Neumora Therapeutics Announces Initiation of Phase 3 Clinical Program for Navacaprant (NMRA-140) in Major Depressive Disorder

July 18, 2023 12:00 PM EDT

In a Phase 2 study, navacaprant (NMRA-140) monotherapy demonstrated statistically significant and clinically meaningful reductions in symptoms of depression and anhedonia in participants with moderate-to-severe MDD

Positive End-of-Phase 2 meeting with U.S. Food and Drug Administration completed in June 2023, enables advancement of navacaprant into Phase 3 studies

Pivotal studies expected to support New Drug Application for navacaprant monotherapy in 2025

WATERTOWN, Mass.--(BUSINESS WIRE)--Neumora Therapeutics, Inc. (Neumora), a clinical-stage biopharmaceutical company redefining neuroscience drug development, today announced the planned initiation of the KOASTAL Program, a Phase 3 pivotal clinical program designed to evaluate the efficacy and safety of navacaprant (NMRA-140) monotherapy for the treatment of major depressive disorder (MDD). The planned initiation follows the successful completion of an End-of-Phase 2 meeting with the U.S. Food and Drug Administration (FDA) and a robust Phase 2 study with navacaprant. Navacaprant is an oral 80 mg once-daily kappa opioid receptor (KOR) antagonist, a novel mechanism of action for the monotherapy treatment of MDD.

“The planned initiation of the KOASTAL program represents an important step toward our goal of bringing a truly novel treatment to people living with MDD,” said Paul L. Berns, co-founder and executive chairman, Neumora. “The data from our Phase 2 study with navacaprant demonstrate its potential as a differentiated antidepressant that may help to manage anhedonia in addition to other core symptoms of depression with a favorable safety profile. These symptoms are among the most challenging to treat and cause significant negative impact on patients’ quality of life. Patients deserve better treatment options for depression, and we are working with urgency to address the serious unmet medical need that remains in MDD.”

The KOASTAL Program will include three Phase 3 randomized, placebo-controlled, double-blind studies, KOASTAL-1, KOASTAL-2, and KOASTAL-3, designed to evaluate the efficacy and safety of navacaprant monotherapy in adult patients with moderate-to-severe MDD who have a Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≥ 25 at baseline. The primary endpoint of these studies will be a change from baseline in MADRS total score at Week 6. The key secondary endpoints will be change from baseline on the Snaith-Hamilton Pleasure Scale (SHAPS) at Week 6, a measure of anhedonia.

- The KOASTAL-1 study is expected to be initiated in 3Q23 and will be conducted in the U.S.
- Neumora expects to initiate the KOASTAL-2 study in 4Q23. The study will be conducted in the U.S., Canada and Latin America.
- Neumora expects to initiate the KOASTAL-3 study in 1Q24. The study will be conducted in the U.S., Asia Pacific, and Europe.

The KOASTAL Program will also include an open-label extension study, KOASTAL-LT, designed to evaluate the long-term safety of navacaprant. Patients will have the opportunity to enroll in the KOASTAL-LT study following participation in the KOASTAL-1, KOASTAL-2, or KOASTAL-3 studies. If successful, these studies are expected to support a New Drug Application (NDA) with the FDA for navacaprant monotherapy in 2025.

“Navacaprant has a novel mechanism of action that modulates multiple neurotransmitters, including dopamine, in reward processing pathways and may offer a differentiated monotherapy treatment option beyond the currently approved agents,” said Sanjay J. Mathew, M.D., vice chair for research and professor of psychiatry and behavioral sciences at Baylor College of Medicine. “I’m excited by the Phase 2 data with navacaprant that demonstrate statistically significant and clinically meaningful improvements in depressive and anhedonic symptoms in traditionally studied moderate-to-severe MDD patients. I’m also impressed with the response in the total population, which included patients with mild MDD, and the well-tolerated safety profile. These data support the important role that the kappa opioid receptor system may have in regulating mood and addressing significant unmet needs for MDD patients.”

Neumora previously completed a Phase 2 clinical trial (NCT04221230) with navacaprant in patients with MDD. The Phase 2 clinical trial was initiated by BlackThorn Therapeutics prior to its acquisition by Neumora and was a double-blind, placebo-controlled, randomized, multicenter trial of once-daily navacaprant monotherapy compared to placebo. The trial originally enrolled only mild-to-moderate MDD patients in the U.S., and Neumora subsequently amended the inclusion criteria to enroll patients with moderate-to-severe MDD, which is the patient population typically studied in MDD clinical trials and the population that will be studied in the KOASTAL Program.

In the prespecified analysis of patients with moderate-to-severe MDD (n = 100, HAMD-17 total score ≥ 22 at baseline), navacaprant demonstrated statistically significant and clinically meaningful improvements in symptoms of depression, as measured by the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score. Navacaprant also demonstrated statistically significant and clinically meaningful improvements in anhedonia as assessed by the SHAPS. Anhedonia is a core feature of MDD that responds poorly to commonly prescribed therapies and is present in approximately 70% of patients with MDD. Topline efficacy results for navacaprant compared to placebo in the moderate-to-severe MDD subgroup are outlined in the following table:

Efficacy Results Summary in Moderate-to-Severe MDD (HAMD-17 total score ≥ 22 at baseline, n = 100)*

Outcome	Week 4 Change from Baseline	Week 8 Change from Baseline
HAMD-17 LSMD (p value)	-3.0 (p = 0.015)	-2.8 (p = 0.037)
SHAPS LSMD (p value)	-2.4 (p = 0.071)	-4.8 (p = 0.001)

**Prespecified statistical sensitivity analysis*
LSMD = difference in LS means of change from baseline between navacaprant and placebo groups

Navacaprant also demonstrated benefit in the total population (n = 171), which included mildly depressed patients with baseline HAMD-17 scores as low as 14. Navacaprant demonstrated a statistically significant and clinically meaningful improvement in depression at Week 4 (HAMD-17 LSMD; -2.7, p = 0.003) and continued to demonstrate improvements but did not achieve statistical significance compared to placebo at Week 8 (HAMD-17 LSMD; -1.7, p = 0.121), which was the primary endpoint of the original study designed by BlackThorn. Additionally, navacaprant demonstrated statistically significant and clinically meaningful improvements in anhedonia as assessed by the SHAPS at Week 4 (SHAPS LSMD; -2.8, p = 0.004) and Week 8 (SHAPS LSMD; -3.4, p= 0.002). These results were consistent with expectations for the population including mild-to-severe patients and support the trial amendments made by Neumora to focus development on the moderate-to-severe population.

In the study, navacaprant was well-tolerated with a favorable safety profile compared to placebo. The incidence of treatment emergent adverse events (TEAEs) in the navacaprant group was 35.3% versus the placebo group at 44.1%. The majority of the TEAEs were mild to moderate, with no severe TEAEs reported in the navacaprant group, and 4.9% severe TEAEs reported in the placebo group. Navacaprant was not associated with reports of sexual dysfunction and weight gain was not observed. No evidence of suicidal behavior was identified as assessed by the Columbia Suicide Severity Rating Scale.

“Major depressive disorder remains one of the most prevalent psychiatric disorders and is associated with high rates of morbidity and functional impairment. Anhedonia, the inability to experience pleasure or joy, impacts a majority of MDD patients and is a complex and challenging symptom that often remains untreated by current antidepressants. A growing body of research suggests that anhedonia is also a core risk factor for suicidal ideation, demonstrating the importance of studying and identifying new treatments that could improve care for impacted patients,” said Roger S. McIntyre, M.D., FRCPC, professor of psychiatry and pharmacology, University of Toronto and executive director of the Brain and Cognition Discovery Foundation in Toronto, Canada. “The Phase 2 navacaprant data are compelling, particularly the significant improvements observed in both depressive and anhedonic symptoms, and I am excited that these benefits will be further studied in the global Phase 3 KOASTAL program.”

About Navacaprant (NMRA-140)

Navacaprant (NMRA-140) is a highly selective, novel kappa opioid receptor (KOR) antagonist being developed as a potential monotherapy treatment for MDD. Navacaprant is an investigational once-daily oral 80 mg medication that is designed to modulate the dopamine and reward processing pathways, which play an important role in the regulation of mood, cognition, reward, and behavior. The KOR system is a well-characterized pathway known to mediate depressive-like states, and modulating this system represents a novel approach to treating MDD and other major neuropsychiatric disorders.

About Major Depressive Disorder (MDD)

Major depressive disorder (MDD) is a chronic psychiatric condition characterized by low mood and impairment in functioning, including episodes where an individual experiences a loss of interest or pleasure in daily activities and has symptoms such as problems with sleep, eating, energy, concentration or sense of self-worth. MDD is estimated to impact over 21 million adults in the United States. Nearly 70% of MDD patients fail to achieve remission with first-line treatment, which can be associated with negative side effects, including weight gain, sexual dysfunction, drowsiness, nausea and insomnia.

Anhedonia is a core feature of MDD impairing the capacity to experience or anticipate pleasure and is present in up to 70% of people with MDD. Anhedonia is associated with poor treatment outcomes and is frequently not resolved with currently approved therapies.

About Neumora

Neumora Therapeutics, Inc. is a clinical-stage biopharmaceutical company founded to confront the global brain disease crisis by taking a fundamentally different approach to the way treatments for brain diseases are developed. Our therapeutic pipeline currently consists of seven clinical and preclinical neuroscience programs that target novel mechanisms of action for a broad range of underserved neuropsychiatric disorders and neurodegenerative diseases. Our work is supported by an integrated suite of translational, clinical, and computational tools to generate insights that can enable precision medicine approaches. Neumora’s mission is to redefine neuroscience drug development by bringing forward the next generation of novel therapies that offer improved treatment outcomes and quality of life for patients suffering from brain diseases.

Neumora has operations in the Greater Boston Area and South San Francisco. For additional information, please visit www.neumoratx.com and follow us on Twitter: @NeumoraTx.

Contacts

Investor Contact:
Helen Rubinstein
Helen.Rubinstein@neumoratx.com

Media Contact:
Katie Engleman
Katie@1abmedia.com