Plus Therapeutics Announces FDA Agreement to Initiate ReSPECT-LM Dose Optimization Trial for REYOBIQ™ in Leptomeningeal Metastases

June 30, 2025

Primary objective to determine optimal dosing schedule for a registrational trial

Trial builds on recommended Phase 2 dose determined in completed Phase 1 trial

Trial benefits from $17.6M award from the Cancer Prevention & Research Institute of Texas

HOUSTON, June 30, 2025 (GLOBE NEWSWIRE) -- Plus Therapeutics, Inc. (Nasdaq: PSTV) (the "Company"), a clinical-stage pharmaceutical company developing targeted radiotherapeutics with advanced platform technologies for central nervous system (CNS) cancers, today announces the initiation of the ReSPECT-LM dose optimization trial for REYOBIQ™ (rhenium Re^{186} obisbemeda) for the treatment of leptomeningeal metastases (LM). The dose optimization trial follows encouraging results from the Company's single-dose escalation trial and is designed to evaluate multiple-dose regimens of REYOBIQ administered at defined intervals via intraventricular catheter (Ommaya reservoir).

"A safe and effective therapeutic to address the epidemic of CNS metastases and specifically leptomeningeal metastases is urgently needed," said Marc H. Hedrick, M.D., Plus Therapeutics President and Chief Executive Officer. "We expect that optimizing the dosing regimen for REYOBIQ in this trial will provide data needed to design and support a follow-on registrational trial."

ReSPECT-LM Dose Optimization Trial Design
The study design is consistent with the FDA's Project Optimus , and aims to optimize treatment dosing for maximum efficacy and safety. The primary objectives of the trial include determining the safety and tolerability of multiple REYOBIQ doses administered via intraventricular catheter at defined intervals in patients with LM from any primary solid tumor cancer and to identify both the maximum tolerated dose and minimum effective dose.

Key additional elements of the trial design include:

- Enrollment of up to 24 patients, evaluating REYOBIQ administered at the recommended Phase 2 dose or R2PD of 44.1 mCi, fractionated across three dosing intervals, with up to six patients per cohort interval:
  - Cohort 1: 56 days
  - Cohort 2: 28 days
  - Cohort 3a: 14 days
  - Cohort 3b: 14 days (6 doses)
- The trial will evaluate both safety, pharmacokinetics/dosimetry, and select efficacy-related endpoints such as objective response rate (ORR), neurologic progression-free survival (PFS), overall survival (OS), changes in neurologic status
- Furthermore, the trial will analyze cerebrospinal fluid (CSF) tumor cell counts via Plus' CNSide CSF assay platform, other pharmacodynamic markers, and compare these to standard CSF cytology

Because of the anticipated pace of enrollment, the trial is being limited initially to only two prestigious and high enrolling cancer centers, both in Texas—the University of Texas Health Science Center at San Antonio (UTHSCSA) and the University of Texas Southwestern Medical Center (UTSW) but may expand to more sites if needed.

The dose optimization study builds on promising results from the Company's single-dose escalation trial. Key highlights include:

- Cohort 4 dose (44.1 mCi) was determined to be the RP2D
- Pharmacodynamic and pharmacokinetic data showed that a single dose of REYOBIQ remained in the CSF for at least 7 days, and delivered up to an average absorbed dose of 253 Gy to the cranial subarachnoid space in Cohort 5
- Neuroimaging results showed a clinical benefit rate[1] of 76%, with 5 of 17 patients (29%) achieving partial responses and 8 (47%) maintaining stable disease through Day 112
- Clinical examination showed a clinical benefit rate in 87% of evaluable patients, with 13 of 15 patients showing a partial response or stable disease based on physician assessment
- No dose-limiting toxicities (DLTs) were observed in the first four cohorts; one Grade 4 DLT (thrombocytopenia) occurred in each of Cohorts 5 and 6
- Biologic signals of early apoptosis, innate immune activation, and increased T-cell activity by Day 28, as observed through RNA sequencing of LM cells
- 5 of 7 patients with over 80% reduction of LM tumor cells in CSF survived at least one year after initial treatment

The Company anticipates presenting these data and additional information from the completed single-dose escalation trial at the upcoming SNO/ASCO CNS Metastases Conference on August 14-16, 2025, in Baltimore, MD. The company will also request an End of Phase 1 Type B meeting with the FDA to align on the clinical development plan and the design of a potential registrational trial.

The ReSPECT-LM dose optimization trial benefits from a $17.6 million grant from the Cancer Prevention & Research Institute of Texas (CPRIT), the

second largest public funding source for cancer research in the world.

About LM
Leptomeningeal metastases (LM) are a rare but severe complication of advanced cancer, affecting the fluid-lined structures of the central nervous system. LM occurs in approximately 5% of patients with metastatic cancer, with breast cancer, lung cancer, and melanoma being the most common sources. Median survival is typically 2-6 months, and effective treatment options are limited, highlighting the urgent need for novel therapies.

About REYOBIQ™ (rhenium Re^{186} obisbemeda)
REYOBIQ™ (rhenium Re^{186} obisbemeda) is a novel injectable radiotherapy specifically formulated to deliver direct targeted high dose radiation in CNS tumors in a safe, effective, and convenient manner to optimize patient outcomes. REYOBIQ™ has the potential to reduce off target risks and improve outcomes for CNS cancer patients, versus currently approved therapies, with a more targeted and potent radiation dose. Rhenium-186 is an ideal radioisotope for CNS therapeutic applications due to its short half-life, beta energy for destroying cancerous tissue, and gamma energy for real-time imaging. REYOBIQ™ is being evaluated for the treatment of recurrent glioblastoma, leptomeningeal metastases, and pediatric brain cancer in the ReSPECT-GBM, ReSPECT-LM, and ReSPECT-PBC clinical trials. ReSPECT-GBM is supported by an award from the National Cancer Institute (NCI), part of the U.S. National Institutes of Health (NIH), and ReSPECT-LM is funded by a three-year $17.6M grant by the Cancer Prevention & Research Institute of Texas (CPRIT). The Company's ReSPECT-PBC clinical trial for pediatric brain cancer is supported by a $3 million grant from the U.S. Department of Defense's Peer Reviewed Cancer Research Program.

About Plus Therapeutics
Headquartered in Houston, Texas, Plus Therapeutics, Inc. is a clinical-stage pharmaceutical company developing targeted radiotherapeutics for difficult-to-treat cancers of the central nervous system with the potential to enhance clinical outcomes. Combining image-guided local beta radiation and targeted drug delivery approaches, the Company is advancing a pipeline of product candidates with lead programs in leptomeningeal metastases (LM), recurrent glioblastoma (GBM), and pediatric brain cancer (PBC). The Company has built a supply chain through strategic partnerships that enable the development, manufacturing, and future potential commercialization of its products. For more information, visit https://plustherapeutics.com/ or contact info@plustherapeutics.com.

Forward-Looking Statements
This press release contains statements that may be deemed "forward-looking statements" within the meaning of U.S. securities laws, including statements regarding clinical trials, expected operations and upcoming developments. All statements in this press release other than statements of historical fact are forward-looking statements. These forward-looking statements may be identified by future verbs, as well as terms such as "expect" "potential," "anticipating," "planning" and similar expressions or the negatives thereof. Such statements are based upon certain assumptions and assessments made by 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 regarding the potential promise of REYOBIQ™, expectations as to the Company's future performance, including the next steps in developing the Company's product candidates; the Company's clinical trials, including statements regarding the timing and characteristics of the ReSPECT-LM single dose and multi-dose clinical trials; the continued evaluation of REYOBIQ™ including through evaluations in additional patient cohorts.

The forward-looking statements included in this press release could differ materially from those expressed or implied by these forward-looking statements because of risks, uncertainties, and other factors that include, but are not limited to, the following: the early stage of the Company's product candidates and therapies; the results of the Company's research and development activities, including uncertainties relating to the clinical trials of its product candidates and therapies; the Company's liquidity and capital resources and its ability to raise additional cash; the outcome of the Company's partnering/licensing efforts, risks associated with laws or regulatory requirements applicable to it; market conditions, product performance, litigation or potential litigation, and competition within the cancer diagnostics and therapeutics field; ability to develop and protect proprietary intellectual property or obtain licenses to intellectual property developed by others on commercially reasonable and competitive terms; challenges associated with radiotherapeutic manufacturing, production and distribution capabilities necessary to support the Company's clinical trials and any commercial level product demand; and material security breach or cybersecurity attack affecting the Company's operations or property. This list of risks, uncertainties, and other factors is not complete. Plus Therapeutics discusses some of these matters more fully, as well as certain risk factors that could affect Plus Therapeutics' business, financial condition, results of operations, and prospects, in its reports filed with the SEC, including Plus Therapeutics' annual report on Form 10-K for the fiscal year ended December 31, 2024, quarterly reports on Form 10-Q, and current reports on Form 8-K. These filings are available for review through the SEC's website at www.sec.gov. Any or all forward-looking statements Plus Therapeutics makes may turn out to be wrong and can be affected by inaccurate assumptions Plus Therapeutics might make or by known or unknown risks, uncertainties, and other factors, including those identified in this press release. Accordingly, you should not place undue reliance on the forward-looking statements made in this press release, which speak only as of its date. The Company assumes no responsibility to update or revise any forward-looking statements to reflect events, trends or circumstances after the date they are made unless the Company has an obligation under U.S. federal securities laws to do so.

Investor Contact
CORE IR
investor@plustherapeutics.com

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[1] Clinical benefit rate defined as complete response + partial response + stable disease