Navitor Pharmaceuticals Commences Phase 1 Clinical Evaluation of NV-5138, a Novel mTORC1 Activator in Patients with Treatment-Resistant Depression

Safety Data and Potential Clinical Efficacy Signal Expected Mid-2019

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Navitor Pharmaceuticals, Inc., the leader in the development of mTORC1-targeted therapeutics designed to help patients live longer and healthier lives, announced today the initiation of Part B of its Phase 1 clinical study with its lead candidate, NV-5138, for treatment-resistant depression (TRD). NV-5138 is a first-in-class, orally-active small molecule that directly activates mTORC1, the gatekeeper of cellular metabolism and renewal, which is suppressed in the brain of people suffering from depression.

"NV-5138's direct activation of mTORC1 may deliver significant advantages over antidepressants that only indirectly activate this master metabolic control switch, offering the potential for rapid-acting antidepressant benefits without the psychotomimetic side effects and abuse potential observed with many N-methyl-D-aspartic-acid (NMDA) receptor targeted therapeutics," said Thomas E. Hughes, Ph.D., Chief Executive Officer of Navitor. "The positive results from the single ascending dose portion of our Phase 1 clinical study of NV-5138 in healthy volunteers support advancement into Part B, and we are now evaluating a single dose of the compound in patients suffering with TRD. We look forward to the initial top-line data from this study in the middle of 2019."

The Phase 1, multicenter, two-part, double-blind, placebo-controlled study is evaluating the safety, tolerability and pharmacokinetics of NV-5138 in up to 88 subjects, including healthy volunteers and patients diagnosed with TRD. In Part A, the single-ascending-dose portion of the study, up to 48 healthy volunteers were randomly assigned to double-blind treatment in six cohorts. In Part B of the study, approximately 40 subjects diagnosed with TRD are being randomized to receive either a single dose of NV-5138 or placebo. Secondary efficacy outcome measures for Part B include standard depression rating and symptomology scores such as the Montgomery-Åsberg Depression Rating Scale (MADRS).

"In multiple standard preclinical models of depressive behavior and cognition, we have shown that a single dose of NV-5138 stimulates mTORC1, enhances protein expression within hours, and increases synaptic growth in key, relevant brain regions, resulting in sustained antidepressant behavioral responses," stated George P. Vlasuk, Ph.D., President and Chief Scientific Officer of Navitor. "These behavioral changes and increases in synaptogenesis were consistent with the effects of NMDA receptor modulators such as ketamine; however, NV-5138 works through direct, post-synaptic activation of the mTORC1 signaling pathway and may therefore offer the potential for an improved safety and tolerability profile. Part B of our Phase 1 trial will offer important insights on the candidate's potential in this difficult-to-treat patient population."

About NV-5138

NV-5138 is an orally bioavailable, small molecule that directly and transiently activates mTORC1, the master modulator of cellular metabolism, which is often suppressed in the brain of patients suffering from depression. NV-5138 binds to and modulates sestrin, a newly discovered

cellular sensor protein for the amino acid leucine, a potent natural activator of mTORC1. As opposed to many other organ systems like skeletal muscle, leucine is a poor activator of mTORC1 in the brain since it is principally used as a metabolic precursor for neurotransmitter and protein synthesis. NV-5138 was designed to avoid the metabolic fate of leucine in the brain and thus serves as an effective activator of mTORC1 in this tissue. Results from preclinical models demonstrate that oral administration of NV-5138 produces rapid upregulation of key synaptic proteins, synaptic remodeling in the prefrontal cortex and hippocampus, sustained antidepressant behavioral responses, cognitive improvements and compound-specific spectral power changes, as measured by quantitative electroencephalography (qEEG). Navitor's strong intellectual property portfolio includes composition of matter patent protection for NV-5138 and related compounds.

About mTORC1

mTORC1, or Complex 1 of the mechanistic target of rapamycin, activity governs the pace and ability of the cell to synthesize protein and other cellular components. Increased mTORC1 activity contributes to a broad array of diseases of aging by increasing protein misfolding and driving cellular stress, inflammation, and fibrosis. In other disease states such as severe depression, inadequate mTORC1 activity contributes to disease pathology by limiting energy utilization and protein synthesis, leading to impaired function. Multiple preclinical studies have shown that mTORC1 activation is required for the efficacy of many rapid-acting antidepressant compounds, including but not limited to modulators of the N-methyl-D-aspartic-acid (NMDA)-mediated signaling pathway like ketamine.[1]

About Navitor

Navitor Pharmaceuticals, Inc. is the leader in the development of mTORC1-targeted therapeutics designed to help patients live longer and healthier lives. The Company's proprietary platform enables true modulation of mTORC1, the gatekeeper of cellular metabolism and renewal, with the first-ever absolutely selective mTORC1 inhibition and the unique ability for mTORC1 activation. Navitor's lead clinical-stage candidate, NV-5138, is a small molecule that directly activates mTORC1 and is being developed for treatment-resistant depression, with additional opportunities in cognition and memory. The Company's NΛValog program, which provides unprecedented selectivity in mTORC1 inhibition, is initially targeting chronic kidney disease and has broad potential application for age-related diseases. For more information, please visit www.navitorpharma.com.