Neuropsychiatric Disorders Portfolio

At Neurocrine Biosciences, our neuropsychiatric disorders portfolio includes early- to mid-stage programs evaluating potential novel therapies for schizophrenia, depression, and anhedonia in major depressive disorder.

Mental health disorders occur in more than 792 million people globally. New treatment options in this space are critical to help lessen the personal, social, and economic toll of these disorders.[1]

Overview

Schizophrenia

Schizophrenia is a serious and complex mental disorder that affects how a person thinks, feels, and behaves. As one of the leading causes of disability worldwide, it often results in significant emotional burden for those who experience symptoms, as well as their family and friends.

The symptoms of schizophrenia fall into three categories:

- **Positive symptoms —** characterized by the addition of something not normally present — include sensory changes, hallucinations, and delusions. Such symptoms can result in psychotic behavior, suggesting lost sense of reality
- **Negative symptoms —** characterized by the absence of something — include emotional and physical disruptions, such as lack of facial expression, slowed speech patterns, decreased motivation, and withdrawal
- **Cognitive symptoms —** characterized by poor mental function — include difficulty paying attention, processing information, and making decisions

Schizophrenia Fast Facts

~30% **patients** living with **schizophrenia in the U.S.** fail to respond to current antipsychotic therapy.[2]

~80% of approximately **3.5 million people living with schizophrenia** in the U.S. experience clinically relevant cognitive symptoms.[3,4]

~40% of patients report bothersome **side effects** **with current antipsychotic medications,** including symptoms of metabolic syndrome and neurologic symptoms.[5,6]

Major Depressive Disorder (MDD)

MDD is a mental health disorder characterized by a persistently depressed mood, loss of interest, lack of enjoyment in daily activities, and decreased energy. MDD is one of the leading causes of disability.

~1/3 of the more than **16 million people** in the U.S. who live with major depressive disorder **do not respond** to available antidepressants.[7,8]

MDD in Anhedonia

Anhedonia results in an inability to experience pleasure from normally enjoyable experiences. It is a core symptom in depression and frequently occurs in people with schizophrenia, bipolar disorder, substance abuse, Parkinson's disease, diabetes, and coronary artery disease.

Anhedonia is a **core symptom** of major depressive disorder.

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Valbenazine

Valbenazine for Add-On Treatment of Schizophrenia

Status: Ongoing Phase 3 study

In the U.S., there are approved treatment options for patients who experience positive symptoms of schizophrenia. Mood stabilizers, antidepressants, and stimulants are sometimes prescribed to mitigate the negative and cognitive symptoms of schizophrenia, but they have been shown to have limited effect and are not specifically approved by the U.S. Food and Drug Administration (FDA) for this purpose.

Valbenazine is a selective vesicular monoamine transporter 2 (VMAT2) inhibitor being developed as a potential add-on treatment for patients with schizophrenia.

Scientists believe that elevated dopamine in an area of the brain called the striatum is associated with symptoms of schizophrenia. Valbenazine may reduce dopamine release for the potential treatment of positive and negative symptoms associated with schizophrenia.

We are currently conducting the Journey™ Study, a Phase 3 study of valbenazine as an add-on treatment in patients with schizophrenia who have inadequate response to antipsychotic treatment.

For more information on the Journey™ Phase 3 study, visit **JourneyResearchStudies.com** or **ClinicalTrials.gov**.

Luvadaxistat

Luvadaxistat for Cognitive Impairment Associated with Schizophrenia

Status: Ongoing Phase 2 study

Luvadaxistat is a potential first-in-class, investigational, selective d-amino acid oxidase (DAAO) inhibitor being developed for the potential treatment of cognitive impairment associated with schizophrenia (CIAS).

In schizophrenia, N-methyl D-aspartate (NMDA) is an important receptor on the surface of PV+ gamma-aminobutyric (GABA) interneurons. D-serine and glutamate are co-agonists, meaning they must both bind to NMDA in order to activate the receptor. In schizophrenia, D-serine is catabolized by DAAO at an increased rate, which reduces D-serine concentrations and subsequently reduces NMDA receptor function. Luvadaxistat may block DAAO, offering the potential to increase D-serine levels and restore NMDA function.

We are currently conducting the ERUDITE™ Phase 2 study of luvadaxistat for patients with CIAS.

For more information about the ERUDITE™ Phase 2 study, please visit **ClinicalTrials.gov**.

NBI-1117568

NBI-1117568 for Schizophrenia

Status: Ongoing Phase 2 study

NBI-1117568 is an investigational, potential first-in-class, oral, investigational muscarinic M4 selective acetylcholine receptor agonist for the potential treatment of adults with schizophrenia.

All currently approved antipsychotic medications are believed to work through direct action on monoaminergic receptors. Muscarinic receptors are central to brain function and have been validated as drug targets in psychosis and cognitive disorders. Highly selective muscarinic agonists represent a novel mechanism of action to target symptoms of schizophrenia.

We are currently conducting a Phase 2 study in adult patients with schizophrenia.

Neurocrine is developing NBI-1117568 for schizophrenia as a part of a strategic collaboration and licensing agreement with Sosei Heptares.

For more information about the Phase 2 study, please visit **ClinicalTrials.gov**.

NBI-1065845

NBI-1065845 for Inadequate Response to Treatment in Major Depressive Disorder

Status: Ongoing Phase 2 study

NBI-1065845 is a potential first-in-class, investigational alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) potentiator being developed for the potential treatment of patients with inadequate response to treatment in major depressive disorder (MDD).

We are currently conducting the SAVITRI™ Phase 2 clinical study to evaluate NBI-1065845 as an adjunctive therapy in patients with MDD who have had an inadequate response to at least one antidepressant treatment.

For more information about the SAVITRI™ Phase 2 study, please visit **studiesonmdd.com** or **ClinicalTrials.gov** once available.

NBI-1065846

NBI-1065846 for Anhedonia in Major Depressive Disorder

Status: Ongoing Phase 2 study

NBI-1065846 is a potential first-in-class, investigational G protein-coupled receptor 139 (GPR139) agonist being developed for the treatment of anhedonia in MDD.

We are currently conducting the TERPSIS™ Phase 2 clinical study to evaluate NBI-1065846 as an adjunctive treatment to oral antidepressant medication(s) in patients with anhedonia in MDD.

For more information about the TERPSIS™ Phase 2 study, please visit **studiesonmdd.com** or **ClinicalTrials.gov**.

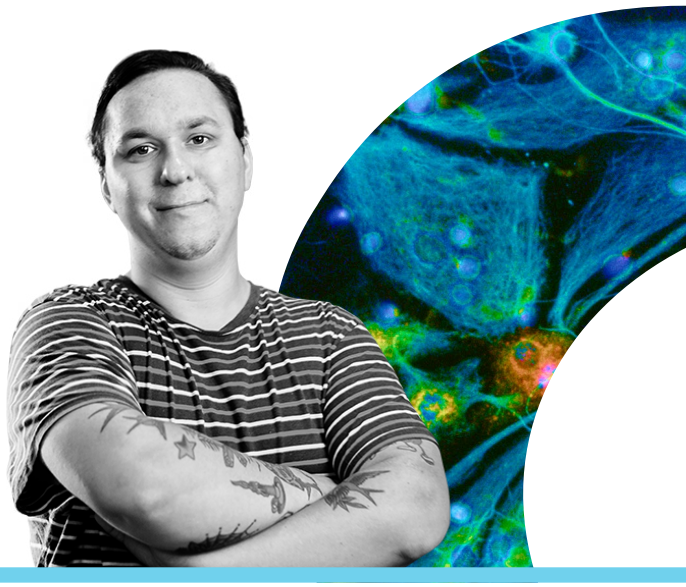
NBI-1070770

NBI-1070770 for Major Depressive Disorder

Status: Ongoing Phase 1 study

NBI-1070770 is an investigational, novel, orally active small molecule that is being developed for the potential treatment of MDD.

We are currently conducting a Phase 1 study to evaluate the safety of NBI-1070770 for the potential treatment of MDD.



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