believe that our cash balance will be sufficient to fund the development and marketing efforts required to reach profitability without raising additional capital from accessible sources of financing in the near future. Our future capital requirements will depend on many factors, including:

- our ability to raise capital to fund our operations on terms acceptable to us, or at all;
- our perceived capital needs with respect to our development programs, and any delays in, adverse events and excessive costs of such programs beyond what we currently anticipate;
- our ability to establish and maintain collaborative and other arrangements with third parties to assist in bringing our product candidates to market and the cost of such arrangements at the time;
- costs associated with operating at our San Antonio, Texas facility;
- the cost of manufacturing our product candidates, including compliance with good manufacturing practices applicable to our product candidates;
- expenses related to the establishment of sales and marketing capabilities for product candidates awaiting approval or products that have been approved;
- competing technological and market developments; and
- our ability to introduce and sell new products.

The amount and timing of our future funding requirements will depend on many factors, including the pace and results of its clinical development efforts.

We have secured capital historically from grant revenue, collaboration proceeds, and debt and equity offerings. To obtain additional capital, we may pursue debt and/or equity offering programs, strategic corporate partnerships, state and federal development programs, licensing arrangements, and sales of assets or debt or equity securities. We cannot be certain that additional

capital will be available on terms acceptable to us, or at all. If we are unsuccessful in our efforts to raise any such additional capital, we may be required to take actions that could materially and adversely harm our business, including a possible significant reduction in our research, development and administrative operations (including reduction of our employee base), the surrender of our rights to some technologies or product opportunities, delay of our clinical trials or regulatory and reimbursement efforts, or curtailment or cessation of operations.

Depending on the type and the terms of any financing we pursue, stockholders' rights and the value of their investment in our common stock could be reduced. A financing could involve one or more types of securities including common stock, convertible debt or warrants to acquire common stock. These securities could be issued at or below the then prevailing market price for our common stock. In addition, if we issue secured debt securities, the holders of the debt would have a claim to our assets that would be prior to the rights of stockholders until the debt is paid. Interest on these debt securities would increase costs and negatively impact operating results. If the issuance of new securities results in diminished rights to holders of our common stock, the market price of our common stock could be negatively impacted.

Pursuant to the purchase agreement (the "2020 Purchase Agreement") and registration rights agreement with Lincoln Park Capital Fund, LLC ("Lincoln Park"), each dated September 30, 2020, we may direct Lincoln Park to purchase up to \$25.0 million worth of shares of our common stock under the 2020 Purchase Agreement over a 36-month period generally in amounts up to 50,000 shares of our common stock, which could be increased to up to 100,000 shares of our common stock depending on the market price of our common stock at the time of sale, provided that Lincoln Park's committed obligation under such single regular purchase did not exceed \$500,000. As of February 24, 2022, we had issued an aggregate 11.7 million shares for gross proceeds of approximately \$20.3 million under the 2020 Purchase Agreement and we have no additional shares of common stock registered that we can issue under the 2020 Purchase Agreement. At this time, we do not intend to register any additional shares of common stock under the 2020 Purchase Agreement.

On January 14, 2022, we entered into an Equity Distribution Agreement (the "Distribution Agreement") with Canaccord Genuity LLC ("Canaccord"), pursuant to which we may issue and sell, from time to time, shares of our common stock having an aggregate offering price of up to \$5,000,000 (the "Shares"), depending on market demand, with Canaccord acting as an agent for sales. Sales of the Shares may be made by any method permitted by law deemed to be an "at the market offering" as defined in Rule 415(a)(4) of the Securities Act of 1933, as amended (the "Securities Act"), including, without limitation, sales made directly on or through the Nasdaq Capital Market ("Nasdaq"). Canaccord will use its commercially reasonable efforts to sell the Shares requested by us to be sold on its behalf, consistent with Canaccord's normal trading and sales practices, under the terms and subject to the conditions set forth in the Distribution Agreement. We have no obligation to sell any of the Shares. We may instruct Canaccord not to sell the Shares if the sales cannot be affected at or above the price designated by us from time to time and we may at any time suspend sales pursuant to the Distribution Agreement.

Failure to raise capital as and when needed, on favorable terms or at all, would have a significant negative impact on our financial condition and our ability to develop our product candidates.

The disruption and volatility in the global capital markets may negatively impact our ability to obtain additional debt financings and modify our existing debt facilities and may increase the risk of non-compliance with covenants under our existing loan agreement.

Under the Loan and Security Agreement, dated May 29, 2015 (the "Loan and Security Agreement"), as amended, with Oxford Finance, LLC ("Oxford"), Oxford made a term loan to us in an aggregate principal amount of \$17.7 million (the "Term Loan") subject to the terms and conditions set forth therein. As of December 31, 2021, the outstanding principal balance of the Term Loan was \$4.0 million. In addition, we are obligated to pay a final payment fee of \$3.2 million at the earlier of the maturity date, acceleration, or payment of the Term Loan.

The Term Loan accrues interest at a floating rate equal to the three-month LIBOR rate (with a floor of 1.00%) plus 7.95% per annum. Beginning November 1, 2021, we began to make payments of principal and accrued interest in equal monthly installments. As required, to amortize the Term Loan through June 1, 2024.

As security for our obligations under the Loan and Security Agreement, we granted a security interest in substantially all of our existing and after-acquired assets, excluding our intellectual property assets, subject to certain exceptions set forth in the Loan and Security Agreement. If we are unable to discharge these obligations, Oxford could foreclose on these assets, which would, at a minimum, have a severe material adverse effect on our ability to operate our business.

Our indebtedness to Oxford could adversely affect our operations and liquidity, by, among other things:

- causing us to use a larger portion of our cash flow to fund interest and principal payments, reducing the availability of cash to fund working capital and capital expenditures and other business activities;
- making it more difficult for us to take advantage of significant business opportunities, such as acquisition opportunities, and to react to changes in market or industry conditions; and

- limiting our ability to borrow additional monies in the future to fund working capital and capital expenditures and for other general corporate purposes.

The Loan and Security Agreement, as amended, requires us to maintain at least \$2.0 million in unrestricted cash and/or cash equivalents and includes certain reporting and other covenants, that, among other things, restrict our ability to (i) dispose of assets, (ii) change the business we conduct, (iii) make acquisitions, (iv) engage in mergers or consolidations, (v) incur additional indebtedness, (vi) create liens on assets, (vii) maintain any collateral account, (viii) pay dividends, (ix) make investments, loans or advances, (x) engage in certain transactions with affiliates, and (xi) prepay certain other indebtedness or amend other financing arrangements. If we fail to comply with any of these covenants or restrictions, such failure may result in an event of default, which if not cured or waived, could result in Oxford causing the outstanding loan amount to become immediately due and payable. If the maturity of our indebtedness is accelerated, we may not have, or be able to timely procure, sufficient cash resources to satisfy our debt obligations, and such acceleration would adversely affect our business and financial condition.

The COVID-19 pandemic has severely impacted the global economic activity and caused significant volatility and negative pressure in the financial markets. This volatility and downturn may affect our business, liquidity position, and financial results. This in turn may negatively impact our ability to remain in compliance with the financial and operating covenants under the Loan and Security Agreement and may restrict our ability to obtain covenant waivers, restructure or amend the terms of our existing debt, or obtain additional debt financing. If the maturity of our indebtedness is accelerated or if we are unable to amend the terms or obtain any necessary waivers under our debt facilities or obtain additional debt or other financing, it would materially and adversely affect our liquidity position and ability to fund our operations. This in turn would materially harm our business and financial conditions.

Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.

We do not expect to make profits in the near future. Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an “ownership change” (generally defined as a greater than 50% change, by value, in its equity ownership over a three year period), the corporation’s ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change taxable income and taxes may be limited. Any “ownership changes” that occur as a result of shifts in stock ownership could limit our ability to use net operating loss carryforwards and other pre-change tax attributes. This change may require us to pay federal income taxes in future years despite generating a loss for federal income tax purposes in prior years.

Risks Related to Our Business and Industry

Our future success is in large part dependent upon our ability to successfully develop our nanomedicine platform and commercialize 186RNL and 188RNL-BAM and any failure to do so could significantly harm our business and prospects.

Our ability to successfully develop and commercialize 186RNL and 188RNL-BAM is subject to a number of risks, including the following:

- we do not have substantive drug development, manufacturing, and commercialization experience, and thus we may be required to hire and rely on significant numbers of scientific, quality, regulatory and other technical personnel with the experience and expertise necessary to develop, manufacture, and commercialize our Plus Therapeutics nanomedicine product candidates. We may be unable to identify, hire and retain personnel with the requisite experience to conduct the operations necessary to obtain regulatory approval and commercialize our RNL product candidates, in which case our business would be materially harmed;
- we intend to find a commercialization partner to share or assume responsibility for marketing, sales, and distribution activities and related costs and expenses for our RNL product candidates. There can be no assurance that we would obtain sufficient capital to fund the development, manufacturing, and commercialization of our nanomedicine program ourselves, or if we do obtain such capital, that our development, manufacturing, and commercialization efforts would be successful; and
- to the extent that we incur unanticipated expenses in our business, are unable to timely obtain sufficient additional capital on terms acceptable to us (or at all) to fund this business, our ability to develop our RNL product candidates could be materially and adversely impacted.

If we are unable to successfully partner with other companies to commercialize our product candidates, our business could materially suffer.

A key part of our business strategy is to leverage strategic partnerships and collaborations to commercialize our product candidates. We do not have the financial, human or other resources necessary to develop, commercialize, launch or sell our therapeutic offerings in all of the geographies that we are targeting, and thus it is important that we identify and partner with third parties who possess the necessary resources to bring our product candidates to market. We expect that any such partners will provide regulatory and reimbursement/pricing expertise, sales and marketing resources, and other expertise and resources vital to the success

of our product offerings in their territories. We further expect, but cannot guarantee, that any such partnering arrangements will include upfront cash payments to us in return for the rights to develop, manufacture, and/or sell our product candidates in specified territories, as well as downstream revenue in the form of milestone payments and royalties. If we are unable to successfully partner with other companies to commercialize our product candidates, our business could materially suffer.

Our current business strategy is high-risk and may not be successful.

Our current business strategy is to aggressively develop our nanomedicine platforms, while simultaneously controlling expenses, which is a high-risk strategy for a number of reasons including the following:

- we do not have prior experience with obtaining regulatory, reimbursement, or other approvals for product candidates such as 186RNL and 188RNL-BAM;
- our nanomedicine product candidates, if commercialized, will compete against established competitive drugs that are marketed and sold by large companies with significant human, technical and financial resources;
- we are not experienced in acquiring and integrating new assets;
- there is an intense and rapidly evolving competitive landscape for our nanomedicine product candidates, including chemotherapies, targeted therapies and immuno-oncology therapies, and as such key assumptions regarding market entry, pricing, and revenue/unit share may not be realized;
- our product candidates may never become commercially viable; and
- we may not be able to prevent other companies from depriving us of market share and profit margins by selling products based on our intellectual property and developments.

If our competitors market or develop products that are marketed more effectively, approved more quickly than our product candidates, or demonstrated to be safer or more effective than our product candidates, our commercial opportunities could be reduced or eliminated.

The life science industry is characterized by rapidly advancing technologies, intense competition, and a strong emphasis on proprietary therapeutics. We face competition from a number of sources, some of which may target the same indications as our products or product candidates, including small and large, domestic and multinational, medical device, biotechnology and pharmaceutical companies, academic institutions, government agencies, and private and public research institutions.

Competitors may have greater experience in developing drugs, conducting clinical trials, obtaining regulatory clearances or approvals, manufacturing and commercialization. It is possible that competitors may obtain patent protection, approval, or clearance from the FDA or achieve commercialization earlier than we can, any of which could have a substantial negative effect on our business. Many of our potential competitors have substantially greater:

- capital resources;
- research and development resources and experience, including personnel and experience;
- product development, clinical trial and regulatory resources and experience;
- sales and marketing resources and experience;
- manufacturing and distribution resources and experience;
- name, brand and product recognition; and
- resources, experience and expertise in prosecution and enforcement of intellectual property rights.

We expect that product candidates in our pipeline, if approved, to compete on the basis of, among other things, product efficacy and safety, time to market, price, coverage, and reimbursement by third-party payers, extent of adverse side effects, and convenience of treatment procedures. One or more of our competitors may develop other products that compete with ours, obtain necessary approvals for such products from the FDA, EMA, Ministry of Health, Labour and Welfare or other agencies, if required, more rapidly than we do or develop alternative products or therapies that are safer, more effective and/or more cost effective than any products developed by us. The competition that we encounter with respect to any of our product candidates that receive the requisite regulatory approval and classification and are marketed may have an effect on our product prices, market share, and results of operations. We may not be able to differentiate any products that we are able to market from those of our competitors, successfully develop or introduce new products that are less costly or offer better results than those of our competitors, or offer purchasers of our products payment and other commercial terms as favorable as those offered by our competitors.

As a result of these factors, our competitors may obtain regulatory approval of their products more quickly than we are able to or may obtain patent protection or other intellectual property rights that limit or block us from developing or commercializing our product candidates. Our competitors may also develop products that are more effective, more useful, better tolerated, subject to fewer or less severe side effects, more widely prescribed or accepted, or less costly than ours and may also be more successful than we are in manufacturing and marketing their products. If we are unable to compete effectively with the marketed therapeutics of our competitors or if such competitors are successful in developing products that compete with any of our product candidates that are approved, our business, results of operations, financial condition, and prospects may be materially adversely affected.

Product development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

Clinical testing of our product candidates is a long, expensive and uncertain process, and the failure or delay of a clinical trial can occur at any stage. Many factors, currently known and unknown, can adversely affect clinical trials and the ability to evaluate a product candidate's efficacy. During the course of treatment, patients can die or suffer other adverse events for reasons that may or may not be related to the proposed product being tested. Even if initial results of preclinical and nonclinical studies or clinical trial results are promising, we may obtain different results in subsequent trials or studies that fail to show the desired levels of safety and efficacy, or we may not obtain applicable regulatory approval for a variety of other reasons.

Further, with respect to the conduct and results of clinical trials generally, in the United States, Europe, Japan, and other jurisdictions, the conduct and results of clinical trials can be delayed, limited, suspended, or otherwise adversely affected for many reasons, including, among others:

- delay or failure in reaching agreement with the FDA or other regulatory authorities outside of the United States on acceptable clinical trial design, or in obtaining authorization to commence a trial;
- delay or failure in reaching agreement on acceptable terms with prospective clinical research organizations ("CRO"), and clinical trial sites;
- delay or failure in obtaining approval of an IRB or ethics committees before a clinical trial can be initiated at a prospective trial site;
- any clinical trial site policies resulting from the COVID-19 pandemic that determine essential and non-essential functions and staff, which may impact the ability of site staff to conduct assessments, or result in delays to the conduct of the assessments, as part of our clinical trial protocols, or the ability to enter assessment results into clinical trial databases in a timely manner;
- withdrawal of clinical trial sites from our clinical trials, including as a result of changing standards of care or the ineligibility of a site to participate;
- clinical results may not meet prescribed endpoints for the studies, produce negative or inconclusive results, or otherwise not provide sufficient data to support the efficacy of our product candidates;
- clinical and nonclinical test results may reveal side effects, adverse events or unexpected safety issues associated with the use of our product candidates;
- emerging of dosing issues;
- lack of adequate funding to continue the clinical trial, including the incurrence of unforeseen costs due to enrollment delays, requirements to conduct additional trials and studies, and increased expenses associated with the services of our CROs, and other third parties;
- inability to design appropriate clinical trial protocols;
- slower than expected rates of subject recruitment and enrollment rates in clinical trials;
- clinical sites or investigators may deviate from trial protocol or fail to conduct the trial in accordance with applicable regulatory requirements, or drop out of a trial;
- regulatory review may not find a product safe or effective enough to merit either continued testing or final approval;
- regulatory authorities may require that we change our studies or conduct additional studies which may significantly delay or make continued pursuit of approval commercially unattractive;
- a regulatory agency may reject our trial data or disagree with our interpretations of either clinical trial data or applicable regulations;
- the cost of clinical trials required for product approval may be greater than what we originally anticipate, and we may decide to not pursue regulatory approval for such a product;
- changes in the standard of care of the indication being studied;
- a regulatory agency may identify problems or other deficiencies in our existing manufacturing processes or facilities or the existing processes or facilities of our collaborators, our contract manufacturers, or our raw material suppliers;
- a regulatory agency may change its formal or informal approval requirements and policies, act contrary to previous guidance, adopt new regulations, or raise new issues or concerns late in the approval process; and
- a regulatory agency may ask us to put a clinical study on hold pending additional safety data (and there can be no assurance that we will be able to satisfy the regulator agencies' requests in a timely manner, which can lead to significant uncertainty in the completion of a clinical study).

We also face clinical trial-related risks with regard to our reliance on other third parties in the performance of many of the clinical trial functions, including CROs that help execute our clinical trials, the hospitals and clinics at which our trials are conducted,

the clinical investigators at the trial sites, and other third-party service providers. Failure of any third-party service provider to adhere to applicable trial protocols, laws and regulations in the conduct of one of our clinical trials could adversely affect the conduct and results of such trial (including possible data integrity issues), which could seriously harm our business.

We, the FDA, other regulatory authorities outside the United States, or an IRB may suspend a clinical trial at any time for various reasons, including if it appears that the clinical trial is exposing participants to unacceptable health risks or if the FDA or one or more other regulatory authorities outside the United States find deficiencies in our IND or similar application outside the United States or the conduct of the trial. If we experience delays in the completion of, or the termination of, any clinical trial of any of our product candidates, the commercial prospects of such product candidate will be harmed, and our ability to generate product revenues from such product candidate will be delayed or inhibited. In addition, any delays in completing our clinical trials will increase our costs, slow down our product candidate development and approval process, and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may harm our business, financial condition, results of operations, cash flows and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Further, regulatory authorities may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after they have reviewed and commented on the design for our clinical trials.

Pre-clinical studies and preliminary and interim data from clinical trials of our product candidates are not necessarily predictive of the results or success of ongoing or future clinical trials of our product candidates.

Pre-clinical studies and any positive preliminary and interim data from our clinical trials of our product candidates may not necessarily be predictive of the results of ongoing or later clinical trials. A number of companies in the pharmaceutical and biotechnology industries, including us and many other companies with greater resources and experience than we, have suffered significant setbacks in clinical trials, even after seeing promising results in prior pre-clinical studies and clinical trials. Even if we are able to complete our planned clinical trials of our product candidates according to our current development timeline, initial positive results from pre-clinical studies and clinical trials of our product candidates may not be replicated in subsequent clinical trials. The design of our later stage clinical trials could differ in significant ways (e.g., inclusion and exclusion criteria, endpoints, statistical analysis plan) from our earlier stage clinical trials, which could cause the outcomes of the later stage trials to differ from those of our earlier stage clinical trials. If we fail to produce positive results in our planned clinical trials of any of our product candidates, the development timeline and regulatory approval and commercialization prospects for our product candidates, and, correspondingly, our business and financial prospects, could be materially adversely affected. If we fail to produce positive results in our planned clinical trials of any of our product candidates, the development timeline and regulatory approval and commercialization prospects for such product candidates, and, correspondingly, our business and financial prospects, could be materially adversely affected.

Because we have limited resources, we may decide to pursue a particular product candidate and fail to advance product candidates that later demonstrate a greater chance of clinical and commercial success.

We are an early-stage company with limited resources and revenues. The product candidates we currently have under development will require significant development, pre-clinical and clinical testing and investment of significant funds before their commercialization. Because of this, we must make strategic decisions regarding resource allocations and which product candidates to pursue. There can be no assurance that we will be able to develop all potentially promising product candidates that we may identify. Based on preliminary results, we may choose to advance a particular product candidate that later fails to be successful, and simultaneously forgo or defer further investment in other product candidates that later are discovered to demonstrate greater promise in terms of clinical and commercial success. If we make resource allocation decisions that later are shown to be inaccurate, our business and prospects could be harmed.

Clinical trial results may fail to support approval of our product candidates.

Even if our clinical trials are successfully completed as planned, the results may not support approval of our product candidates under the laws and regulations of the FDA or other regulatory authorities outside the United States. The clinical trial process may fail to demonstrate that our product candidates are both safe and/or effective for their intended uses. Pre-clinical and clinical data and analyses are often able to be interpreted in different ways. Even if we view our results favorably, if a regulatory authority has a different view, we may still fail to obtain regulatory approval of our product candidates. This, in turn, would significantly adversely affect our business prospects.

If third parties are not able to successfully perform due to the impact of the COVID-19 pandemic or otherwise, we may not be able to successfully complete clinical development, obtain regulatory approval or commercialize our product candidates and our business could be substantially harmed.

We rely on third parties in the performance of many of the clinical trial functions, including CROs, which help execute our clinical trials, the hospitals and clinics at which our trials are conducted, the clinical investigators at the trial sites, and other third-party

service providers. Failure of any third-party service provider to adhere to applicable trial protocols, laws and regulations in the conduct of one of our clinical trials could adversely affect the conduct and results of such trial (including possible data integrity issues), which could seriously harm our business. The COVID-19 pandemic has placed a strain on hospitals and clinics, CROs, and other providers of clinical and medical supplies and equipment. This in turn could impact the ability of third parties such as hospitals to support our clinical trials or perform other services in support of our clinical programs. In addition, third parties may not prioritize our clinical trials relative to those of other customers due to resource or other constraints as a result of the COVID-19 pandemic. We may experience enrollment at a slower pace at certain of our clinical trial sites than initially anticipated. Further, our clinical trial sites may be required to suspend enrollment due to travel restrictions, workplace safety concerns, quarantine, facility closures, and other governmental restrictions. Some of our clinical trial sites have imposed limited accessibility to conduct clinical monitoring and training on-site. As a result, results from our clinical trials may be delayed, which in turn would have a material adverse impact on our clinical trial plans and timelines and impair our ability to successfully complete clinical development, obtain regulatory approval, or commercialize our product candidates. This in turn would substantially harm our business and operations.

We also rely on third-party expertise to support us in this area. We have entered into contracts with third-party manufacturers to manufacture, supply, store and distribute supplies of our product candidates for our clinical trials. If any of our product candidates receives FDA approval, we expect to rely on third-party contractors to manufacture our drugs. We have no current plans to build internal manufacturing capacity for any product candidate, and we have no long-term supply arrangements.

Our reliance on third-party manufacturers exposes us to potential risks, such as the following:

- we may be unable to contract with third-party manufacturers on acceptable terms, or at all, because the number of potential manufacturers is limited. Potential manufacturers of any product candidate that is approved will be subject to FDA compliance inspections and any new manufacturer would have to be qualified to produce our products;
- our third-party manufacturers might be unable to formulate and manufacture our drugs in the volume and of the quality required to meet our clinical and commercial needs, if any;
- our third-party manufacturers may not perform as agreed or may not remain in the contract manufacturing business for the time required to supply our clinical trials through completion or to successfully produce, store and distribute our commercial products, if approved;
- drug manufacturers are subject to ongoing periodic unannounced inspection by the FDA and other government agencies to ensure compliance with cGMP and other government regulations and corresponding foreign standards. We do not have control over third-party manufacturers' compliance with these regulations and standards, but we may ultimately be responsible for any of their failures;
- if any third-party manufacturer makes improvements in the manufacturing process for our products, we may not own, or may have to share, the intellectual property rights to such improvements; and
- a third-party manufacturer may gain knowledge from working with us that could be used to supply one of our competitors with a product that competes with ours.

Each of these risks could delay or have other adverse impacts on our clinical trials and the approval and commercialization of our product candidates, potentially resulting in higher costs, reduced revenues or both.

We may have difficulty enrolling, or fail to enroll patients, in our clinical trials, which could delay or prevent clinical trials of our drug candidates.

Identifying and enrolling patients to participate in clinical trials of our product candidates is essential to our success. The timing of our clinical trials depends in part on the rate at which we can recruit patients to participate in clinical trials of our product candidates, and we may experience delays in our clinical trials if we encounter difficulties in enrollment. The eligibility criteria of our planned clinical trials may further limit the available eligible trial participants as we require that patients have specific characteristics that we can measure or meet the criteria to assure their conditions are appropriate for inclusion in our clinical trials. We may not be able to identify, recruit and enroll a sufficient number of patients to complete our clinical trials in a timely manner because of the perceived risks and benefits of the drug candidate under study, the availability and efficacy of competing therapies and clinical trials, and the willingness of physicians to participate in our planned clinical trials. If patients are unwilling to participate in our clinical trials for any reason, the timeline for conducting trials and obtaining regulatory approval of our drug candidates may be delayed.

If we experience delays in the completion of, or termination of, any clinical trials of our drug candidates, the commercial prospects of our product candidates could be harmed, and our ability to generate product revenue from any of these product candidates could be delayed or prevented. In addition, any delays in completing our clinical trials would likely increase our overall costs, impair product candidate development and jeopardize our ability to obtain regulatory approval relative to our current plans. Any of these occurrences may materially and adversely harm our business, financial condition, and prospects.

Our success depends in substantial part on our ability to obtain regulatory approvals for our RNL product candidates. However, we cannot be certain that we will receive regulatory approval for these product candidates or our other product candidates.

We have only a limited number of product candidates in development, and our business depends substantially on their successful development and commercialization. Our product candidates will require development, regulatory review and approval in multiple jurisdictions, substantial investment, access to sufficient commercial manufacturing capacity and significant marketing efforts before we can generate any revenue from sales of our product candidates. The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of products are subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries, whose regulations differ from country to country.

We are not permitted to market our product candidates in the United States until we receive approval from the FDA, or in any foreign countries until we receive the requisite approval from the regulatory authorities of such countries (including centralized marketing authorization from EMA), and we may never receive such regulatory approvals. Obtaining regulatory approval for a product candidate is a lengthy, expensive and uncertain process, and may not be obtained. Any failure to obtain regulatory approval of any of our product candidates would limit our ability to generate future revenue (and any failure to obtain such approval for all of the indications and labeling claims we deem desirable could reduce our potential revenue), would potentially harm the development prospects of our product candidates and would have a material and adverse impact on our business.

Even if we successfully obtain regulatory approvals to market our product candidates, our revenue will be dependent, in part, on our ability to commercialize such products as well as the size of the markets in the territories for which we gain regulatory approval. If the markets for our product candidates are not as significant as we estimate, our business and prospects will be harmed.

If a product candidate is not approved in a timely fashion on commercially viable terms, or if development of any product candidate is terminated due to difficulties or delays encountered in the regulatory approval process, it could have a material adverse effect on our business, and we may become more dependent on the development of other proprietary products and/or our ability to successfully acquire other products and technologies. There can be no assurance that any product candidate will receive regulatory approval in a timely manner, or at all.

If a particular product candidate causes significant adverse events, then we may be unable to receive regulatory approval or market acceptance for such product candidate.

We may experience numerous unforeseen events during, or as a result of, the testing process that could delay or prevent commercialization of any of our product candidates, including the occurrence of significant adverse events in clinical trials. Such significant adverse events could lead to clinical trial challenges, such as difficulties in patient recruitment, retention, and adherence, potential product liability claims, and possible trial termination by us, regulatory authorities, and/or an IRB or ethics committees. These types of clinical trial challenges could delay or prevent regulatory approval of our product candidate. Significant adverse events may also lead regulatory authorities to require additional warnings on the label for such product, require us to conduct additional costly post-marketing studies, require us to develop a REMS, among other possible requirements. If the product candidate has already been approved, such approval may be withdrawn. Any delay in, denial, or withdrawal of marketing approval for one of our product candidates will adversely affect our financial position. Even if our product candidates receive marketing approval, undesirable side effects may limit the product's commercial viability. Patients may not wish to use our product, physicians may not prescribe our product, and our reputation may suffer. Any of these events may significantly harm our business and financial prospects.

If our product candidates and technologies receive regulatory approval but do not achieve broad market acceptance, especially by physicians, the revenue that we generate will be limited.

The commercial success of any of our approved products or technologies will depend upon the acceptance of these products and technologies by physicians, patients and the medical community. The degree of market acceptance of these products and technologies will depend on a number of factors, including, among others:

- acceptance by physicians and patients of the product as a safe and effective treatment;
- any negative publicity or political action related to our or our competitors' products or technologies;
- the relative convenience and ease of administration;
- the prevalence and severity of adverse side effects;
- demonstration to authorities of the pharmacoeconomic benefits;
- demonstration to authorities of the improvement in burden of illness;
- limitations or warnings contained in a product's approved labeling;
- payers' level of restrictions and/or barriers to coverage;
- the clinical indications for which a product is approved;

- availability and perceived advantages of alternative treatments;
- the effectiveness of our or future collaborators' sales, marketing and distribution strategies; and
- pricing and cost effectiveness.

We expect physicians' inertia and skepticism to also be a significant barrier as we attempt to gain market penetration with our future products. We believe we will continue to need to finance lengthy time-consuming clinical studies to provide evidence of the medical benefit of our products and resulting therapies in order to overcome this inertia and skepticism.

Overall, our efforts to educate the medical community on the benefits of any of our products or technologies for which we obtain marketing approval from the FDA or other regulatory authorities and gain broad market acceptance may require significant resources and may never be successful. If our products and technologies do not achieve an adequate level of acceptance by physicians, pharmacists and patients, we may not generate sufficient revenue from these products to become or remain profitable.

All potential applications of our product candidates are investigational, which subjects us to development and marketing risks.

Our product candidates are at various stages of development. Successful development and market acceptance of our products is subject to developmental risks, including risk of negative clinical data from current and anticipated trials, failure of inventive imagination, ineffectiveness, lack of safety, unreliability, manufacturing hurdles, failure to receive necessary regulatory clearances or approvals, high commercial cost, preclusion or obsolescence resulting from third parties' proprietary rights or superior or equivalent products, competition from copycat products and general economic conditions affecting purchasing patterns. There can be no assurance that we or our partners will successfully develop and commercialize our product candidates, or that our competitors will not develop competing technologies that are superior or less expensive. Failure to successfully develop and market our product candidates would have a substantial negative effect on our results of operations and financial condition. If we are unable to establish or sustain coverage and adequate reimbursement for any future product candidates from third-party payors, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those product candidates, if approved.

If we or any party to a key collaboration, licensing, development, acquisition or similar arrangement fails to perform material obligations, or commit a breach, under such arrangement, or any arrangement is terminated for any reason, there could be an adverse effect on our business.

We are currently party to certain licensing, collaboration and acquisition agreements under which we may make or receive future payments in the form of milestone payments, maintenance fees, royalties and/or minimum product purchases. Our collaborators may not devote the attention and resources to such efforts to be successful. The termination of a key collaboration agreement by one of our collaborators could materially impact our ability to enter into additional collaboration agreements with new collaborators on favorable terms.

On March 29, 2020, we entered into an exclusive license agreement with NanoTx for the global rights to develop and commercialize NanoTx's glioblastoma treatment, 186RNL. Under the license agreement with NanoTx, we are required to use commercial reasonable efforts to develop the 186RNL product candidate acquired under the license agreement. Further, we are subject to future milestone, earn-out and other payments to NanoTx all of which are tied to our commercialization and sale activities for product candidates. If we are unsuccessful in our efforts to develop these assets, or if NanoTx and we were to enter into a dispute over the terms of our agreement, then our business could be seriously harmed.

On December 31, 2021, we entered into an exclusive license agreement with UT Health Science Center at San Antonio for the global rights to develop and commercialize Rhenium-188 NanoLiposome biodegradable alginate microspheres (188RNL-BAM). Under the license agreement with UT Health Science at San Antonio, we are required to use commercial reasonable efforts to develop the 188RNL-BAM product candidate acquired under the license agreement. Further, we are subject to future milestone, earn-out and other payments to UT Health Science Center San Antonio all of which are tied to our commercialization and sale activities for product candidates. If we are unsuccessful in our efforts to develop these assets, or if UT Health Science Center San Antonio and we were to enter into a dispute over the terms of our agreement, then our business could be seriously harmed.

If we breach any of the agreements under which we license the use, development and commercialization rights to our product candidates or technology from third parties, we could lose license rights that are important to our business. Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. Disputes may arise between us and our licensors regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patents and other intellectual property rights to third parties under collaborative development relationships;

- our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates, and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- whether and the extent to which inventors are able to contest the assignment of their rights to our licensors.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms or at all, we may be unable to successfully develop and commercialize the affected product candidates. In addition, if disputes arise as to ownership of licensed intellectual property, our ability to pursue or enforce the licensed patent rights may be jeopardized. If we or our licensors fail to adequately protect this intellectual property, our ability to commercialize our products could suffer.

We and our product candidates are subject to extensive regulation, and the requirements to obtain regulatory approvals in the United States and other jurisdictions can be costly, time-consuming and unpredictable. If we or our partners are unable to obtain timely regulatory approval for our product candidates, our business may be substantially harmed.

The worldwide regulatory process for our nanomedicine drug candidates can be lengthy and expensive, with no guarantee of approval.

Before any new drugs may be introduced to the U.S. market, the manufacturer generally must obtain FDA approval through either an ANDA process for generic drugs off patent that allow for bioequivalence to an existing RLD or the lengthier NDA process, which typically requires multiple successful and successive clinical trials to generate clinical data supportive of safety and efficacy along with extensive pharmacodynamic and pharmacokinetic preclinical testing to demonstrate safety. Our RNL product candidates are subject to the FDA's 505(b)(1) NDA process. NDA drugs can take significant time due to the preclinical and clinical trial requirements.

There are numerous risks arising out of the regulation of our nanomedicine product candidates include the following:

- we can provide no assurances that our current and future oncology drugs will meet all of the stringent government regulation in the United States under the Federal Food, Drug and Cosmetic Act, and/or in international markets such as Europe, by the EMA under its Medicinal Products Directive;
- our nanomedicine product candidates, if approved, will still be subject to post-market reporting requirements for instances where the drug may have caused or contributed to the death or serious injury, or serious adverse events;
- there are no assurances that our product candidates will not have safety or effectiveness problems occurring after the drugs reach the market;
- there are no assurances that regulatory authorities will not take steps to prevent or limit further marketing of the drug due to safety concerns; and
- it is possible that the new legislation in our priority markets will yield additional regulatory requirements for therapeutic drugs for our nanomedicine product candidates.

We will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant expense, and if we or collaborators fail to comply with such requirements, regulatory agencies may take action against us or them, which could significantly harm our business.

Approved drug products are subject to ongoing regulatory requirements and oversight, including requirements related to manufacturing, quality control, conduct of post-marketing studies, labeling, packaging, storage, distribution, safety surveillance, import, export, advertising, promotion, recordkeeping and reporting. Regulatory authorities subject a marketed product, its manufacturer, and the manufacturing facilities to continual review and periodic inspections. We, our collaborators, and our and their respective contractors, suppliers and vendors, will be subject to ongoing regulatory requirements, including complying with regulations and laws regarding advertising, promotion and sales of products (including applicable anti-kickback, fraud and abuse and other health care laws and regulations), required submissions of safety and other post-market information and reports, registration requirements, Clinical Good Manufacturing Practices (cGMP) regulations (including requirements relating to quality control and quality assurance, as well as the corresponding maintenance of records and documentation), and the requirements regarding the distribution of samples to physicians and recordkeeping requirements. Regulatory agencies may change existing requirements or adopt new requirements or policies. We, our collaborators, and our and their respective contractors, suppliers, and vendors, may be slow to adapt or may not be able to adapt to these changes or new requirements.

Failure to comply with regulatory requirements may result in any of the following:

- restrictions on the marketing of our product candidates or manufacturing processes;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- voluntary or mandatory recall;
- fines;
- suspension or withdrawal of regulatory approvals;

- suspension or termination of any of our ongoing clinical trials;
- refusal to permit the import or export of our product candidates;
- refusal to approve pending applications or supplements to approved applications that we submit;
- product seizure;
- injunctions; or
- imposition of civil or criminal penalties.

Changing, new and/or emerging government regulations, including healthcare legislative reform measures, may adversely affect us.

Our nanoparticle and microparticle technologies and pipeline oncology products are being developed under existing government criteria, which are subject to change in the future. Clinical and/or pre-clinical criteria and cGMP manufacturing requirements may change and additional regulatory burdens may be imposed. Any regulatory review committees and advisory groups and any contemplated new guidelines may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we may be required to consult with these regulatory and advisory groups and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a product candidate to market could decrease our ability to generate sufficient revenue to maintain our business. Divergence in regulatory criteria for different regulatory agencies in international jurisdictions could result in the repeat of clinical studies and/or preclinical studies to satisfy local territory requirements, resulting in the repeating of studies and/or delays in the regulatory process. Some territories may require clinical data in their indigenous population, resulting in the repeat of clinical studies in whole or in part. Some territories may object to the formulation ingredients in the final finished product and may require reformulation to modify or remove objectionable components; resulting in delays in regulatory approvals. Such objectionable reformulations include, but are not limited to, human or animal components, Bovine Spongiform Encephalopathy and/or Transmissible Spongiform Encephalopathy risks, banned packaging components, prohibited chemicals, and banned substances. There can be no assurances that the FDA or foreign regulatory authorities will accept our pre-clinical and/or clinical data.

Anticipated or unanticipated changes in the way or manner in which the FDA or other regulators regulate products or classes and groups of products can delay, further burden, or alleviate regulatory pathways that were once available to other products. There are no guarantees that such changes in the FDA's or other regulators' approach to the regulatory process will not deleteriously affect some or all of our product candidates or product applications.

In the United States and in some other jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the health care system that could prevent or delay marketing approval of our drug candidates, restrict or regulate post-approval activities, or affect our ability to profitably sell any drug candidates for which we obtain marketing approval, if any. Further, any increased scrutiny of the FDA's approval process for drugs and biological products may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements. There also are a number of state and local legislative and regulatory efforts related to drug pricing, including drug price transparency laws that apply to pharmaceutical manufacturers, which may have an impact on our business.

In addition, the Drug Supply Chain Security Act enacted in 2013 imposes new obligations on manufacturers of pharmaceutical products related to product tracking and tracing, and that law is expected to be fully implemented over a ten-year period. Most recently, in December 2019, the Further Consolidated Appropriations Act for 2020 was signed into law (P.L. 116-94) that includes a piece of bipartisan legislation called the Creating and Restoring Equal Access to Equivalent Samples Act of 2019 or the "CREATES Act." The CREATES Act aims to address the concern articulated by both the FDA and others in the industry that some brand manufacturers have improperly restricted the distribution of their products, including by invoking the existence of a REMS for certain products, to deny generic and biosimilar product developers access to samples of brand products. The CREATES Act establishes a private cause of action that permits a generic or biosimilar product developer to sue the brand manufacturer to compel it to furnish the necessary samples on "commercially reasonable, market-based terms." Whether and how generic and biosimilar product developments will use this new pathway, as well as the likely outcome of any legal challenges to provisions of the CREATES Act, remain highly uncertain and its potential effects on our future commercial products are unknown. Other legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals, if any, of our drug candidates, may be or whether such changes will have any other impacts on our business. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing conditions and other requirements.

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

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

Adequate coverage and reimbursement from third party payors may not be available for our products and we may be unable to successfully contract for coverage from pharmacy benefit managers and other organizations; conversely, to secure coverage from these organizations, we may be required to pay rebates or other discounts or other restrictions to reimbursement, either of which could diminish our sales or adversely affect our ability to sell our products profitably.

In both U.S. and non-U.S. markets, our ability to successfully commercialize and achieve market acceptance of our products depends in significant part on adequate financial coverage and reimbursement from third party payors, including governmental payors (such as the Medicare and Medicaid programs in the U.S.), managed care organizations and private health insurers. Without third party payor reimbursement, patients may not be able to obtain or afford prescribed medications. In addition, reimbursement guidelines and incentives provided to prescribing physicians by third party payors may have a significant impact on the prescribing physicians' willingness and ability to prescribe our products. The demand for, and the profitability of, our products could be materially harmed if the state Medicaid programs, Medicare program, other healthcare programs in the U.S. or elsewhere, or third party commercial payors in the U.S. or elsewhere deny reimbursement for our products, limit the indications for which our products will be reimbursed, or provide reimbursement only on unfavorable terms. In particular, we cannot predict to what extent the evolving effects of the COVID-19 pandemic may disrupt global healthcare systems and access to our products, result in a widespread loss of individual health insurance coverage due to unemployment, result in a shift from commercial payor coverage to government payor coverage, or result in an increase in demand for patient assistance and/or free drug programs, any of which could adversely affect net revenue.

As part of the overall trend toward cost containment, third party payors often require prior authorization for, and require reauthorization for continuation of, prescription products or impose step edits, which require prior use of another medication, usually a generic or preferred brand, prior to approving coverage for a new or more expensive product. Such restrictive conditions for reimbursement and an increase in reimbursement-related activities can extend the time required to fill prescriptions and may discourage patients from seeking treatment. We cannot predict actions that third party payors may take, or whether they will limit the access and level of reimbursement for our products or refuse to provide any approvals or coverage. From time to time, third party payors have refused to provide reimbursement for our products, and others may do so in the future.

Third party payors increasingly examine the cost-effectiveness of pharmaceutical products, in addition to their safety and efficacy, when making coverage and reimbursement decisions. We may need to conduct expensive pharmacoeconomic and/or clinical studies in order to demonstrate the cost-effectiveness of our products. If our competitors offer their products at prices that provide purportedly lower treatment costs than our products, or otherwise suggest that their products are safer, more effective or more cost-effective than our products, this may result in a greater level of access for their products relative to our products, which would reduce our sales and harm our results of operations. In some cases, for example, third party payors try to encourage the use of less expensive generic products through their prescription benefit coverage and reimbursement and co-pay policies. Because some of our products compete in a market with both branded and generic products, obtaining and maintaining access and reimbursement coverage for our products may be more challenging than for products that are new chemical entities for which no therapeutic alternatives exist.

Some intellectual property that we have in-licensed has been discovered through government funded programs and thus may be subject to federal regulations such as "march-in" rights, certain reporting requirements and a preference for U.S.-based companies. Compliance with such regulations may limit our exclusive rights and limit our ability to contract with non-U.S. manufacturers.

Some of the intellectual property rights we have licensed are generated through the use of U.S. government funding and are therefore subject to certain federal regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future product candidates pursuant to the Bayh-Dole Act of 1980, or Bayh-Dole Act, and implementing regulations. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S.

government has the right to require us or our licensors to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). The U.S. government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. These time limits have recently been changed by regulation and may change in the future. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. To the extent any of our current or future intellectual property is generated through the use of U.S. government funding, the provisions of the Bayh-Dole Act may similarly apply.

Orphan drug designation may not ensure that we will enjoy market exclusivity in a particular market, and if we fail to obtain or maintain orphan drug designation or other regulatory exclusivity for some of our product candidates, our competitive position would be harmed.

A product candidate that receives orphan drug designation can benefit from potential commercial benefits following approval. Under the U.S. Orphan Drug Act, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, defined as affecting a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, the EMA's Committee for Orphan Medicinal Products, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 10,000 persons in the European Union. Currently, this designation provides market exclusivity in the U.S. and the European Union for seven years and ten years, respectively, if a product is the first such product approved for such orphan indication. This market exclusivity does not, however, pertain to indications other than those for which the drug was specifically designated in the approval, nor does it prevent other types of drugs from receiving orphan designations or approvals in these same indications. Further, even after an orphan drug is approved, the FDA can subsequently approve a drug with similar chemical structure for the same condition if the FDA concludes that the new drug is clinically superior to the orphan product or a market shortage occurs. In the European Union, orphan exclusivity may be reduced to six years if the drug no longer satisfies the original designation criteria or can be lost altogether if the marketing authorization holder consents to a second orphan drug application or cannot supply enough drug, or when a second applicant demonstrates its drug is "clinically superior" to the original orphan drug. In September 2020, the FDA granted both Orphan Drug designation and Fast Track designation to 180RNL for the treatment of patients with glioblastoma.

If we experience an interruption in supply from a material sole source supplier, our business may be harmed

We acquire some of our components and other raw materials from sole source suppliers. If there is an interruption in supply of our raw materials from a sole source supplier, for any reason, including due to disruption caused by the COVID-19 pandemic, there can be no assurance that we will be able to obtain adequate quantities of the raw materials within a reasonable time or at commercially reasonable prices. Interruptions in supplies due to pricing, timing, availability, or other issues with our sole source suppliers could have a negative impact on our ability to manufacture products and product candidates, which in turn could adversely affect the development and commercialization of our nanomedicine product candidates and cause us to potentially breach our supply or other obligations under our agreements with certain other counterparties.

We are dependent on sole source suppliers to manufacture the active pharmaceutical ingredients (API) and certain other components of our nanomedicine product candidates. There is no assurance that these sole source suppliers will enter into supply agreements with us to provide contractual assurance to us around supply and pricing. Regardless of whether a sole source supplier enters into a written supply arrangement with us, such supplier could still delay, suspend, or terminate supply of raw materials to us for a number of reasons, including manufacturing or quality issues, payment disputes with us, bankruptcy or insolvency, or other occurrences.

The COVID-19 pandemic has placed a significant strain on the pharmaceutical and medical industries, manufacturers of clinical supplies, and healthcare-related supplies and resources in general. For instance, we have experienced increased difficulties in obtaining certain materials for manufacturing that are also components of COVID-19 vaccine candidates. The impact of the COVID-19 pandemic has exacerbated the risks to which we are subject due to our reliance on third-party (and in some cases, sole source) suppliers. Additionally, our suppliers may experience operational difficulties, and resource constraints due to the impact of the COVID-19 pandemic. If our third-party suppliers were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to provide our product candidates to patients in clinical trials would be jeopardized. Any delay or interruption in the procurement 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.

If a sole source supplier ceases supply of raw materials necessary, there is no guarantee that we will find an alternative supplier for the necessary raw materials on terms acceptable to us, or at all. Further the qualification process for a new vendor could take months or years, and any such day in qualification could significantly harm our business.

We may engage in strategic transactions that could impact our liquidity, increase our expenses, and present significant distractions to our management.

From time to time, we may consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing of products, product candidates or technologies. Growth of the nanomedicine business will require significant management time and attention. Further, the future growth of our business will depend in part on our ability to in-license or otherwise acquire the rights to additional product candidates or technologies. We cannot assure you that we will be able to in-license or acquire the rights to any product candidates or technologies from third parties on acceptable terms or at all.

Additional potential transactions that we may consider include a variety of different business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non-recurring or other charges, may increase our near and long-term expenditures and may pose significant integration challenges or disrupt our management or business, which could adversely affect our operations and financial results. For example, these transactions may entail numerous operational and financial risks, including:

- exposure to unknown liabilities;
- disruption of our business and diversion of our management's time and attention in order to develop acquired products, product candidates or technologies;
- incurrence of substantial debt or dilutive issuances of equity securities to pay for acquisitions;
- higher than expected acquisition and integration costs;
- write-downs of assets or goodwill or impairment charges;
- increased amortization expenses;
- difficulty and cost in combining the operations and personnel of any acquired businesses with our operations and personnel;
- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and
- inability to retain key employees of any acquired businesses.

In addition, strategic transactions, including acquisitions and divestitures, may expose us to litigation risks. On June 22, 2021, we were named as a defendant in an action brought by Lorem Vascular, Pte. Ltd. ("Lorem") in the District Court for the District of Delaware. The complaint alleges false representations were made to Lorem regarding the manufacturing facility in the United Kingdom (the "UK Facility") that Lorem purchased from us under the Equity Purchase Agreement, dated March 29, 2019, between us and Lorem (the "Lorem Agreement"). Lorem also claims that false representations were made regarding the UK Facility's certification to sell and distribute devices in the European Union and export such devices to China. In connection with these allegations, Lorem claims entitlement to at least \$6,000,000 in compensatory damages and operational costs and expenses (collectively, the "Lorem Claim"). We believe that the claims from Lorem are without merit and we intend to vigorously defend the case and on August 12, 2021, we filed a Motion to Dismiss asking the District Court to dismiss the Lorem Claim. Lorem filed an opposition on September 9, 2021, which we responded to on September 30, 2021. On February 7, 2022, a hearing was held on our Motion to Dismiss and the presiding judge ruled against the Motion to Dismiss. We are moving forward with discovery in the case.

The in-licensing and acquisition of these technologies is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire product candidates or technologies that we may consider attractive. In addition, companies that perceive us to be a competitor may be unwilling to license rights to us. Furthermore, we may be unable to identify suitable product candidates or technologies within our area of focus. If we are unable to successfully obtain rights to suitable product candidates or technologies undertake or to successfully complete any additional transactions of the nature described above, our business, financial condition and prospects could suffer. In addition, even if we are able to successfully complete any additional transactions of the nature described above, any additional transactions that we do complete could have a material adverse effect on our business, results of operations, financial condition, and prospects.

We must maintain quality controls and compliance with manufacturing standards.

The manufacture of our product candidates is, and the manufacture of any future drug and/or cell-related therapeutic products would be, subject to periodic inspection by regulatory authorities and distribution partners. The manufacture of drug and device products for human use is subject to regulation and inspection from time to time by the FDA for compliance with the FDA's cGMP, Quality System Regulations ("QSRs"), as well as equivalent requirements and inspections by state and non-U.S. regulatory

authorities. There can be no assurance that the FDA or other authorities will not, during the course of an inspection of existing or new facilities, identify what they consider to be deficiencies in our compliance with QSRs or other requirements and request, or seek remedial action.

Failure to comply with such regulations or a potential delay in attaining compliance may adversely affect our manufacturing activities and could result in, among other things, injunctions, civil penalties, FDA refusal to grant pre- market approvals or clearances of future or pending product submissions, fines, recalls or seizures of products, total or partial suspensions of production and criminal prosecution. There can be no assurance that after such occurrences that we will be able to obtain additional necessary regulatory approvals or clearances on a timely basis, if at all. Delays in receipt of or failure to receive such approvals or clearances, or the loss of previously received approvals or clearances could have a substantial negative effect on our results of operations and financial condition.

If we are unable to identify, hire and/or retain key personnel, or if any of our personnel were to test positive for COVID-19, we may not be able to sustain or grow our business.

We maintain a very small executive team. Our ability to operate successfully and manage our potential future growth depends significantly upon our ability to attract, retain, and motivate highly skilled and qualified research, technical, clinical, regulatory, sales, marketing, managerial and financial personnel. We compete for talent with numerous companies, as well as universities and non-profit research organizations. In the future, we may hire a significant number of scientists, quality and regulatory personnel, and other technical staff with the requisite expertise to support and expand our nanomedicine business. The manufacturing of our oncology drug assets is a highly complex process that requires significant experience and know-how. If we are unable to attract personnel with the necessary skills and experience to reestablish and expand our nanomedicine business, which is currently conducted out of our San Antonio, Texas facility, our business could suffer.

Our future success also depends on the personal efforts and abilities of the principal members of our senior management and scientific staff to provide strategic direction, manage our operations, and maintain a cohesive and stable environment. In particular, we are highly dependent on our executive officers, especially Marc Hedrick, M.D., our Chief Executive Officer. Given his leadership, extensive technical, scientific, and financial expertise and management and operational experience, if we were unable to retain the services of Dr. Hedrick for any reason, it would materially and adversely impact our business and operations. Further, the loss of services of Dr. Hedrick or any other executive officer could result in product development delays or the failure of our collaborations with current and future collaborators, which, in turn, may hurt our ability to develop and commercialize products and generate revenue. We do not maintain key man life insurance on the lives of any of the members of our senior management. The loss of key personnel for any reason or our inability to hire, retain, and motivate additional qualified personnel in the future could prevent us from sustaining or growing our business. In addition, if any of our personnel were to test positive for COVID-19, it would likely significantly impair our operations. The loss of services of any of our personnel, including Dr. Hedrick, particularly for an extended period due to COVID-19 or otherwise, would likely result in product development delays or the failure of our collaborations with current and future collaborators, which, in turn, may impede or delay our ability to develop and commercialize products and generate revenue. In addition, it could also result in difficulty to obtain additional funding for our development of products and our future operations.

We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability if our insurance coverage for those claims is inadequate.

The clinical use of our product candidates exposes us to the risk of product liability claims. This risk exists even if a product or product candidate is approved for commercial sale by applicable regulatory authorities and manufactured in facilities regulated by such authorities. Our product candidates are designed to affect important bodily functions and processes. Any side effects, manufacturing defects, misuse, or abuse associated with our product candidates could result in injury to a patient or even death. For example, 186RNL and 188RNL-BAM are cytotoxic, or toxic to living cells, and, if incorrectly or defectively manufactured or labeled, or incorrectly dosed or otherwise used in a manner not contemplated by its label, could result in patient harm and even death. In addition, a liability claim may be brought against us even if our product candidates merely appear to have caused an injury.

Product liability claims may be brought against us by consumers, health care providers, pharmaceutical companies or others selling or otherwise coming into contact with our products or product candidates, if approved, among others. If we cannot successfully defend ourselves against product liability claims, we will incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- the inability to commercialize our product candidates;
- decreased demand for our product candidates, if approved;
- impairment of our business reputation;
- product recall or withdrawal from the market;
- withdrawal of clinical trial participants;
- costs of related litigation;

- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants; or
- loss of revenue.

We have obtained product liability insurance coverage for clinical trials with a \$10 million per occurrence and annual aggregate coverage limit. Our insurance coverage may not be sufficient to cover all of our product liability related expenses or losses and may not cover us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost, in sufficient amounts or upon adequate terms to protect us against losses due to product liability. If we determine that it is prudent to increase our product liability coverage, we may be unable to obtain this increased product liability insurance on commercially reasonable terms or at all. Large judgments have been awarded in class action or individual lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could decrease our cash and have a material adverse effect on our business, results of operations, financial condition and prospects.

A failure to adequately protect private health information could result in severe harm to our reputation and subject us to significant liabilities, each of which could have a material adverse effect on our business.

Throughout the clinical trial process, we may obtain the private health information of our trial subjects. There are a number of state, federal and international laws protecting the privacy and security of health information and personal data. The Healthcare Information Portability and Accountability Act ("HIPAA") imposes privacy, security, breach reporting obligations, and mandatory contractual terms on covered entity health care providers, health plans, and health care clearinghouses, as well as their "business associates" – certain persons or covered entities that create, receive, maintain, or transmit protected health information in connection with providing a specified service or performing a function on behalf of a covered entity. We could potentially be subject to criminal penalties if we, our affiliates, or our agents knowingly use or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA. Most states have laws requiring notification of affected individuals and state regulators (breach notification laws) in the event of a breach of personal information, which is a broader class of information than the health information protected by HIPAA. Many state laws impose significant data security requirements, such as encryption or mandatory contractual terms to ensure ongoing protection of personal information. Additionally, in California, the California Consumer Privacy Act ("CCPA") establishes certain requirements for data use and sharing transparency and creates new data privacy rights for California residents. The CCPA and its implementing regulations have already been amended multiple times since their enactment. In November 2020, California voters approved the California Privacy Rights Act ("CPRA") ballot initiative which introduced significant amendments to the CCPA and established and funded a dedicated California privacy regulator, the California Privacy Protection Agency ("CPPA"). The amendments introduced by the CPRA go into effect on January 1, 2023, and new implementing regulations are expected to be introduced by the CPPA. Failure to comply with the CCPA may result in, among other things, significant civil penalties and injunctive relief, or statutory or actual damages. In addition, California residents have the right to bring a private right of action in connection with certain types of incidents. These claims may result in significant liability and damages. Activities outside of the U.S. implicate local and national data protection standards, impose additional compliance requirements and generate additional risks of enforcement for non-compliance. The European Union's General Data Protection Regulation ("GDPR"), which imposes fines of up to EUR 20 million or 4% of the annual global revenue of a noncompliant company, whichever is greater, Canada's Personal Information Protection and Electronic Documents Act and other data protection, privacy and similar national, state/provincial and local laws may also restrict the access, use and disclosure of patient health information abroad. We may be required to expend significant capital and other resources to ensure ongoing compliance with applicable privacy and data security laws, to protect against security breaches and hackers, or to alleviate problems caused by such breaches. Compliance with these laws is difficult, constantly evolving, time consuming, and requires a flexible privacy framework and substantial resources. Compliance efforts will likely be an increasing and substantial cost in the future.

We and our collaborators must comply with environmental laws and regulations, including those pertaining to use of hazardous and biological materials in our business, and failure to comply with these laws and regulations could expose us to significant liabilities.

We and our collaborators are subject to various federal, state, and local environmental laws, rules and regulations, including those relating to discharge of materials into the air, water and ground, those relating to manufacturing, storage, use, transportation and disposal of hazardous and biological materials, and those relating to the health and safety of employees with respect to laboratory activities required for the development of our products and activities. In particular, our nanomedicine products and processes involve the controlled storage, use and disposal of certain cytotoxic, or toxic to living cells, materials. Even if we and these suppliers and collaborators comply with the standards prescribed by law and regulation, the risk of accidental contamination or injury from hazardous materials, or other violations of applicable environmental laws, rules or regulations cannot be completely eliminated. In the event of any violation of such laws, rules or regulations, we could be held liable for any damages that result, and any liability could exceed the limits or fall outside the coverage of any insurance we may obtain and could exceed our financial resources. We may not be able to maintain insurance on acceptable terms, or at all. We may incur significant costs in complying with environmental laws, rules and regulations.

Risks Relating to Our Intellectual Property

Our success depends in part on our ability to protect our intellectual property.

Our success depends in part on our ability to obtain and maintain patent, trademark, and trade secret protection of our platform technology and current product candidates, including but not limited to our nanomedicine product candidates, including 186RNL and 188RNL-BAM, as well as successfully defending our intellectual property against third-party challenges. Our ability to stop unauthorized third parties from making, using, selling, offering to sell, or importing our platform technology and/or our product candidates is dependent upon the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities.

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. For example:

- we, NanoTx, or UT Health Science Center at San Antonio, as the case may be, might not have been the first to file patent applications for the covered inventions;
- it is possible that our pending patent applications will not result in issued patents;
- it is possible that there are dominating patents to our product candidates of which we are not aware;
- it is possible that there are prior public disclosures that could invalidate our patents, of which we are not aware;
- it is possible that others may circumvent our patents;
- it is possible that there are unpublished applications or patent applications maintained in secrecy that may later issue with claims covering our product candidates or technology similar to ours;
- the claims of our patents or patent applications, if and when issued, may not cover our system or products, or our system or product candidates;
- our owned or in-licensed issued patents may not provide us with any competitive advantages, or may be narrowed in scope, be held invalid or unenforceable as a result of legal administrative challenges by third parties;
- others may be able to make or use compounds that are the same or similar to the 186RNL or 188RNL-BAM product candidates but that are not covered by the claims of our patents;
- we may not be able to detect infringement against our patents, which may be especially difficult for manufacturing processes or formulation patents, such as the patents/applications related to 186RNL or 188 RNL-BAM;
- the active pharmaceutical ingredient (API) used in 186RNL, 186-Re, is routinely produced in nuclear reactors or at a particle accelerator and is commercially available as 186-Re Sulfide for isotropic radiation synovectomy of medium sized joints and in developing countries as 186-Re-HEDP for bone pain palliation;
- we may not develop additional proprietary technologies for which we can obtain patent protection; or
- the patents of others may have an adverse effect on our business.

The patent positions of pharmaceutical, biopharmaceutical and medical device 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 patents in these fields has emerged to date in the United States. There have been recent changes regarding how patent laws are interpreted, and both the USPTO and Congress have recently made significant changes to the patent system. There have been three U.S. Supreme Court decisions that now show a trend of the Supreme Court which is distinctly negative on patents. The trend of these decisions along with resulting changes in patentability requirements being implemented by the USPTO could make it increasingly difficult for us to obtain and maintain patents on our product candidates. We cannot accurately predict future changes in the interpretation of patent laws or changes to patent laws which might be enacted into law. Those changes may materially affect our patents, our ability to obtain patents and/or the patents and applications of our collaborators and licensors. The patent situation in these fields 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 or narrow the scope of our patent protection. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in the patents we own or to which we have a license or third-party patents.

Intellectual property law outside the United States is uncertain and in many countries is currently undergoing review and revisions. The laws of some countries do not protect our patent and other intellectual property rights to the same extent as United States laws. Third parties may attempt to oppose the issuance of patents to us in foreign countries by initiating opposition proceedings. Opposition proceedings against any of our patent filings in a foreign country could have an adverse effect on our corresponding patents that are issued or pending in the United States. It may be necessary or useful for us to participate in proceedings to determine the validity of our patents or our competitors' patents that have been issued in countries other than the United States. This could result in substantial costs, divert our efforts and attention from other aspects of our business, and could have a material adverse effect on our results of operations and financial condition.

Failure to obtain or maintain patent protection or protect trade secrets, for any reason (or third-party claims against our patents, trade secrets, or proprietary rights, or our involvement in disputes over our patents, trade secrets, or proprietary rights, including involvement in litigation), could have a substantial negative effect on our results of operations and financial condition.

We may not be able to protect our trade secrets.

We may rely on trade secrets to protect our technology, especially with respect to the nanomedicine products, as well as in areas where we do not believe patent protection is appropriate or obtainable. Trade secrets are difficult to protect, and we have limited control over the protection of trade secrets used by our collaborators and suppliers. Although we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors, outside scientific collaborators, and other advisors may unintentionally or willfully disclose our information to competitors. Enforcing a claim that a third party illegally obtained and is using any of our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, state laws in the United States vary, and their courts as well as courts outside the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods, and know-how. If our confidential or proprietary information is divulged to or acquired by third parties, including our competitors, our competitive position in the marketplace will be harmed and our ability to successfully penetrate our target markets could be severely compromised.

We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

As is common in the device, biotechnology and pharmaceutical industries, we employ individuals who were previously employed at other device, biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management, which would adversely affect our financial condition.

We may incur substantial costs as a result of litigation or other proceedings relating to patent and other intellectual property rights, and we may be unable to protect our rights to our product candidates and technology.

Litigation may be necessary to enforce or confirm the ownership of any patents issued or licensed to us, or to determine the scope and validity of third-party proprietary rights, which would result in substantial costs to us and diversion of effort on our part. If our competitors claim technology also claimed by us and prepare and file patent applications in the United States, we may have to participate in interference proceedings declared by the USPTO or a foreign patent office to determine priority of invention, which could result in substantial costs to and diversion of effort, even if the eventual outcome is favorable to us. Any such litigation or interference proceeding, regardless of outcome, could be expensive and time-consuming.

Successful challenges to our patents through oppositions, reexamination proceedings or interference proceedings could result in a loss of patent rights in the relevant jurisdiction. If we are unsuccessful in actions we bring against the patents of other parties, and it is determined that we infringe the patents of third-parties, we may be subject to litigation, prevented from commercializing potential products in the relevant jurisdiction and/or may be required to obtain licenses to those patents or develop or obtain alternative technologies, any of which could harm our business. Furthermore, if such challenges to our patent rights are not resolved in our favor, we could be delayed or prevented from entering into new collaborations or from commercializing certain products, which could adversely affect our business and results of operations.

Competitors or third parties may infringe on or upon our patents. We may be required to file patent infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or is unenforceable or that the third party's technology does not in fact infringe upon our patents. An adverse determination of any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our related pending patent applications at risk of not issuing.

Litigation may fail and, even if successful, may result in substantial costs and be a distraction to our management. We may not be able to prevent misappropriation of our proprietary rights, particularly in countries outside the United States where patent rights may be more difficult to enforce. Further, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential or sensitive information could be compromised by disclosure in the event of litigation. In addition, during the course of litigation there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise the funds necessary to continue our operations or otherwise have a material adverse effect on our business, results of operations, financial condition, and prospects.

If we are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in that litigation would have a material adverse effect on our business.

Our commercial success will also depend, in part, on our ability to avoid infringing on patents issued by others. There may be issued patents of third parties of which we are currently unaware, that are infringed or are alleged to be infringed by our product candidate or proprietary technologies. Because some patent applications in the United States may be maintained in secrecy until the patents are issued, patent applications in the United States and many foreign jurisdictions are typically not published until eighteen months after filing, and publications in the scientific literature often lag behind actual discoveries, we cannot be certain that others have not filed patent applications for technology covered by our owned and in-licensed issued patents or our pending applications, or that we or, if applicable, a licensor were the first to invent the technology. Our competitors may have filed, and may in the future file, patent applications covering our product candidates or technology similar to ours. Any such patent application may have priority over our patent applications or patents, which could further require us to obtain rights to issued patents covering such technologies.

We may be exposed to, or threatened with, future litigation by third parties having patent or other intellectual property rights alleging that our product candidates and/or proprietary technologies infringe their intellectual property rights. These lawsuits are costly and could adversely affect our results of operations and divert the attention of managerial and technical personnel. There is a risk that a court would decide that we or our commercialization partners are infringing the third party's patents and would order us or our partners to stop the activities covered by the patents. In addition, there is a risk that a court will order us or our partners to pay the other party damages for having violated the other party's patents.

If a third-party's patent were found to cover our product candidates, proprietary technologies or their uses, we could be enjoined by a court and required to pay damages and could be unable to commercialize our product candidates or use our proprietary technologies unless we or they obtained a license to the patent. A license may not be available to us on acceptable terms, if at all. In addition, during litigation, the patent holder could obtain a preliminary injunction or other equitable relief which could prohibit us from making, using or selling our product candidates, technologies or methods pending a trial on the merits, which could be years away.

Risks Relating to the Securities Markets and an Investment in our Common Stock

Our stockholders may experience substantial dilution in the value of their investment if we issue additional shares of our capital stock, including in connection with the sale or issuance of our common stock by Canaccord.

Our charter allows us to issue up to 100,000,000 shares of our common stock and to issue and designate the rights of, without stockholder approval, up to 5,000,000 shares of preferred stock. To raise additional capital, we may in the future sell additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that are lower than the prices paid by existing stockholders, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders, which could result in substantial dilution to the interests of existing stockholders.

On January 14, 2022, we entered into the Distribution Agreement with Canaccord, pursuant to which we may issue and sell, from time to time, the Shares, depending on market demand, with Canaccord acting as an agent for sales. Sales of the Shares may be made by any method permitted by law deemed to be an "at the market offering" as defined in Rule 415(a)(4) of the Securities Act, including, without limitation, sales made directly on or through the Nasdaq. Canaccord will use its commercially reasonable efforts to sell the Shares requested by us to be sold on its behalf, consistent with Canaccord's normal trading and sales practices, under the terms and subject to the conditions set forth in the Distribution Agreement. We have no obligation to sell any of the Shares. We may instruct Canaccord not to sell the Shares if the sales cannot be effected at or above the price designated by us from time to time and we may at any time suspend sales pursuant to the Distribution Agreement.

Future sales of our common stock may depress our share price.

As of December 31, 2021, we had 15,510,025 shares of our common stock outstanding. Sales of a number of shares of common stock in the public market could cause the market price of our common stock to decline. We may also sell additional common stock or securities convertible into or exercisable or exchangeable for common stock in subsequent public or private offerings or other transactions, which may adversely affect the market price of our common stock.

The market price of our common stock may be volatile and fluctuate significantly, which could result in substantial losses for stockholders.

The market price of our common stock has been, and may continue to be, subject to significant fluctuations. Among the factors that may cause the market price of our common stock to fluctuate are the risks described in this "Risk Factors" section and other factors, including:

- fluctuations in our operating results or the operating results of our competitors;
- the outcome of clinical trials involving the use of our product candidates, including our sponsored trials;
- changes in estimates of our financial results or recommendations by securities analysts;
 - variance in our financial performance from the expectations of securities analysts;
- changes in the estimates of the future size and growth rate of our markets;
- changes in accounting principles or changes in interpretations of existing principles, which could affect our financial results;
- conditions and trends in the markets we currently serve or which we intend to target with our product candidates;
 - changes in general economic, industry and market conditions;
- the impact of the COVID-19 impact, including the magnitude, severity, duration, and uncertainty of the downturn in the domestic and global economies and financial markets;
 - success of competitive products and services;
 - changes in market valuations or earnings of our competitors;
- announcements of significant new products, contracts, acquisitions or strategic alliances by us or our competitors;
 - our continuing ability to list our securities on an established market or exchange;
 - the timing and outcome of regulatory reviews and approvals of our product candidates;
 - the commencement or outcome of litigation involving our company, our general industry or both;
 - changes in our capital structure, such as future issuances of securities or the incurrence of additional debt;
 - actual or expected sales of our common stock by the holders of our common stock; and
 - the trading volume of our common stock.

In addition, the financial markets may experience a loss of investor confidence or otherwise experience continued volatility and deterioration due to the COVID-19 pandemic. A loss of investor confidence may result in extreme price and volume fluctuations in our common stock that are unrelated or disproportionate to the operating performance of our business, our financial condition or results of operations, which may materially harm the market price of our common stock and result in substantial losses for stockholders. Further, although our common stock is traded on the Nasdaq, there is currently a limited market for our common stock and an active market may never develop. An active trading market in our common stock may not develop.

We may be or become the target of securities litigation, which is costly and time-consuming to defend.

In the past, following periods of market volatility in the price of a company's securities, the reporting of unfavorable news or continued decline in a company's stock price, security holders have often instituted class action litigation. The market value of our securities has steadily declined over the past several years for a variety of reasons discussed elsewhere in this "Risk Factors" section, which heightens our litigation risk. If we face such litigation, we could incur substantial legal costs and our management's attention could be diverted from the operation of our business, causing our business to suffer. Any adverse determination in any such litigation or any amounts paid to settle any such actual or threatened litigation could require that we make significant payments.

We may issue debt and equity securities or securities convertible into equity securities, any of which may be senior to our common stock as to distributions and in liquidation, which could negatively affect the value of our common stock.

In the future, we may attempt to increase our capital resources by entering into debt or debt-like financing that is unsecured or secured by up to all of our assets, or by issuing additional debt or equity securities, which could include issuances of secured or unsecured commercial paper, medium-term notes, senior notes, subordinated notes, guarantees, preferred stock, hybrid securities, or securities convertible into or exchangeable for equity securities. In the event of our liquidation, our lenders and holders of our debt and preferred securities would receive distributions of our available assets before distributions to the holders of our common stock. Because our decision to incur debt and issue securities in future offerings may be influenced by market conditions and other factors beyond our control, we cannot predict or estimate the amount, timing or nature of our future offerings or debt financings. Further, market conditions could require us to accept less favorable terms for the issuance of our securities in the future.

We could be delisted from Nasdaq, which would seriously harm the liquidity of our stock and our ability to raise capital.

Nasdaq requires listing issuers to comply with certain standards in order to remain listed on its exchange. If, for any reason, Nasdaq should delist our securities from trading on its exchange and we are unable to obtain listing on another reputable national securities exchange, a reduction in some or all of the following may occur, each of which could materially adversely affect our stockholders.

For example, if at any time the bid price of our common stock closes at below \$1.00 per share for more than 30 consecutive trading days, we may be subject to delisting from the Nasdaq. If we receive a delisting notice, we would have 180 calendar days to regain compliance (subject to any additional 180-day compliance period which may be available to us), which would mean having a bid price above the minimum of \$1.00 for at least 10 consecutive days in the 180-day period. During this 180-day period, we would anticipate reviewing our options to regain compliance with the minimum bid requirements, including conducting a reverse stock split. To the extent that we are unable to resolve any listing deficiency, there is a risk that our common stock may be delisted from Nasdaq, which would adversely impact liquidity of our common stock and potentially result in even lower bid prices for our common stock. On February 22, 2022, the closing price of our common stock was \$1.01 per share.

If, for any reason, Nasdaq were to delist our securities from trading on its exchange and we are unable to obtain listing on another reputable national securities exchange, a reduction in some or all of the following may occur, each of which could materially adversely affect our stockholders:

- the liquidity and marketability of our common stock;
- the market price of our common stock;
- our ability to obtain financing for the continuation of our operations;
- the number of institutional and general investors that will consider investing in our common stock;
- the number of market makers in our common stock;
- the availability of information concerning the trading prices and volume of our common stock; and
- the number of broker-dealers willing to execute trades in shares of our common stock.

In addition, if we cease to be eligible to trade on Nasdaq, we may have to pursue trading on a less recognized or accepted market, such as the over the counter markets, our stock may be traded as a “penny stock” which would make transactions in our stock would be more difficult and cumbersome, and we may be unable to access capital on favorable terms or at all, as companies trading on alternative markets may be viewed as less attractive investments with higher associated risks, such that existing or prospective institutional investors may be less interested in, or prohibited from, investing in our common stock. This may also cause the market price of our common stock to further decline.

Our charter documents contain anti-takeover provisions.

Certain provisions of our amended and restated certificate of incorporation and amended and restated bylaws could discourage, delay or prevent a merger, acquisition or other change of control that stockholders may consider favorable. These provisions could also prevent or frustrate attempts by our stockholders to replace or remove members of our Board of Directors. Stockholders who wish to participate in these transactions may not have the opportunity to do so. These provisions:

- authorize our Board of Directors to issue without stockholder approval up to 5,000,000 shares of preferred stock, the rights of which will be determined at the discretion of the Board of Directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and cannot be taken by written consent;
- establish advance notice requirements for stockholder nominations to our Board of Directors or for stockholder proposals that can be acted on at stockholder meetings; and
- limit who may call stockholder meetings.

We are governed by the provisions of Section 203 of the Delaware General Corporation Law, which may, unless certain criteria are met, prohibit large stockholders, in particular those owning 15% or more of the voting rights on our common stock, from merging or combining with us for a prescribed period of time.

We presently do not intend to pay cash dividends on our common stock.

We have never paid cash dividends in the past, and we currently anticipate that no cash dividends will be paid on the common stock in the foreseeable future. Furthermore, our Loan and Security Agreement with Oxford currently prohibits our issuance of cash dividends. This could make an investment in our common stock inappropriate for some investors, and may serve to narrow our potential sources of additional capital. While our dividend policy will be based on the operating results and capital needs of the business, it is anticipated that all earnings, if any, will be retained to finance the future expansion of our business.

If securities and/or industry analysts fail to continue publishing research about our business, if they change their recommendations adversely, or if our results of operations do not meet their expectations, our stock price and trading volume could decline.

The trading market for our common stock may be influenced by the research and reports that industry or securities analysts publish about us or our business. If one or more of these analysts cease coverage of our company or fail to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline. In

addition, it is likely that in some future period our operating results will be below the expectations of securities analysts or investors. If one or more of the analysts who cover us downgrade our stock, or if our results of operations do not meet their expectations, our stock price could decline.

General Risk Factors

The COVID-19 pandemic could adversely affect our business, results of operations, and financial condition.

The COVID-19 pandemic has caused a significant downturn in the worldwide economy, the severity, magnitude, and duration of which is uncertain. While we cannot presently predict the future scope and severity of current or any potential business shutdowns or disruptions related to COVID-19, if we or any of the third parties with whom we engage, including the suppliers, manufacturers and other third parties in our global supply chain, clinical trial sites, clinical research organizations, patients who may be candidates for clinical trials, regulators, surgeons, potential business development partners and other third parties with whom we conduct business, were to experience prolonged shutdowns or other business disruptions, our ability to conduct our business in the manner and on the timelines presently planned could be materially and negatively impacted. Further, any sustained disruption in the capital markets from the pandemic could negatively impact our ability to raise capital.

To the extent the pandemic adversely affects our business, results of operations, financial condition and cash flows, it may also heighten many of the other risks described herein as well as in any amendment or update to our risk factors reflected in subsequent filings with the SEC.

The ultimate impact of the Pandemic on our business, results of operations, financial condition and cash flows is dependent on future developments, which are still highly uncertain and cannot be predicted with confidence, including the duration of the Pandemic, as well as the timing and phasing of business reopening.

We may face business disruption and related risks resulting from the COVID-19 pandemic and the invocation of the Defense Production Act, either of which could have a material adverse effect on our business.

Our development programs could be disrupted and materially adversely affected by the COVID-19 pandemic. As a result of measures imposed by the governments in affected regions, many commercial activities, businesses and schools have been suspended as part of quarantines and other measures intended to contain this outbreak. The spread of COVID-19 worldwide has resulted in the International Health Regulations Emergency Committee of the World Health Organization declaring the outbreak of COVID-19 as a “public health emergency of international concern,” and the World Health Organization characterizing COVID-19 as a pandemic. International stock markets have also been significantly impacted and their volatility reflect the uncertainty associated with the potential economic impact of the outbreak. The volatility in the Dow Industrial Average since the end of February 2020 has been largely attributed to the effects of the COVID-19 pandemic. While we have not experienced any significant impact on our business as a result of the COVID-19 pandemic, we continue to assess the potential impact the COVID-19 pandemic may have on our ability to effectively conduct our commercialization efforts and development programs and otherwise conduct our business operations as planned. There can be no assurance that we will not be further impacted by the COVID-19 pandemic or by any action taken by the federal government under the Defense Production Act, including downturns in business sentiment generally or in our industry and business in particular.

Increased information technology security threats and more sophisticated and targeted computer crime could pose a risk to our systems, networks, and products.

Increased global information technology security threats and more sophisticated and targeted computer crime pose a risk to the security of our systems and networks and the confidentiality, availability and integrity of our data and communications. While we attempt to mitigate these risks by employing a number of measures, including employee refreshers, monitoring of our networks and systems, and maintenance of backup and protective systems, our systems, networks and products remain potentially vulnerable to advanced persistent threats. Depending on their nature and scope, such threats could potentially lead to the compromising of confidential information and communications, improper use of our systems and networks, manipulation and destruction of data, defective products, production downtimes and operational disruptions, which in turn could adversely affect our reputation, competitiveness and results of operations.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

We have two lease agreements for our San Antonio, Texas locations. The leases for these properties will expire in February 2025. We also lease certain office space in Austin, Texas under a month-to-month operating lease agreement. We also have a lease agreement for office space in Charlottesville, Virginia. We pay an aggregate of approximately \$16,000 in rent per month for these properties.

Item 3. Legal Proceedings

On June 22, 2021, the Company was named as a defendant in an action brought by Lorem Vascular, Pte. Ltd. (“Lorem”) in the District Court for the District of Delaware. The complaint alleges false representations were made to Lorem regarding the manufacturing facility in the United Kingdom (the “UK Facility”) that Lorem purchased from the Company under the Equity Purchase Agreement, dated March 29, 2019, between the Company and Lorem (the “Lorem Agreement”). Lorem also claims that false representations were made regarding the UK Facility’s certification to sell and distribute devices in the European Union and export such devices to China. In connection with these allegations, Lorem claims entitlement to at least \$6,000,000 in compensatory damages and operational costs and expenses (collectively, the “Lorem Claim”). The Company believes that the claims from Lorem are without merit and intends to vigorously defend the case and on August 12, 2021, the Company filed a Motion to Dismiss asking the District Court to dismiss the Lorem Claim. Lorem filed an opposition on September 9, 2021, which the Company responded to on September 30, 2021. On February 7, 2022, a hearing was held on the Company’s Motion to Dismiss and the presiding judge ruled against the Motion to Dismiss. The Company is moving forward with discovery in this case.

Refer to Note 7 of the Consolidated Financial Statements included in this Form 10-K.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Prices

Market Information

Our common stock is traded on the Nasdaq Capital Market under the symbol "PSTV". As of February 14, 2022, we had approximately 20 record holders of our common stock. Because many of our shares are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of individual stockholders represented by these record holders.

Equity Compensation Plan Information

The following table gives information as of December 31, 2021 about shares of our common stock that may be issued upon the exercise of outstanding options, and shares remaining available for issuance under all of our equity compensation plans:

Plan Category	Number of securities to be issued upon exercise of outstanding options and rights (a)	Weighted-average exercise price of outstanding options and rights (b)	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column(a)) (c)
Equity compensation plans not approved by security holders (1)	160,353	\$ 16.04	90,389
Equity compensation plans approved by security holders (2)	1,010,537	\$ 3.26	640,212
Total	1,170,890	\$ 5.01	730,601

(1) Represents (i) options outstanding that were issued under the 2004 Stock Option and Stock Purchase Plan which expired in August 2004 and (ii) the 2015 New Employee Incentive Plan.

(2) See Notes to the Consolidated Financial Statements included elsewhere herein for a description of our 2020 Stock Incentive Plan.

Material Features of the Amended and Restated 2015 New Employment Incentive Plan and the 2020 Stock Incentive Plan

The 2015 Plan was adopted by the Company on December 29, 2015 pursuant to Rule 5653(c)(4) of the Nasdaq. The 2015 Plan was subsequently amended by the Board in May 2016 and January 2020.

Awards granted under the 2015 Plan were intended to constitute "employment inducement awards" under Nasdaq Listing Rule 5635(c)(4) and, therefore, the 2015 Plan was intended to be exempt from the Nasdaq Listing Rules regarding stockholder approval of stock option and stock purchase plans. The 2015 Plan provides for issuance of 133 shares. In January 2017, the Company amended the 2015 Plan to add 500 shares to its share pool. In February 2020, the Company amended the 2015 Plan to add 250,000 shares of stock to its share pool. The 2015 Plan provides for the grant of restricted stock unit awards, restricted stock awards, performance awards, unrestricted securities, stock-equivalent units, stock appreciation units, securities or debentures convertible into common stock or other forms. These awards may be granted to individuals who were then new employees, or were commencing employment with us or one of our subsidiaries following a bona fide period of non-employment with us, and for whom such awards were granted as a material inducement to commencing employment with us or one of our subsidiaries.

The 2015 Plan is administered by the Compensation Committee. The plan administrator has discretion to take action under the 2015 Plan, such as determining the purchase price, performance measures, any repurchase rights, as well as make adjustment to the terms of any Award to reflect, or related to, such changes in the capital structure of the Company or distributions as it deems appropriate, including modification of performance goals, performance award formulas, and performance periods.

On June 16, 2020, the stockholders of the Company approved the Company's 2020 Stock Incentive Plan (the "2020 Plan"), which replaced the Company's 2014 Equity Incentive Plan. The 2020 Plan provides for the issuance of up to 550,000 shares of common stock, and the number of shares available for issuance are increased to the extent that awards granted under the 2020 Plan and the Company's 2014 Equity Incentive Plan are forfeited or expire (except as otherwise provided in the 2020 Plan). On May 17, 2021, the stockholders of the Company approved an amendment and restatement to the 2020 Plan to increase the total number of shares of common stock reserved for issuance under the 2020 Plan by 1,000,000 shares.

The 2020 Plan provides for the direct award or sale of shares of common stock (including restricted stock), the award of stock units and stock appreciation rights, and the grant of both incentive stock options to purchase common stock intended to qualify for preferential tax treatment under Section 422 of the Code and nonstatutory stock options to purchase common stock that do not qualify for such treatment under the Code. All employees (including officers) and directors of the Company or any subsidiary and any consultant who performs services for the Company or a subsidiary are eligible to purchase shares of common stock and to receive awards of shares or grants of nonstatutory stock options, stock units and stock appreciation rights. Only employees are eligible to receive grants of incentive stock options.

The 2020 Plan is administered by the Compensation Committee. Subject to the limitations set forth in the 2020 Plan, the Compensation Committee has the authority to determine, among other things, to whom awards will be granted, the number of shares subject to awards, the term during which an option, stock unit or stock appreciation right may be exercised and the rate at which the awards may vest or be earned, including any performance criteria to which they may be subject. The Compensation Committee also has the authority to determine the consideration and methodology of payment for awards.

Item 6. [Reserved]

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

Our Management's Discussion and Analysis of Financial Condition and Results of Operations includes the following sections:

- Overview that discusses our business and some of the relevant trends.
- Results of Operations that includes a detailed discussion of our revenue and expenses.
- Liquidity and Capital Resources which discusses key aspects of our statements of cash flows, changes in our financial position and our financial commitments.

Overview

Plus Therapeutics, Inc. is a U.S. pharmaceutical company developing innovative, targeted radiotherapeutics for adults and children with rare and difficult-to-treat cancers. Our novel radioactive drug formulations and therapeutic candidates are designed to deliver safe and effective doses of radiation to tumors. To achieve this, we have developed innovative approaches to drug formulation, including encapsulating radionuclides such as Rhenium isotopes with nanoliposomes and microspheres. Our formulations are intended to achieve elevated patient absorbed radiation doses and extended retention times such that the clearance of the isotope occurs after significant radiation decay, which will contribute and provide less normal tissue/organ exposure and improved safety margins.

Traditional approaches to radiation therapy for cancer such as external beam radiation have many disadvantages including continuous treatment for 4-6 weeks (which is onerous for patients), that the radiation damages healthy cells and tissue, and that the amount of radiation delivered is very limited and, therefore, is frequently inadequate to fully destroy the cancer.

Our targeted radiotherapeutic platform and unique investigational drugs have the potential to overcome these disadvantages by directing higher, more powerful radiation doses at the tumor—and only the tumor—potentially in a single treatment. By minimizing radiation exposure to healthy tissues while simultaneously maximizing efficacy, we hope to reduce the toxicity of radiation for patients, improving their quality and life expectancy. Our radiotherapeutic platform, combined with advances in surgery, nuclear medicine, interventional radiology, and radiation oncology, affords us the opportunity to target a broad variety of cancer types.

Our lead radiotherapeutic candidate, Rhenium-186 NanoLiposome ("¹⁸⁶RNL") is designed specifically to target central nervous system (CNS) cancers including recurrent glioblastoma, leptomeningeal metastases, and pediatric brain cancers by direct localized delivery utilizing approved standard-of-care tissue access such conduction enhanced delivery ("CED") and intraventricular brain catheters (Ommaya reservoir). Our recently acquired radiotherapeutic candidate, Rhenium-188 NanoLiposome Biodegradable Alginate Microsphere ("¹⁸⁸RNL-BAM") is designed to treat many solid organ cancers including primary and secondary liver cancers.

Our headquarters and manufacturing facilities are Texas are in proximity to world-class cancer institutions and researchers. Our dedicated team of engineers, physicians, scientists, and other professionals are committed to advancing our targeted radiotherapeutic technology for the benefit of cancer patients and healthcare providers worldwide and our current pipeline is focused on treating rare and difficult-to-treat cancers with significant unmet medical needs.

Pipeline

Our most advanced investigational drug, ¹⁸⁶RNL, is a patented radiotherapy potentially useful for patients with central nervous system (CNS) and other cancers. Preclinical study data describing the use of ¹⁸⁶RNL for several cancer targets have been published in peer-reviewed journals. Besides glioblastoma, leptomeningeal metastases, and pediatric brain cancer, ¹⁸⁶RNL has been reported to have potential applications for head and neck cancer, ovarian cancer, breast cancer and peritoneal metastases.

The ¹⁸⁶RNL technology was part of a licensed radiotherapeutic portfolio that we acquired from NanoTx, Corp. ("NanoTx") on May 7, 2020. The licensed radiotherapeutic has been evaluated in preclinical studies for several cancer targets and we have an active \$3.0 million award from U.S. National Institutes of Health/National Cancer Institute which will provide financial support for the continued clinical development of ¹⁸⁶RNL for recurrent glioblastoma through the completion of a Phase 2 clinical trial including enrollment of up to 55 patients. Thus far, 23 patients have been treated in the Phase 1 clinical trial and the Phase 2 clinical trial has not yet been initiated.

We are currently conducting the ReSPECT-GBM and ReSPECT-LM clinical trials for recurrent glioblastoma (GBM) and leptomeningeal metastases (LM), respectively. In addition, we anticipate seeking FDA IND approval for the ReSPECT-PBC clinical trial for pediatric brain cancer (PBC) in late 2022 or early 2023.

¹⁸⁶RNL versus External Beam Radiation Therapy

¹⁸⁶RNL is a novel injectable radiotherapy designed to deliver targeted, high dose radiation directly into glioblastoma tumors in a safe, effective, and convenient manner that may ultimately prolong patient survival. ¹⁸⁶RNL is composed of the radionuclide Rhenium-186 and a nanoliposomal carrier, and is infused in a highly targeted fashion, directly into the tumor via precision brain mapping and convection enhanced delivery (CED). Potential benefits of ¹⁸⁶RNL compared to standard external beam radiotherapy or EBRT include:

- The ¹⁸⁶RNL radiation dose delivered to patients may be up to 20 times greater than what is possible with commonly used external beam radiation therapy (EBRT).
- ¹⁸⁶RNL can be visualized in real-time during administration, possibly giving clinicians better control of radiation dosing and distribution.
- ¹⁸⁶RNL potentially more effectively treats the bulk tumor and microscopic disease that has already invaded healthy tissue.
- ¹⁸⁶RNL is infused directly into the targeted tumor, bypassing the blood-brain barrier, which reduces radiation exposure to healthy cells, in contrast to EBRT which passes through normal tissue to reach the tumor, continuing its path through the tumor, hence being less targeted and selective.
- ¹⁸⁶RNL is given during a single, short, in-patient hospital visit, and is available in all hospitals with nuclear medicine and neurosurgery, while EBRT requires out-patient visits 5 days a week for approximately 4-6 weeks.

ReSPECT-GBM Trial for Recurrent GBM

Glioblastoma is the most common, complex, and aggressive primary brain cancer in adults. Annually in the U.S., there are 12,900 glioblastoma (GBM) cases diagnosed and approximately 10,000 patients succumb to the disease each year. The average life expectancy with primary glioblastoma is less than 24 months, with a one-year survival rate of 40.8% and a five-year survival rate of only 6.8%. GBM often causes and presents with headaches, seizures, vision changes and other significant neurological complications. Despite the best available medical treatments to eliminate the initial brain tumor, some microscopic disease frequently remains, with tumor regrowth within months. Approximately 90% or more of patients with primary GBM experience tumor recurrence. Complete surgical removal of GBM is not typically possible and GBM is often resistant or quickly develops resistance to most available therapies. Even today, the treatment of GBM remains a significant challenge and it has been nearly a decade since the FDA approved a new therapy for this disease.

For recurrent GBM, there are few currently approved treatments that in the aggregate, provide only marginal survival benefit. Furthermore, these therapies are associated with significant side effects, which limit dosing and prolonged use.

While EBRT has been shown to be safe and effective in many malignancies including glioblastoma but the maximum possible administered dose is limited by toxicity to the normal tissues surrounding the malignancy. In contrast, targeted radiopharmaceuticals that precisely deliver radiation in the form of beta particles such as Iodine-131 for thyroid cancer, are known to be very safe and effective and minimize exposure to normal cells and tissues.

Interim results from our ongoing Phase 1/2a ReSPECT-GBM trial, suggest beta particle energy from our lead investigational drug ¹⁸⁶RNL may also have utility in treating glioblastoma and other malignancies. More specifically, the preliminary data from ReSPECT-GBM indicates that radiation, in the form of high energy beta particles or electrons, can be effective against glioblastoma. Thus far, we have been able to deliver up to 740 Gy of absorbed radiation to tumor tissue without significant or dose limiting toxicities. In comparison, current EBRT protocols for recurrent glioblastoma typically recommend a total maximum dose of about 35 Gy.

In September 2020, the U.S. Food and Drug Administration ("FDA") granted both Orphan Drug designation and Fast Track designations to ¹⁸⁶RNL for the treatment of patients with glioblastoma.

¹⁸⁶RNL is presently under clinical investigation in a multicenter, sequential cohort, open-label, volume and dose escalation study of the safety, tolerability, and distribution of ¹⁸⁶RNL given by CED to patients with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment (NCT01906385). The study uses a modified Fibonacci dose escalation, followed by a planned expansion at the maximum tolerated dose (MTD) / maximum feasible dose (MFD) to determine efficacy. The trial is funded through Phase 2 in large part by a NIH/NCI grant. The planned enrollment in the NIH/NCI grant is 21 patients in the dose-escalation part of the study and 34 patients in the expansion cohort. The study is in its 8th dosing administration cohort and is under development and internal review to potentially advance to a Phase 2 or registration trial.

At the Society for Neuro-Oncology Annual Meeting in November 2021, Plus presented patient data which at that time included the results for 22 patients treated in the ReSPECT trial. The trial, thus far, has shown that CED in recurrent GBM patients is

feasible. Median absorbed dose to the tumor volume across all subjects in the first eight cohorts (n=22) was 267.5 Gy (range 8.9-740). In a subset of patients in whom tumor coverage was greater than or equal to 75%, the median absorbed dose was 405 Gy (range 146-593). By contrast, the median absorbed doses to the whole brain and the total body across all subjects were 0.55 Gy (range 0.001-2.728) and 0.09 Gy (range 0.001-0.182), respectively. Small doses, as delivered to the body, are typically well-tolerated. Based on observed and reported patient protocol activity and all available adverse event (AE) data, ¹⁸⁶RNL has been well-tolerated. No AEs with an outcome of death or study drug-related serious AEs have been reported. Furthermore, no patient was discontinued from the study because of an AE. All AEs have been mild or moderate (Grade 1 or 2) in intensity, except for one case of Grade 3 vasogenic edema, which was considered by the investigator to be unrelated to the study drug. AEs considered by the investigator to be at least possibly related to ¹⁸⁶RNL have included Grade 1 to 2 skin and soft tissue infection, intermittent cephalgia, neck and jaw pain, nausea with or without vomiting, constipation, increased lethargy, difficulty walking (gait disturbance), worsening double vision, and dysuria. Scalp discomfort and tenderness related to the surgical procedure has also been reported.

In the 22 subjects with recurrent GBM receiving a single administration of ¹⁸⁶RNL, the mean & median OS for all 22 patients as of November 2021 was 48.1 & 33.1 weeks, respectively, with 7 patients alive. In a subset of 13 patients receiving a presumed therapeutic absorbed radiation dose to the tumor (>100 Gy), the mean & median OS was 64.8 & 47.1 weeks, respectively, with 7 of 13 patients alive. In contrast, in 9 patients receiving a presumed sub-therapeutic absorbed radiation dose to the tumor (<100 Gy), the mean and median OS was 23.9 & 22.3 weeks, respectively. A Kaplan-Meier curve comparing patients with presumed therapeutic vs. sub-therapeutic radiation dose to the tumor showed a statistically significant difference between the groups (p=.0002). It is hypothesized that targeted infusion of ¹⁸⁶RNL into the tumor by CED, bypassing the blood-brain barrier and normal brain and external tissues, significantly spares normal tissues from radiation exposure and potential toxicity and concentrates radiation to the tumor and surrounding region of interest.

ReSPECT-LM Clinical Trial for Leptomeningeal Metastases

Leptomeningeal Metastases or LM is a rare complication of cancer in which the disease spreads to the membranes (meninges) surrounding the brain and spinal cord. The incidence of LM is growing and occurs in approximately 5% of people with late-stage cancer, or 110,000 people in the U.S. each year. It is highly lethal with an average 1-year survival of just 7%. LM occurs with cancers that are most likely to spread to the central nervous system. The most common cancers to spread to the leptomeninges are breast cancer, lung cancer, melanoma and gastrointestinal cancers--though most solid tumors have the potential for LM spread.

The ReSPECT-LM Phase 1 clinical trial (ClinicalTrials.gov NCT05034497) is predicated in part upon preclinical studies in which tolerance to doses of ¹⁸⁶RNL as high as 1,075 Gy was shown in animal models with LM without significant observed toxicity. Furthermore, treatment led to marked reduction in tumor burden in both C6 and MDA-231 LM models.

In October 2021, the FDA announced clearance of our Investigational New Drug (IND) application for ¹⁸⁶RNL for the treatment of LM. Subsequently, in November 2021, the FDA granted a Fast Track designation for ¹⁸⁶RNL for the treatment of leptomeningeal metastases. The Company initiated the trial and began screening patients for the ReSPECT-LM Phase 1 clinical trial in Q4 2021.

The ReSPECT-LM multi-center, sequential cohort, open-label, dose escalation study is evaluating the safety, tolerability, and distribution of ¹⁸⁶RNL via intrathecal infusion to the ventricle of patients with LM after standard surgical, radiation, and/or chemotherapy treatment. The primary endpoint of the study is the incidence and severity of adverse events and dose limiting toxicities.

ReSPECT-PBC Clinical Trial for Pediatric Brain Cancer

In August 2021, we announced plans for treating pediatric brain cancer at the 2021 American Association of Neurological Surgeons (AANS) Annual Scientific Meeting. In July 2021, we reported that we had received FDA feedback pertaining to a pre-IND meeting briefing package in which the FDA stated that we are not required to perform any additional preclinical or toxicology studies.

Currently, the Company plans to investigate the use of ¹⁸⁶RNL in 2 pediatric brain cancers. High-grade glioma (HGG) is a rare, fast-growing CNS tumor that forms in glial cells of the brain and spinal cord. It can be found almost anywhere within the CNS, but is most commonly within the supratentorium in children ages 15-19. HGG tumors in children act differently from those in adults, causing headaches, seizures, and difficulty achieving developmental milestones depending on the tumor location. Approximately 360-400 children are diagnosed with HGG annually in North America and the 5-year survival rate is approximately 20%. In contrast to HGG, ependymoma is a rare, slow- or fast-growing (depending on the grade) primary CNS tumor that forms in ependymal cells in the brain and spinal cord—and may spread throughout the CNS, though infrequently. All ependymomas can recur, but patients are often tumor-free for years before testing shows tumor regrowth, either at the initial tumor site or elsewhere within the CNS. Symptoms

depend on tumor location and size, usually including irritability, sleeplessness, vomiting, nausea, back pain, arm/leg weakness, and headaches.

Approximately 250 children are diagnosed with ependymoma annually in the U.S. while 71% of children with Grade II and 57% with Grade III survive 5 years from diagnosis.

Based on the aggregate preclinical and clinical work completed to date in adult recurrent glioblastoma, we hypothesized that ¹⁸⁶RNL may offer potential clinical benefit for PBCs, such as high-grade glioma and ependymoma. We intend to submit an IND application to the FDA for ¹⁸⁶RNL for the treatment of PBC (high-grade glioma and ependymoma) in late 2022 or early 2023.

Rhenium-188 NanoLiposome Biodegradable Alginate Microsphere Technology

In January 2022, we announced that we licensed Biodegradable Alginate Microsphere (BAM) patents and technology from The University of Texas Health Science Center at San Antonio (“UT Health Science Center at San Antonio”) to expand our tumor targeting capabilities and precision radiotherapeutics pipeline. We intend to combine our Rhenium NanoLiposome technology with the BAM technology to create a novel radioembolization technology. Initially, we intend to utilize the Rhenium-188 isotope, ¹⁸⁸RNL-BAM for the intra-arterial embolization and local delivery of a high dose of targeted radiation for a variety of solid organ cancers such as hepatocellular cancer, hepatic metastases, pancreatic cancer and many others.

Preclinical data from an *ex vivo* embolization experiment in which Tc-BAM was intra-arterially delivered to a bovine kidney perfusion model was presented at the recent 2021 Society of Interventional Radiology (SIR) Annual Scientific Meeting. The study concluded that the technology required for radiolabeling BAM could successfully deliver, embolize and retain radiation in the target organ. ¹⁸⁸RNL-BAM is a preclinical investigational drug we intend to further develop and move into clinical trials. Specifically, in 2022, we intend to transfer the ¹⁸⁸RNL-BAM technology from UT Health Science Center at San Antonio, fabricate and scale the drug product, and complete certain preclinical studies to support a future FDA IND submission. Our likely initial clinical target is liver cancer which is the 6th most common and 3rd deadliest cancer worldwide. It is a rare disease with increasing U.S. annual incidence (42,000) and deaths (30,000).

Recent Developments

UT Health Science Center San Antonio (UTHSA) License Agreement

On December 31, 2021, we entered into an exclusive license agreement with UT Health Science Center at San Antonio for the global rights to develop and commercialize Rhenium-188 NanoLiposome biodegradable alginate microspheres (¹⁸⁸RNL-BAM). Under the license agreement with UT Health Science Center at San Antonio, we are required to use commercial reasonable efforts to develop the ¹⁸⁸RNL-BAM product candidate acquired under the license agreement. Further, we are subject to future milestone, earn-out and other payments to UT Health Science Center at San Antonio all of which are tied to our commercialization and sale activities for product candidates.

Piramal Master Services Agreement

On January 8, 2021, we entered into a Master Services Agreement (the “MSA”) with Piramal Pharma Solutions, Inc. (“Piramal”), for Piramal to perform certain services related to the development, manufacture, and supply of our RNL-Liposome Intermediate Drug Product. The MSA includes the transfer of analytical methods, development of microbiological methods, process transfer and optimization, intermediate drug product manufacturing, and stability studies for us. The transfer will be performed at Piramal’s facility located in Lexington, Kentucky. The parties contemplate that the MSA will lead to clinical and commercial supply agreements between us and Piramal.

The MSA has a term of five years and will automatically renew for successive one-year terms unless either party notifies the other no later than six months prior to the original term or any additional terms of its intention to not renew the MSA. We have the right to terminate the MSA for convenience upon thirty days’ prior written notice. Either party may terminate the MSA upon an uncured material breach by the other party or upon the bankruptcy or insolvency of the other party.

Recent Financings

Refer to the “Liquidly and Capital Resources” section below for information on our recent financings.

Exercise of Warrants

In February 2021, certain warrant holders exercised warrants to purchase 896,500 shares of our common stock for total exercise proceeds of \$2.0 million.

Results of Operations

Development revenue

We did not recognize any revenue or related costs during 2021. We recognized a total of \$0.3 million in revenue for the year ended December 31, 2020, as well as \$0.3 million in qualified expenditures for those periods. Our Biomedical Advanced Research and Development Authority (“BARDA”) contract was terminated in December 2019 and the contract close out process was completed during 2020.

Research and development expenses

Research and development expenses include costs associated with the design, development, testing, and enhancement of our product candidates, payment of regulatory fees, laboratory supplies, pre-clinical studies, and clinical studies.

The following table summarizes the components of our research and development expenses for the years ended December 31, 2021 and 2020 (in thousands):

	<u>Years ended December 31,</u>	
	2021	2020
Research and development	\$ 5,248	\$ 2,668
Share-based compensation	75	32
Total research and development expenses	\$ 5,323	\$ 2,700

The increase in research and development expenses of \$2.6 million for the year ended December 31, 2021 as compared to the same period in 2020 was due primarily to an increase in developments costs of 186RNL of \$2.2 million as we ramp up to plan for the pivotal trial, an increase in personnel costs including recruiting expenses and share-based compensation of \$0.3 million due to increased headcount and grants of share based awards, and an increase in other professional services of \$0.1 million.

We expect aggregate research and development expenditures to increase in absolute dollars during 2022 due to the expected costs of development of the 186RNL™ therapy acquired from NanoTx and development expenses related to 188 RNL-BAM.

In process research and development acquired from UT Heather Science Center at San Antonio and NanoTx

In process research and development acquired from UT Heather Science Center at San Antonio in the amount of \$250,000 represents the upfront cash payment. In process research and development acquired from NanoTx in the amount of \$781,000 represents the upfront cash payment of \$400,000 and fair value of 230,769 shares of common stock, with fair value of \$1.65 per share, issued to NanoTx in accordance with the terms of the License Agreement.

General and administrative expenses

General and administrative expenses include costs for administrative personnel, legal and other professional expenses, and general corporate expenses. The following table summarizes the general and administrative expenses for the years ended December 31, 2021 and 2020 (in thousands):

	<u>Years ended December 31,</u>	
	2021	2020
General and administrative	\$ 6,322	\$ 6,191
Share-based compensation	531	215
Total general and administrative expenses	\$ 6,853	\$ 6,406

General and administrative expenses increased by \$0.4 million during the year ended December 31, 2021, as compared to the same period in 2020, primarily due to an increase of share-based compensation expenses of \$0.3 million as more share-based awards were granted during 2021 as well as increased grant date fair value of the awards, as compared with 2020.

We expect general and administrative expenditures to remain generally consistent in 2022 as compared with the year ended December 31, 2021, subject to litigation cost which is not predictable at this time.

Share-based compensation expenses

Share-based compensation expenses include charges related to options and restricted stock awards issued to employees, directors and non-employees. We measure stock-based compensation expenses based on the grant-date fair value of any awards granted to our employees. Such expense is recognized over the requisite service period.

The following table summarizes the components of our share-based compensation expenses for the years ended December 31, 2021 and 2020 (in thousands):

	Years ended December 31,	
	2021	2020
Research and development	\$ 75	\$ 32
General and administrative	531	215
Total share-based compensation	\$ 606	\$ 247

The increases in our share-based compensation was due to increases in grants of share-based options during 2021 as compared to 2020, as well as higher grant-date fair value of share-based awards during 2021 compared with 2020. Refer to Note 13 for weighted average assumptions used in valuation of our stock options as of the grant date.

Financing items

The following table summarizes interest income, interest expense, and other income and expense for the years ended December 31, 2021 and 2020 (in thousands):

	Years ended December 31,	
	2021	2020
Interest income	19	50
Interest expense	(932)	(1,107)
Change in fair value of liability instruments	6	2,400
Total	\$ (907)	\$ 1,343

The decrease in interest expense for the year ended December 31, 2021 as compared to the same period in 2020 was primarily due to the repayments of debt principal of \$0.3 million in 2021 and \$5.3 million in 2020, respectively. The changes in fair value of our warrant liabilities are primarily due to reclassification of liability-classified warrants to equity during 2020 (see Note 12), as well as fluctuations in the valuation inputs for the warrants. See Note 3 to the consolidated financial statements included elsewhere herein for disclosure and discussion of our warrant liabilities.

We expect interest expense in 2022 to decrease as compared with 2021 due to scheduled debt principal repayments starting on November 1, 2021. As disclosed in Note 12 to the consolidated financial statements included elsewhere herein, in 2020 we entered into revised Series U warrant agreements with certain Series U warrant holders. The amended Series U warrants meet the requirements for equity classification under authoritative accounting guidance and are no longer subject to fair value accounting post amendment. The remaining Series U warrants accounted for as liabilities are immaterial.

Liquidity and Capital Resources

Short-term and long-term liquidity

The following is a summary of our key liquidity measures at December 31, 2021 and 2020 (in thousands):

	As of December 31,	
	2021	2020
Cash and cash equivalents	\$ 18,400	\$ 8,346
Current assets	\$ 19,724	\$ 9,175
Current liabilities	5,870	8,539
Working capital	\$ 13,854	\$ 636

For the periods presented, operating losses have been funded primarily from outside sources of invested capital in our common stock, proceeds raised from the Loan and Security Agreement. We believe that our cash and cash equivalents of \$18.4 million at December 31, 2021 and the net proceeds of approximately \$7.9 million received so far during 2022 from the issuance of

common stock will enable the Company to fund its current and planned operations for at least the next twelve months and beyond from the date these consolidated financial statements were issued.

We have had, and we will continue to have, an ongoing need to raise additional cash from outside sources to fund our future clinical development programs and other operations. Our inability to raise additional cash would have a material and adverse impact on operations and would cause us to default on our loan.

On January 14, 2022, we entered into an Equity Distribution Agreement (the “2022 Distribution Agreement”) with Canaccord Genuity LLC (the “Agent”, or “Canaccord”), pursuant to which we may issue and sell, from time to time, shares of its common stock having an aggregate offering price of up to \$5,000,000 (the “Shares”), depending on market demand, with the Agent acting as an agent for sales. Sales of the Shares may be made by any method permitted by law deemed to be an “at the market offering” as defined in Rule 415(a)(4) of the Securities Act of 1933, as amended (the “Securities Act”), including, without limitation, sales made directly on or through the Nasdaq. As of the date of filing of this Form 10-K, we issued 1,000,000 shares under the 2022 Distribution Agreement for net proceeds of approximately \$0.9 million.

On October 23, 2020, we entered into the 2020 Distribution Agreement with Canaccord, pursuant to which we could issue and sell, from time to time, our common stock in “at the market” offerings, depending on market demand, with Canaccord acting as an agent for sales. During the year ended December 31, 2020, we issued 1,616,331 shares under the 2020 Distribution Agreement for net proceeds of approximately \$3.2 million. During 2021, we issued 2,179,193 shares under the 2020 Distribution Agreement for net proceeds of \$6.3 million. As of December 31, 2021, there were no remaining shares to issue and sell under the 2020 Distribution Agreement.

On September 30, 2020, we entered into the 2020 Purchase Agreement and a registration rights agreement with Lincoln Park, pursuant to which Lincoln Park committed to purchase up to \$25.0 million of our common stock. During the year ended December 31, 2020, we issued 353,113 shares, excluding 180,701 shares issued as commitment fee, under the 2020 Purchase Agreement for net proceeds of approximately \$0.7 million. During 2021, we issued 5,685,186 shares of our common stock under the 2020 Purchase Agreement for total proceeds of \$12.5 million. During January 2022, we issued 5,665,000 shares of common stock for net proceeds of approximately \$7.0 million under the 2020 Purchase Agreement. We no longer have any additional shares of common stock registered to sell under the 2020 Purchase Agreement, and at this time, we do not intend to register any additional shares of common stock under the 2020 Purchase Agreement.

On March 29, 2020, we entered into the Ninth Amendment, pursuant to which, among other things, Oxford agreed to defer the start date of principal repayment to November 1, 2021. In addition, on April 1, 2020, we made a \$5.0 million paydown of principal upon execution of the Ninth Amendment. As a result of this Ninth Amendment, the term of the Term Loan has been extended from September 1, 2021 to June 1, 2024, with all other major terms remained consistent.

Capital Resources

We continue to seek additional capital through strategic transactions and other financing alternatives. Without additional capital, current working capital and cash generated from sales will not provide adequate funding for research and product development activities at their current levels. If sufficient capital is not raised, we will at a minimum need to significantly reduce or curtail our research and development and other operations, and this would negatively affect our ability to achieve corporate growth goals. Although the stock markets and our stock price have recovered to some extent in recent weeks, there may likely be continued market volatility due to the pandemic or other events, which could cause our stock price to decline. This in turn will likely negatively impact our ability to raise funds through equity-related financings. Further, a continued global economic downturn may impair our ability to obtain additional financing through other means, such as strategic transactions or debt financing. The overall deterioration of the credit and financial markets due to the COVID-19 pandemic will likely generally reduce our ability to obtain additional financing to fund our operations.

Should we be unable to raise additional cash from outside sources or if we are unable to do so in a timely manner or on commercially reasonable terms, it would have a material adverse impact on our operations.

Cash (used in) provided by operating, investing and financing activities for the years ended December 31, 2021 and 2020 is summarized as follows (in thousands):

	Years Ended December 31,	
	2021	2020
Net cash used in operating activities	\$ (10,280)	\$ (8,434)
Net cash used in investing activities	(82)	(493)
Net cash provided by (used in) financing activities	20,416	(319)
Net increase (decrease) in cash and cash equivalents	\$ 10,054	\$ (9,246)

Operating activities

Net cash used in operating activities for the year ended December 31, 2021 was \$10.3 million compared to \$8.4 million in the same period of 2020. Overall, our operational cash use increased during the year ended December 31, 2021 as compared to the same period in 2020, due primarily to increased expenditures for our research and development activities.

Investing activities

Net cash used in investing activities for the year ended December 31, 2021 were related to purchases of fixed assets of \$144,000, offset by proceeds of \$62,000 from sale of property and equipment. Net cash used in investing activities for year ended December 31, 2020 was primarily related to cash payments of \$0.4 million made for in process research and development assets from NanoTx, and \$0.1 million for purchases of fixed assets.

Financing Activities

Net cash provided by financing activities for year ended December 31, 2021 was primarily related to sales of common stock of \$18.7 million, net of offering cost through the 2020 Purchase Agreement with Lincoln Park and the Distribution Agreement with Canaccord, as well as \$2.0 million from exercise of warrants, offset by principal repayment of the Oxford term loan of \$0.3 million. Net cash used for financing activities for the year ended December 31, 2020 was related to repayment of \$5.3 million of the Term Loan in April 2020 (consisting of \$5.0 million principal and \$0.3 million of related final payment), and cash payments of \$0.1 million for our finance leases, offset by cash proceeds received from issuance of common stock of \$4.0 million and warrant exercises of \$1.1 million.

Critical Accounting Policies and Significant Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires us to make estimates and assumptions that affect the reported amounts of our assets, liabilities, revenue, and expenses, and that affect our recognition and disclosure of contingent assets and liabilities.

While our estimates are based on assumptions we consider reasonable at the time they were made, our actual results may differ from our estimates, perhaps significantly. If results differ materially from our estimates, we will make adjustments to our financial statements prospectively as we become aware of the necessity for an adjustment.

We believe it is important for you to understand our most critical accounting policies, which are included in Note 2 of the consolidated financial statements in Item 8.

Recent Accounting Pronouncements

See Note 2 to the Consolidated Financial Statements included elsewhere herein for disclosure and discussion of new accounting standards.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

Not applicable.

Item 8. Financial Statements and Supplementary Data

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PART I. FINANCIAL INFORMATION**Item 1. Financial Statements****Report of Independent Registered Public Accounting Firm**

Shareholders and Board of Directors

Plus Therapeutics, Inc.

Austin, Texas

Opinion on the Consolidated Financial Statements

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

Basis for Opinion

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

We conducted our audits 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

Critical audit matters are matters arising from the current period audit of the financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective, or complex judgments. We determined that there are no critical audit matters.

/s/ BDO USA, LLP

We have served as the Company's auditor since 2016.

Austin, Texas

February 24, 2022

PLUS THERAPEUTICS, INC.
CONSOLIDATED BALANCE SHEETS
(in thousands, except share and par value data)

	As of December 31,	
	2021	2020
Assets		
Current assets:		
Cash and cash equivalents	\$ 18,400	\$ 8,346
Other current assets	1,324	829
Total current assets	<u>19,724</u>	<u>9,175</u>
Property and equipment, net	1,477	1,820
Operating lease right-use-of assets	341	636
Goodwill	372	372
Intangible assets, net	51	86
Other assets	16	16
Total assets	<u>\$ 21,981</u>	<u>\$ 12,105</u>
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable and accrued expenses	\$ 4,151	\$ 2,081
Operating lease liability	111	123
Term loan obligation, current	1,608	6,335
Total current liabilities	<u>5,870</u>	<u>8,539</u>
Noncurrent operating lease liability	269	528
Term loan obligation	5,005	—
Warrant liability	1	7
Total liabilities	<u>11,145</u>	<u>9,074</u>
Commitments and contingencies (Note 7)		
Stockholders' equity:		
Preferred stock, \$0.001 par value; 5,000,000 shares authorized; 1,952 and 1,954 shares issued and outstanding in 2021 and 2020, respectively	—	—
Common stock, \$0.001 par value; 100,000,000 shares authorized; 15,510,025 and 6,749,028 shares issued and outstanding in 2021 and 2020, respectively	16	7
Additional paid-in capital	457,730	436,535
Accumulated deficit	(446,910)	(433,511)
Total stockholders' equity	<u>10,836</u>	<u>3,031</u>
Total liabilities and stockholders' equity	<u>\$ 21,981</u>	<u>\$ 12,105</u>

See Accompanying Notes to these Consolidated Financial Statements

PLUS THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(in thousands, except share and per share data)

	For the Years Ended December 31,	
	2021	2020
Development revenue:		
Government contracts and other	\$ —	\$ 303
	<hr/>	<hr/>
Operating expenses:		
Research and development	5,323	2,700
In process research and development acquired	250	781
General and administrative	6,853	6,406
Loss on disposal of property and equipment	66	—
Total operating expenses	<hr/> 12,492	<hr/> 9,887
Operating loss	<hr/> (12,492)	<hr/> (9,584)
Other income (expense):		
Interest income	19	50
Interest expense	(932)	(1,107)
Change in fair value of liability instruments	6	2,400
Total other expense	<hr/> (907)	<hr/> 1,343
Net loss	<hr/> <hr/> \$ (13,399)	<hr/> <hr/> \$ (8,241)
Net loss per share, basic and diluted	\$ (1.11)	\$ (1.86)
Basic and diluted weighted average shares used in calculating net loss per share attributable to common stockholders	12,089,186	4,427,835

See Accompanying Notes to these Consolidated Financial Statements

PLUS THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
FOR THE YEARS ENDED DECEMBER 31, 2021 and 2020
(in thousands, except share data)

	Convertible preferred stock		Common stock		Additional paid-in capital	Accumulated deficit	Total stockholders' equity
	Shares	Amount	Shares	Amount			
Balance at December 31, 2019	1,959	\$ —	3,880,588	\$ 4	\$ 426,426	\$ (425,270)	\$ 1,160
Share-based compensation	—	—	—	—	247	—	247
Issuance of common stock, net of offering costs of \$0.6 million	—	—	2,150,113	2	3,880	—	3,882
Issuance of common stock for exercise of warrants	—	—	487,521	1	1,097	—	1,098
Reclassification of warrant liabilities	—	—	—	—	4,504	—	4,504
Issuance of common stock for in process research and development acquired from NanoTX Therapeutics	—	—	230,769	—	381	—	381
Conversion of Series B convertible preferred stock into common stock	(5)	—	37	—	—	—	—
Net loss	—	—	—	—	—	(8,241)	(8,241)
Balance at December 31, 2020	1,954	—	6,749,028	7	436,535	(433,511)	3,031
Share-based compensation	—	—	—	—	606	—	606
Sale of common stock, net of offering costs of \$0.3 million	—	—	7,864,379	8	18,573	—	18,581
Issuance of common stock for exercise of warrants	—	—	896,500	1	2,016	—	2,017
Conversion of Series B convertible preferred stock into common stock	(2)	—	118	—	—	—	—
Net loss	—	—	—	—	—	(13,399)	(13,399)
Balance at December 31, 2021	1,952	\$ —	15,510,025	\$ 16	\$ 457,730	\$ (446,910)	\$ 10,836

See Accompanying Notes to these Consolidated Financial Statements

PLUS THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	For the Years Ended December 31,	
	2021	2020
Cash flows used in operating activities:		
Net loss	\$ (13,399)	\$ (8,241)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	395	366
Amortization of deferred financing costs and debt discount	546	584
In process research and development acquired	250	781
Change in fair value of liability instruments	(6)	(2,400)
Loss on disposal of property and equipment	66	—
Share-based compensation expense	606	247
Inventory write off	—	107
Non-cash lease expense	24	3
Increases (decreases) in cash caused by changes in operating assets and liabilities:		
Accounts receivable	—	1,169
Other current assets	(496)	126
Other assets	—	58
Accounts payable and accrued expenses	1,734	(1,234)
Other long-term liabilities	—	—
Net cash used in operating activities	(10,280)	(8,434)
Cash flows from (used in) investing activities:		
Purchases of property and equipment and intangible assets	(144)	(93)
Proceeds from sale of property and equipment	62	—
In process research and development acquired from NanoTx Therapeutics	—	(400)
Net cash used in investing activities	(82)	(493)
Cash flows from financing activities:		
Principal payments of long-term obligations	(268)	(5,307)
Payment of financing lease liability	(8)	(117)
Proceeds from exercise of warrants	2,017	1,098
Proceeds from sale of common stock	18,675	4,007
Net cash provided by (used in) financing activities	20,416	(319)
Net increase (decrease) in cash and cash equivalents	10,054	(9,246)
Cash and cash equivalents at beginning of period	8,346	17,592
Cash and cash equivalents at end of period	\$ 18,400	\$ 8,346
Supplemental disclosure of cash flows information:		
Cash paid during period for:		
Interest	\$ 388	\$ 567
Supplemental schedule of non-cash investing and financing activities:		
Unpaid offering cost	\$ 219	\$ 125
Issuance costs paid in common stock	\$ —	\$ 463
Common stock issued in payment for in process research and development	\$ —	\$ 381
Reclassification of warrants liability to equity	\$ —	\$ 4,504

See Accompanying Notes to these Consolidated Financial Statements

PLUS THERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS
DECEMBER 31, 2021

1. Organization and Operations

The Company

Plus Therapeutics, Inc. is a clinical-stage pharmaceutical company focused on the development, manufacture and commercialization of complex and innovative treatments for patients battling cancer and other life-threatening diseases.

Principles of Consolidation

The accompanying consolidated financial statements include the Company's accounts and those of its subsidiaries. All significant intercompany transactions and balances have been eliminated in consolidation.

Certain Risks and Uncertainties

The Company's prospects are subject to the risks and uncertainties frequently encountered by companies in the early stages of development and commercialization, especially those companies in rapidly evolving and technologically advanced industries such as the biotech/medical device field. The Company's future viability largely depends on its ability to complete development of new products and receive regulatory approvals for those products. No assurance can be given that the Company's new products will be successfully developed, regulatory approvals will be granted, or acceptance of these products will be achieved.

Liquidity

The Company incurred net losses of \$13.4 million for the year ended December 31, 2021, and as of December 31, 2021, the Company had an accumulated deficit of \$446.9 million and cash and cash equivalents of \$18.4 million. Additionally, the Company used net cash of \$10.3 million to fund its operating activities for the year ended December 31, 2021. In addition, as discussed in Note 14, the full magnitude of the coronavirus pandemic on the Company's financial condition, liquidity and future results of operations is uncertain. The Company expect that its research and development expenditures will increase in absolute dollars in 2022.

As disclosed in more detail in Note 12, the Company had entered into various financing agreements during 2020 through January 2022, and raised capital by issuing its common stock. The Company believes its current cash and cash equivalents will be sufficient to fund its operations for at least the next 12 months from the date these consolidated financial statements are issued.

The Company continues to seek additional capital through strategic transactions and from other financing alternatives. If sufficient capital is not raised, the Company will at a minimum need to significantly reduce or curtail its research and development and other operations, and this would negatively affect its ability to achieve corporate growth goals.

2. Summary of Significant Accounting Policies

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 affecting the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements, and the reported amounts of revenue and expenses during the reporting period. The most significant estimates and critical accounting policies involve reviewing assets for impairment, determining the assumptions used in measuring share-based compensation expense, valuing warrants and valuing allowances for doubtful accounts.

Actual results could differ from these estimates. Management's estimates and assumptions are reviewed regularly, and the effects of revisions are reflected in the consolidated financial statements in the periods they are determined to be necessary.

Cash and cash equivalents

The Company considers all highly liquid investments with maturities of three months or less at the time of purchase to be cash equivalents.

Cash and cash equivalents include cash in readily available checking and savings accounts. The Company held no investments as of December 31, 2021 and 2020. The Company maintains deposits in federally insured financial institutions in excess of federally insured limits. The Company has not experienced any losses in such accounts and believes it is not exposed to significant risk on its cash balances due to the financial position of the depository institution in which those deposits are held.

Financial Instruments

Financial instruments include cash equivalents, accounts receivable, other current assets, accounts payable, accrued expenses, other liabilities and long-term debt. The carrying values of cash equivalents, accounts receivable, other current assets, accounts payable, accrued expenses, other liabilities generally approximate fair value due to the short-term nature of these instruments. Based on level 3 inputs and the borrowing rates current available for loans with similar terms, the Company believes the fair value of the long-term debt is materially consistent with its carrying value.

Property and Equipment

Property and equipment are stated at cost, net of accumulated depreciation. Depreciation expense, which includes the amortization of capitalized leasehold improvements, is provided for on a straight-line basis over the estimated useful lives of the assets, or the life of the lease, whichever is shorter, and range from three to five years. When assets are sold or otherwise disposed of, the cost and related accumulated depreciation are removed from the accounts and the resulting gain or loss, if any, is included in operations. Maintenance and repairs are charged to operations as incurred.

Impairment

The Company assesses its property and equipment for potential impairment when there is a change in circumstances that indicates carrying values of assets may not be recoverable. Such long-lived assets are deemed to be impaired when the undiscounted cash flows expected to be generated by the asset (or asset group) are less than the asset's carrying amount. Any required impairment loss would be measured as the amount by which the asset's carrying value exceeds its fair value and would be recorded as a reduction in the carrying value of the related asset and a charge to operating expense. The Company recognized no impairment losses during any of the periods presented in these financial statements.

Goodwill

The Company's goodwill represents the excess of the cost over the fair value of net assets acquired from its business combinations. The determination of the value of goodwill arising from business combinations requires extensive use of accounting estimates and judgments to allocate the purchase price to the fair value of the net tangible and intangible assets acquired.

Goodwill is not amortized; however, it is assessed for impairment using fair value measurement techniques on an annual basis or more frequently if facts and circumstance warrant such a review. Goodwill is considered to be impaired if the Company determines that the carrying value of the reporting unit exceeds its fair value.

The Company performs its impairment test annually during the fourth quarter by comparing the Company's estimated fair value, calculated from the Company's market capitalization, to its carrying amount. The Company's annual evaluation for impairment of goodwill consists of one reporting unit. The Company completed its most recent annual evaluation for impairment as of December 31, 2021 and determined that no impairment existed.

Warrant Liability

Warrants are accounted for in accordance with the applicable authoritative accounting guidance as either liabilities or as equity instruments depending on the specific terms of the agreements. Liability-classified instruments are recorded at fair value at each reporting period with any change in fair value recognized as a component of change in fair value of warrant liabilities in the consolidated statements of operations and comprehensive loss.

Revenue Recognition

The Company did not have any revenue or related costs during 2021. Prior to 2021, the Company earned revenue for performing tasks under research and development agreements with governmental agencies like BARDA. Revenue derived from reimbursement of direct out-of-pocket expenses for research costs associated with government contracts were recorded as government contract and other within development revenue. Government contract revenue was recorded at the gross amount of the reimbursement. The costs associated with these reimbursements were reflected as a component of research and development

expense in the Company's statements of operations. The Company recognized \$0.3 million in BARDA revenue for the year ended December 31, 2020.

The BARDA Agreement was terminated by the U.S. Department of Health and Human Services effective in December 2019 and the contract close out process was completed during 2020.

Research and Development

Research and development expenditures, which are charged to operations in the period incurred, include costs associated with the design, development, testing and enhancement of the Company's products, regulatory fees, the purchase of laboratory supplies, and pre-clinical and clinical studies as well as salaries and benefits for our research and development employees.

Also included in research and development expenditures are costs incurred to support the government reimbursement contract, including \$0.3 million qualified expenses that were incurred for the years ended December 31, 2020, related to the BARDA Agreement. There was no BARDA related costs during the year ended December 31, 2021.

Acquired In-Process Research and Development (IPR&D)

Acquired IPR&D represents the value assigned to research and development assets that have not reached technological feasibility. Upon the acquisition of IPR&D, the Company completes an assessment of whether the acquisition constitutes the purchase of a single asset or group of assets. The Company considers multiple factors in this assessment, including the nature of the technology acquired, the presence or absence of separate cash flows, the development process and stage of completion, quantitative significance, and the Company's rationale for entering into the transaction.

If the Company acquires a business as defined under applicable accounting standards, then the acquired IPR&D is capitalized as an intangible asset on the consolidated balance sheets and recorded at fair value. If the Company acquires an asset or group of assets that do not meet the definition of a business under applicable accounting standards, then the acquired IPR&D is expensed as research and development in the consolidated statements of operations and comprehensive loss on its acquisition date. Future costs to develop these assets are recorded to research and development expense as they are incurred until such time that the asset or group of assets reaches technological feasibility, if ever.

Deferred Financing Costs and Other Debt-Related Costs

Deferred financing costs are capitalized, recorded as an offset to debt balances and amortized to interest expense over the term of the associated debt instrument using the effective interest method. If the maturity of the debt is accelerated because of default or early debt repayment, then the amortization would be accelerated.

Income Taxes

Income taxes are accounted for under the asset and liability method. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases and operating loss and tax credit carry forwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income (loss) in the years in which those temporary differences are expected to be recovered or settled. Due to our history of losses, a full valuation allowance has been recognized against our deferred tax assets.

The Company's policy is to recognize interest and penalties related to income tax matters in income tax expense. For the years ended December 31, 2021 and 2020, the Company has not recorded any interest or penalties related to income tax matters. The Company does not foresee any material changes to unrecognized tax benefits within the next twelve months.

Share-Based Compensation

The Company recognizes the fair value of all share-based payment awards in our statements of operations over the requisite vesting period of each award, which approximates the period during which the employee and non-employee director is required to provide service in exchange for the award. The Company estimates the fair value of these options using the Black-Scholes option pricing model using assumptions for expected volatility, expected term, and risk-free interest rate. Expected volatility is based primarily on historical volatility and is computed using daily pricing observations for recent periods that correspond to the expected term of the options. The expected term is calculated based on historical data for and applied to all employee awards as a single group as the Company does not expect (nor does historical data suggest) substantially different exercise or post-vesting termination behavior amongst our employee population. The risk-free interest rate is the interest rate for treasury instruments with maturities that approximate the expected term.

Segment Information

For the years ended December 31, 2021 and 2020, the Company is managed as a single operating segment, therefore we report our results in one operating segment.

Loss Per Share

Basic per share data is computed by dividing net income or loss applicable to common stockholders by the weighted average number of common shares outstanding during the period. Diluted per share data is computed by dividing net income or loss applicable to common stockholders by the weighted average number of common shares outstanding during the period increased to include, if dilutive, the number of additional common shares that would have been outstanding as calculated using the treasury stock method. Potential common shares were related entirely to outstanding but unexercised options, warrants and convertible preferred stocks for all periods presented.

The Company excluded all potentially dilutive securities from the calculation of diluted loss per share attributable to common stockholders for the years ended December 31, 2021 and 2020, as their inclusion would be antidilutive.

Concentration Risk

Although the Company's contracts with its vendors are not exclusive, the Company currently uses sole source providers for core materials used in its clinical trials.

Recently Issued and Recently Adopted Accounting Pronouncements

Recently Issued Accounting Pronouncements

In June 2016, the FASB issued ASU 2016-13, Financial Instruments -- Credit Losses (Topic 326), Measurement of Credit Losses on Financial Instruments. The standard amends the impairment model by requiring entities to use a forward-looking approach based on expected losses to estimate credit losses for most financial assets and certain other instruments that aren't measured at fair value through net income. For available-for-sale debt securities, entities will be required to recognize an allowance for credit losses rather than a reduction in carrying value of the asset. Entities will no longer be permitted to consider the length of time that fair value has been less than amortized cost when evaluating when credit losses should be recognized. This new guidance is effective in the first quarter of 2023 for calendar-year SEC filers that are smaller reporting companies as of the one-time determination date. Early adoption is permitted. The Company plans to adopt the new guidance on January 1, 2023, and it does not expect that adoption of this standard will have a material impact on its consolidated financial statements and related disclosures.

In August 2020, the FASB issued ASU 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) ("ASU 2020-06"). ASU 2020-06 eliminates the beneficial conversion and cash conversion accounting models for convertible instruments. It also amends the accounting for certain contracts in an entity's own equity that are currently accounted for as derivatives because of specific settlement provisions. In addition, ASU 2020-06 modifies how particular convertible instruments and certain contracts that may be settled in cash or shares impact the diluted EPS computation. The amendments in ASU 2020-06 are effective for smaller reporting companies as defined by the SEC for fiscal years beginning after December 15, 2023, including interim periods within those fiscal years. Early adoption is permitted, but no earlier than fiscal years beginning after December 15, 2020. The Company is currently evaluating the impact of ASU 2020-06 on its financial statements.

Recently Adopted Accounting Pronouncements

In December 2019, the FASB issued ASU No. 2019-12, Income Taxes, Simplifying the Accounting for Income Taxes ("ASU 2019-12"). The new guidance eliminates certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. It also clarifies and simplifies other aspects of the accounting for income taxes. ASU 2019-12 became effective for the Company on January 1, 2021. Adoption of ASU 2019-12 did not have a material impact on the Company's consolidated financial statements.

3. Fair Value Measurements

Fair value measurements are market-based measurements, not entity-specific measurements. Therefore, fair value measurements are determined based on the assumptions that market participants would use in pricing the asset or liability. We follow a three-level hierarchy to prioritize the inputs used in the valuation techniques to derive fair values. The basis for fair value measurements for each level within the hierarchy is described below:

- Level 1: Quoted prices in active markets for identical assets or liabilities.
- Level 2: Quoted prices for similar assets or liabilities in active markets; quoted prices for identical or similar instruments in markets that are not active; and model-derived valuations in which all significant inputs are observable in active markets.
- Level 3: Valuations derived from valuation techniques in which one or more significant inputs are unobservable in active markets.

Warrants issued by the Company in connection with the sale of common stock in a registration offering in September 2019 (“Series U Warrants”) were classified as liabilities at issuance. The Series U warrants were marked to market at each subsequent reporting date as non-operating income or loss in the statement of operations. As described in more detail in Note 12, during 2020 the Company amended the terms of 3,522,500 Series U Warrants such that those amended Series U Warrants met the requirements to be classified within stockholders’ equity and were no longer required to be re-measured at fair value at each balance sheet date.

Expected volatility was computed using daily pricing observations of traded shares of the Company for recent periods that correspond to the expected term of the warrants. The Company believes this method produces an estimate that is representative of our expectations of future volatility over the expected term of these warrants. The Company currently has no reason to believe future volatility over the expected remaining life of these warrants is likely to differ materially from historical volatility. The expected life is based on the remaining contractual term of the warrants. The risk-free interest rate is the U.S. Treasury bond rate as of the valuation date. Because some of the inputs to our valuation model are either not observable or are not derived principally from or corroborated by observable market data by correlation or other means, the warrant liability is classified as Level 3 in the fair value hierarchy. Fluctuations in the fair value of the warrants are impacted by unobservable inputs. Significant increases (decreases) in this input in isolation would result in a significantly higher (lower) fair value measurement.

The Company estimated the fair value of the liability-classified Series U Warrants on the issuance date as well as at each subsequent balance sheet date with the Black Scholes model. The assumptions used in the Black Scholes option pricing model to determine the fair value of the Series U warrants were as follows:

	As of December 31, 2021	As of December 31, 2020
Expected term	2.75 years	3.75 years
Common stock market price	\$ 1.05	\$ 2.02
Risk-free interest rate	0.91%	0.24%
Expected volatility	143.2%	149.0%
Resulting fair value (per warrant)	\$ 0.58	\$ 1.56

The following table summarizes the change in our Level 3 warrant liability value (in thousands):

Warrant liability	Years ended December 31,	
	2021	2020
Beginning balance	\$ 7	\$ 6,929
Change in fair value of warrants	(6)	(2,418)
Reclassification to equity	—	(4,504)
Ending balance	<u>\$ 1</u>	<u>\$ 7</u>

On September 30, 2020, the Company committed to issue 180,701 shares to Lincoln Park as a committee fee (“Commitment Shares”) in connection with the 2020 Purchase Agreement, and these shares were issued on October 2, 2020. The change in fair value of the Commitment Shares between September 30, 2020 and the issuance date, in the amount of \$18,000 and calculated using the closing stock prices on respective dates, was recorded in change in fair value of liability-classified instruments on the statement of operations and comprehensive income/loss for the year ended December 31, 2020.

Nonfinancial Assets and Liabilities

The Company applies fair value techniques on a non-recurring basis, if and when necessary, associated with: (1) valuing potential impairment losses related to goodwill which are accounted for pursuant to the authoritative guidance for intangibles—goodwill and other; and (2) valuing potential impairment losses related to long-lived assets which are accounted for pursuant to the authoritative guidance for property, plant and equipment.

5. Loss per Share

The following were excluded from the diluted loss per share calculation for the periods presented because their effect would be anti-dilutive:

	For the Year Ended December 31,	
	2021	2020
Outstanding stock options	1,170,890	531,336
Preferred stock	422,867	422,985
Outstanding warrants	2,141,378	3,113,625
Total	3,735,135	4,067,946

6. Composition of Certain Financial Statement Captions

Other Current Assets

As of December 31, 2021 and 2020, other current assets were comprised of the following (in thousands):

	December 31,	
	2021	2020
Prepaid services	\$ 622	\$ 131
Prepaid insurance	695	639
Other	7	59
	<u>\$ 1,324</u>	<u>\$ 829</u>

Property and Equipment, net

As of December 31, 2021 and 2020, property and equipment, net, were comprised of the following (in thousands):

	December 31,	
	2021	2020
Office and computer equipment	\$ 1,231	\$ 1,525
Leashold improvements	1,661	1,682
	<u>2,892</u>	<u>3,207</u>
Less accumulated depreciation	(1,415)	(1,387)
	<u>\$ 1,477</u>	<u>\$ 1,820</u>

Depreciation expense totaled \$0.4 million for each of the years ended December 31, 2021 and 2020, respectively.

Intangible Assets, net

As of December 31, 2021, intangible assets included the net book value of costs incurred for software upgrades.

Accounts Payable and Accrued Expenses

As of December 31, 2021 and 2020, accounts payable and accrued expenses were comprised of the following (in thousands):

	December 31,	
	2021	2020
Accounts payable	\$ 2,611	\$ 789
Accrued payroll and bonus	781	738
Accrued professional fees	189	276
Accrued vacation and compensation	252	245
Finance lease obligation -- current	—	10
Other current liabilities	122	23
Accrued R&D studies	196	—
	<u>\$ 4,151</u>	<u>\$ 2,081</u>

7. Commitments and Contingencies

Leases

At the inception of a contractual arrangement, the Company determines whether the contract contains a lease by assessing whether there is an identified asset and whether the contract conveys the right to control the use of the identified asset in exchange for consideration over a period of time. If both criteria are met, the Company calculates the associated lease liability and corresponding right-of-use asset upon lease commencement using a discount rate based on the rate implicit in the lease or an incremental borrowing rate commensurate with the term of the lease. Lease renewable options are included in the estimation of lease term when it is reasonably certain that the Company will exercise such options.

The Company records lease liabilities within current liabilities or long-term liabilities based upon the length of time associated with the lease payments. The Company records its operating lease right-of-use assets as long-term assets. Right-of-use assets for financing leases are recorded within property and equipment, net in the Balance Sheet. Leases with an initial term of 12 months or less are not recorded on the Balance Sheet. Instead, the Company recognizes lease expense for these leases on a straight-line basis over the lease term.

The Company leases laboratory, office and storage facilities in San Antonio, Texas, under operating lease agreements that expire in 2025. The Company also leases certain office space in Austin, Texas under a month-to-month operating lease agreement.

On March 1, 2021, the Company entered into a lease agreement for office space in Charlottesville, Virginia (the "Charlottesville Lease"). The Charlottesville Lease has a term of 12 months and is renewable for four additional one-year periods. The minimum lease payment is \$30,000 for the first twelve months, subject to a 3% annual increase if and when the lease is renewed. The lease commencement date is April 1, 2021. The Company measured the operating lease right-of-use asset and related lease liability related to the Charlottesville Lease as of the lease commencement date.

In addition, the Company has entered into leases for certain equipment under various operating and finance leases. The lease agreements generally provide for periodic rent increases, and renewal and termination options. The Company's lease agreements do not contain any material variable lease payments, residual value guarantees or material restrictive covenants.

During 2021, contractual terms of all finance leases had expired and the Company did not have any right-of-use assets or lease liabilities relating to finance leases as of December 31, 2021. The lease agreements generally provide for periodic rent increases, and renewal and termination options. The Company's lease agreements do not contain any material variable lease payments, residual value guarantees or material restrictive covenants.

Certain leases require the Company to pay taxes, insurance, and maintenance. Payments for the transfer of goods or services such as common area maintenance and utilities represent non-lease components. The Company elected the package of practical expedients and therefore does not separate non-lease components from lease components.

The table below summarizes the Company's lease liabilities and corresponding right-of-use assets (in thousands, except years and rates):

	2021	2020
Assets		
Operating	\$ 341	\$ 636
Financing	—	7
Total leased assets	<u><u>\$ 341</u></u>	<u><u>\$ 643</u></u>
Liabilities		
Current:		
Operating	\$ 111	\$ 123
Financing	—	10
Noncurrent:		
Operating	269	528
Total lease liabilities	<u><u>\$ 380</u></u>	<u><u>\$ 661</u></u>
Weighted-average remaining lease term (years) - operating leases	2.86	6.57
Weighted-average remaining lease term (years) - finance leases	—	0.42
Weighted-average discount rate - operating leases	9.00%	7.79%
Weighted-average discount rate - finance leases	N/A	5.00%

The table below summarizes the Company's lease costs from its consolidated statements of operations, and cash payments from its consolidated statements of cash flows.

	Year Ended December 31,	
	2021	2020
Lease expense:		
Operating lease expense	\$ 211	\$ 210
Finance lease expense:		
Depreciation of right-of-use assets	7	127
Interest expense on lease liabilities	—	4
Total lease expense	<u>218</u>	<u>341</u>
Cash payment information:		
Operating cash used for operating leases	\$ 206	\$ 204
Financing cash used for financing leases	8	117
Total cash paid for amounts included in the measurement of lease liabilities	<u>214</u>	<u>321</u>

Total rent expenses for each of the years ended December 31, 2021 and 2020 was \$0.2 million, which includes leases in the table above, month-to-month operating leases, and common area maintenance charges.

The Company's future minimum annual lease payments under operating and financing leases at December 31, 2021 are as follows (in thousands):

	Operating Leases
2022	\$ 159
2023	137
2024	113
2025	18
Thereafter	—
Total minimum lease payments	<u>427</u>
Less: amount representing interest	<u>(47)</u>
Present value of obligations under leases	380
Less: current portion	(111)
Noncurrent lease obligations	<u>269</u>

Piramal Master Services Agreement

On January 8, 2021, the Company entered into a Master Services Agreement (the "MSA") with Piramal Pharma Solutions, Inc. ("Piramal"), for Piramal to perform certain services related to the development, manufacture, and supply of the Company's 186RNL-Liposome Intermediate Drug Product. The MSA includes the transfer of analytical methods, development of microbiological methods, process transfer and optimization, intermediate drug product manufacturing, and stability studies for the Company, which has been initiated at Piramal's facility located in Lexington, Kentucky.

The MSA has a term of five years and will automatically renew for successive one-year terms unless either party notifies the other no later than six months prior to the original term or any additional terms of its intention to not renew the MSA. The Company has the right to terminate the MSA for convenience upon thirty days' prior written notice. Either party may terminate the MSA upon an uncured material breach by the other party or upon the bankruptcy or insolvency of the other party.

Other Commitments and Contingencies

The Company has entered into agreements with various research organizations for pre-clinical and clinical development studies, which have provisions for cancellation. Under the terms of these agreements, the vendors provide a variety of services including conducting research, recruiting and enrolling patients, monitoring studies and data analysis. Payments under these agreements typically include fees for services and reimbursement of expenses. The timing of payments due under these agreements is

estimated based on current study progress. As of December 31, 2021, the Company did not have any clinical research study obligations.

Legal proceedings

On June 22, 2021, the Company was named as a defendant in an action brought by Lorem Vascular, Pte. Ltd. ("Lorem") in the District Court for the District of Delaware. The complaint alleges false representations were made to Lorem regarding the manufacturing facility in the United Kingdom (the "UK Facility") that Lorem purchased from the Company under the Equity Purchase Agreement, dated March 29, 2019, between the Company and Lorem (the "Lorem Agreement"). Lorem also claims that false representations were made regarding the UK Facility's certification to sell and distribute devices in the European Union and export such devices to China. In connection with these allegations, Lorem claims entitlement to at least \$6,000,000 in compensatory damages and operational costs and expenses (collectively, the "Lorem Claim"). The Company believes that the claims from Lorem are without merit and intends to vigorously defend the case and on August 12, 2021, the Company filed a Motion to Dismiss asking the District Court to dismiss the Lorem Claim. Lorem filed an opposition on September 9, 2021, which the Company responded to on September 30, 2021. On February 7, 2022, a hearing was held on the Company's Motion to Dismiss and the presiding judge ruled against the Motion to Dismiss. The Company is moving forward with discovery in this case.

The Company is subject to various claims and contingencies related to legal proceedings. Due to their nature, such legal proceedings involve inherent uncertainties including, but not limited to, court rulings, negotiations between affected parties and governmental actions. Management assesses the probability of loss for such contingencies and accrues a liability and/or discloses the relevant circumstances, as appropriate.

8. Term Loan Obligations

On May 29, 2015, the Company entered into the Loan and Security Agreement (the "Loan and Security Agreement"), pursuant to which Oxford Finance, LLC ("Oxford") funded an aggregate principal amount of \$17.7 million (the "Term Loan"), subject to the terms and conditions set forth in the Loan and Security Agreement. The Term Loan accrues interest at a floating rate of at least 8.95% per annum, comprised of a three-month LIBOR rate with a floor of 1.00% plus 7.95%. Pursuant to the Loan and Security Agreement, as amended, the Company is required to make interest only payments through May 1, 2021 and thereafter it is required to make payments of principal and accrued interest in equal monthly installments sufficient to amortize the Term Loan through June 1, 2024, the maturity date. At maturity of the Term Loan, or earlier repayment in full following voluntary prepayment or upon acceleration, the Company is required to make a final payment in an aggregate amount equal to approximately \$3.2 million. In connection with the Term Loan, on May 29, 2015, the Company issued to Oxford warrants to purchase an aggregate of 188 shares of the Company's common stock at an exercise price of \$5,175 per share. These warrants became exercisable as of November 30, 2015 and will expire on May 29, 2025 and, following the authoritative accounting guidance, are equity classified and its respective fair value was recorded as a discount to the debt.

From September 2017 to March 2019, the Company entered into a total of seven amendments to the Term Loan which, amongst other things, extended the interest only period, required repayment of \$3.1 million using the proceeds received from sale of the Company's former UK and Japan subsidiaries in April 2019, increased the final payment, increased the final payment fee upon maturity or early repayment of the Term Loan, and increased the minimum liquidity covenant level to \$2.0 million.

On March 29, 2020, the Company entered into the Ninth Amendment of the Loan and Security Agreement (the "Ninth Amendment"), pursuant to which Oxford agreed to defer the start date of principal repayment from May 1, 2020 to May 1, 2021 and extended the term of the Term Loan from September 1, 2021 to June 1, 2024. The principal repayment start date was further deferred to November 1, 2021. In addition, pursuant to the Ninth Amendment, on April 1, 2020, the Company made a \$5.0 million paydown of principal upon execution of the Ninth Amendment and \$0.3 million of related final payment. After giving effect to this payment, \$4.3 million of principal remains outstanding under the Term Loan. In addition, an amendment fee of \$1.0 million will be payable in connection with the Amendment at the earlier of the maturity date, acceleration of the loans and the making of certain prepayments. All other major terms remained consistent.

Under authoritative guidance, the Ninth Amendment does not meet the criteria to be accounted for as a troubled debt restructuring. In addition, the Company performed a quantitative analysis and determined that the terms of the new debt and original debt instrument are not substantially different. Accordingly, the Ninth Amendment is accounted for as debt modification. A new effective interest rate that equates the revised cash flows to the carrying amount of the original debt is computed and applied prospectively.

The Term Loan, as amended, is collateralized by a security interest in substantially all of the Company's existing and subsequently acquired assets, including its intellectual property assets, subject to certain exceptions set forth in the Loan and Security Agreement, as amended. The intellectual property asset collateral will be released upon the Company achieving a certain liquidity level when the total principal outstanding under the Loan and Security Agreement is less than \$3 million. As of

December 31, 2021, there was \$4.0 million principal amount outstanding under the Term Loan, excluding the \$3.2 million final payment fee, and the Company was in compliance with all of the debt covenants under the Loan and Security Agreement.

The Company's interest expense for the year ended December 31, 2021 and 2020 was \$0.9 million and \$1.1 million, respectively. Interest expense is calculated using the effective interest method; therefore it is inclusive of non-cash amortization in the amount of \$0.5 million and \$0.6 million for the year ended December 31, 2021 and 2020, respectively, related to the amortization of the debt discount, deferred financing costs, and accretion of final payment.

The Loan and Security Agreement, as amended, contains customary indemnification obligations and customary events of default, including, among other things, the Company's failure to fulfill certain obligations under the Term Loan, as amended, and the occurrence of a material adverse change, which is defined as a material adverse change in the Company's business, operations, or condition (financial or otherwise), a material impairment of the prospect of repayment of any portion of the loan. In the event of default by the Company or a declaration of material adverse change by its lender, under the Term Loan, the lender would be entitled to exercise its remedies thereunder, including the right to accelerate the debt, upon which the Company may be required to repay all amounts then outstanding under the Term Loan, which could materially harm the Company's financial condition. As of December 31, 2021, the Company has not received any notification or indication from Oxford to invoke the material adverse change clause.

Additional details relating to the outstanding Term Loan as of December 31, 2021 and 2020 are presented in the following table (in thousands):

Year ended December 31, 2021

Origination Date	Original Loan Amount	Interest Rate**	Current Monthly Payment***	Amended expiration date	Remaining Principal (Face Value)
May 2015	\$ 17,700	8.95%	\$ 134	June 1, 2024	\$ 4,021

Year ended December 31, 2020

Origination Date	Original Loan Amount	Interest Rate**	Current Monthly Payment*	Amended expiration date	Remaining Principal (Face Value)
May 2015	\$ 17,700	8.95%	\$ 32	May 31, 2024	\$ 4,289

* Monthly payment as of December 2020, which reflects interest only

** 3 month LIBOR rate with a floor of 1% plus 7.95%

*** Monthly payment as of December 2021, which reflects principal and interest

As of December 31, 2021, the future contractual principal and final fee payments on all of our debt obligations are as follows (as thousands):

Years Ending December 31,

2022	\$ 1,608
2023	1,608
2024	3,996
Total	\$ 7,212

Reconciliation of Face Value to Book Value as of December 31, 2021

Total debt obligations, including final payment fee (Face Value)	\$ 7,212
Less: Debt discount	(599)
Total obligation	6,613
Less: Current portion	1,608
Term loan obligation	\$ 5,005

9. Income Taxes

The Company has recorded a full valuation allowance against its net deferred tax assets and due to our net losses for the years ended December 31, 2021 and 2020, there was no provision or benefit for income taxes recorded.

A reconciliation of the total income tax provision tax rate to the statutory federal income tax rates of 21% for the years ended December 31, 2021 and 2020, respectively, is as follows:

	2021	2020
Income tax expense (benefit) at federal statutory rate	(21.0)%	(21.0)%
Change in valuation allowance	0.9%	23.6%
Income tax expense (benefit) at state statutory rate	(0.6)%	(8.9)%
Stock compensation	0.7%	6.9%
NOLs expiring and adjustments to NOL	20.3%	6.0%
Research credit	(0.8)%	(1.1)%
Return to provision	0.5%	1.0%
Change in state rate	—	(0.5)%
Mark to market adjustment	—	(6.1)%
Other, net	—	0.1%
	<u>0.0%</u>	<u>0.0%</u>

The tax effects of temporary differences that give rise to significant portions of our deferred tax assets and deferred tax liabilities as of December 31, 2021 and 2020 are as follows (in thousands):

	2021	2020
Deferred tax assets:		
Accrued expenses	\$ 41	\$ 128
Stock based compensation	164	168
Net operating loss carryforwards	95,310	95,114
Income tax credit carryforwards	8,864	8,756
Property and equipment, principally due to differences in depreciation	19	16
Intangible assets	451	556
Other, net	82	182
	<u>104,931</u>	<u>104,920</u>
Valuation allowance	(104,857)	(104,742)
Total deferred tax assets, net of allowance	74	178
Deferred tax liabilities:		
Other	(74)	(178)
Total deferred tax liability	(74)	(178)
Net deferred tax assets (liability)	<u>\$ —</u>	<u>\$ —</u>

The Company has established a valuation allowance against its net deferred tax assets due to the uncertainty surrounding the realization of such assets. The Company periodically evaluates the recoverability of the deferred tax assets. At such time as it is determined that it is more likely than not that deferred tax assets are realizable, the valuation allowance will be reduced. The Company has recorded a full valuation allowance of \$104.9 million as of December 31, 2021 as it does not believe it is more likely than not our net deferred tax assets will be realized. The Company increased its valuation allowance by approximately \$0.1 million during the year ended December 31, 2021.

At December 31, 2021, we had federal, and state tax loss carry forwards of approximately \$395.7 million, and \$175.8 million, respectively. The federal and state net operating loss carry forwards begin to expire in 2023 and 2028, respectively, if unused. The federal net operating loss carryover includes \$45.5 million of net operating losses generated after 2017. Federal net operating losses generated from 2018 onwards carryover indefinitely and may generally be used to offset up to 80% of future taxable income. At December 31, 2020, we had federal and state tax credit carry forwards of approximately \$6.5 million and \$5.5 million, respectively, before reduction for uncertain tax positions. The Company has not performed a formal research and development credit study with respect to these credits. The federal credits will begin to expire in 2022, if unused, and the state credits carry forward indefinitely.

Pursuant to the Internal Revenue Code ("IRC") of 1986, as amended, specifically IRC §382 and IRC §383, The Company's ability to use net operating loss and R&D tax credit carry forwards ("tax attribute carry forwards") to offset future taxable income is limited if we experience a cumulative change in ownership of more than 50% within a three-year testing period. The Company has not completed an ownership change analysis pursuant to IRC Section 382 for taxable years ended after December 31, 2007. If ownership changes within the meaning of IRC Section 382 are identified as having occurred subsequent to 2007, the amount of remaining tax attribute carry forwards available to offset future taxable income and income tax expense in future

years may be significantly restricted or eliminated. Further, the Company's deferred tax assets associated with such tax attributes could be significantly reduced upon realization of an ownership change within the meaning of IRC §382.

The Company follows the provisions of income tax guidance which provides recognition criteria and a related measurement model for uncertain tax positions taken or expected to be taken in income tax returns. The guidance requires that a position taken or expected to be taken in a tax return be recognized in the financial statements when it is more likely than not that the position would be sustained upon examination by tax authorities. Tax positions that meet the more likely than not threshold are then measured using a probability weighted approach recognizing the largest amount of tax benefit that is greater than 50% likely of being realized upon ultimate settlement. The Company has not recognized any liability for uncertain tax positions as of December 31, 2021 and 2020.

Following is a tabular reconciliation of the unrecognized tax benefits activity during the years ended December 31, 2021 and 2020 (in thousands):

	2021	2020
Unrecognized Tax Benefits – Beginning	\$ 2,223	\$ 2,234
Gross decreases – tax positions in prior period	(44)	(44)
Gross increase – current-period tax positions	69	33
Unrecognized Tax Benefits – Ending	<u>\$ 2,248</u>	<u>\$ 2,223</u>

The unrecognized tax benefit amounts are reflected in the determination of the Company's deferred tax assets. If recognized, none of these amounts would affect the Company's effective tax rate, since it would be offset by an equal reduction in the deferred tax asset valuation allowance. The Company does not foresee material changes to its liability for uncertain tax benefits within the next twelve months.

The Company did not recognize interest related to unrecognized tax benefits in interest expense and penalties in operating expenses as of December 31, 2021.

The Company's material tax jurisdictions are the United States and California. To its knowledge, the Company is currently not under examination by the Internal Revenue Service or any other taxing authority.

The Company's tax years for 2018 (federal) and 2017 (CA) remain open to examination by the taxing authority. While not open to examination, the tax attributes generated in tax years 2002 (federal) and 1997 (CA) and forward are subject to adjustment by the taxing authorities if utilized in tax years which are still open to examination.

10. Employee Benefit Plan

The Company implemented a 401(k) retirement savings and profit sharing plan (the "Plan") effective January 1, 1999. During 2021, the Company commenced safe harbor matching contribution for up to 4% of eligible employee contributions. Total matching contribution under the Plan amounted to approximately \$40,000 for the year ended December 31, 2021. The Company made no matching contribution to the Plan in 2020.

11. License Agreements

UT Health Science Center at San Antonio ("UTHSA") License Agreement

On December 31, 2021, the Company entered into a Patent and Know-How License Agreement (the "UTHSA License Agreement") with The University of Texas Health Science Center at San Antonio, pursuant to which UTHSA granted the Company an irrevocable, perpetual, exclusive, fully paid-up license, with the right to sublicense and to make, develop, commercialize and otherwise exploit certain patents, know-how and technology related to the development of biodegradable alginate microspheres (BAM) containing nanoliposomes loaded with imaging and/or therapeutic payloads.

Pursuant to the UTHSA License Agreement, the Company is required to make an upfront payment of \$250,000, which was recorded as in process research and development acquired in the statement of operations for the year ended December 31, 2021. The upfront payment was paid in cash in January 2022. Furthermore, the Company may pay up to \$30.3 million in development and sales milestone payments and a tiered single digit royalty on U.S. and European sales. In addition, the Company is obligated to pay a \$50,000 annual maintenance fee starting 2024, as well as low single digit of sales-based royalty under the UTHSA License Agreement.

NanoTx License Agreement

On March 29, 2020, the Company and NanoTx, Corp. ("NanoTx") entered into a Patent and Know-How License Agreement (the "NanoTx License Agreement"), pursuant to which NanoTx granted the Company an irrevocable, perpetual, exclusive, fully

paid-up license, with the right to sublicense and to make, develop, commercialize and otherwise exploit certain patents, know-how and technology related to the development of radiolabeled nanoliposomes.

On May 7, 2020, all closing conditions under the NanoTx License Agreement were satisfied and the Company paid an upfront payment of \$400,000 in cash and issued 230,769 shares of its common stock to NanoTx. Cash and the fair value of common stock issued totaled \$781,000 and is recorded as in-process research and development expenses, pursuant to authoritative literature for asset acquisition, in the consolidated statement of operations and comprehensive loss for the year ended December 31, 2020. Pursuant to the terms of the NanoTx License Agreement, the Company may be required to pay up to \$136.5 million in development and sales milestone payments and a tiered single-digit royalty on U.S. and European sales.

12. Stockholders' Equity

Preferred Stock

The Company has authorized 5,000,000 shares of preferred stock, par value \$0.001 per share. The Company's Board of Directors is authorized to designate the terms and conditions of any preferred stock the Company issues without further action by the common stockholders. On September 21, 2021, Series A 3.6% Convertible Preferred Stock was eliminated. There were no shares of Series A 3.6% Convertible Preferred Stock immediately prior to September 21, 2021, or December 31, 2020. There were 1,014 and 1,016 shares of Series B Convertible Preferred Stock outstanding as of December 31, 2021 and December 31, 2020, respectively. There were 938 shares of Series C Preferred Stock outstanding as of each of December 31, 2021 and December 31, 2020.

As of December 31, 2021, there were 938 outstanding shares of Series C Preferred Stock that can be converted into an aggregate of 416,889 shares of common stock, and 1,014 shares of Series B Convertible Preferred Stock that can be converted into an aggregate of 5,978 shares of common stock.

Warrants

On September 25, 2019, the Company completed an underwritten public offering. The Company issued 289,000 shares of its common stock, along with pre-funded warrants to purchase 2,711,000 shares of its common stock and Series U Warrants to purchase 3,450,000 shares of its common stock at \$5.00 per share. The Series U Warrants have a term of five years from the issuance date. In addition, the Company issued warrants to H.C. Wainwright & Co., LLC, as representatives of the underwriters, to purchase 75,000 shares of its common stock at \$6.25 per share with a term of 5 years from the issuance date, in the form of Series U Warrants (the "Representative Warrants").

In accordance with authoritative guidance, the pre-funded warrants are classified as equity. The Series U Warrants and the Representative Warrants are classified at issuance as liabilities due to a contingent obligation for the Company to settle the Series U Warrants with cash upon certain change in control events.

Between April and September 2020, the Company entered into revised warrant agreements with the holders of 3,447,500 Series U Warrants (the "Warrant Amendments"). In return for reducing the strike price of the warrants to \$2.25 per share, the warrant holders agreed to amend the settlement provisions upon a fundamental transaction such that the warrants would meet the requirements to be classified within stockholders' equity. In September 2020, the Company entered into revised warrant agreements for the Representative Warrants that reduced the strike price of the warrants to \$2.81 per share, and the warrant holders agreed to amend the settlement provisions upon a fundamental transaction such that the Representative Warrants would meet the requirements to be classified within stockholders' equity. Accordingly, approximately \$4.5 million of warrant liability was reclassified to stockholders' equity on the respective effective date of the Warrant Amendments. In addition, approximately \$0.7 million of other income representing change in the fair value of amended warrants from April 1, 2020 to the respective effective date of the Warrant Amendments is recorded in the consolidated statement of operations for the year ended December 31, 2020.

As of December 31, 2021, there were 2,141,000 outstanding Series U Warrants (of which 2,138,500 warrants were equity classified) which can be exercised into an aggregate of 2,141,000 shares of common stock.

Common Stock

Lincoln Park Purchase Agreements

On September 30, 2020, the Company entered into the 2020 Purchase Agreement and registration rights agreement pursuant to which Lincoln Park committed to purchase up to \$25.0 million of the Company's common stock. Under the terms and subject to the conditions of the 2020 Purchase Agreement, the Company had the right, but not the obligation, to sell to Lincoln Park, and Lincoln Park was obligated to purchase up to \$25.0 million of the Company's common stock. Such sales of common stock by the Company were subject to certain limitations, and may occur from time to time, at the Company's sole discretion, over

the 36-month period commencing on November 6, 2020, subject to the satisfaction of certain conditions.

The 2020 Purchase Agreement provided that the number of shares the Company may sell to Lincoln Park on any single business day in a regular purchase is 50,000, but that amount could be increased up to 100,000 shares, depending upon the market price of the Company's common stock at the time of sale and subject to a maximum limit of \$500,000 per regular purchase. The purchase price per share for each such regular purchase was based on prevailing market prices of the Company's common stock immediately preceding the time of sale as computed under the 2020 Purchase Agreement. In addition to regular purchases, the Company could also direct Lincoln Park to purchase other amounts as accelerated purchases or as additional accelerated purchases if the closing sale price of the common stock exceeded certain threshold prices as set forth in the 2020 Purchase Agreement. There are no trading volume requirements or restrictions under the Lincoln Park Purchase Agreement. There is no upper limit on the price per share that Lincoln Park must pay for common stock under a regular purchase or an accelerated purchase and in no event will shares be sold to Lincoln Park on a day when the Company's common stock closing sale price is less than \$0.25 per share.

On June 16, 2020, the Company received stockholder approval to permit issuances of the Company's common stock (including the issuance of more than 19.99% of the Company's common stock) to Lincoln Park pursuant to the 2020 Purchase Agreement. Based on the closing price of the Company's common stock of \$1.05 per share on March 16, 2020, the maximum number of shares the Company can issue and sell under the 2020 Purchase Agreement is approximately 23.8 million shares. Accordingly, the Company requested and received stockholder approval for the issuance of up to 23.8 million shares of the Company's common stock under the 2020 Purchase Agreement. The Company would seek additional stockholder approval before issuing more than 23.8 million shares.

Lincoln Park had no right to require the Company to sell any shares of common stock to Lincoln Park, but Lincoln Park was obligated to make purchases as the Company directed, subject to certain conditions.

During the year ended December 31, 2020, the Company issued 353,113 shares, excluding 180,701 shares issued as a commitment fee, of common stock under the 2020 Purchase Agreement for total net proceeds of approximately \$0.7 million. During the year ended December 31, 2021, the Company issued 5,685,186 shares of its common stock under the 2020 Purchase Agreement for net proceeds of approximately \$12.5 million. As described in Note 15, subsequent to January 1, 2022, the Company issued approximately 5,665,000 shares of its common stock for net proceeds of \$7.0 million. The Company no longer had any additional shares of common stock registered to sell under the 2020 Purchase Agreement.

At-the-market Issuances

On January 14, 2022, the Company entered into an Equity Distribution Agreement (the "2022 Distribution Agreement") with Canaccord Genuity LLC (the "Agent"), pursuant to which the Company may issue and sell, from time to time, shares of its common stock having an aggregate offering price of up to \$5,000,000 Share, with the Agent acting as an agent for sales. The Agent will use its commercially reasonable efforts to sell the Shares requested by the Company to be sold on its behalf. The Company has no obligation to sell any of the Shares. The Company has no obligation to sell any of the Shares. The Company may instruct the Agent not to sell the Shares if the sales cannot be effected at or above the price designated by us from time to time and the Company may at any time suspend sales pursuant to the 2022 Distribution Agreement. As described in Note 15, subsequent to January 1, 2022, the Company issued 1,000,000 shares under the 2022 Distribution Agreement for net proceeds of approximately \$0.9 million.

On October 23, 2020, the Company entered into the 2020 Distribution Agreement with Canaccord Genuity LLC ("Canaccord"), pursuant to which the Company issued and sold the ATM Shares, depending on market demand, with Canaccord acting as an agent for sales. The Company had no obligation to sell any of the ATM Shares and it could instruct Canaccord not to sell the ATM Shares if the sales could not be effected at or above the price the Company designated from time to time and the Company could at any time suspend sales pursuant to the 2020 Distribution Agreement.

During the year ended December 31, 2020, the Company issued 1,616,331 shares under the 2020 Distribution Agreement for net proceeds of approximately \$3.2 million. During the year ended December 31, 2021, the Company issued 2,179,193 shares under the 2020 Distribution Agreement for net proceeds of \$6.3 million. As of December 31, 2021, there were no remaining shares that may be issued and sold under the 2020 Distribution Agreement.

13. Stock-based Compensation

On February 6, 2020, the Company amended the Company's 2015 New Employee Incentive Plan (the "2015 Plan") to increase the total number of shares of common stock reserved for issuance under the plan by 250,000 shares. Awards may only be granted under the 2015 Plan to employees who were not previously an employee or director of the Company, or following a bona fide period of non-employment, as a material inducement to entering into employment with the Company. As of December 31, 2021, there were 90,389 shares of common stock remaining and available for future issuances under the 2015 Plan.

On June 16, 2020, the stockholders of the Company approved the Company's 2020 Stock Incentive Plan (the "2020 Plan"), which replaced the Company's 2014 Equity Incentive Plan. The 2020 Plan provides for the award or sale of shares of common stock (including restricted stock), the award of stock units and stock appreciation rights, and the grant of both incentive stock options to purchase common stock. The 2020 Plan provides for the issuance of up to 550,000 shares of common stock, and the number of shares available for issuance will be increased to the extent that awards granted under the 2020 Plan and the Company's 2014 Equity Incentive Plan are forfeited or expire (except as otherwise provided in the 2020 Plan). On May 17, 2021, the stockholders of the Company approved an amendment and restatement to the 2020 Plan to increase the total number of shares of common stock reserved for issuance under the 2020 Plan by 1,000,000 shares. As of December 31, 2021, there were 640,212 shares of common stock remaining and available for future issuances under the 2020 Plan.

Stock Options

Generally, options issued under the 2020 Plan are subject to a two-year or four-year vesting schedule with 25% of the options vest on one year anniversary of the grant date, and have a contractual term of 10 years.

A summary of activity for the year ended December 31, 2021 is as follows:

	Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Balance as of December 31, 2020	531,336	\$ 10.01		
Granted	680,227	\$ 2.52		
Cancelled/forfeited	(40,673)	\$ 16.69		
Balance as of December 31, 2021	1,170,890	\$ 5.01	9.00	\$ -
Vested and expected to vest at December 31, 2021	378,010	\$ 10.37	8.70	\$ -
Exercisable at December 31, 2021	1,089,944	\$ 5.16	9.00	\$ -

The Company settles exercises of stock options with newly issued shares of its common stock. There were no stock options exercised in 2021 or 2020.

The fair value of each option awarded during the years ended December 31, 2021 and 2020 was estimated on the date of grant using the Black-Scholes-Merton option valuation model based on the following weighted-average assumptions:

	December 31, 2021	December 31, 2020
Expected term	6 years	5.8 years
Risk-free interest rate	1.00%	0.58%
Expected volatility	127.0%	128.6%
Dividends	0%	0%
Resulting fair value	\$ 2.23	\$ 1.87

The weighted average risk-free interest rate represents the interest rate for treasury constant maturity instruments published by the Federal Reserve Board. If the term of available treasury constant maturity instruments is not equal to the expected term of an employee option, we use the weighted average of the two Federal Reserve securities closest to the expected term of the employee option.

The dividend yield has been assumed to be zero as the Company (a) has never declared or paid any dividends and (b) does not currently anticipate paying any cash dividends on its outstanding shares of common stock in the foreseeable future.

The following table summarizes share-based compensation recognized during the years ended December 31, 2021 and 2020 in the statement of operations and comprehensive loss:

	Years ended December 31,	
	2021	2020
Research and development	\$ 75	\$ 32
General and administrative	531	215
Total share-based compensation	<u>\$ 606</u>	<u>\$ 247</u>

As of December 31, 2021, the total compensation cost related to non-vested stock options and stock awards not yet recognized for all our plans is approximately \$1.5 million, which is expected to be recognized as a result of vesting under service conditions over a weighted average period of 2.9 years.

14. COVID-19 Pandemic and CARES Act

A novel strain of coronavirus (COVID-19) was declared a global pandemic by the World Health Organization in March 2020. COVID-19 has presented substantial public health and economic challenges and is affecting economies, financial markets and business operations around the world. International and U.S. governmental authorities in impacted regions have taken action in an effort to slow the spread of COVID-19, including issuing varying forms of “stay-at-home” orders, and restricting business functions outside of one’s home. In response, the Company put restrictions on employee travel and working from its executive offices with many employees continuing their work remotely. While the Company has implemented additional health and safety precautions and protocols in response to the pandemic and government guidelines, the Company has not experienced a significant impact on its business and operations. However, the Company may experience disruptions that could adversely impact its business operations as well as its preclinical studies and clinical trials. The Company is currently continuing the clinical trials it has underway in sites across the U.S., and, although there has been no significant impact to date, the Company expects that COVID-19 precautions may directly or indirectly impact the timeline for some of its clinical trials. Some of the Company’s clinical trial sites, including those located in areas severely impacted by the pandemic, have placed new patient enrollment into clinical trials on hold. In addition, some clinical trial sites have imposed limited accessibility to conduct clinical monitoring and training on-site. The Company considered the impacts of COVID-19 on the assumptions and estimates used to prepare its consolidated financial statements and determined that there were no material adverse impacts on the Company’s results of operations and financial position at December 31, 2021. The full extent to which the COVID-19 pandemic will directly or indirectly impact its business, results of operations and financial condition, will depend on future developments that are highly uncertain, including as a result of new information that may emerge concerning COVID-19 and the actions taken to contain or treat it, as well as the economic impact on local, regional, national and international markets.

In response to the COVID-19 pandemic, the CARES Act was signed into law on March 27, 2020. The CARES Act, among other things, includes tax provisions relating to refundable payroll tax credits, deferment of employer’s social security payments, net operating loss utilization and carryback periods, modifications to the net interest deduction limitations and technical corrections to tax depreciation methods for qualified improvement property (QIP). The CARES Act had no material impact on the Company’s income tax provision for the year ended December 31, 2021. The Company continues to evaluate the impact of the CARES Act on its financial position, results of operations and cash flows.

15. Subsequent Events

From January 1, 2022 through the date of filing of this Form 10-K, the Company issued approximately 5,665,000 shares of its common stock for net proceeds of \$7.0 million under the 2020 Purchase Agreement. In addition, the Company issued 1,000,000 shares under the 2022 Distribution Agreement for net proceeds of approximately \$0.9 million.

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

Not applicable.

Item 9A. Controls and Procedures**(a) Evaluation of Disclosure Controls and Procedures**

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our reports filed or furnished pursuant to the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer (our principal executive officer) and Chief Financial Officer (our principal accounting officer and principal financial officer), as appropriate, to allow for timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and management necessarily is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

As required by Rule 13a-15(b) under the Exchange Act, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of our disclosure controls and procedures, as such term is defined under Rule 13a-15(e) promulgated under the Securities Exchange Act of 1934, as amended, as of the end of the period covered by this Annual Report on Form 10-K. Based on the foregoing, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures as of the end of the period covered by this Annual Report were effective.

(b) Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) or 15d-15(f) under the Securities Exchange Act of 1934 as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our Board of Directors, management and other personnel, 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 and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures are being made only in accordance with authorizations of management and our Board of Directors; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

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.

Under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, we have conducted an evaluation of the effectiveness of our internal control over financial reporting as of the end of the fiscal year covered by this Annual Report on Form 10-K based on the criteria set forth in *Internal Control - Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Based on our evaluation, management concluded that our internal control over financial reporting was effective as of December 31, 2021 based on the COSO criteria.

This report does not include an attestation report on internal control over financial reporting by the Company's independent registered public accounting firm since the Company is a smaller reporting company under the rules of the SEC.

(c) Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting during the quarter ended December 31, 2021 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspection

Not Applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item will be set forth under the captions “Election of Directors – Directors and Nominees,” “Executive Officers,” “Certain Relationships and Related Transactions – Section 16(a) Beneficial Ownership Reporting Compliance,” “Code of Business Conduct and Ethics” and “Corporate Governance – Board Committees” in our definitive proxy statement to be filed with the SEC, in connection with our 2022 annual meeting of stockholders (the “Proxy Statement”), which is expected to be filed not later than 120 days after the end of our fiscal year ended December 31, 2021, and is incorporated in this report by reference.

Item 11. Executive Compensation.

The information required by this item will be set forth under the captions “Executive Compensation”, “Corporate Governance — Compensation Committee Interlocks and Insider Participation,” “Corporate Governance – Compensation Committee Report” and “Corporate Governance — Non-Employee Director Compensation” in the Proxy Statement and is incorporated herein by reference.

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

The information required by this item will be set forth under the caption “Security Ownership of Certain Beneficial Owners and Management” and “Executive Compensation — Equity Compensation Plan Information” in the Proxy Statement and is incorporated herein by reference.

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

The information required by this item will be set forth under the captions “Certain Relationships and Related Person Transactions” and “Corporate Governance — Board Independence” in the Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

The information required by this item will be set forth under the caption “Audit Matters — Principal Accounting Fees and Services” in the Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) (1) Financial Statements.

The responses to this portion of Item 15 are set forth under Part II, Item 8 above.

(a) (2) Financial Statement Schedules.

None.

(a) (3) Exhibits.

List of Exhibits required by Item 601 of Regulation S-K. See Item 15(b) below.

(b) Exhibits.

The exhibits listed in the accompanying "Exhibit Index" are filed, furnished or incorporated by reference as part of this Annual Report, as indicated.

Item 16. Form 10-K Summary.

None.

EXHIBIT INDEX
PLUS THERAPEUTICS, INC.

Exhibit Number	Exhibit Title	Filed with this Form 10-K	Form	Incorporated by Reference File No.	Date Filed
3.1	<u>Composite Certificate of Incorporation</u>		10-K	001-34375 Exhibit 3.1	03/11/2016
3.2	<u>Certificate of Amendment to Amended and Restated Certificate of Incorporation</u>		8-K	001-34375 Exhibit 3.1	05/10/2016
3.3	<u>Certificate of Amendment to Amended and Restated Certificate of Incorporation</u>		8-K	001-34375 Exhibit 3.1	05/23/2018
3.4	<u>Certificate of Amendment to Amended and Restated Certificate of Incorporation</u>		8-K	001-34375 Exhibit 3.1	07/29/2019
3.5	<u>Certificate of Amendment to Amended and Restated Certificate of Incorporation</u>		8-K	001-34375 Exhibit 3.1	08/06/2019
3.6	<u>Certificate of Designation of Preferences, Rights and Limitations of Series A 3.6% Convertible Preferred Stock</u>		8-K	001-34375 Exhibit 3.1	10/08/2014
3.7	<u>Certificate of Designation of Preferences, Rights and Limitations of Series B Convertible Preferred Stock</u>		8-K	001-34375 Exhibit 3.1	11/28/2017
3.8	<u>Certificate of Designation of Preferences, Rights and Limitations of Series C Convertible Preferred Stock</u>		8-K	001-34375 Exhibit 3.1	07/25/2018
3.9	<u>Amended and Restated Bylaws of Plus Therapeutics, Inc.</u>		8-K	001-34375 Exhibit 3.2	09/21/2021
3.10	<u>Certification of Elimination of Series A Preferred Stock</u>		8-K	001-34375 Exhibit 3.2	09/21/2021
4.1	<u>Description of Securities</u>		10-K	001-34375 Exhibit 4.1	03/30/2020
4.2	<u>Form of Common Stock Certificate</u>		10-K	001-34375 Exhibit 4.33	03/09/2018
4.3	<u>Form of Series U Warrant</u>		S-1/A	333-229485 Exhibit 4.37	09/16/2019
4.4	<u>Form of Warrant Amendment Agreement</u>		8-K	011-34375 Exhibit 4.1	04/23/2020
4.5	<u>Form of Underwriters' Warrant Amendment Agreement</u>		8-K	011-34375 Exhibit 4.1	10/05/2020
10.1+	<u>Patent and Know-How License Agreement, dated March 29, 2020, by and between Plus Therapeutics, Inc. and NanoTx, Corp.</u>		8-K	011-34375 Exhibit 10.1	3/30/2020
10.2+	<u>Patent & Technology License Agreement, dated December 31, 2021, between Plus Therapeutics, Inc. and the University of Texas Health Science Center at San Antonio</u>	X			
10.3	<u>Distribution Agreement, dated January 14, 2022, by and among Plus Therapeutics, Inc. and Canaccord Genuity LLC</u>		8-K	011-34375 Exhibit 1.1	1/14/2022
10.4	<u>Purchase Agreement between Lincoln Park Capital Fund, LLC and Plus Therapeutics, Inc.</u>		8-K	011-34375 Exhibit 10.1	10/06/2020
10.5	<u>Registration Rights Agreement between Plus Therapeutics, Inc. and Lincoln Park Capital Fund, LLC, dated September 30, 2020.</u>		8-K	001-34375 Exhibit 10.2	10/06/2020
10.6+	<u>Asset Purchase Agreement by and between Plus Therapeutics, Inc. and Azaya Therapeutics, Inc., effective January 16, 2017.</u>		10-K	001-34375 Exhibit 10.40	03/24/2017

10.7	Loan and Security Agreement, dated May 29, 2015, by and between Plus Therapeutics, Inc. and Oxford Finance, LLC.	10-Q	001-34375 Exhibit 10.4	08/10/2015
10.8	First Amendment to Loan and Security Agreement, dated September 20, 2017, by and between Plus Therapeutics, Inc. and Oxford Finance, LLC.	S-1/A	333-219967 Exhibit 10.45	10/03/2017
10.9	Second Amendment to Loan and Security Agreement, dated June 19, 2018, by and between Plus Therapeutics, Inc. and Oxford Finance, LLC.	10-Q	001-34375 Exhibit 10.3	08/14/2018
10.10	Third Amendment to Loan and Security Agreement, dated August 31, 2018, by and between Plus Therapeutics, Inc. and Oxford Finance, LLC.	S-1	333-227485 Exhibit 10.51	09/21/2018
10.11	Fourth Amendment to Loan and Security Agreement dated December 31, 2018, by and between Plus Therapeutics, Inc. and Oxford Finance, LLC.	S-1	333-229485 Exhibit 10.52	02/01/2019
10.12	Fifth Amendment to Loan and Security Agreement dated February 13, 2019, by and between Plus Therapeutics, Inc. and Oxford Finance, LLC.	10-K	001-34375 Exhibit 10.55	03/29/2019
10.13	Sixth Amendment to Loan and Security Agreement dated March 4, 2019, by and between Plus Therapeutics, Inc. and Oxford Finance, LLC.	10-K	001-34375 Exhibit 10.56	03/29/2019
10.14	Seventh Amendment to Loan and Security Agreement dated April 24, 2019, by and between Plus Therapeutics, Inc. and Oxford Finance, LLC.	10-Q	001-34375 Exhibit 10.3	05/14/2019
10.15	Eight Amendment to Loan and Security Agreement dated July 15, 2019, by and between Plus Therapeutics, Inc. and Oxford Finance, LLC.	10-Q	001-34375 Exhibit 10.2	08/15/2019
10.16+	Ninth Amendment to Loan and Security Agreement, dated March 29, 2020 by and between Plus Therapeutics, Inc. and Oxford Finance, LLC.	8-K	011-34375 Exhibit 10.2	3/30/2020
10.17#	Amended and Restated Employment Agreement between Marc Hedrick and Plus Therapeutics, Inc.	10-Q	001-34375 Exhibit 10.6	5/16/2020
10.18#	Amended and Restated Employment Agreement between Andrew Sims and Plus Therapeutics, Inc.	10-Q	001-34375 Exhibit 10.7	5/16/2020
10.19#	LaFrance Employment Agreement	8-K	001-34375 Exhibit 10.1	09/13/2021
10.20#	2015 New Employee Incentive Plan.	8-K	001-34375 Exhibit 10.1	01/05/2016
10.21#	First Amendment to the Plus Therapeutics, Inc. 2015 New Employee Incentive Plan, dated Jan. 26, 2017.	10-K	001-34375 Exhibit 10.42	03/24/2017
10.22#	Second Amendment to the Plus Therapeutics, Inc. 2015 New Employee Incentive Plan, dated February 6, 2020.	10-K	001-34375 Exhibit 10.25	03/30/2020
10.23#	Form of Notice of Grant of Stock Option under the 2015 New Employee Incentive Plan.	S-8	333-210211 Exhibit 99.5	03/15/2016
10.24#	Form of Stock Option Agreement under the 2015 New Employee Incentive Plan.	S-8	333-210211 Exhibit 99.4	03/15/2016
10.25#	Plus Therapeutics, Inc. 2020 Stock Incentive Plan, as amended and restated.	8-K	001-34375 Exhibit 10.1	05/17/2021
10.26#	Form of Notice of Grant and Stock Option Agreement under the 2020 Stock Incentive Plan.	X		
10.27+	Master Services Agreement between Piramal Pharma Solutions, Inc. and Plus Therapeutics, Inc.	10-K	001-334275 Exhibit 10.24	02/22/2021

10.28#	<u>Form of Indemnification Agreement</u>	8-K	001-34375 Exhibit 10.1	02/06/2020
10.29#	<u>Form of Agreement for Acceleration and/or Severance</u>	10-K	001-34375 Exhibit 10.113	03/11/2016
23.1	<u>Consent of BDO USA, LLP, Independent Registered Public Accounting Firm</u>	X		
24.1	<u>Power of Attorney (see signature page)</u>	X		
31.1	<u>Certification of Principal Executive Officer Pursuant to Securities Exchange Act Rule 13a-14(a), as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002</u>	X		
31.2	<u>Certification of Principal Financial and Accounting Officer Pursuant to Securities Exchange Act Rule 13a-14(a), as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002</u>	X		
32.1	<u>Certifications Pursuant to 18 U.S.C. Section 1350/ Securities Exchange Act Rule 13a-14(b), as adopted pursuant to Section 906 of the Sarbanes -Oxley Act of 2002</u>	X		
101.INS	Inline XBRL Instance Document	X		
101.SCH	Inline XBRL Schema Document	X		
101.CAL	Inline XBRL Calculation Linkbase Document	X		
101.DEF	Inline XBRL Definition Linkbase Document	X		
101.LAB	Inline XBRL Label Linkbase Document	X		
101.PRE	Inline XBRL Presentation Linkbase Document	X		
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)	X		

Indicates management contract or compensatory plan or arrangement.
+ *Portions of this exhibit have been excluded pursuant to Item 601(b)(1)(iv).*

SIGNATURES

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

PLUS THERAPEUTICS, INC.

By: /s/ Marc H. Hedrick, MD
Marc. H. Hedrick, MD
President & Chief Executive Officer

February 24, 2022

POWER OF ATTORNEY

KNOW ALL BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Andrew Sims and Desiree Smith, and each of them, as his or her true and lawful attorneys-in-fact and agents, each with the full power of substitution, for him or her and in his or her name, place, or stead, in any and all capacities, to sign any and all amendments to this Report, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this Annual Report on Form 10-K has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

SIGNATURE	TITLE	DATE
<u>/s/ Richard J. Hawkins</u> Richard J. Hawkins	<i>Chairman of the Board</i>	February 24, 2022
<u>/s/ Marc H. Hedrick, MD</u> Marc H. Hedrick, MD	<i>President & Chief Executive Officer (Principal Executive Officer)</i>	February 24, 2022
<u>/s/ Andrew Sims</u> Andrew Sims	<i>Chief Financial Officer and VP of Finance (Principal Financial and Accounting Officer)</i>	February 24, 2022
<u>/s/ An van Es-Johansson, MD</u> An van Es-Johansson, MD	<i>Director</i>	February 24, 2022
<u>/s/ Greg Petersen</u> Greg Petersen	<i>Director</i>	February 24, 2022
<u>/s/ Howard Clowes</u> Howard Clowes	<i>Director</i>	February 24, 2022
<u>/s/ Robert Lenk</u> Robert Lenk	<i>Director</i>	February 24, 2022