# NeuroRx, Inc. Completes Phase 2b/3 Feasibility Enrollment for First Glx-Targeted Oral Drug Targeting Suicidal Bipolar Depression

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WILMINGTON, Del. - NeuroRx, Inc., a clinical stage biopharma company has completed the feasibility enrollment phase of its 2b/3 clinical trial of NRX-101 for the treatment of suicidal bipolar depression. The study is designed to test the hypothesis that NRX-101 is superior to standard of care in maintaining remission from depression and suicidal ideation in patients who present to emergency departments with Severe Bipolar Depression and Acute Suicidal Ideation and Behavior. NRX-101 was awarded FAST TRACK designation by the FDA in August 2017 as an experimental agent for the treatment of Severe Bipolar Depression with Acute Suicidal Ideation or Behavior. In April 2018, the FDA issued a Special Protocol Agreement (SPA)1 to NeuroRx for a pivotal trial of NRX-101.

Patients enrolled in the clinical trial had Montgomery Asberg Depression Rating Scores of 30 or higher and Columbia Suicide Severity Rating Scale scores of 4 or 5 and are considered to be at highest risk of potential suicide. These patients would otherwise be provided psychiatric hospitalization on a voluntary or involuntary basis and considered for Electroconvulsive Therapy. Patients who suffer from bipolar depression are at far greater risk of suicide than those with major depressive disorder and are believed to represent between 25% and 40% of those who tragically end their lives each year in the United States. Tragically, 20% of those diagnosed with bipolar disorder are believed to take their lives at some point.

“Suicide has become a national epidemic and the 10th leading cause of death. We at NeuroRx embarked on this mission to develop a first-in-class drug for patients with suicidal depression because these patients represent an acute unmet medical need. We are losing 100 Americans each day, 22 of whom are veterans and soldiers,” said Jonathan Javitt, MD, MPH, CEO and Chairman of NeuroRx.

NRX-101 (D-cycloserine/lurasidone fixed dose combination) is the first oral drug demonstrated in human volunteers to raise glutamine/glutamate (abbreviated Glx) in the anterior cingulate cortex of the brain on Magnetic Resonance Spectroscopy. Reduced levels of Glx have been reported in multiple studies of patients with depression and PTSD and increased Glx is correlated with improvement in depression as measured by rating scales. Increased Glx has also been demonstrated with intravenous ketamine and ECT, but not with any known SSRI antidepressant. As a result, the US Food and Drug Administration (FDA) issued NeuroRx a Letter of Support related to the treatment of depression under the Biomarker program of the 21st Century Cures Act. Specifically, the FDA stated:

*“published and nonpublished data submitted by NeuroRx to FDA suggests that measurement of Glx has the potential to be developed as a pharmacodynamic biomarker…There is evidence that NMDA-blocking drugs may result in increased Glx, but this effect has not been observed in drugs targeting the serotonin pathway.”*

The purpose of the phase 2b/3 feasibility phase is to determine whether patients with suicidal bipolar depression can safely be enrolled and monitored throughout a six-week trial that begins in the hospital setting and transitions to the outpatient setting as soon as the patient is deemed stable by treating physicians. Twelve patients were enrolled at hospitals in Alabama, North Carolina, and Florida, and were treated initially in the hospital with intravenous ketamine or placebo. Those who responded to initial treatment were randomized to receive oral NRX-101 or lurasidone alone (the standard of care) on an outpatient basis. No drug-related Serious Adverse Events were observed in the feasibility phase and study sites were able to demonstrate a concordance between the rating scores determined by on-site evaluators and by a central master rater. The ongoing clinical trial remains blinded and will likely include a complete feasibility assessment by the study’s Data Safety and Monitoring Committee prior to initiating the pivotal phase 2b/3 efficacy study later this year.

The pivotal phase under the Special Protocol Agreement is targeted to involve 150 patients at 10 or more study sites. As noted on Clinicaltrials.gov, the study will be led by Prof. Andrew Nierenberg, Professor of Psychiatry at Harvard Medical School, and co-chaired by Profs. Sanjay Matthew of Baylor Medical School and Richard Shelton of University of Alabama Birmingham. “This is the first trial that attempts to offer a potentially safe and effective oral treatment to a population of patients for whom there is no currently-indicated drug” said Prof. Nierenberg who serves as Head of Bipolar Research at Harvard’s Mass General Hospital.

In addition to the planned phase 2b/3 efficacy study, NeuroRx is initiating further biomarker studies in depression and PTSD to attempt to demonstrate the association between increased Glx associated with oral NRX-101 and decreased measures of depression and suicidal ideation.

*About Bipolar Depression and Acute Suicidal Ideation & Behavior*

Bipolar disorder, which affects 5.7 million Americans, is characterized by significant changes in mood, from mania or hypomania,

to depression, often quite severe. The depressive phase, which is called “bipolar depression,” can trigger suicidal thoughts and behaviors. Standard-of-care consists of hospitalized observation and electroconvulsive therapy (ECT). Unfortunately, most commonly-used antidepressants bear an FDA-mandated warning label identifying their potential to increase the risk of suicide.

Each day, approximately 100 Americans, 22 of whom are Veterans and Soldiers, and more than 2,100 people worldwide, end their lives by suicide, according to American Foundation for Suicide Prevention (AFSP) and the World Health Organization (WHO). Although only 10% of all people with depression have bipolar depression, NeuroRx estimates that bipolar depression accounts for nearly half of all suicides each year. Estimates indicate that 50% or more of individuals with bipolar disorder attempt suicide and that 11% or more succumb to suicide.

*About NRX-101*

NRX-101 is the first oral antidepressant drug demonstrated to raise Glutamate/Glutamine (Glx) in the brain. It is a patented, oral, fixed-dose combination of two FDA approved drugs: d-cycloserine, a N-methyl-D-aspartate (NMDA) receptor modulator, and lurasidone, a 5-HT2a receptor antagonist. In August 2017, NRX-101 was awarded FAST TRACK designation for treatment of Acute Suicidal Ideation and Behavior in patients with Bipolar Depression and has now entered a pivotal phase 2b/3 trial led by investigators from Harvard, Columbia, Baylor, and UAB.

Statistically significant results from two Phase II clinical studies, have been published in peer-reviewed journals. The studies showed a 50% reduction in symptoms of depression in patients with major depressive disorder and suicidal bipolar depression, and a 75% reduction in suicidal ideation in bipolar patients. Biomarker studies using MR Spectroscopy have demonstrated increases in Glx that approximate those demonstrated with intravenous ketamine and exceed the neurochemical changes achieved with electroconvulsive therapy.

NeuroRx has now received a Biomarker Letter of Support and a Special Protocol Agreement from the US Food and Drug Administration for its phase 2b/3 clinical trials. The Company has signed a Cooperative Research and Development Agreement with the US Dept. of Veterans Affairs to study the effects of NRX-101 in veterans with suicidal depression and PTSD.

*About NeuroRx, Inc.*

NeuroRx draws upon 30 years of basic science and clinical expertise in the role of the N-methyl-D-aspartate (NMDA), a receptor that regulates human thought processes, particularly depression and suicidality. The company is privately- funded and led by former senior executives of Johnson and Johnson, Pfizer, Lilly, and Bristol Meyer Squibb.

1 A special protocol agreement is the mechanism by which FDA reviews in advance the study design, endpoints, and statistical analysis plan of a clinical trial in order to determine whether the proposed study may meet the requirements for a New Drug Application. A small minority of drugs that enter phase 3 studies are awarded Special Protocol Agreements.

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