NEWS RELEASE

Navitor Pharmaceuticals Initiates a Clinical Study of NV-5138, a Novel, Oral Small Molecule for Treatment-Resistant Depression

NV-5138 is a specific and direct activator of mTORC1, a cellular pathway required for the efficacy of many rapid acting antidepressants

CAMBRIDGE, Mass., June 26, 2018 – Navitor Pharmaceuticals, Inc., a biopharmaceutical company targeting the mTORC1 pathway to develop novel therapeutics that help patients live longer and healthier lives, announced today the initiation of a Phase 1 clinical study with its lead pipeline candidate, NV-5138, for treatment-resistant depression (TRD). NV-5138 is a novel small molecule that directly activates mTORC1, a master cellular regulator that has recently been shown to be a central signaling pathway required for the efficacy of several rapid acting antidepressants. NV-5138 is initially being evaluated in TRD but may offer future potential for the treatment in the broader disease category of major depressive disorder (MDD.)

"We are enthusiastic about initiating clinical development with NV-5138 for major depressive disorder, as we believe this novel activator of mTORC1 has the potential to offer a unique approach to meeting many of the unmet needs of this serious and chronic disease. Millions of patients with depression do not adequately respond to standard pharmacological therapies which can take weeks or months before patients experience their effects, if at all, "said George P. Vlasuk, PhD, President and Chief Executive Officer of Navitor. "We see the development of NV-5138 in MDD/TRD as a pioneering advance toward realizing the therapeutic potential of modulating the mTORC1 signaling pathway to treat a wide range of chronic human diseases."

The Phase 1, multicenter, two-part, double-blind, placebo-controlled study will evaluate 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 will be randomly assigned to double-blind treatment in six dosage-level cohorts. Within each cohort, six subjects will be randomized to receive NV-5138 and two subjects will be randomized to receive placebo. In Part B of the study, approximately 40 subjects diagnosed with TRD will be randomly assigned to double-blind treatment at a single dosage level that will be established based on data from Part A of the study. Other prespecified outcome measures to be evaluated in Part B include standard depression rating and symptomology scores such as the Montgomery-Åsberg Depression Rating Scale (MADRS).

"Initiation of this clinical study is supported by preclinical studies demonstrating the potential of NV-5138 as an oral treatment for depression through activation of mTORC1, a cellular pathway that appears to underlie the beneficial effects of several in a new class of rapidly acting antidepressants," said Maurizio Fava, MD, Director of the Division of Clinical Research of the Massachusetts General Hospital (MGH) Research Institute and member of the Navitor Clinical Advisory Board.

Previously, Navitor has presented preclinical results on the efficacy of NV-5138 in multiple models of depression-like behavior, which demonstrated that NV-5138 produced behavioral responses and concomitant increases in new synapses (synaptogenesis) consistent with a rapid-acting antidepressant through transient,

direct activation of the mTORC1 signaling pathway in the brain. Navitor leveraged multiple preclinical observations that have shown mTORC1 activation is required for the efficacy of many rapid-acting antidepressant compounds including several modulators of the NMDA (N-methyl-D-aspartic acid)-mediated signaling pathway like ketamine, which is an active area of innovative drug development for depression.[1,2]

About Treatment Resistant Depression and Treatment Options

Treatment-resistant depression (TRD) is a subset of major depressive disorder (MDD) that refers to depressive episodes that are not adequately controlled by standard antidepressant therapy. Several studies including a postmortem analysis of healthy and severely depressed patients as well as multiple pre-clinical settings have suggested an association between the activity of mTORC1 pathway signaling and depression. Standard antidepressant therapies, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are only modestly effective and have a very slow onset typically taking 6-8 weeks to show efficacy. Newer drugs that antagonize or otherwise modulate the presynaptic glutamate N-methyl-D-aspartic acid (NMDA) receptor, have demonstrated the potential for improved efficacy with a rapid onset of antidepressant effects (days as opposed to weeks) and today there are several NMDA modulators in clinical development for depression, including ketamine and related agents. Unfortunately, presynaptic NMDA receptor modulation can cause significant side effects including dissociation (hallucination) and has abuse potential.

About Rapid Acting Antidepressants and mTORC1 Activity

New antidepressant drugs that modulate the presynaptic glutamate N-methyl-D-aspartic acid (NMDA) receptor, have demonstrated the potential for improved efficacy with a rapid onset of antidepressant effects (days as opposed to weeks) and today there are several NMDA modulators in clinical development for depression, including ketamine and related agents. Since the initial observations connecting NMDA receptor modulation and depression, scientists have demonstrated that these agents increase production of key synaptic signaling proteins resulting in synaptogenesis and have also elucidated the mechanism that underlies the therapeutic antidepressant benefit seen with these agents in specific pre-clinical settings. This new research demonstrates that presynaptic NMDA receptor modulation transiently activates the postsynaptic mTORC1 signaling pathway and this activation is required to initiate the cellular processes like protein synthesis that lead to the synaptogenesis and antidepressant effects of these agents. Although the initial target engagement of these agents occurs within a short time frame of a few hours, this transient activation of mTORC1 results in sustained, long-lasting synaptic and behavioral effects that persist for days to even weeks after a single treatment.

About NV-5138

NV-5138 is an orally bioavailable, small molecule that is designed to directly and transiently activate mTORC1 activity by binding to and modulating a newly discovered cellular sensor protein for the amino acid leucine, which is a potent natural activator of mTORC1. Unlike leucine, oral administration of NV-5138 results in significant mTORC1 pathway activation in the brain since it is not broken down or incorporated into new proteins. These properties make NV-5138 a unique agent with which to evaluate the role of mTORC1 in brain disorders, such as depression, where mTORC1 activity is often suppressed. Results from preclinical models demonstrate that NV-5138 produces rapid upregulation of key synaptic proteins, synaptogenesis and sustained antidepressant behavioral responses via the transient and direct activation of the mTORC1 signaling

pathway. Since NV-5138 does not directly modulate the NMDA receptor pathway, it may not have the side effects and abuse potential observed with several NMDA receptor therapeutics currently in development. NV-5138 is currently being clinically studied for the treatment of major depressive disorder (MDD) with an initial focus on treatment-resistant depression (TRD).

About Navitor

Navitor Pharmaceuticals, Inc. is realizing the potential of modulating mTORC1, the master regulator of cellular function, to develop a pipeline of therapeutics that help patients live longer and healthier lives. Our industry leading team is unlocking the promise of recent discoveries in mTORC1 biology to address a broad range of chronic diseases. Our initial clinical application is a first-in-class drug to address unmet needs in depression. For more information, please visit www.navitorpharma.com.

1. Duman, RS and Aghajanian, GK. *Science*. 2012 October 5; 338(6103): 68–72.

2. Scheung, L, et al., *Frontiers in Neuroscience*. 2015 July 21; 9 (249).

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