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, 2022
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.
(Exact name of Registrant as Specified in Its Charter)

DELAWARE	**33-0827593**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**
4200 MARATHON BLVD. SUITE 200, AUSTIN, TX	**78756**
(Address of principal executive offices)	**(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	☐	Accelerated Filer	☐
Non-Accelerated Filer	☒	Smaller reporting company	☒
Emerging growth company	☐		

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

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

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

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

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

The aggregate market value of the common stock of the registrant held by non-affiliates of the registrant on June 30, 2022, the last business day of the registrant's most recently completed second fiscal quarter, was $12.1 million based on the closing sales price of the registrant's common stock on June 30, 2022 as reported on the Nasdaq Capital Market, of $0.54 per share.

As of February 17, 2023, there were 35,109,885 shares of the registrant's common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the registrant's definitive proxy statement for its 2023 Annual Meeting of Stockholders, which will be filed with the United States Securities and Exchange Commission within 120 days of December 31, 2022, 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; our strategic collaborations and license agreements, intellectual property, FDA and EMA 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 could be delisted from Nasdaq, which would seriously harm the liquidity of our stock and our ability to raise capital.
- 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. Furthermore, the 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 rhenium (^{186}Re) obisbemeda and ^{188}RNL-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 success depends in substantial part on our ability to obtain regulatory approvals for our rhenium (^{186}Re) obisbemeda and ^{188}RNL-BAM product candidates. However, we cannot be certain that we will receive regulatory approval for these product candidates or our other product candidates.
- Reliance on government funding for our programs may impose requirements that limit our ability to take certain actions, and subject it to potential financial penalties, which could materially and adversely affect its business, financial condition and results of operations.
- 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.
- Clinical trial results may fail to support approval of our product candidates.
- If third parties we engage are not able to successfully perform, 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.
- 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.
- 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.

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 or issuance of our common stock to Lincoln Park and the sale of the shares of common stock acquired by Lincoln Park and the sale of our common stock by Canaccord.
- The market price of our common stock may be volatile and fluctuate significantly, which could result in substantial losses for stockholders, and future sales of our common stock may depress our share price.
- 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.

PART I

Item 1. Business

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

General

Plus Therapeutics, Inc. is a U.S. pharmaceutical company developing targeted radiotherapeutics with advanced platform technologies for central nervous system ("CNS") 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 extend retention times such that the clearance of the isotope occurs after significant and essentially complete 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 four to six 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 locoregional delivery and, thereby, efficacy, we hope to reduce the radiation toxicity for patients, improving their quality of life 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}Re) obisbemeda (formerly, "^{186}RNL"), is designed specifically to CNS cancers including recurrent glioblastoma ("GBM"), leptomeningeal metastases ("LM"), and pediatric brain cancers ("PBC") by direct localized delivery utilizing approved standard-of-care tissue access such as with convection-enhanced delivery ("CED") and intraventricular brain(Ommaya reservoir) catheters. Our recently acquired radiotherapeutic candidate, Rhenium-188 NanoLiposome Biodegradable Alginate Microsphere ("^{188}RNL-BAM") is designed to treat many solid organ cancers including primary and secondary liver cancers by intra-arterial injection.

Our headquarters and manufacturing facilities are 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.

In addition to its headquarters in Austin, we have an established, GMP-validated research and development and manufacturing facility in San Antonio, Texas, tailored to produce cGMP rhenium (186Re) obisbemeda. We have built a robust supply chain through strategic partnerships that enable the development, manufacturing and future potential commercialization of our products. Our current supply chain and key partners are positioned to supply cGMP rhenium (186Re) obisbemeda for ongoing and planned Phase 2 and Phase 3 clinical trials in patients with GBM, LM and PBC..

Pipeline

Our most advanced investigational drug, rhenium (^{186}Re) obisbemeda, is a patented radiotherapy potentially useful for patients with CNS and other cancers. Preclinical study data describing the use of rhenium (^{186}Re) obisbemeda for several cancer targets have been published in peer-reviewed journals and reported at a variety of medical society peer-reviewed meetings. Besides GBM, LM and PBC, rhenium (^{186}Re) obisbemeda has been reported to have potential applications for head and neck cancer, ovarian cancer, breast cancer and peritoneal metastases.

The Rhenium (186Re) Obisbemeda 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 is expected to provide financial support for the continued clinical development of rhenium (^{186}Re) obisbemeda for recurrent GBM through the completion of a Phase 2 clinical trial, including enrollment of up to 55 patients. As of February 23, 2023, 26 patients have been treated in the Phase 1 clinical trial and the Phase 2 clinical trial has been initiated with the first patient treated. In addition, we anticipate obtaining FDA IND approval for the ReSPECT-PBC clinical trial for PBC in early 2023.

On August 29, 2022, we announced feedback from a Type C meeting with the FDA regarding Chemistry, Manufacturing and Controls ("CMC") practices. The meeting focused on our Current Good Manufacturing Practice ("cGMP") clinical and commercial manufacturing process for our lead investigational targeted radiotherapeutic, BMEDA-chelated Rhenium (186Re) Obisbemeda, for recurrent GBM.

The FDA indicated agreement with our proposed application of cGMP guidance for radiotherapeutics, small molecule drug products and liposome drug products for our novel rhenium (^{186}Re) obisbemeda in support of ongoing and future GBM clinical trials, manufacturing scale up, and commercialization. Alignment with the FDA includes support of our proposed controls and release strategy for new drug substance and new drug product. Because this product is identical for recurrent GBM and LM adult development and pediatric brain tumors, we believe this FDA alignment and feedback will apply to rhenium (^{186}Re) obisbemeda used in other clinical development programs, including LM and PBC.

Rhenium (^{186}Re) obisbemeda *versus External Beam Radiation Therapy for Recurrent GBM*

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

- The rhenium (^{186}Re) obisbemeda radiation dose delivered to patients may be up to 20 times greater than what is possible with commonly used external beam radiation therapy ("EBRT"), which, unlike EBRT and proton beam devices, spares normal tissue and the brain from radiation exposure.
- Rhenium (^{186}Re) obisbemeda can be visualized in real-time during administration, possibly giving clinicians better control of radiation dosing, distribution and retention.
- Rhenium (^{186}Re) obisbemeda potentially more effectively treats a bulk tumor and microscopic disease that has already invaded healthy tissue.
- Rhenium (^{186}Re) obisbemeda is infused directly into the targeted tumor by CED catheter insertion using MRI guided software to avoid critical patient neurological structures and neural pathways and also bypasses the blood brain barrier, which delivers the therapeutic product where it is needed. Importantly, it 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.
- Rhenium (^{186}Re) obisbemeda 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 five days a week for approximately four to six weeks.

ReSPECT-GBM Trial for Recurrent GBM

Recurrent GBM is the most common, complex, and aggressive primary brain cancer in adults. In the U.S., there are more than 13,000 GBM cases diagnosed and approximately 10,000 patients succumb to the disease each year. The average length of overall survival ("OS") for GBM patients is eight months, with a one-year survival rate of 40.8% and a five-year survival rate of only 6.8% and these estimates varies and are lower in some publications. GBM routinely presents with headaches, seizures, vision changes and other significant neurological complications, with a significant compromise in quality of life. Despite the best available medical treatments, the disease remains incurable. Even after efforts to manage the presenting signs and symptoms and completely resect the initial brain tumor, some microscopic disease almost always remains and tumor regrowth occurs within months. Approximately 90% or more of patients with primary GBM experience tumor recurrence. Complete surgical removal of GBM is usually not possible and GBM is often resistant or quickly develops resistance to most available current and investigational 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, and these more recent approvals have not improved GBM patients OS over past decades, and a significant unmet medical need persists.

For recurrent GBM, there are few currently approved treatments, which 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 has temporary efficacy in many malignancies including GBM, typically at absorbed, fractionated radiation dose of ~30 Gray in GBM, this maximum possible administered dose is always limited by toxicity to the normal tissues surrounding the malignancy and because EBRT requires fractionation to manage toxicity and maximum EBRT limits are typically reached before long-term efficacy reached. Because of this limitation EBRT cannot provide a cure or long term control of GBM and GBM always recurs within months after EBRT. In contrast, locally delivered and targeted radiopharmaceuticals that precisely deliver radiation in the form of beta particles such as Iodine-131 for thyroid cancer, are known to be safe and effective and minimize exposure to normal cells and tissues especially with optimal targeting and avoidance of normal tissue. The locally delivered rhenium (^{186}Re) obisbemeda is designed for and provides patient tolerability and safety. Though no head-to-head trial with chemo, immune,

EBRT or systemic radiopharmaceutical products have been conducted, patient tolerability and safety considerations have been reported as expected.

Interim results from our ongoing Phase 1/2a ReSPECT-GBM trial (ClinicalTrials.gov NCT01906385) show that the beta particle energy from our lead investigational drug rhenium (^{186}Re) obisbemeda has provided preliminary positive data and utility in treating GBM and potential other malignancies. More specifically, the preliminary data from our Phase 1/2a ReSPECT-GBM trial suggests 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 tissue in humans, without significant or dose limiting toxicities and with what we believe has the capability to go higher if required. In comparison, current EBRT protocols for recurrent GBM typically recommend a total maximum radiation dose of about ~30-35 Gray.

In September 2020, the FDA granted both Orphan Drug designation and Fast Track designations to rhenium (^{186}Re) obisbemeda for the treatment of patients with GBM. In November 2021, the FDA granted Fast Track designation for rhenium (^{186}Re) obisbemeda for the treatment of LM.

Rhenium (^{186}Re) obisbemeda is under clinical investigation in a multicenter, sequential cohort, open-label, volume and dose escalation study of the safety, tolerability, and distribution of rhenium (186Re) obisbemeda given by CED catheters to patients with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment (NCT01906385). The study uses a standard, modified 3x3 Fibonacci dose escalation, followed by a planned Phase 2 expansion trial at the maximum tolerated dose ("MTD") / maximum feasible dose ("MFD") or non-dose limiting toxicity ("DLT") if MTD is not reached, to determine efficacy. The trial is funded through Phase 2 in large part by a NIH/NCI grant. These investigations have not reached DLT or MTD/MFD and the study is in its eighth dosing administration cohort. Due to the observation of a preliminary efficacy signal, we have initiated in parallel a Phase 2, non-DLT dose trial pursuant to the currently funded NIH/NCI Grant. This trial will begin at the current non-DLT rhenium (186Re) obisbemeda dose and will expand exploring higher radiation doses in larger volumes to treat larger tumors. Additionally, two or more rhenium (186Re) obisbemeda administrations, if indicated, will be evaluated, and reviewed with the FDA, as well as expanded safety, imaging and efficacy data to support a planned future registrational trial. This in turn will provide a path to a registration trial.

On September 6, 2022, we announced a summary of our Type C clinical meeting with the FDA that focused on the ReSPECT-GBM trial. The FDA agreed with us that the ReSPECT-GBM clinical trial should proceed to the planned Phase 2. The key focus areas of clinical investigation of the Phase 2 trial will be 1) further dose exploration, including both increased dosing and multiple doses, and 2) collecting additional safety and efficacy data to inform the design of a future registrational trial. Because no DLT administered doses were observed, the FDA and we also agreed to continue to dose cohort eight. There was further agreement with the FDA that in a planned future registrational trial, overall survival should be used as the primary endpoint. We agreed with the FDA to hold future meeting(s) to consider the use of external data to augment the use of a control arm in the registrational trial.

At the European Society for Medical Oncology Congress, held September 9 to 13, 2022, we presented updated data from the ReSPECT-GBM trial, which evaluated 23 adult patients with recurrent GBM across eight cohorts of increasing dose and treated over a seven-year period. Key findings include:

- No DLTs have been observed and the procedure was very well tolerated with a strong safety profile. Minimal systemic radiation has been observed and the majority of adverse events have been mild or moderate and considered causally unrelated to rhenium (186Re) obisbemeda.
- Improved median overall survival ("OS") rates correlated with the absorbed radiation tumor dose. When patients were stratified based on receipt of either a therapeutic or a subtherapeutic absorbed dose of radiation to the tumor, a statistically significant improvement in survival was observed. Specifically, patients receiving a therapeutic absorbed radiation dose (>100 Gray) had a median OS of 22.9 months (95% CI of 8.8-42.3) compared to those receiving a subtherapeutic absorbed radiation dose (<100 Gray) whose median OS was 5.6 months (95% CI of 1.6-9.4). Currently, three patients remain alive, all in the therapeutic group.
- Feasibility to deliver up to at least 20 times more radiation to the tumor than the standard of care, EBRT. A maximum of 32.2 mCi in 12.3 mL of volume has been delivered in and near the tumors, and a maximum average absorbed dose of radiation of 740 Gray was successfully administered in a single procedure.
- Average absorbed radiation dose to the tumor increased in latter dosing cohorts with greater administered doses of rhenium (186Re) obisbemeda β-particle radiation, larger drug CED infusate volumes, more catheters used (up to four versus one), and higher convection flow rates. In cohorts five and later, 82% of patients received a therapeutic radiation dose of >100Gray.
- Single-photon emission computerized tomography and (SPECT)/CT scanning were used during treatment to compute tumor coverage and dosimetry. Post treatment imaging analyses, including MRI, relative cerebral blood volume (rCBV) analysis

and treatment response assessment maps (TRAMs) correlated with a positive tumor response and confirmed the presence of pseudoprogression in patients with positive tumor responses.

At the Society for Neuro-Oncology Annual Meeting in November 2022, we presented patient data, which at that time included the results for 24 patients treated in the ReSPECT-GBM trial. As of the date of this report, rhenium (186Re) obisbemeda given by CED in recurrent GBM patients was observed in the trial to be feasible and well tolerated. Across all subjects in the first eight cohorts (n=24), the median absorbed dose to the tumor volume increased as cohorts evaluated progressed, with patients receiving >100Gy absorbed dose showing significant survival benefit versus patients receiving <100Gy absorbed dose. Importantly, in a subset of patients where tumor coverage was greater than or equal to 75%, the median absorbed dose was 405 Gy (range 146-593). By contrast, given the protocol dose escalation design where early cohorts often had much lower doses, the absorbed doses were adequate for small tumors even with low doses. Small, absorbed doses to specific organs and whole body, are typically well-tolerated. Based on observed and reported patient protocol activity and all available adverse event (AE) data, rhenium (186Re) obisbemeda has been well-tolerated with AEs related to CED insertion that were limited and fully recovered. No AEs with an outcome of death, study discontinuation or study drug-related serious AEs have been reported. 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 rhenium (186Re) obisbemeda 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 24 subjects with recurrent GBM receiving a single administration of rhenium (186Re) obisbemeda, the median OS for all 24 patients as of November 2022 was 8.8 months, with four patients alive. In a subset of 13 patients receiving a presumed therapeutic absorbed radiation dose to the tumor (>100 Gy), the mean OS was 22.9 months, respectively, with seven of 13 patients alive. In contrast, in nine patients receiving a presumed sub-therapeutic absorbed radiation dose to the tumor (<100 Gy), the mean and median OS was 23.9 and 22.3 weeks, respectively. A Kaplan-Meier curve comparing patients with presumed therapeutic (>100 Gy) versus sub-therapeutic (<100 Gy) radiation dose to the tumor showed a statistically significant difference between the groups (p=.0003). It is hypothesized that targeted infusion of rhenium (186Re) obisbemeda into the tumor by CED, which exposure and potential toxicity and concentrates radiation to the tumor and surrounding region of interest. On January 18, 2023, we announced that the first patient has been dosed in the ReSPECT-GBM Phase 2b dose expansion clinical trial evaluating rhenium obisbemeda for the treatment of recurrent GBM. The Phase 2b trial is expected to enroll up to 31 total patients with small- to medium-sized tumors in approximately 24 months.

ReSPECT-LM Clinical Trial for Leptomeningeal Metastases (LM)

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%, or more, of people with late-stage cancer, or 110,000 people in the U.S. each year. It is highly lethal with an average one-year survival of just 7%. All solid cancers have the potential to spread to the central nervous system and leptomeninges resulting in LM.

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

Upon receiving acceptance of our Investigational New Drug application and Fast Track designation by the FDA for rhenium (186Re) obisbemeda for the treatment of LM, we initiated the trial and began screening patients for the ReSPECT-LM Phase 1 clinical trial in Q4 2021.

The ReSPECT-LM is a multi-center, sequential cohort, open-label, dose escalation study evaluating the safety, tolerability, and efficacy of a single-dose application of rhenium (186Re) obisbemeda administered through 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.

On March 31, 2022, we entered into a Sales Order (the "Sales Order") with Medidata Solutions, Inc. ("Medidata"), pursuant to which Medidata built a Synthetic Control Arm® (SCA) platform that facilitates the use of historical clinical data to incorporate into our Phase 2 clinical trial of rhenium (186Re) obisbemeda in GBM. The Sales Order had a term of six (6) months. Work under this Sales Order has been completed.

On September 19, 2022, we entered into a Cancer Research Grant Contract (the "CPRIT Contract"), effective as of August 31, 2022, with CPRIT, pursuant to which CPRIT will provide us a grant of up to $17.6 million (the "CPRIT Grant") over a three-year period to fund the continued development of rhenium (^{186}Re) obisbemeda for the treatment of patients with LM through Phase 2 of the ReSPECT LM clinical trial. The CPRIT Grant is subject to customary CPRIT funding conditions, including, but not limited to, a matching fund requirement (one dollar from us for every two dollars awarded by CPRIT), revenue sharing obligations upon

commercialization of rhenium (^{186}Re) obisbemeda based on specific dollar thresholds until CPRIT receives the aggregate amount of 400% of the proceeds awarded under the CPRIT Grant, and certain reporting requirements.

Interim results showed that treatment with rhenium (^{186}Re) obisbemeda decreased CSF tumor cell count/ml and was well tolerated by all four LM patients. rhenium (^{186}Re) obisbemeda was administered through a standard intraventricular catheter (Ommaya Reservoir), redistributed throughout the CSF, and was retained in the leptomeninges at least through day seven. All four patients have shown prompt and durable rhenium (^{186}Re) obisbemeda distribution throughout the subarachnoid space. A single dose of rhenium (^{186}Re) obisbemeda at 6.6 millicurie ("mCi") in 5.0 mL, in Cohort 1, achieved absorbed doses of 18.7 to 29.0 Gy to the ventricles and cranial subarachnoid spaces, respectively. Cohort 2 is in progress with a 13.2 mCi administered dose in 5ml and was also well tolerated. All four patients experienced a decreased CSF cell count ranging from 46% to 92%. Three patients remain alive**,** as the first patient in Cohort 1 has died, due to primary tumor progression. A single dose of rhenium (^{186}Re) obisbemeda was well-tolerated with limited AEs and no patients had definite treatment related AEs. Additionally, there were no AEs greater than Grade 1 that were even possibly related to treatment. Cohort 2 was completed on January 26, 2023 and Cohort 3 is expected to enroll in late February/early March 2023 after a protocol defined follow-up 28-day period. Besides continued dose escalation, repeated dosing will be explored.

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.

It is estimated that in 2022 there were approximately 25,050 new brain and other central nervous system cases diagnosed (1.3% of all cancers) and 18,280 deaths (3.0% of all cancer related deaths). The average annual age adjusted mortality rate (“AAAMR”) for children aged 0-14 for malignant brain (and other CNS) tumors is 0.71/100,000, making it the most common cause of death and cancer death in this age group. The 2021 World Health Organization Classification of CNS Tumors (“WHO CNS5”) classifies gliomas, glioneuronal tumors, and neuronal tumors into six different families: (1) adult-type diffuse gliomas; (2) pediatric-type diffuse low-grade gliomas; (3) pediatric-type diffuse high-grade gliomas (“HGG”); (4) circumscribed astrocytic gliomas; (5) glioneuronal and neuronal tumors; and (6) ependymomas.

Since the initial FDA feedback and receiving important adult GBM data and experience with rhenium (^{186}Re) obisbemeda and follow-up communications with the FDA, we plan to submit a pediatric brain tumor IND to investigate the use of rhenium (^{186}Re) obisbemeda in two pediatric brain cancers in early 2023.

Pediatric high-grade gliomas can be found almost anywhere within the CNS; however, they are most commonly found within the supratentorium. The highest incidence of supratentorial, high-grade gliomas in pediatrics appears to occur in children aged 15 to 19 years, with a median age of approximately nine years. Overall, pediatric high grade glioma confers a three-year progression free survival (“PFS”) of 11 ± 3% and three-year overall survival (“OS”) of 22% ±5%. One-year PFS is as low as 40% in recent trials. Ependymomas are slow-growing central nervous system tumors that involve the ventricular system. Diagnosis is based on MRI and biopsy and survival rate depends on tumor grade and how much of the tumor can be removed. Grade II pathology was associated with significantly improved OS compared to Grade III (anaplastic) pathology (five-year OS = 71 ± 5% vs. 57 ± 10%; p = 0.026). Gross total resection compared to subtotal resection was associated with significantly improved OS (five-year OS = 75 ± 5% vs. 54 ± 8%; p = 0.002).

Overall, pediatric HGG and ependymoma are extremely difficult-to-treat pediatric brain tumors, frequently aggressive, and in recurrent settings, carry an extremely poor prognosis.

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, ^{188}RNL-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 Technetium99m-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. ^{188}RNL-BAM is a preclinical investigational drug we intend to further develop and move into clinical trials. Specifically, in 2022 we transferred the ^{188}RNL-BAM technology from UT Health Science Center at San Antonio, and began planning to develop the drug product and complete early preclinical studies to support a future FDA IND submission. Our intended initial clinical target is liver

cancer which is the sixth most common and third deadliest cancer worldwide. It is a rare disease with increasing U.S. annual incidence (42,000) and deaths (30,000).

Licensing

On June 22, 2022, we announced a multi-year laboratory services agreement with Biocept, Inc. ("Biocept") to employ their cerebrospinal fluid ("CSF") assay, CNSide, in Plus Therapeutics' ReSPECT-LM Phase 1/2a dose-escalation trial of Rhenium-186 NanoLiposome for the treatment of patients with ("LM").

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 Heath 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 directly into the intra-arterial vascular system via commonly utilized and standard interventional vascular catheters and techniques that allow precise placement into the arterial blood vessels feeding tumors. Once injected, BAM technology provides a dual therapeutic delivery—blocking blood flow to the tumors by alginate microsphere tumor capillary embolization with simultaneous delivery of very high doses of cytotoxic compounds including radiation, such as nanoliposome encapsulated bi-functionally chelated Re-188, for an extended time. Weeks later, the delivered BAM are physiologically metabolized allowing excretion from the body. Rhenium-188 is an attraction and ideal therapeutic isotope for this application because of it's 16.9 hour half-life, 2.12MEV β-decay and ~3.8mm tissue path-length, and simultaneous 155Kev γ-decay that allow simultaneous SPECT/CT imaging with commonly available imaging equipment to easily and non-invasively monitor product administration, delivery and dosimetry absorbed dose evaluation.

We currently anticipate that we will initially focus on developing ^{188}RNL-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 ^{188}RNL 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 five-year overall survival of only 20%. We estimate that 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 ^{188}RNL-BAM technology incorporates Rhenium-188, or ^{188}Re, a unique isotope for radiotherapeutic embolization owing to its emission of a high energy [2.12Mev] electron (beta particle, 16.9 hour half-life with a 3.8mm decay path length. ^{188}Re also emits 155kev 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 ^{188}Re through the kidneys, which may minimize bone marrow toxicity.

The transaction terms include an upfront payment in cash. We are also required to pay development and sales milestone payments, if achieved, and a tiered single-digit royalty on U.S. and European sales. In addition, we may be obligated to pay an annual maintenance fee beginning in 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 $0.4 million in cash and $0.3 million in our voting stock. The transaction terms also included success-based milestone and royalty payments contingent on key clinical, regulatory and sales milestones, as well as the requirement to pay 15% of any non-dilutive monetary awards or grants received from external agencies to support product development of the nanoliposome encapsulated BMEDA-chelated radioisotope, which includes grants from the CPRIT.

The licensed NanoTx portfolio benefits from proprietary nanoliposome-encapsulated technology to encapsulate radionuclides allowing direct local delivery for several cancer targets.

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 Kolitz 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 $3 million award from NIH/NCI which is expected to financially support the continued clinical development of rhenium (^{186}Re) obisbemeda 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 manufactures to support clinical trials and commercial release. Upon approval of our drug candidates, we expect our manufacturing capabilities to 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 is designed to enable 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") is entitled to 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 rhenium (186Re) obisbemeda 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 rhenium (186Re) obisbemeda may come from a single or combination therapy in the future.

Recurrent Glioblastoma

EnGeneIC, Berg, Istari, AstraZeneca, Novartis, PharmAbcine, Kairos, Midatech, Oncovir, Infuseon, Astellas, NanoPharmaceuticals, Erasca, OX2, Crimson BioPharm, TMUNITY, Pfizer, Arcus, Photolitec, Samus, DNAtrix, ImmVira, BerGenBio, Boston Scientific, BeiGene, GSK, Bristol Myers Squibb, Lilly, Sumitomo, QED, Chimerix, Accenda, Oblato, VBI, INIGHTEC, Sonalasense, VBL, Medicenna, Mimiva, Carthera, Gilead, CNS Pharmaceuticals, VAXIMM, Incyte, Celularity, Medicinova, Karyopharm, Nerviano Medical Sciences, Merck, Telix, Neonc, Nuvation Bio, Aadi, ERC, Kazia, Xoft, Basilea, Vigo, Biohaven, Bayer, Kintara, and others have reported drug development programs at various clinical stages for recurrent GBM.

Leptomeningeal Metastases

Angiochem, Y-mAbs, Roche, Bristol Myers Squibb, Merck, Kazia, AstraZeneca, Pfizer, Memorial Sloan Kettering, University of Virginia, Wake Forest University, University of Alabama Birmingham, and others have reported drug development programs at various clinical stages for LM.

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 PBC.

Competition for ^{188}RNL-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.

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. rhenium (186Re) obisbemeda and ^{188}RNL 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 rhenium (186Re) obisbemeda. This has the potential to extend patent coverage for this product for up to another five years. The '160 Patent covers rhenium (186Re) obisbemeda and ^{188}RNL and their method of manufacture. 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.

^{188}RNL is also covered by U.S. Patent Appl. No. 17/611,929 titled Radiotherapeutic Microspheres, to which we have a license. This application is directed to a method of producing liposome containing alginate microspheres. This application was filed on November 17, 2021, and any patent granted from or claiming priority to it is expected to expire in May 2040, not including any patent term adjustment or patent term extension. The patent family also contains applications in Canada, Israel, India, Japan, Mexico, Saudi Arabia, Thailand, South Africa, Vietnam, Philippines, China, European Patent Office, Brazil, Singapore, Indonesia, Malaysia, Australia, and New Zealand.

^{188}RNL is also covered by PCT/US2022/018992 titled Loading Alginate Microspheres, to which we have a license. This application is directed to a method for post-manufacture loading of a liposome-containing hydrogel microsphere. This application was filed March 4, 2022, and any patent granted from or claiming priority to it is expected to expire in March 2042.

We co-own and license PCT Application No. PCT/US2021/059969 and U.S. Patent Appl. No. 17/746,853, titled Radiolabeled Liposomes and Methods of Use Thereof, which are directed to methods of treating cancer comprising administering 186Re and 188Re nanoliposomes via CED. These applications were filed on November 18, 2021 and May 17, 2022, respectively, and any patents issued from or claiming priority to them are expected to expire in November 2041, not including any patent term adjustment or patent term extension.

We co-own and license PCT Application No. PCT/US2023/11564, titled Radiolabeled Liposomes and Methods of Use for Treating Leptomeningeal Metastases, which is directed to methods of treating Leptomeningeal Metastases comprising administering ^{186}Re and/or ^{188}Re nanoliposomes via an intraventricular reservoir. This application was filed on January 25, 2023, and any patent issued claiming priority to it 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. Manufactures 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 consider 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 six 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 aged 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 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, 2022, we had 17 full-time employees. Of these full-time employees, ten 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.

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 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, 2022, we incurred net losses of $20.3 million and our net cash used in operating activities was $13.0 million. As of December 31, 2022, our accumulated deficit was $467.2 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 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. 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 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.

On May 24, 2022, we received written notice (the "Notification Letter") from the Listings Qualifications Department of The Nasdaq Stock Market LLC ("Nasdaq") that because the closing bid price for our common stock has fallen below $1.00 per share for 30 consecutive business days, we no longer complied with the minimum bid price requirement pursuant to Nasdaq Listing Rule 5550(a)(2) (the "Minimum Bid Requirement"). Nasdaq's notice had no immediate effect on the listing or trading of our common stock. The Notification Letter stated that we had 180 days, or until November 21, 2022, to demonstrate our compliance with the Minimum Bid Requirement. On November 22, 2022, we received a second letter from Nasdaq advising that we had been granted an additional 180 calendar days, or to May 22, 2023, to regain compliance with the Minimum Bid Requirement, in accordance with Nasdaq Listing Rule 5810(c)(3)(A).

We intend to continue to actively monitor the closing bid price of our common stock and will evaluate available options to regain compliance with the Minimum Bid Requirement. Specifically, we have confirmed to Nasdaq that, if necessary, we will implement a reverse stock split of our outstanding common stock (if approved by our stockholders) to attempt to regain compliance. If we do not regain compliance within the additional compliance period, Nasdaq will provide notice that our common stock will be subject to delisting. We would then be entitled to appeal that determination to a Nasdaq hearings panel. There can be no assurance that we will regain compliance with the Minimum Bid Requirement during the 180-day additional compliance period or maintain compliance with the other Nasdaq listing requirements.

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 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.

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.

On September 9, 2022, we entered into an Equity Distribution Agreement (the "September 2022 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, depending on market demand, with Canaccord acting as an agent for sales. Sales of our common stock 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.

On August 2, 2022, we entered into a purchase agreement (the "2022 Purchase Agreement") and registration rights agreement pursuant to which Lincoln Park Capital Fund ("Lincoln Park") committed to purchase up to $50.0 million shares of our common stock. Under the terms and subject to the conditions of the 2022 Purchase Agreement, we have the right, but not the obligation, to sell to Lincoln Park, and Lincoln Park is obligated to purchase up to $50.0 million shares of our common stock, provided that we cannot sell more than 57.5 million shares pursuant to the 2022 Purchase Agreement. Sales of common stock by us are subject to certain limitations, and can occur from time to time, at our sole discretion, over the 36-month period commencing on August 17, 2022, subject to the satisfaction of certain conditions. As consideration for Lincoln Park's irrevocable commitment to purchase shares of our common stock upon the terms of and subject to satisfaction of the conditions set forth in the Purchase Agreement, we paid $0.1 million in cash as an Initial Commitment Fee and issued 492,698 Commitment Shares to Lincoln Park in consideration for its commitment to purchase shares of our common stock at our direction under the Purchase Agreement.

On August 17, 2022, a registration statement was declared effective covering the resale of up to 9,500,000 shares of our common stock comprised of (i) the 492,698 Commitment Shares, and (ii) up to 9,007,302 shares that we have reserved for issuance and

sale to Lincoln Park under the Purchase Agreement. We cannot sell more shares under the 2022 Purchase Agreement without registering additional shares.

Even with the arrangements described above, we will need to complete additional financing transactions in order to continue operations. These arrangements may also not be sufficient in the near-term. Given, among other things, the current status of the capital markets and our recent stock price performance, the September 2022 Distribution Agreement and the 2022 Purchase Agreement and other financing strategies we may pursue may not be sufficient to fund our operations in the near term. There can be no assurances that we will be able to secure additional financing, or if available, that it will be sufficient to meet our needs or be on favorable terms. Additionally, our cost of capital will depend upon numerous factors including, but not limited to, the strength of the financial markets, global market conditions, including inflationary pressures, interest rate fluctuations, our recovery and financial performance, the recovery and performance of our industry in general and the size, scope and timing of our financial needs. If we are unable to access current financings or secure future financings, including for any of the foregoing reasons, it will have a negative impact on our cash flows and our ability to meet our financial obligations. 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 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, 2022, the outstanding principal balance of the Term Loan was $2.4 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, 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 global markets have experienced significant volatility and a continued 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. We have undergone "ownership changes" as a result of shifts in stock ownership in the past, which significantly limited our ability to use net operating loss carryforwards and other pre-change tax attributes. Any additional ownership change within the definition of Section 382 would further limit our ability to use net operating loss carryforwards and other 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 rhenium (186Re) obisbemeda and ^{188}RNL-BAM and any failure to do so could significantly harm our business and prospects.

Our ability to successfully develop and commercialize rhenium (186Re) obisbemeda and ^{188}RNL-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 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 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 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 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, rhenium (186Re) obisbemeda. Under the license agreement with NanoTx, we are required to use commercial reasonable efforts to develop the rhenium (186Re) obisbemeda 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 (^{188}RNL-BAM). Under the license agreement with UT Health Science at San Antonio, we are required to use commercial reasonable efforts to develop the ^{188}RNL-BAM product candidate acquired under the license agreement. Further, we are subject to future milestone, earn-out and other payments to UT Heath 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 Heath 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.

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 rhenium (186Re) obisbemeda and ^{188}RNL-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.

Reliance on government funding for our programs may impose requirements that limit our ability to take certain actions, and subject it to potential financial penalties, which could materially and adversely affect its business, financial condition and results of operations.

A significant portion of our funding will come from grants received from CPRIT. The CPRIT Grant includes provisions that reflect the government's substantial rights and remedies, many of which are not typically found in commercial contracts, including powers of the government to potentially require repayment of all or a portion of the grant award proceeds, in certain cases with interest, in the event we violate certain covenants pertaining to various matters that include any potential relocation outside of the State of Texas. After the CPRIT Grant ends, we are not permitted to retain any unused grant award proceeds without CPRIT's approval, but our obligation to pay CPRIT sales-based royalty, if and when commercialization is achieved, and other obligations, including our obligation to repay the disbursed grant proceeds under certain circumstances, to maintain certain records and documentation, to notify CPRIT of certain unexpected adverse events and our obligation to use reasonable efforts to ensure that any new or expanded preclinical testing, clinical trials, commercialization or manufacturing related to any aspect to our CPRIT project take place in Texas, survive the termination of the agreement.

Our award from CPRIT requires us to pay CPRIT a portion of our revenues from sales of certain products by us, or received from our licensees or sublicensees, at tiered percentages of revenue in the low- to mid-single digits until the aggregate amount of such payments equals 400% of the grant award proceeds, and thereafter at a rate of 0.5% for as long as we maintain government exclusivity, subject to our right, under certain circumstances, to make a one-time payment in a specified amount to CPRIT to terminate such payment obligations. In addition, the grant contract also contains a provision that provides for repayment to CPRIT of some amount not to exceed the full amount of the grant proceeds under certain specified circumstances involving relocation of our principal place of business outside Texas.

The CPRIT Grant requires us, as a Texas-based company, to meet certain criteria, including among other things, that we maintain our headquarters in Texas and use certain vendors, consultants and employees that are located in Texas. If we fail to maintain compliance with any such requirements that may apply to us now or in the future, we may be subject to potential liability and to termination of our contracts, and potentially full repayment of the CPRIT Grant.

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;
- 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 we engage are not able to successfully perform, 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. 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.

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.

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. 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.

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 rhenium (186Re) obisbemeda for the treatment of patients with GBM. In November 2021, the FDA granted Fast Track designation to rhenium (186Re) obisbemeda for the treatment of patients with LM.

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, 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.

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.

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, 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. The loss of services of any of our personnel, including Dr. Hedrick, particularly for an extended period, 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, rhenium (186Re) obisbemeda and ^{188}RNL-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 went into effect on January 1, 2023. 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 rhenium (186Re) obisbemeda and ^{188}RNL-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 rhenium (186Re) obisbemeda or ^{188}RNL-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 rhenium (186Re) obisbemeda or ^{188} RNL-BAM;
- the active pharmaceutical ingredient ("API") used in rhenium (186Re) obisbemeda, 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 Unites 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 to Lincoln Park and the sale of the shares of common stock acquired by Lincoln Park and the sale 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 August 2, 2022, we entered into the 2022 Purchase Agreement with Lincoln Park, pursuant to which Lincoln Park committed to purchase up to $50.0 million (the "Commitment Amount") of our common stock, subject to certain limitations. As consideration for Lincoln Park's irrevocable commitment to purchase shares of our common stock upon the terms of and subject to satisfaction of the conditions set forth in the 2022 Purchase Agreement, upon execution of the 2022 Purchase Agreement, we agreed to pay Lincoln Park an initial commitment fee equal to 1.5% of the Commitment Amount. The initial commitment fee was paid upon execution of the 2022 Purchase Agreement through the issuance of 492,698 shares of common stock and $0.1 million in cash. An additional commitment fee equal to 2.5% of the remainder of the Commitment Amount will be paid if and when we sell over $25.0 million of our common stock under the 2022 Purchase Agreement. The additional commitment fee may be paid in cash, common stock, or a combination of cash and common stock.

The remaining shares of our common stock that may be issued under the 2022 Purchase Agreement may be sold by us to Lincoln Park at our discretion from time to time over a 36-month period commencing August 17, 2022, subject to satisfaction of certain conditions. The purchase price for the shares that we may sell to Lincoln Park under the 2022 Purchase Agreement will fluctuate based on the price of our common stock. Depending on market liquidity at the time, sales of such shares may cause the trading price of our common stock to fall.

If and when we do sell shares to Lincoln Park, after Lincoln Park has acquired the shares, Lincoln Park may resell all or some of those shares at any time or from time to time in its discretion. Therefore, sales to Lincoln Park by us could result in substantial dilution to the interests of other holders of our common stock. Additionally, the sale of a substantial number of shares of our common stock to Lincoln Park, or the anticipation of such sales, could make it more difficult for us to sell equity or equity-related securities in the future at a time and at a price that we might otherwise wish to effect sale.

On September 9, 2022, we entered into the September 2022 Distribution Agreement with 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, 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. Sales pursuant to the September 2022 Distribution Agreement, if any, could result in substantial dilution to the interest of other holders of our common stock. Depending on market liquidity at the time, sales of such shares may cause the trading price of our common stock to fall.

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

As of December 31, 2022, we had 33,601,373 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;
- 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. 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.

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

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 one lease agreement for our San Antonio, Texas locations. The lease for this property 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, 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 alleged false representations were made to Lorem regarding the manufacturing facility in the United Kingdom (the “UK Facility”) that Lorem purchased from us under the Asset and Equity Purchase Agreement, dated March 29, 2019, between us and Lorem (the “Lorem Agreement”). Lorem also claimed 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 claimed entitlement to at least $6,000,000 in compensatory damages and operational costs and expenses (collectively,

the “Lorem Claim”). On December 9, 2022, we entered into a settlement agreement (the “Settlement Agreement”) with Lorem to settle the Lorem Claim. Under the terms of the Settlement Agreement, we made a payment to Lorem, and Lorem moved to dismiss the lawsuit with prejudice. The Settlement Agreement released us from all claims made by Lorem. The parties to the Settlement Agreement recognized that it did not constitute an admission of liability, wrongdoing, or any matter of fact or law. As of December 31, 2022, we accrued the settlement amount, as well as the accounts that we have confirmed to be recoverable under our insurance claims on the matter. The net amount of $1.4 million that was not recoverable under our insurance has been reflected as an expense in the year ended December 31, 2022. The full settlement amount was paid in January 2023. All legal costs incurred related to the Lorem Claim were expensed. The Settlement was conditioned on the customary terms contained in the Settlement Agreement and was approved by the Court and the case was dismissed on January 17, 2023.

Refer to Note 7 of the 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 17, 2023, we had approximately 16 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, 2022 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	Weighted-average exercise price of outstanding options and rights	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column(a))
	(a)	(b)	(c)
Equity compensation plans not approved by security holders (1)	160,095	$ 13.42	90,389
Equity compensation plans approved by security holders (2)	1,014,921	$ 3.14	2,635,717
Total	1,175,016	$ 4.54	2,726,106

(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 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

We adopted the 2015 Plan 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 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 our capital structure or distributions as we deem appropriate, including modification of performance goals, performance award formulas, and performance periods. As of December 31, 2022, there were 90,389 shares of common stock remaining and available for issuance under the 2015 Plan.

On June 16, 2020, our stockholders approved our 2020 Stock Incentive Plan (the "2020 Plan"), which replaced the Company's 2014 Equity Incentive Plan. The 2020 Plan, as amended, provides for the issuance of up to 3,550,000 shares of common stock, plus the number of shares available for issuance is increased to the extent that awards granted under the 2020 Plan and the 2014 Equity Incentive Plan are forfeited or expire (except as otherwise provided in the 2020 Plan).

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 us 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.

Share Repurchase Program

On August 15, 2022, we announced that our Board of Directors had approved a share repurchase program pursuant to which we were authorized to repurchase up to $2.0 million of our outstanding common stock. The timing and amount of any shares repurchased will be determined based on our evaluation of market conditions and other factors. Repurchases may be made from time to time on the open market over the course of 12 months. We are not obligated to acquire any shares and the program may be discontinued or suspended at any time. Through the date of filing of this Form 10-K, we have not repurchased any of its common stock under this share repurchase program.

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 targeted radiotherapeutics with advanced platform technologies for central nervous system ("CNS") 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 extend retention times such that the clearance of the isotope occurs after significant and essentially complete 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 four to six 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 locoregional delivery and, thereby, efficacy, we hope to reduce the radiation toxicity for patients, improving their quality of life 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}Re) obisbemeda (formerly, "^{186}RNL"), is designed specifically to CNS cancers including recurrent glioblastoma ("GBM"), leptomeningeal metastases ("LM"), and pediatric brain cancers ("PBC") by direct localized delivery utilizing approved standard-of-care tissue access such as with convection-enhanced delivery ("CED") and intraventricular brain(Ommaya reservoir) catheters. Our recently acquired radiotherapeutic candidate, Rhenium-188 NanoLiposome Biodegradable Alginate Microsphere ("^{188}RNL-BAM") is designed to treat many solid organ cancers including primary and secondary liver cancers by intra-arterial injection.

Our headquarters and manufacturing facilities are 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.

In addition to its headquarters in Austin, we have an established, GMP-validated research and development and manufacturing facility in San Antonio, Texas, tailored to produce cGMP rhenium (186Re) obisbemeda. We have built a robust supply chain through strategic partnerships that enable the development, manufacturing and future potential commercialization of our products. Our current supply chain and key partners are positioned to supply cGMP rhenium (186Re) obisbemeda for ongoing and planned Phase 2 and Phase 3 clinical trials in patients with GBM, LM and PBC..

Pipeline

Our most advanced investigational drug, rhenium (^{186}Re) obisbemeda, is a patented radiotherapy potentially useful for patients with CNS and other cancers. Preclinical study data describing the use of rhenium (^{186}Re) obisbemeda for several cancer targets have been published in peer-reviewed journals and reported at a variety of medical society peer-reviewed meetings. Besides GBM, LM and PBC, rhenium (^{186}Re) obisbemeda has been reported to have potential applications for head and neck cancer, ovarian cancer, breast cancer and peritoneal metastases.

The Rhenium (186Re) Obisbemeda 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 is expected to provide financial support for the continued clinical development of rhenium (^{186}Re) obisbemeda for recurrent GBM through the completion of

a Phase 2 clinical trial, including enrollment of up to 55 patients. As of February 23, 2023, 26 patients have been treated in the Phase 1 clinical trial and the Phase 2 clinical trial has been initiated with the first patient treated. In addition, we anticipate obtaining FDA IND approval for the ReSPECT-PBC clinical trial for PBC in early 2023.

On August 29, 2022, we announced feedback from a Type C meeting with the FDA regarding Chemistry, Manufacturing and Controls ("CMC") practices. The meeting focused on our Current Good Manufacturing Practice ("cGMP") clinical and commercial manufacturing process for our lead investigational targeted radiotherapeutic, BMEDA-chelated Rhenium (186Re) Obisbemeda, for recurrent GBM.

The FDA indicated agreement with our proposed application of cGMP guidance for radiotherapeutics, small molecule drug products and liposome drug products for our novel rhenium (^{186}Re) obisbemeda in support of ongoing and future GBM clinical trials, manufacturing scale up, and commercialization. Alignment with the FDA includes support of our proposed controls and release strategy for new drug substance and new drug product. Because this product is identical for recurrent GBM and LM adult development and pediatric brain tumors, we believe this FDA alignment and feedback will apply to rhenium (^{186}Re) obisbemeda used in other clinical development programs, including LM and PBC.

Rhenium (^{186}Re) obisbemeda *versus External Beam Radiation Therapy for Recurrent GBM*

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

- The rhenium (^{186}Re) obisbemeda radiation dose delivered to patients may be up to 20 times greater than what is possible with commonly used external beam radiation therapy ("EBRT"), which, unlike EBRT and proton beam devices, spares normal tissue and the brain from radiation exposure.
- Rhenium (^{186}Re) obisbemeda can be visualized in real-time during administration, possibly giving clinicians better control of radiation dosing, distribution and retention.
- Rhenium (^{186}Re) obisbemeda potentially more effectively treats a bulk tumor and microscopic disease that has already invaded healthy tissue.
- Rhenium (^{186}Re) obisbemeda is infused directly into the targeted tumor by CED catheter insertion using MRI guided software to avoid critical patient neurological structures and neural pathways and also bypasses the blood brain barrier, which delivers the therapeutic product where it is needed. Importantly, it 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.
- Rhenium (^{186}Re) obisbemeda 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 five days a week for approximately four to six weeks.

ReSPECT-GBM Trial for Recurrent GBM

Recurrent GBM is the most common, complex, and aggressive primary brain cancer in adults. In the U.S., there are more than 13,000 GBM cases diagnosed and approximately 10,000 patients succumb to the disease each year. The average length of overall survival ("OS") for GBM patients is eight months, with a one-year survival rate of 40.8% and a five-year survival rate of only 6.8% and these estimates varies and are lower in some publications. GBM routinely presents with headaches, seizures, vision changes and other significant neurological complications, with a significant compromise in quality of life. Despite the best available medical treatments, the disease remains incurable. Even after efforts to manage the presenting signs and symptoms and completely resect the initial brain tumor, some microscopic disease almost always remains and tumor regrowth occurs within months. Approximately 90% or more of patients with primary GBM experience tumor recurrence. Complete surgical removal of GBM is usually not possible and GBM is often resistant or quickly develops resistance to most available current and investigational 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, and these more recent approvals have not improved GBM patients OS over past decades, and a significant unmet medical need persists.

For recurrent GBM, there are few currently approved treatments, which 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 has temporary efficacy in many malignancies including GBM, typically at absorbed, fractionated radiation dose of ~30 Gray in GBM, this maximum possible administered dose is always limited by toxicity to the normal tissues surrounding the malignancy and because EBRT requires fractionation to manage toxicity and maximum EBRT limits are typically reached before long-term efficacy reached. Because of this limitation EBRT cannot provide a cure or long term control of

GBM and GBM always recurs within months after EBRT. In contrast, locally delivered and targeted radiopharmaceuticals that precisely deliver radiation in the form of beta particles such as Iodine-131 for thyroid cancer, are known to be safe and effective and minimize exposure to normal cells and tissues especially with optimal targeting and avoidance of normal tissue. The locally delivered rhenium (^{186}Re) obisbemeda is designed for and provides patient tolerability and safety. Though no head-to-head trial with chemo, immune, EBRT or systemic radiopharmaceutical products have been conducted, patient tolerability and safety considerations have been reported as expected.

Interim results from our ongoing Phase 1/2a ReSPECT-GBM trial (ClinicalTrials.gov NCT01906385) show that the beta particle energy from our lead investigational drug rhenium (^{186}Re) obisbemeda has provided preliminary positive data and utility in treating GBM and potential other malignancies. More specifically, the preliminary data from our Phase 1/2a ReSPECT-GBM trial suggests 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 tissue in humans, without significant or dose limiting toxicities and with what we believe has the capability to go higher if required. In comparison, current EBRT protocols for recurrent GBM typically recommend a total maximum radiation dose of about ~30-35 Gray.

In September 2020, the FDA granted both Orphan Drug designation and Fast Track designations to rhenium (^{186}Re) obisbemeda for the treatment of patients with GBM. In November 2021, the FDA granted Fast Track designation for rhenium (^{186}Re) obisbemeda for the treatment of LM.

Rhenium (^{186}Re) obisbemeda is under clinical investigation in a multicenter, sequential cohort, open-label, volume and dose escalation study of the safety, tolerability, and distribution of rhenium (186Re) obisbemeda given by CED catheters to patients with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment (NCT01906385). The study uses a standard, modified 3x3 Fibonacci dose escalation, followed by a planned Phase 2 expansion trial at the maximum tolerated dose (“MTD”) / maximum feasible dose (“MFD”) or non-dose limiting toxicity (“DLT”) if MTD is not reached, to determine efficacy. The trial is funded through Phase 2 in large part by a NIH/NCI grant. These investigations have not reached DLT or MTD/MFD and the study is in its eighth dosing administration cohort. Due to the observation of a preliminary efficacy signal, we have initiated in parallel a Phase 2, non-DLT dose trial pursuant to the currently funded NIH/NCI Grant. This trial will begin at the current non-DLT rhenium (186Re) obisbemeda dose and will expand exploring higher radiation doses in larger volumes to treat larger tumors. Additionally, two or more rhenium (186Re) obisbemeda administrations, if indicated, will be evaluated, and reviewed with the FDA, as well as expanded safety, imaging and efficacy data to support a planned future registrational trial. This in turn will provide a path to a registration trial.

On September 6, 2022, we announced a summary of our Type C clinical meeting with the FDA that focused on the ReSPECT-GBM trial. The FDA agreed with us that the ReSPECT-GBM clinical trial should proceed to the planned Phase 2. The key focus areas of clinical investigation of the Phase 2 trial will be 1) further dose exploration, including both increased dosing and multiple doses, and 2) collecting additional safety and efficacy data to inform the design of a future registrational trial. Because no DLT administered doses were observed, the FDA and we also agreed to continue to dose cohort eight. There was further agreement with the FDA that in a planned future registrational trial, overall survival should be used as the primary endpoint. We agreed with the FDA to hold future meeting(s) to consider the use of external data to augment the use of a control arm in the registrational trial.

At the European Society for Medical Oncology Congress, held September 9 to 13, 2022, we presented updated data from the ReSPECT-GBM trial, which evaluated 23 adult patients with recurrent GBM across eight cohorts of increasing dose and treated over a seven-year period. Key findings include:

- No DLTs have been observed and the procedure was very well tolerated with a strong safety profile. Minimal systemic radiation has been observed and the majority of adverse events have been mild or moderate and considered causally unrelated to rhenium (186Re) obisbemeda.
- Improved median overall survival (“OS”) rates correlated with the absorbed radiation tumor dose. When patients were stratified based on receipt of either a therapeutic or a subtherapeutic absorbed dose of radiation to the tumor, a statistically significant improvement in survival was observed. Specifically, patients receiving a therapeutic absorbed radiation dose (>100 Gray) had a median OS of 22.9 months (95% CI of 8.8-42.3) compared to those receiving a subtherapeutic absorbed radiation dose (<100 Gray) whose median OS was 5.6 months (95% CI of 1.6-9.4). Currently, three patients remain alive, all in the therapeutic group.
- Feasibility to deliver up to at least 20 times more radiation to the tumor than the standard of care, EBRT. A maximum of 32.2 mCi in 12.3 mL of volume has been delivered in and near the tumors, and a maximum average absorbed dose of radiation of 740 Gray was successfully administered in a single procedure.
- Average absorbed radiation dose to the tumor increased in latter dosing cohorts with greater administered doses of rhenium (186Re) obisbemeda β-particle radiation, larger drug CED infusate volumes, more catheters used (up to four versus one),

and higher convection flow rates. In cohorts five and later, 82% of patients received a therapeutic radiation dose of >100Gray.

- Single-photon emission computerized tomography and (SPECT)/CT scanning were used during treatment to compute tumor coverage and dosimetry. Post treatment imaging analyses, including MRI, relative cerebral blood volume (rCBV) analysis and treatment response assessment maps (TRAMs) correlated with a positive tumor response and confirmed the presence of pseudoprogression in patients with positive tumor responses.

At the Society for Neuro-Oncology Annual Meeting in November 2022, we presented patient data, which at that time included the results for 24 patients treated in the ReSPECT-GBM trial. As of the date of this report, rhenium (186Re) obisbemeda given by CED in recurrent GBM patients was observed in the trial to be feasible and well tolerated. Across all subjects in the first eight cohorts (n=24), the median absorbed dose to the tumor volume increased as cohorts evaluated progressed, with patients receiving >100Gy absorbed dose showing significant survival benefit versus patients receiving <100Gy absorbed dose. Importantly, in a subset of patients where tumor coverage was greater than or equal to 75%, the median absorbed dose was 405 Gy (range 146-593). By contrast, given the protocol dose escalation design where early cohorts often had much lower doses, the absorbed doses were adequate for small tumors even with low doses. Small, absorbed doses to specific organs and whole body, are typically well-tolerated. Based on observed and reported patient protocol activity and all available adverse event (AE) data, rhenium (186Re) obisbemeda has been well-tolerated with AEs related to CED insertion that were limited and fully recovered. No AEs with an outcome of death, study discontinuation or study drug-related serious AEs have been reported. 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 rhenium (186Re) obisbemeda 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 24 subjects with recurrent GBM receiving a single administration of rhenium (186Re) obisbemeda, the median OS for all 24 patients as of November 2022 was 8.8 months, with four patients alive. In a subset of 13 patients receiving a presumed therapeutic absorbed radiation dose to the tumor (>100 Gy), the mean OS was 22.9 months, respectively, with seven of 13 patients alive. In contrast, in nine patients receiving a presumed sub-therapeutic absorbed radiation dose to the tumor (<100 Gy), the mean and median OS was 23.9 and 22.3 weeks, respectively. A Kaplan-Meier curve comparing patients with presumed therapeutic (>100 Gy) versus sub-therapeutic (<100 Gy) radiation dose to the tumor showed a statistically significant difference between the groups (p=.0003). It is hypothesized that targeted infusion of rhenium (186Re) obisbemeda into the tumor by CED, which exposure and potential toxicity and concentrates radiation to the tumor and surrounding region of interest. On January 18, 2023, we announced that the first patient has been dosed in the ReSPECT-GBM Phase 2b dose expansion clinical trial evaluating rhenium obisbemeda for the treatment of recurrent GBM. The Phase 2b trial is expected to enroll up to 31 total patients with small- to medium-sized tumors in approximately 24 months.

ReSPECT-LM Clinical Trial for Leptomeningeal Metastases (LM)

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%, or more, of people with late-stage cancer, or 110,000 people in the U.S. each year. It is highly lethal with an average one-year survival of just 7%. All solid cancers have the potential to spread to the central nervous system and leptomeninges resulting in LM.

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

Upon receiving acceptance of our Investigational New Drug application and Fast Track designation by the FDA for rhenium (186Re) obisbemeda for the treatment of LM, we initiated the trial and began screening patients for the ReSPECT-LM Phase 1 clinical trial in Q4 2021.

The ReSPECT-LM is a multi-center, sequential cohort, open-label, dose escalation study evaluating the safety, tolerability, and efficacy of a single-dose application of rhenium (186Re) obisbemeda administered through 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.

On March 31, 2022, we entered into a Sales Order (the “Sales Order”) with Medidata Solutions, Inc. (“Medidata”), pursuant to which Medidata built a Synthetic Control Arm® (SCA) platform that facilitates the use of historical clinical data to incorporate into our Phase 2 clinical trial of rhenium (186Re) obisbemeda in GBM. The Sales Order had a term of six (6) months. Work under this Sales Order has been completed.

On September 19, 2022, we entered into a Cancer Research Grant Contract (the "CPRIT Contract"), effective as of August 31, 2022, with CPRIT, pursuant to which CPRIT will provide us a grant of up to $17.6 million (the "CPRIT Grant") over a three-year period to fund the continued development of rhenium (^{186}Re) obisbemeda for the treatment of patients with LM through Phase 2 of the ReSPECT LM clinical trial. The CPRIT Grant is subject to customary CPRIT funding conditions, including, but not limited to, a matching fund requirement (one dollar from us for every two dollars awarded by CPRIT), revenue sharing obligations upon commercialization of rhenium (^{186}Re) obisbemeda based on specific dollar thresholds until CPRIT receives the aggregate amount of 400% of the proceeds awarded under the CPRIT Grant, and certain reporting requirements.

Interim results showed that treatment with rhenium (^{186}Re) obisbemeda decreased CSF tumor cell count/ml and was well tolerated by all four LM patients. rhenium (^{186}Re) obisbemeda was administered through a standard intraventricular catheter (Ommaya Reservoir), redistributed throughout the CSF, and was retained in the leptomeninges at least through day seven. All four patients have shown prompt and durable rhenium (^{186}Re) obisbemeda distribution throughout the subarachnoid space. A single dose of rhenium (^{186}Re) obisbemeda at 6.6 millicurie ("mCi") in 5.0 mL, in Cohort 1, achieved absorbed doses of 18.7 to 29.0 Gy to the ventricles and cranial subarachnoid spaces, respectively. Cohort 2 is in progress with a 13.2 mCi administered dose in 5ml and was also well tolerated. All four patients experienced a decreased CSF cell count ranging from 46% to 92%. Three patients remain alive**,** as the first patient in Cohort 1 has died, due to primary tumor progression. A single dose of rhenium (^{186}Re) obisbemeda was well-tolerated with limited AEs and no patients had definite treatment related AEs. Additionally, there were no AEs greater than Grade 1 that were even possibly related to treatment. Cohort 2 was completed on January 26, 2023 and Cohort 3 is expected to enroll in late February/early March 2023 after a protocol defined follow-up 28-day period. Besides continued dose escalation, repeated dosing will be explored.

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.

It is estimated that in 2022 there were approximately 25,050 new brain and other central nervous system cases diagnosed (1.3% of all cancers) and 18,280 deaths (3.0% of all cancer related deaths). The average annual age adjusted mortality rate ("AAAMR") for children aged 0-14 for malignant brain (and other CNS) tumors is 0.71/100,000, making it the most common cause of death and cancer death in this age group. The 2021 World Health Organization Classification of CNS Tumors ("WHO CNS5") classifies gliomas, glioneuronal tumors, and neuronal tumors into six different families: (1) adult-type diffuse gliomas; (2) pediatric-type diffuse low-grade gliomas; (3) pediatric-type diffuse high-grade gliomas ("HGG"); (4) circumscribed astrocytic gliomas; (5) glioneuronal and neuronal tumors; and (6) ependymomas.

Since the initial FDA feedback and receiving important adult GBM data and experience with rhenium (^{186}Re) obisbemeda and follow-up communications with the FDA, we plan to submit a pediatric brain tumor IND to investigate the use of rhenium (^{186}Re) obisbemeda in two pediatric brain cancers in early 2023.

Pediatric high-grade gliomas can be found almost anywhere within the CNS; however, they are most commonly found within the supratentorium. The highest incidence of supratentorial, high-grade gliomas in pediatrics appears to occur in children aged 15 to 19 years, with a median age of approximately nine years. Overall, pediatric high grade glioma confers a three-year progression free survival ("PFS") of 11 ± 3% and three-year overall survival ("OS") of 22% ±5%. One-year PFS is as low as 40% in recent trials. Ependymomas are slow-growing central nervous system tumors that involve the ventricular system. Diagnosis is based on MRI and biopsy and survival rate depends on tumor grade and how much of the tumor can be removed. Grade II pathology was associated with significantly improved OS compared to Grade III (anaplastic) pathology (five-year OS = 71 ± 5% vs. 57 ± 10%; p = 0.026). Gross total resection compared to subtotal resection was associated with significantly improved OS (five-year OS = 75 ± 5% vs. 54 ± 8%; p = 0.002).

Overall, pediatric HGG and ependymoma are extremely difficult-to-treat pediatric brain tumors, frequently aggressive, and in recurrent settings, carry an extremely poor prognosis.

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, ^{188}RNL-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 Technetium99m-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. ^{188}RNL-BAM is a preclinical investigational drug we intend to further develop and move into clinical trials. Specifically, in 2022 we transferred the ^{188}RNL-BAM technology from UT Health Science Center at San Antonio, and began planning to develop the drug product and complete early preclinical studies to support a future FDA IND submission. Our intended initial clinical target is liver cancer which is the sixth most common and third deadliest cancer worldwide. It is a rare disease with increasing U.S. annual incidence (42,000) and deaths (30,000).

Recent Developments

Grant Agreement with CPRIT

On September 19, 2022, we entered into a Cancer Research Grant Contract (the "CPRIT Contract"), effective as of August 31, 2022, with CPRIT, pursuant to which CPRIT will provide us a grant of up to $17.6 million (the "CPRIT Grant") over a three-year period to fund the continued development of rhenium (^{186}Re) obisbemeda for the treatment of patients with LM. The CPRIT Grant is subject to customary CPRIT funding conditions, including, but not limited to, a matching fund requirement (one dollar from Plus Therapeutics for every two dollars awarded by CPRIT), revenue sharing obligations upon commercialization of rhenium (^{186}Re) obisbemeda based on specific dollar thresholds until CPRIT receives the aggregate amount of 400% of the proceeds awarded under the CPRIT Grant, and certain reporting requirements.

Services Agreement and Statement of Work with Biocept

On June 22, 2022, we announced a multi-year laboratory services agreement with Biocept, Inc. ("Biocept") to employ their cerebrospinal fluid ("CSF") assay, CNSide, in Plus Therapeutics' ReSPECT-LM Phase 1/2a dose-escalation trial of Rhenium-186 NanoLiposome for the treatment of patients with ("LM").

Services Agreement and Sales Order with Medidata

On March 31, 2022, we entered into a Sales Order (the "Sales Order") with Medidata Solutions, Inc. ("Medidata"), pursuant to which Medidata will build a Synthetic Control Arm® (SCA) platform that facilitates the use of historical clinical data to incorporate into our Phase 2 clinical trial of rhenium (^{186}Re) obisbemeda in GBM. The Sales Order had a term of six (6) months. Work under this Sales Order has been completed.

UT Health Science Center San Antonio (UTHSCSA) 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 ^{188}RNL-BAM. Under the license agreement with UT Health Science Center at San Antonio, we are required to use commercial reasonable efforts to develop the ^{188}RNL-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.

Recent Financings

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

Results of Operations

Grant Revenue

We recognized $0.2 million of grant revenue during the year ended December 31, 2022, which represents CPRIT's share of the costs incurred for our rhenium (^{186}Re) obisbemeda development for the treatment of patients with LM.

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, 2022 and 2021 (in thousands):

	Years ended December 31,	
	2022	2021
Research and development	$ 9,611	$ 5,248
Share-based compensation	87	75
Total research and development expenses	$ 9,698	$ 5,323

The increase in research and development expenses of $4.4 million for the year ended December 31, 2022 as compared to the same period in 2021 was due primarily to an increase of $1.6 million in development costs relating to the development of cGMP rhenium (^{186}Re) obisbemeda drug, an increase of $1.6 million in other expenses which includes the development of the SCA, an increase of $0.8 million related to personnel related expenses, an increase of $0.3 million in licensing payments under the NanoTx agreement for grant revenue received (Note 7), and an increase of $0.1 million in depreciation expenses.

We expect aggregate research and development expenditures to remain consistent during 2023 as compared to the year ended December 31, 2022, due to an increase in licensing payments offset by reduced research and development spend.

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, 2022 and 2021 (in thousands):

	Years ended December 31,	
	2022	2021
General and administrative	$ 9,719	$ 6,322
Share-based compensation	519	531
Total general and administrative expenses	$ 10,238	$ 6,853

General and administrative expenses increased by $3.4 million during the year ended December 31, 2022, as compared to the same period in 2021, primarily due to $1.4 million settlement cost for Lorem claim (Note 6 of the financial statements), an increase of $1.5 million in legal fees and other professional expenses due to increased costs related to Lorem litigation, an increase of $0.2 million of personnel expenses and an increase of $0.3 million in travel and other expenses.

We expect general and administrative expenditures to remain generally consistent in 2023 as compared with the year ended December 31, 2022, exclusive of the impact of the one-time legal settlement costs and settlement related legal expenses in 2022.

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 share-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, 2022 and 2021 (in thousands):

	Years ended December 31,	
	2022	2021
Research and development	$ 87	$ 75
General and administrative	519	531
Total share-based compensation	$ 606	$ 606

Our share-based compensation expenses, which are impacted by grants of share-based options, vesting schedule of such grants, as well as grant-date fair value of share-based awards, remained consistent from 2021 to 2022.

Other Income (Expense)

The following table summarizes interest income, interest expense, and other income and expense for the years ended December 31, 2022 and 2021 (in thousands):

	Years ended December 31,	
	2022	2021
Interest income	$ 147	$ 19
Interest expense	(711)	(932)
Change in fair value of liability instruments	1	6
Total	$ (563)	$ (907)

The decrease in interest expense for the year ended December 31, 2022 as compared to the same period in 2021 was primarily due to the repayments of debt principal of $1.6 million in 2022 and $0.3 million in 2021, respectively.

We expect interest expense in 2023 to decrease as compared with 2022 due to scheduled debt principal repayments which began on November 1, 2021.

Liquidity and Capital Resources

Short-term and long-term liquidity

The following is a summary of our key liquidity measures at December 31, 2022 and 2021 (in thousands):

	As of December 31,	
	2022	2021
Cash and cash equivalents	$ 18,120	$ 18,400
Current assets	$ 21,817	$ 19,724
Current liabilities	11,852	5,870
Working capital	$ 9,965	$ 13,854

For the periods presented, operating losses have been funded primarily from outside sources of invested capital in our common stock. We believe that our cash and cash equivalents of $18.1 million at December 31, 2022 will enable us to fund our current and planned operations for at least the next twelve months and beyond from the date our 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 September 19, 2022, we entered into the CPRIT Contract, pursuant to which CPRIT will provide us with the CPRIT Grant of $17.6 million subject to the terms of the CPRIT Contract, to fund approximately two-thirds of the continued development of rhenium (^{186}Re) obisbemeda for the treatment of patients with LM.

On September 9, 2022, we entered into an Equity Distribution Agreement (the “September 2022 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, depending on market demand, with Canaccord acting as an agent for sales. Sales of our common stock 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. Canaccord will use its commercially reasonable efforts to sell common stock that we requested to be sold on our behalf, consistent with Canaccord's normal trading and sales practices, under the terms and subject to the conditions set forth in the September 2022 Distribution Agreement. We will pay Canaccord a commission of up to 3.0% of the gross sale of shares of common stock. We have no obligation to sell any of our common stock. We may instruct Canaccord not to sell any common stock 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 September 2022 Distribution Agreement. During the period from September 9, 2022 to December 31, 2022, we issued 1,031,371 shares under the September 2022 Distribution Agreement for net proceeds of approximately $0.6 million. From January 1, 2023 to the date of filing of this Form 10-K, we issued 1,812,785 shares under the September 2022 Distribution Agreement for net proceeds of approximately $0.7 million.

On August 2, 2022, we entered into a purchase agreement (the “2022 Purchase Agreement”) and registration rights agreement pursuant to which Lincoln Park committed to purchase up to $50.0 million shares of our common stock. Under the terms and subject to the conditions of the 2022 Purchase Agreement, we have the right, but not the obligation, to sell to Lincoln Park, and Lincoln Park is obligated to purchase up to $50.0 million shares of our common stock, provided that we cannot sell more than 57.5 million shares pursuant to the 2022 Purchase Agreement. Sales of common stock by us are subject to certain limitations, and can occur from time to time, at our sole discretion, over the 36-month period commencing on August 17, 2022, subject to the satisfaction of certain conditions. Actual sales of shares of common stock to Lincoln Park under the 2022 Purchase Agreement depend on a variety of factors to be determined by us from time to time, including, among others, market conditions, the trading price of the common stock and determinations by us as to the appropriate sources of funding for us and our operations. As consideration for Lincoln Park’s irrevocable commitment to purchase shares of our common stock upon the terms of and subject to satisfaction of the conditions set forth in the Purchase Agreement, we paid $0.1 million in cash as an Initial Commitment Fee and issued 492,698 Commitment Shares to Lincoln Park in consideration for its commitment to purchase shares of our common stock at our direction under the Purchase Agreement.

On August 17, 2022, a registration statement was declared effective covering the resale of up to 9,500,000 shares of our common stock comprised of (i) the 492,698 Commitment Shares, and (ii) up to 9,007,302 shares that we have reserved for issuance and sale to Lincoln Park under the Purchase Agreement. An additional commitment fee equal to 2.5% of the remainder of the $50 million will be paid if and when we sell over $25.0 million of our common stock under the 2022 Purchase Agreement. The additional commitment fee may be paid in cash, common stock, or a combination thereof. We cannot sell more shares under the 2022 Purchase Agreement without registering additional shares.

During the period from August 17, 2022 to December 31, 2022, we issued 4,000,000 shares under the 2022 Purchase Agreement for net proceeds of approximately $3.2 million. From January 1, 2023 to the date of filing of this Form 10-K, we did not issue any shares under the 2022 Purchase Agreement.

On January 14, 2022, we entered into an Equity Distribution Agreement (the "January 2022 Distribution Agreement") with Canaccord, pursuant to which we could issue and sell, from time to time, shares of our common stock in "at the market" offerings, having an aggregate offering price of up to $5,000,000, depending on market demand, with Canaccord acting as an agent for sales. During the year ended December 31, 2022, we issued 6,902,279 shares under the January 2022 Distribution Agreement for net proceeds of approximately $4.8 million. The January 2022 Distribution Agreement was terminated after all available registered shares were fully utilized.

On October 23, 2020, we entered into an Equity Distribution Agreement (the "2020 Distribution Agreement") with Canaccord, pursuant to which we could issue and sell, from time to time, shares of our common stock in "at the market" offerings, having an aggregate offering price of up to $10,000,000, depending on market demand, with Canaccord acting as an agent for sales. During 2021, we issued 2,179,193 shares under the 2020 Distribution Agreement for net proceeds of $6.3 million. The 2020 Distribution Agreement has been terminated.

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 2021, we issued 5,685,186 shares of our common stock under the 2020 Purchase Agreement for total proceeds of $12.5 million. During the year ended December 31, 2022, we issued 5,665,000 shares of common stock for net proceeds of approximately $7.0 million under the 2020 Purchase Agreement. The 2020 Purchase Agreement has been terminated.

We continue to seek additional capital through strategic transactions and other financing alternatives. Without additional capital, current working capital and cash generated from grants will not provide adequate funding for research and product development activities at their current levels. If sufficient capital is not raised in the future, we eventually may 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. There may be continued market volatility due to the pandemic, downturn in the global economy, or other events, which could cause our stock price to decline. This in turn would likely negatively impact our ability to raise funds through equity-related financings.

Should we be unable in the future 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, 2022 and 2021 is summarized as follows (in thousands):

	Years Ended December 31,	
	2022	2021
Net cash used in operating activities	$ (12,972)	$ (10,280)
Net cash used in investing activities	(759)	(82)
Net cash provided by financing activities	13,451	20,416
Net increase (decrease) in cash and cash equivalents	$ (280)	$ 10,054

Material Cash Obligations

On September 19, 2022, we entered into the CPRIT Contract, effective as of August 31, 2022, pursuant to which we will continue the development of rhenium (^{186}Re) obisbemeda for the treatment of patients with LM, with CPRIT providing matching funds for approximately two-thirds of the total development costs, subject to various funding conditions. The CPRIT contract is effective for three years, unless otherwise terminated per terms of the contract. CPRIT may require us to repay some or all of the disbursed CPRIT grant proceeds (with interest not to exceed 5% annually) in the event of the early termination of the CPRIT Contract.

We are also obligated to make ongoing payments against the remaining principal and interest payments of approximately $6.0 million in total under the Term Loan with Oxford through the maturity date of June 1, 2024 (See Note 5 of the accompanying financial

statements for more information). In addition, as described in more detail in Note 7 of the accompanying financial statements, we are obligated to make operating lease payments for our office and laboratory space and we may be required to make payments under certain of our other contractual agreements.

Operating activities

Net cash used in operating activities for the year ended December 31, 2022 was $13.0 million compared to $10.3 million in the same period of 2021. Overall, our operational cash use increased during the year ended December 31, 2022 as compared to the same period in 2021, due primarily to increased expenditures for our research and development activities.

Investing activities

Net cash used in investing activities for year ended December 31, 2022 was primarily related to cash payments of $0.5 million made for purchases of fixed assets and intangible assets, and $0.3 million paid for in-process research and development. Net cash used in investing activities for the year ended December 31, 2021 was related to purchases of fixed assets of $0.1 million, offset by proceeds of $0.1 million from sale of property and equipment.

On August 15, 2022, we announced that our Board of Directors had approved a share repurchase program pursuant to which we were authorized to repurchase up to $2.0 million of our outstanding common stock. The timing and amount of any shares repurchased will be determined based on our evaluation of market conditions and other factors. Repurchases may be made from time to time on the open market over the course of 12 months. We are not obligated to acquire any shares and the program may be discontinued or suspended at any time. Through the date of filing of this Form 10-K, we have not repurchased any of its common stock under this share repurchase program.

Financing Activities

Net cash provided by financing activities for year ended December 31, 2022 was primarily related to sales of common stock of $15.1 million, net of offering cost through the Purchase Agreements with Lincoln Park and the Distribution Agreements with Canaccord, offset by principal repayment of the Oxford term loan of $1.6 million.

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.

Critical Accounting 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. On an on-going basis, we evaluate our estimates and judgments, including those related to impairment assessment of our grants and awards, indefinite lived intangible assets, and share-based compensation. We base our estimates on historical experience, known trends and events, and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

Grants and Awards

We determined that grants and awards are out of the scope of ASC Topic 606, *Revenue from Contracts with Customers* (“ASC 606”) because the funding entities do not meet the definition of a “customer”, as defined by ASC 606, as there is no transfer of control of goods or services. With respect to each grant or award, we determine if it has a collaboration in accordance with ASC Topic 808, *Collaborative Arrangements* (“ASC 808”). To the extent the grant or award is within the scope of ASC 808, we recognize the award upon achievement of certain milestones as credits to research and development expenses. For grant and awards outside the scope of ASC 808, we apply ASC 606 or International Accounting Standards No. 20, *Accounting for Government Grants and Disclosure of Government Assistance*, by analogy, and revenue is recognized when we incur expenses related to the grants for the amount we are entitled to under the provisions of the contract.

We also consider the guidance in ASC Topic 730, *Research and Development* (“ASC 730”), which requires an assessment, at the inception of the grant or award, of whether the agreement is a liability. If we are obligated to repay funds received regardless of the outcome of the related research and development activities, then we are required to estimate and recognize that liability. Alternatively, if we are not required to repay the funds, then payments received are recorded as revenue or contra-expense as the expenses are incurred.

Deferred grant or award liability represents award funds received or receivable for which the allowable expenses have not yet been incurred as of the balance sheet date.

Impairment of Goodwill

We perform our goodwill impairment analysis at the reporting unit level. For the years ended December 31, 2022 and 2021, our company has one reporting unit. We perform our annual impairment analysis by either doing a qualitative assessment of a reporting unit's fair value from the last quantitative assessment to determine if there is potential impairment, or comparing a reporting unit's estimated fair value to its carrying amount. If a quantitative assessment is performed the evaluation includes management estimates of cash flow projections based on internal future projections and/or use of a market approach by looking at market values of comparable companies. Our market capitalization is also considered as a part of this analysis.

In accordance with our accounting policy, we completed the annual evaluation for impairment of goodwill as of December 31, 2022 using the qualitative method and determined that no impairment existed.

Share-based Compensation

Compensation expense related to stock options granted is measured at the grant date based on the estimated fair value of the award and is recognized on an accelerated attribution method over the requisite service period. We determine the estimated fair value of each stock option on the date of grant using the Black-Scholes valuation model which uses assumptions regarding a number of complex and subjective variables. The risk-free interest rate is based on the U.S. Treasury yield for a period consistent with the expected term of the option in effect at the time of the grant. Expected volatility is based on an analysis of the historical volatility of our common stock. The expected term represents the period that we expect our stock options to be outstanding. The expected term assumption is estimated using the simplified method set forth in the U.S. Securities and Exchange Commission's (the "SEC") Staff Accounting Bulletin 110, which is the mid-point between the option vesting date and the expiration date. We have never declared or paid dividends on our common stock and have no plans to do so in the foreseeable future. Changes in these assumptions may lead to variability with respect to the amount of stock compensation expense we recognize related to stock options.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

Not applicable.

Item 8. Financial Statements and Supplementary Data

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 Financial Statements
We have audited the accompanying balance sheets of Plus Therapeutics, Inc. (the "Company") as of December 31, 2022 and 2021, the related 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 "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, 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 financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

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

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

Critical Audit 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 23, 2023

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

	As of December 31,	
	2022	2021
Assets		
Current assets:		
Cash and cash equivalents	$ 18,120	$ 18,400
Other current assets	3,697	1,324
Total current assets	21,817	19,724
Property and equipment, net	1,324	1,477
Operating lease right-use-of assets	248	341
Goodwill	372	372
Intangible assets, net	94	51
Other assets	12	16
Total assets	$ 23,867	$ 21,981
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable and accrued expenses	$ 10,134	$ 4,151
Operating lease liability	110	111
Term loan obligation, current	1,608	1,608
Total current liabilities	11,852	5,870
Noncurrent operating lease liability	141	269
Term loan obligation	3,786	5,005
Deferred grant liability	1,643	—
Warrant liability	—	1
Total liabilities	17,422	11,145
Commitments and contingencies (Note 6)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 5,000,000 shares authorized; 1,952 shares issued and outstanding as of December 31, 2022 and 2021	—	—
Common stock, $0.001 par value; 100,000,000 shares authorized; 33,601,373 and 15,510,025 shares issued and outstanding as of December 31, 2022 and 2021, respectively	34	16
Additional paid-in capital	473,596	457,730
Accumulated deficit	(467,185)	(446,910)
Total stockholders' equity	6,445	10,836
Total liabilities and stockholders' equity	$ 23,867	$ 21,981

See Accompanying Notes to these Financial Statements

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

	For the Years Ended December 31,	
	2022	**2021**
Grant revenue	$ 224	$ —
Operating expenses:		
Research and development	9,698	5,323
In process research and development acquired	—	250
General and administrative	10,238	6,853
Loss on disposal of property and equipment	—	66
Total operating expenses	19,936	12,492
Operating loss	(19,712)	(12,492)
Other income (expense):		
Interest income	147	19
Interest expense	(711)	(932)
Change in fair value of liability instruments	1	6
Total other expense	(563)	(907)
Net loss	$ (20,275)	$ (13,399)
Net loss per share, basic and diluted	$ (0.77)	$ (1.11)
Basic and diluted weighted average shares used in calculating net loss per share attributable to common stockholders	26,255,256	12,089,186

See Accompanying Notes to these Financial Statements

PLUS THERAPEUTICS, INC.
STATEMENTS OF STOCKHOLDERS' EQUITY
FOR THE YEARS ENDED December 31, 2022 and 2021
(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, 2020	1,954	$ —	6,749,028	$ 7	$ 436,535	$ (433,511)	$ 3,031
Share-based compensation	—	—	—	—	606	—	606
Sale of common stock, net	—	—	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
Share-based compensation	—	—	—	—	606	—	606
Sale of common stock, net	—	—	18,091,348	18	15,260	—	15,278
Net loss	—	—	—	—	—	(20,275)	(20,275)
Balance at December 31, 2022	1,952	$ —	33,601,373	$ 34	$ 473,596	$ (467,185)	$ 6,445

See Accompanying Notes to these Financial Statements

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

	For the Years Ended December 31,	
	2022	**2021**
Cash flows used in operating activities:		
Net loss	$ (20,275)	$ (13,399)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	619	395
Amortization of deferred financing costs and debt discount	389	546
In process research and development acquired	—	250
Change in fair value of liability instruments	(1)	(6)
Loss on disposal of property and equipment	—	66
Share-based compensation expense	606	606
Amortization of operating lease right-of-use assets	93	24
Increases (decreases) in cash caused by changes in operating assets and liabilities:		
Other current assets	(2,369)	(496)
Accounts payable and accrued expenses	6,452	1,734
Change in operating lease liabilities	(129)	—
Other long-term liabilities	1,643	—
Net cash used in operating activities	(12,972)	(10,280)
Cash flows used in investing activities:		
Purchases of property and equipment and intangible assets	(509)	(144)
In process research and development acquired	(250)	—
Proceeds from sale of property and equipment	—	62
Net cash used in investing activities	(759)	(82)
Cash flows from financing activities:		
Principal payments of long-term obligations	(1,608)	(268)
Payment of finance lease liability	—	(8)
Proceeds from exercise of warrants	—	2,017
Proceeds from sale of common stock	15,059	18,675
Net cash provided by financing activities	13,451	20,416
Net increase (decrease) in cash and cash equivalents	(280)	10,054
Cash and cash equivalents at beginning of period	18,400	8,346
Cash and cash equivalents at end of period	$ 18,120	$ 18,400
Supplemental disclosure of cash flows information:		
Cash paid during period for:		
Interest	$ 327	$ 388
Supplemental schedule of non-cash investing and financing activities:		
Unpaid offering cost	$ —	$ 219

See Accompanying Notes to these Financial Statements

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.

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 $20.3 million for the year ended December 31, 2022, and as of December 31, 2022, the Company had an accumulated deficit of $467.2 million and cash and cash equivalents of $18.1 million. Additionally, the Company used net cash of $13.0 million to fund its operating activities for the year ended December 31, 2022. The Company expects that its research and development expenditures will increase in absolute dollars in 2023 and beyond.

As disclosed in more detail in Note 12, the Company has entered into various financing agreements 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 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 in the future, the Company may eventually 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.

On May 24, 2022, the Company received notice from The Nasdaq Stock Market LLC ("Nasdaq") that, because the closing bid price for the Company's common stock had fallen below $1.00 per share for 30 consecutive business days, the Company no longer complied with the minimum bid price requirement pursuant to Nasdaq Listing Rule 5550(a)(2) (the "Minimum Bid Requirement").

Nasdaq's notice had no immediate effect on the listing or trading of the Company's common stock. On November 22, 2022, the Company received a second letter from Nasdaq advising that the Company had been granted an additional 180 calendar days, or to May 22, 2023, to regain compliance with the Minimum Bid Requirement, in accordance with Nasdaq Listing Rule 5810(c)(3)(A).

The Company intends to continue to actively monitor the closing bid price of its common stock and will evaluate available options to regain compliance with the Minimum Bid Requirement. Specifically, the Company has confirmed to Nasdaq that, if necessary, it will implement a reverse stock split of its outstanding common stock (if approved by the Company's stockholders) to attempt to regain compliance. If the Company does not regain compliance within the additional compliance period, Nasdaq will provide notice that the Company's common stock will be subject to delisting. The Company would then be entitled to appeal that determination to a Nasdaq hearings panel. There can be no assurance that the Company will regain compliance with the Minimum Bid Requirement during the 180-day additional compliance period or maintain compliance with the other Nasdaq listing requirements.

2. Summary of Significant Accounting Policies

Use of Estimates

The preparation of 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 grant revenue recognition, reviewing assets for impairment, and determining the assumptions used in measuring share-based compensation expense.

Actual results could differ from these estimates. Management's estimates and assumptions are reviewed regularly, and the effects of revisions are reflected in the 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, 2022 and 2021. 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, other current assets, accounts payable, accrued expenses, other liabilities and long-term debt. The carrying values of cash equivalents, 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 currently 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, 2022 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 statements of operations and comprehensive loss.

Grant Receivable and Revenue Recognition

In applying the provisions of Accounting Standards Codification ("ASC") Topic 606, Revenue from Contracts with Customers ("ASC 606"), the Company has determined that government grants are out of the scope of ASC 606 because the funding entities do not meet the definition of a "customer", as defined by ASC 606, as there is not considered to be a transfer of control of goods or services. With respect to the grant, the Company determines if it has a collaboration in accordance with ASC Topic 808, Collaborative Arrangements ("ASC 808"). For grants outside the scope of ASC 808, the Company applies ASC 606 or International Accounting Standards No. 20, Accounting for Government Grants and Disclosure of Government Assistance, by analogy, and revenue is recognized when the Company incurs expenses related to the grant for the amount the Company is entitled to under the provisions of the contract.

The Company also considers the guidance in ASC Topic 730, Research and Development ("ASC 730"), which requires an assessment, at the inception of the grant, of whether the agreement is a liability. If the Company is obligated to repay funds received regardless of the outcome of the related research and development activities, then the Company is required to estimate and recognize that liability. Alternatively, if the Company is not required to repay the funds, then payments received are recorded as revenue or contra-expense as the expenses are incurred.

Deferred grant liability represents grant funds received or receivable for which the allowable expenses have not yet been incurred as of the balance sheet date.

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.

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.

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, 2022 and 2021, 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, 2022 and 2021, the Company is managed as a single operating segment, and therefore reports its 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, 2022 and 2021, 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 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 will adopt the new guidance for the quarter beginning on January 1, 2023, and it does not expect that adoption of this standard will have a material impact on its financial statements and related disclosures.

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. The Company follows

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.

Certain warrants issued in an underwritten public offering in September 2019 ("Series U Warrants") are classified as liability instruments. The Company estimated the fair value of the Series U Warrants with the Black Scholes model. Because some of the inputs to the Company's 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.

Liability-classified Series U Warrants are marked to market as of each balance sheet date until they are exercised or upon expiration, with the changes in fair value recorded as non-operating income or loss in the statements of operations. As of December 31, 2022 and 2021, the fair value of the Series U Warrants was immaterial, and the change in the fair value of liability classified Series U Warrants during year ended December 31, 2022 and 2021 was immaterial.

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.

4. 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,	
	2022	2021
Outstanding stock options	1,175,016	1,170,890
Preferred stock	422,867	422,867
Outstanding warrants	2,141,378	2,141,378
Total	3,739,261	3,735,135

5. Composition of Certain Financial Statement Captions

Other Current Assets

As of December 31, 2022 and 2021, other current assets were comprised of the following (in thousands):

	December 31,	
	2022	2021
Prepaid services	$ 2,999	$ 622
Prepaid insurance	698	695
Other	—	7
	$ 3,697	$ 1,324

Property and Equipment, net

As of December 31, 2022 and 2021, property and equipment, net, were comprised of the following (in thousands):

	December 31,	
	2022	2021
Office and computer equipment	$ 1,474	$ 1,231
Leasehold improvements	1,810	1,661
	3,284	2,892
Less accumulated depreciation	(1,960)	(1,415)
	$ 1,324	$ 1,477

Depreciation expense totaled $0.5 million and $0.4 million for the year ended December 31, 2022 and 2021, respectively.

Intangible Assets, net

As of December 31, 2022, intangible assets included the net book value of costs incurred for software upgrades. Amortization expenses totaled $0.1 million and $32 thousand for the year ended December 31, 2022 and 2021, respectively.

Accounts Payable and Accrued Expenses

As of December 31, 2022 and 2021, accounts payable and accrued expenses were comprised of the following (in thousands):

	December 31,	
	2022	2021
Accounts payable	$ 8,364	$ 2,611
Accrued payroll and bonus	989	781
Accrued professional fees	147	189
Accrued vacation and compensation	325	252
Accrued R&D studies	309	196
Other current liabilities	—	122
	$ 10,134	$ 4,151

6. 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 finance leases are recorded within property and equipment, net in the balance sheets. Leases with an initial term of 12 months or less are not recorded on the balance sheets. Instead, the Company recognizes lease expense for these leases on a straight-line basis over the lease term in the statements of operations.

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 and certain office space in Charlottesville, Virginia (the “Charlottesville Lease”). The Charlottesville Lease has a term of 12 months and the Company has the ability to renew for three additional one-year periods. The Charlottesville Lease is currently set to expire on March 31, 2023. 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 of April 1, 2021. In addition, the Company has entered into leases for certain equipment under various operating and finance leases. 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, 2022 or 2021. The Company’s existing operating 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 Company's operating lease liabilities and corresponding right-of-use assets are included in the balance sheets. As of December 31, 2022, the weighted average discount rate used to measure operating lease liabilities and the operating leases remaining term were 9% and 2.03 years, respectively.

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

	Year Ended December 31,	
	2022	2021
Lease expense:		
Operating lease expense	$ 159	$ 211
Finance lease expense:		
Depreciation of right-of-use assets	—	7
Total lease expense	$ 159	$ 218
Cash payment information:		
Operating cash used for operating leases	$ 159	$ 206
Financing cash used for financing leases	—	8
Total cash paid for amounts included in the measurement of lease liabilities	$ 159	$ 214

Total rent expenses for each of the years ended December 31, 2022 and 2021 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 finance leases at December 31, 2022 are as follows (in thousands):

	Operating Leases
2023	137
2024	113
2025	18
Total minimum lease payments	$ 268
Less: amount representing interest	(17)
Present value of obligations under leases	251
Less: current portion	(110)
Noncurrent lease obligations	$ 141

Services Agreement and Sales Order with Medidata

On March 31, 2022, the Company and Medidata Solutions, Inc. ("Medidata") entered into a Sales Order (the "Sales Order"), pursuant to which Medidata will build a Synthetic Control Arm® (SCA) platform that facilitates the use of historical clinical data to incorporate into the Company's Phase 2 clinical trial of rhenium (^{186}Re) obisbemeda in recurrent glioblastoma ("GBM"). The Sales Order is governed under the terms of a services agreement (the "Services Agreement"), dated November 5, 2021. The Sales Order had a term of six (6) months, and work under the Sales Order has been completed. Costs related to the Sales Order of $1.5 million were expensed in the statement of operations for the year ended December 31, 2022.

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 rhenium (^{186}Re) obisbemeda-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, 2022, 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 alleged 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 Asset and Equity Purchase Agreement, dated March 29, 2019, between the Company and Lorem (the "Lorem Agreement"). Lorem also claimed 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 claimed entitlement to at least $6,000,000 in compensatory damages and operational costs and expenses (collectively, the "Lorem Claim"). On December 9, 2022, the Company entered into a settlement agreement (the "Settlement Agreement") with Lorem to settle the Lorem Claim. Under the terms of the Settlement Agreement, the Company made a payment to Lorem, and Lorem moved to dismiss the lawsuit with prejudice. The Settlement Agreement released us from all claims made by Lorem. The parties to the Settlement Agreement recognized that it did not constitute an admission of liability, wrongdoing, or any matter of fact or law. The Settlement was conditioned on the customary terms contained in the Settlement Agreement and was approved by the Court and the case was dismissed on January 17, 2023. As of December 31, 2022, the Company accrued the settlement amount, as well as the accounts that the Company has confirmed to be recoverable under its insurance claims on the matter. The net amount of $1.4 million that was not recoverable under the Company's insurance has been reflected as an expense in the year ended December 31, 2022. The full settlement amount was paid in January 2023. All legal costs related to the Lorem Claim were expensed as incurred.

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.

7. 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 was required to make an upfront payment, 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 of $0.3 million was paid in cash in January 2022.

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.

The transaction terms included an upfront payment of $0.4 million in cash and $0.3 million in the Company's voting stock. The transaction terms also included success-based milestone and royalty payments contingent on key clinical, regulatory and sales milestones, as well as the requirement to pay 15% of any non-dilutive monetary awards or grants received from external agencies

to support product development of the nanoliposome encapsulated BMEDA-chelated radioisotope, which includes grants from the Cancer Prevention & Research Institute of Texas ("CPRIT"). As of December 31, 2022, the Company accrued $0.3 million of payments due to NanoTx as a result of the CPRIT grant received (Note 9).

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 was 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 their respective fair value was recorded as a discount to the debt.

The Term Loan 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, 2022, there was $2.4 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 years ended December 31, 2022 and 2021 was $0.7 million and $0.9 million, respectively. Interest expense is calculated using the effective interest method; therefore it is inclusive of non-cash amortization in the amount of $0.4 million and $0.5 million for the year ended December 31, 2022 and 2021, respectively, related to the amortization of the debt discount, deferred financing costs, and accretion of final payment.

The Loan and Security Agreement 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, 2022, 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, 2022 and 2021 are presented in the following table (in thousands):

Year ended December 31, 2022

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	$ 2,412

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

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

*** Monthly payment reflects principal and interest*

As of December 31, 2022, the future contractual principal and final fee payments on all of our debt obligations are as follows (as thousands):

Years Ending December 31,		
2023	$	1,608
2024		3,996
Total	$	5,604

Reconciliation of Face Value to Book Value as of December 31, 2022		
Total debt obligations, including final payment fee (Face Value)	$	5,604
Less: Debt discount		(210)
Total obligation		5,394
Less: Current portion		(1,608)
Term loan obligation -- noncurrent	$	3,786

9. Grant Revenue

On September 19, 2022, the Company entered into the CPRIT Contract, effective as of August 31, 2022, with CPRIT, pursuant to which CPRIT will provide the Company a grant of up to $17.6 million (the “CPRIT Grant”) over a three-year period to fund the continued development of rhenium (^{186}Re) obisbemeda for the treatment of patients with leptomeningeal metastases (“LM”). The CPRIT Grant is subject to customary CPRIT funding conditions, including, but not limited to, a matching fund requirement (one dollar for every two dollars awarded by CPRIT), revenue sharing obligations upon commercialization of rhenium (^{186}Re) obisbemeda based on specific dollar thresholds and tiered low single digit royalty rates until CPRIT receives the aggregate amount of 400% of the proceeds awarded under the CPRIT Grant, and certain reporting requirements.

The CPRIT Contract will terminate on August 30, 2025, unless terminated earlier by (a) the mutual written consent of all parties to the CPRIT Contract, (b) CPRIT for an event of default by the Company, (c) CPRIT, if the funds allocated to the CPRIT Grant become legally unavailable during the term of the CPRIT Contract and CPRIT is unable to obtain additional funds for such purposes, and (d) the Company for convenience. CPRIT may require the Company to repay some or all of the disbursed CPRIT Grant proceeds (with interest not to exceed 5% annually) in the event of the early termination of the CPRIT Contract by CPRIT for an event of default by the Company or by the Company for convenience.

The Company will retain ownership over any intellectual property developed under the contract ("Project Result"). With respect to non-commercial use of any Project Result, the Company agreed to grant to CPRIT a nonexclusive, irrevocable, royalty-free, perpetual, worldwide license with right to sublicense any necessary additional intellectual property rights to exploit all Project Results by CPRIT, other governmental entities and agencies of the State of Texas, and private or independent institutions of higher education located in Texas, for education, research and other non-commercial purposes.

The Company determined that the CPRIT Contract is not in the scope of ASC 808 or ASC 606. Applying ASC 606 by analogy, the Company recognizes proceeds received under the CPRIT Contract as grant revenue on the statement of operations when related costs are incurred. The Company recognized $0.2 million in grant revenue from the CPRIT Contract during the year ended December 31, 2022.

10. Income Taxes

Pursuant to the Internal Revenue Code (“IRC”) of 1986, as amended, specifically IRC §382 ("Section 382") and IRC §383, the Company’s ability to use net operating loss ("NOLs") and R&D tax credit carry forwards (“tax attribute carry forwards”) to offset future taxable income is limited if the Company experiences a cumulative change in ownership of more than 50% within a three-year testing period. In preparation of the financial statements as of and for the year ended December 31, 2022, the Company performed an ownership change analysis and concluded that it was probable that an ownership change within the meaning of IRC §382 occurred prior to December 31, 2020.

As a result, the Company has determined that approximately $346.8 million for federal NOL carryforwards and $173.0 million for state NOL carryforwards were subject to limitation. Consequently, approximately $84.9 million of deferred tax assets related to NOL carryforwards were eliminated. In addition, deferred tax assets related to federal and state research and development credits of approximately $6.0 million and $5.5 million were eliminated, resulting in a total reduction of deferred tax assets of $8.4 million, which was completely offset by a corresponding adjustment to the Company's valuation allowance. The deferred tax assets relating to net operating loss carryforwards and income tax credit carryforwards and the related valuation allowance as

of December 31, 2021 reflected in the table below have been adjusted to give effect to this. These revisions had no impact on the Company's balance sheet, statement of operations or statement of cash flows.

The Company's use of federal and state NOLs and research credits could be limited further by the provisions of Section 382 depending upon the timing and amount of additional equity securities that the Company has issued or will issue. State NOL carryforwards may be similarly limited. If a change in ownership were to have occurred, NOL and tax credits carryforwards could be eliminated or restricted. If eliminated, the related asset would be removed from the deferred tax asset schedule with a corresponding reduction in the valuation allowance. Due to the existence of the valuation allowance, limitations created by ownership changes, if any, will not impact the Company's effective tax rate.

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, 2022 and 2021, 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, 2022 and 2021, respectively, is as follows:

	2022	2021
Income tax expense (benefit) at federal statutory rate	(21.0)%	(21.0)%
Change in valuation allowance	22.5%	(699.5)%
Income tax expense (benefit) at state statutory rate	(0.2)%	(0.6)%
Share based compensation	0.9%	0.7%
NOLs expiring and adjustments to NOL	0.5%	720.7%
Research credit	(2.5)%	(0.8)%
Return to provision	(0.1)%	0.5%
Change in state rate	(0.1)%	—
	0.0%	(0.0)%

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, 2022 and 2021 are as follows (in thousands):

	2022	2021
Deferred tax assets:		
Accrued expenses	$ 262	$ 41
Share based compensation	107	164
Net operating loss carryforwards	12,605	10,404
Income tax credit carryforwards	956	447
Property and equipment, principally due to differences in depreciation	89	19
Intangible assets	2,073	451
Other, net	53	82
	16,145	11,608
Valuation allowance	(16,092)	(11,534)
Total deferred tax assets, net of allowance	53	74
Deferred tax liabilities:		
Other	(53)	(74)
Total deferred tax liability	(53)	(74)
Net deferred tax assets (liability)	$ —	$ —

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 $16.1 million as of December 31, 2022 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 $4.6 million during the year ended December 31, 2022.

At December 31, 2022, the Company had federal and state tax loss carry forwards of approximately $59.6 million, and $1.8 million, respectively. The federal net operating loss carry forwards begin to expire in 2037, if unused. The state net operating loss carries over indefinitely. The federal net operating loss carryover includes $56.2 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, 2022, the Company had federal tax credit carry forwards of approximately $1.2 million, before reduction for uncertain tax positions. The federal credits will begin to expire in 2039, if unused.

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, 2022 and 2021.

Following is a tabular reconciliation of the unrecognized tax benefits activity during the years ended December 31, 2022 and 2021 (in thousands):

	2022	2021
Unrecognized Tax Benefits – Beginning	$ 81	$ 2,223
Gross decreases – tax positions in prior period	(1)	(2,211)
Gross increase – current-period tax positions	129	69
Unrecognized Tax Benefits – Ending	$ 209	$ 81

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 for the year ended December 31, 2022.

The Company files income tax returns with the United States and various state jurisdictions. To its knowledge, the Company is currently not under examination by the Internal Revenue Service or any other taxing authority.

With few exceptions, the Company's tax years prior to 2019 are no longer open to examination by the taxing authority. While not open to examination, the tax attributes generated in tax years 2017 and forward remain subject to adjustment by the taxing authorities if utilized in tax years which are still open to examination.

11. Employee Benefit Plan

The Company implemented a 401(k) retirement savings and profit sharing plan (the "Plan") effective January 1, 1999. During 2022, the Company commenced safe harbor matching contribution for up to 4% of eligible employee contributions. Total matching contribution under the Plan amounted to approximately $100,000 and $40,000 for the year ended December 31, 2022 and 2021, respectively.

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 issued prior to September 21, 2021. There were 1,014 shares of Series B Convertible Preferred Stock and 938 shares of Series C Preferred Stock outstanding as of each of December 31, 2022 and 2021, respectively.

As of December 31, 2022, 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 five years from the issuance date, in the form of Series U Warrants (the "Representative Warrants").

As of December 31, 2022, there were 2,141,000 outstanding Series U Warrants which can be exercised into an aggregate of 2,141,000 shares of common stock.

Common Stock

Lincoln Park Purchase Agreements

On August 2, 2022, the Company entered into a purchase agreement (the "2022 Purchase Agreement") and registration rights agreement pursuant to which Lincoln Park committed to purchase up to $50.0 million of the Company's common stock. Under the terms and subject to the conditions of the 2022 Purchase Agreement, the Company has the right, but not the obligation, to sell to Lincoln Park, and Lincoln Park is obligated to purchase up to $50.0 million of the Company's common stock. Such sales of common stock by the Company are subject to certain limitations, and can occur from time to time, at the Company's sole discretion, over the 36-month period commencing on August 17, 2022, subject to the satisfaction of certain conditions. Lincoln Park has no right to require the Company to sell any shares of common stock to Lincoln Park, but Lincoln Park is obligated to make purchases as the Company directs, subject to certain conditions.

On May 16, 2022, the Company received stockholder approval for purposes of the Nasdaq listing rules to permit issuances of up to 57.5 million shares of the Company's common stock (including the issuance of more than 19.99% of the Company's common stock) to Lincoln Park, and it was pursuant to that approval that the Company entered into the 2022 Purchase Agreement.

Upon execution of the 2022 Purchase Agreement, the Company paid $0.1 million in cash as the initial commitment fee, and issued 492,698 shares as the initial commitment shares, to Lincoln Park as consideration for its irrevocable commitment to purchase shares of the Company's common stock at its direction under the Purchase Agreement. The Company has agreed to pay an additional commitment fee, which it may elect to pay in cash and/or shares of its common stock, upon receipt of $25.0 million aggregate gross proceeds from sales of common stock to Lincoln Park under the 2022 Purchase Agreement.

On August 17, 2022, a registration statement was declared effective to cover the resale of up to 9,500,000 shares of the Company's common stock comprised of (i) the 492,698 initial commitment shares, and (ii) up to 9,007,302 that the Company has reserved for issuance and sale to Lincoln Park under the Purchase Agreement from time to time from and after the date of this prospectus. The Company cannot sell more shares under the 2022 Purchase Agreement without registering additional shares.

Actual sales of shares of common stock to Lincoln Park under the 2022 Purchase Agreement depend on a variety of factors to be determined by the Company from time to time, including, among others, market conditions, the trading price of the common stock and determinations by the Company as to the appropriate sources of funding for the Company and its operations. The net proceeds under the 2022 Purchase Agreement to the Company depend on the frequency and prices at which the Company sells shares of its stock to Lincoln Park.

During the period from August 17, 2022 to December 31, 2022, the Company issued 4,000,000 shares under the 2022 Purchase Agreement for net proceeds of approximately $3.2 million. From January 1, 2023 to the date of filing of these financial statements, the Company did not issue any shares under the 2022 Purchase Agreement.

On September 30, 2020, the Company entered into a purchase agreement (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 could 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.

On June 16, 2020, the Company received stockholder approval for purposes of the Nasdaq listing rules to permit issuances of up to 23.8 million shares of the Company's common stock (including the issuance of more than 19.99% of the Company's common stock) to Lincoln Park, and it was pursuant to that approval that the Company entered into the 2020 Purchase Agreement.

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 directs, subject to certain conditions.

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. During the year issued December 31, 2022, the Company issued 5,665,000 shares of its common stock under the 2020 Purchase Agreement for net proceeds of approximately $7.0 million. The Company no longer has any additional shares of common stock registered to sell under the 2020 Purchase Agreement.

At-the-market Issuances

On September 9, 2022, the Company entered into an Equity Distribution Agreement (the "September 2022 Distribution Agreement") with Canaccord Genuity LLC ("Canaccord"), 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, depending on market demand, with Canaccord acting as an agent for sales. Sales of the Company's common stock 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. Canaccord will use its commercially reasonable efforts to sell common stock requested by the Company 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 September 2022 Distribution Agreement. The Company has no obligation to sell any of its common stock. The Company may instruct Canaccord not to sell any common stock if the sales cannot be effected at or above the price designated by the Company from time to time and the Company may at any time suspend sales pursuant to the September 2022 Distribution Agreement. During the period from September 9, 2022 to December 31, 2022, the Company issued 1,031,371 shares under the September 2022 Distribution Agreement for net proceeds of approximately $0.6 million. From January1, 2023 to the date of filing of this Form 10-K, the Company issued 1,812,785 shares under the September 2022 Distribution Agreement for net proceeds of approximately $0.7 million.

The Company is obligated to pay Canaccord a commission of up to 3.0% of the gross proceeds from the sale of its common stock under the September 2022 Distribution Agreement. The Company has also agreed to reimburse Canaccord for its reasonable documented out-of-pocket expenses, including fees and disbursements of its counsel, in the amount of $50,000. In addition, the Company has agreed to provide customary indemnification rights to Canaccord.

The Offering will terminate upon the earlier of (1) the issuance and sale of all shares of the Company's common stock subject to the September 2022 Distribution Agreement, or (2) the termination of the Distribution Agreement as permitted therein, including by either party at any time without liability of any party.

On January 14, 2022, the Company entered into an Equity Distribution Agreement (the "January 2022 Distribution Agreement") with Canaccord, pursuant to which the Company could issue and sell, from time to time, shares of its common stock having an aggregate offering price of up to $5,000,000 shares, with Canaccord acting as an agent for sales. The Company had no obligation to sell any of the Company's shares and it could instruct Canaccord not to sell any shares if the sales could not be effected at or above the price designated by the Company from time to time and the Company could at any time suspend sales pursuant to the January 2022 Distribution Agreement. During the year ended December 31, 2022, the Company issued 6,902,279 shares under the January 2022 Distribution Agreement for net proceeds of approximately $4.8 million. The January 2022 Distribution Agreement has been terminated after all available registered shares were fully utilized.

Share Repurchase Program

On August 15, 2022, the Company announced that its Board of Directors has approved a share repurchase program pursuant to which the Company is authorized to repurchase up to $2.0 million of the Company's outstanding common stock. The timing and amount of any shares repurchased will be determined based on the Company's evaluation of market conditions and other factors, including consent of Oxford. Repurchases may be made from time to time on the open market over the course of 12 months. The Company is not obligated to acquire any shares and the program may be discontinued or suspended at any time. Through the date of filing of this Form 10-K, the Company has not repurchased any of its common stock under this share repurchase program.

13. Share-based Compensation

Under the Company's 2015 New Employee Incentive Plan (the "2015 Plan"), awards may only be granted 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, 2022, there were 90,389 shares of common stock remaining and available for future issuances under the 2015 Plan.

The Company's 2020 Stock Incentive Plan (the "2020 Plan"), which replaced the Company's 2014 Equity Incentive 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 to directors, officers, employees and consultants of the Company. The 2020 Plan, as amended, provides for the issuance of up to 3,550,000 shares of common stock, plus the number of shares available for issuance is 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). As of December 31, 2022, there were 2,635,717 shares remaining and available for future issuances under the 2020 Plan.

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

A summary of activity for the year ended December 31, 2022 is as follows:

	Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Balance as of December 31, 2021	1,170,890	$ 5.01	9.00	
Granted	13,000	$ 0.53		
Cancelled/forfeited	(8,874)	$ 60.08		
Balance as of December 31, 2022	1,175,016	$ 4.54	8.00	$ -
Vested and expected to vest at December 31, 2022	1,135,664	$ 4.57	8.00	$ -
Exercisable at December 31, 2022	671,892	$ 6.11	7.84	$ -

The Company settles exercises of stock options with newly issued shares of its common stock. There were no stock options exercised in 2022 or 2021.

The fair value of each option awarded during the years ended December 31, 2022 and 2021 was estimated on the date of grant using the Black-Scholes-Merton option valuation model based on the following weighted-average assumptions:

	December 31, 2022	December 31, 2021
Expected term	6.0 years	6.0 years
Risk-free interest rate	2.83%	1.00%
Expected volatility	123.4%	127.0%
Dividends	0%	0%
Resulting fair value	$ 0.47	$ 2.23

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, the Company uses 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, 2022 and 2021 in the statement of operations and comprehensive loss:

	Years ended December 31,	
	2022	2021
Research and development	$ 87	$ 75
General and administrative	519	531
Total share-based compensation	$ 606	$ 606

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 $0.9 million, which is expected to be recognized as a result of vesting under service conditions over a weighted average period of 2.2 years.

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, 2022 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, 2022 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, 2022, 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	Incorporated by Reference		
			Form	File No.	Date Filed
3.1	Composite Certificate of Incorporation.		10-K	001-34375 Exhibit 3.1	03/11/2016
3.2	Certificate of Amendment to Amended and Restated Certificate of Incorporation.		8-K	001-34375 Exhibit 3.1	05/10/2016
3.3	Certificate of Amendment to Amended and Restated Certificate of Incorporation.		8-K	001-34375 Exhibit 3.1	05/23/2018
3.4	Certificate of Amendment to Amended and Restated Certificate of Incorporation.		8-K	001-34375 Exhibit 3.1	07/29/2019
3.5	Certificate of Amendment to Amended and Restated Certificate of Incorporation.		8-K	001-34375 Exhibit 3.1	08/06/2019
3.6	Certificate of Designation of Preferences, Rights and Limitations of Series B Convertible Preferred Stock.		8-K	001-34375 Exhibit 3.1	11/28/2017
3.7	Certificate of Designation of Preferences, Rights and Limitations of Series C Convertible Preferred Stock.		8-K	001-34375 Exhibit 3.1	07/25/2018
3.8	Amended and Restated Bylaws of Plus Therapeutics, Inc.		8-K	001-34375 Exhibit 3.2	09/21/2021
4.1	Description of Securities.		10-K	001-34375 Exhibit 4.1	03/30/2020
4.2	Form of Common Stock Certificate.		10-K	001-34375 Exhibit 4.33	03/09/2018
4.3	Form of Series U Warrant.		S-1/A	333-229485 Exhibit 4.37	09/16/2019
4.4	Form of Warrant Amendment Agreement.		8-K	011-34375 Exhibit 4.1	04/23/2020
4.5	Form of Underwriters' Warrant Amendment Agreement.		8-K	011-34375 Exhibit 4.1	10/05/2020
10.1+	Patent and Know-How License Agreement, dated March 29, 2020, by and between Plus Therapeutics, Inc. and NanoTx, Corp.		8-K	011-34375 Exhibit 10.1	3/30/2020
10.2+	Patent & Technology License Agreement, dated December 31, 2021, between Plus Therapeutics, Inc. and the University of Texas Health Science Center at San Antonio.		10-K	011-34375 Exhibit 10.2	2/24/2022
10.3	Distribution Agreement, dated September 9, 2022, by and between Plus Therapeutics, Inc. and Canaccord Genuity LLC.		8-K	011-34375 Exhibit 1.1	09/09/2022
10.4	Purchase Agreement between Lincoln Park Capital Fund, LLC and Plus Therapeutics, Inc., dated August 2, 2022.		8-K	011-34375 Exhibit 10.1	08/08/2022
10.5	Registration Rights Agreement between Plus Therapeutics, Inc. and Lincoln Park Capital Fund, LLC, dated August 2, 2022.		8-K	001-34375 Exhibit 10.2	08/08/2022
10.6	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
10.7	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

10.8	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
10.9	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
10.10	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
10.11	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
10.12	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
10.13	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
10.14	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
10.15+	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
10.16#	Amended and Restated Employment Agreement between Marc Hedrick and Plus Therapeutics, Inc.	10-Q	001-34375 Exhibit 10.6	5/16/2020
10.17#	Amended and Restated Employment Agreement between Andrew Sims and Plus Therapeutics, Inc.	10-Q	001-34375 Exhibit 10.7	5/16/2020
10.18#	Employment Agreement, dated December 8, 2021, by and between Plus Therapeutics, Inc. and Normal LaFrance	8-K	001-34375 Exhibit 10.1	09/13/2021
10.19#	2015 New Employee Incentive Plan.	8-K	001-34375 Exhibit 10.1	01/05/2016
10.20#	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
10.21#	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
10.22#	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
10.23#	Form of Stock Option Agreement under the 2015 New Employee Incentive Plan.	S-8	333-210211 Exhibit 99.4	03/15/2016
10.24#	Plus Therapeutics, Inc. 2020 Stock Incentive Plan, as amended and restated.	8-K	001-34375 Exhibit 10.1	05/17/2021
10.25#	Form of Notice of Grant and Stock Option Agreement under the 2020 Stock Incentive Plan.	10-K	001-34375 Exhibit 10.26	02/24/2022
10.26+	Master Services Agreement between Piramal Pharma Solutions, Inc. and Plus Therapeutics, Inc.	10-K	001-334275 Exhibit 10.24	02/22/2021
10.27#	Form of Indemnification Agreement.	8-K	001-34375 Exhibit 10.1	02/06/2020
10.28#	Form of Agreement for Acceleration and/or Severance.	10-K	001-34375 Exhibit 10.113	03/11/2016

10.29	Medidata Services Agreement and Statement of Work.		10-Q	001-34375 Exhibit 10.1	04/21/2022
10.30	Cancer Research Grant Contract, effective August 31, 2022, by and between the Cancer Prevention and Research Institute of Texas and Plus Therapeutics, Inc.		8-K	001-34375 Exhibit 10.1	09/22/2022
23.1	Consent of BDO USA, LLP, Independent Registered Public Accounting Firm.	X			
24.1	Power of Attorney (see signature page).	X			
31.1	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.	X			
31.2	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.	X			
32.1	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.	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 23, 2023

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
/s/ Richard J. Hawkins Richard J. Hawkins	*Chairman of the Board*	February 23, 2023
/s/ Marc H. Hedrick, MD Marc H. Hedrick, MD	*President & Chief Executive Officer (Principal Executive Officer)*	February 23, 2023
/s/ Andrew Sims Andrew Sims	*Chief Financial Officer and VP of Finance (Principal Financial and Accounting Officer)*	February 23, 2023
/s/ An van Es-Johansson, MD An van Es-Johansson, MD	*Director*	February 23, 2023
/s/ Greg Petersen Greg Petersen	*Director*	February 23, 2023
/s/ Howard Clowes Howard Clowes	*Director*	February 23, 2023
/s/ Robert Lenk Robert Lenk	*Director*	February 23, 2023

EXHIBIT 23.1

Consent of Independent Registered Public Accounting Firm

Plus Therapeutics, Inc.
Austin, Texas

We hereby consent to the incorporation by reference in the Registration Statements on Forms S-1 (Nos. 333-229485, 333-227485, 333-226205, 333-224502, 333-219967, 333-215365, 333-210628 and 333-249728, 333-253612, 333-259325 and 333-266684), Forms S-3 (Nos. 333-217988, 333-172787, 333-169822, 333-157023, 333-140875, 333-134129, 333-153233, 333-159912, 333-192409, 333-200090, 333-195846, 333-216947 and 333-249410) and Forms S-8 (Nos. 333-223566, 333-210211, 333-202858, 333-181764, 333-122691, 333-82074 and 333-239548) of Plus Therapeutics, Inc. (the "Company") of our report dated February 23, 2023, relating to the consolidated financial statements, which appears in this Annual Report on Form 10-K.

/s/ BDO USA, LLP

Austin, Texas

February 23, 2023

EXHIBIT 31.1

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

I, Marc H. Hedrick, certify that:

1. I have reviewed this Annual Report on Form 10-K of Plus Therapeutics, Inc.;

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

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

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

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

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

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

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

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

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

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

Date: February 23, 2023
/s/ Marc H. Hedrick, MD
Marc. H. Hedrick,
President & Chief Executive Officer

EXHIBIT 31.2

Certification of Principal Financial Officer Pursuant to
Securities Exchange Act Rule 13a-14(a)
As Adopted Pursuant to
Section 302 of the Sarbanes-Oxley Act of 2002

I, Andrew Sims, certify that:

1. I have reviewed this Annual Report on Form 10-K of Plus Therapeutics, Inc.;

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

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

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

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

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

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

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

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

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

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

Date: February 23, 2023
/s/ Andrew Sims
Andrew Sims
Chief Financial Officer

EXHIBIT 32.1

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

In connection with the Annual Report on Form 10-K of Plus Therapeutics, Inc. for the year ended December 31, 2022 as filed with the Securities and Exchange Commission on February 23, 2023, (the "Report"), Marc H. Hedrick, as President & Chief Executive Officer of Plus Therapeutics, Inc., and Andrew Sims, as Chief Financial Officer of Plus Therapeutics, Inc., each hereby certifies, respectively, that:

1. The Report fully complies with the requirements of Section 13(a) of the Securities Exchange Act of 1934.

2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Plus Therapeutics, Inc.

By: /s/ Marc H. Hedrick, MD

Dated: February 23, 2023

Marc H. Hedrick, MD
President & Chief Executive Officer

By: /s/ Andrew Sims

Dated: February 23, 2023

Andrew Sims
Chief Financial Officer