Sequential Treatment With IV Ketamine Followed by Combined Oral D-Cycloserine + Lurasidone (NRX-101) for Severe Bipolar Depression and Suicidality: Preclinical and Clinical Findings

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ABSTRACT

Background: N-methyl-D-aspartate (NMDAR) antagonists produce potent anti-depressive and anti-suicidal effects in humans but their clinical utility is limited by psychotomimetic side effects and lack of orally available medications. D-cycloserine (DCS) is a NMDAR-glycine-site mixed agonist/antagonist that has shown efficacy at high doses (1000 mg) in human clinical studies in treatment-resistant depression (TRD) and suicidality. Lurasidone is an atypical antipsychotic approved for the treatment of bipolar depression. Here, we evaluated effects of combined DCS + lurasidone (NRX-101) in rodent depression, psychosis, and anxiety/akathisia assays. In parallel, we evaluated the ability of oral NRX-101 to maintain effects of acute ketamine administration in patients with severe bipolar depression with acute suicidal ideation and behavior (ASIB).

Methods, Preclinical: The combined ketamine + DCS/lurasidone was assessed in animal models of depression (Forced swim test, FST), psychosis (AMPH-induced locomotor activity, LMA), anxiety/akathisia (Elevated plus maze, EPM), and abuse potential (self-administration). All studies were performed by Psychogenics, Inc. (Tarrytown, NJ). Animals (Male C57BL/6J mice) were studied in groups of n=10. Each animal was used only once.

Methods, Clinical: Patients with severe bipolar depression that were acutely suicidal of either sex (n=21) were first administered intravenous ketamine vs. placebo. Responders were then randomized to receive co-formulated DCS+lurasidone (NRX-101) vs. lurasidone alone. Depression was assessed using MADRS-scores derived from the BISS. Suicidality was assessed using the CSSRS. Clinical PK data

Outcome measures

- Primary: Montgomery-Asberg Depression Rating Scale from the Bipolar Inventory of Symptoms Scale (BISBIS-derived MADRS)
- Secondary: Columbia Suicide Severity Rating Scale (C-SSRS)

Inclusion criteria:

- Age: 18-55; sex (n=21) were first administered intravenous ketamine vs. placebo. Responders were then randomized to NRX-101 vs. lurasidone alone.

Exclusion criteria:

- Atypical antipsychotics discontinued at study initiation
- Pregnancy/unstable medical conditions
- Treatment with >1 mood stabilizer (e.g. lithium, valproic acid, carbamazepine)
- Concomitant psychotherapy allowed if stable for 3 months
- Bipolar depression based upon MINI 7.0.2

Concurrent medications

- Allowed to continue on prior antidepressants/mood stabilizers
- Adjunct antipsychotics continued at study initiation
- Target dose: 950 mg DCS/66 mg lurasidone
- DCS: 375 mg DCS/53.3 mg lurasidone, 5 day up-titrations
- Lurasidone: 200 mg DCS/31.25 mg lurasidone for agitation/titration responses
- EPM ("anxiety")

Clinical PK data

- Peak levels were assessed 2-hr following day 2 (375 mg/d) and day 42 (950 mg/d) administration.
- Trough levels were assessed 2-hr following day 2 (375 mg/d) and day 42 (950 mg/d) administration.
- As expected, peak levels at full-dose (day 42) were ~25 µg/mL.
- Trough levels differed by ~40% from peak levels.

Clinical study: patient flow (CONSORT)

Stage 1: 28 subjects were randomized 3:1 to either ketamine or placebo
Stage 2: Ketamine responders (n=15) were randomized 2:1 to NRX-101 vs. lurasidone alone

Clinical study: Results

Statistical analyses compared individuals who received ketamine followed by lurasidone alone (standard of care, SOC) vs. those who received ketamine followed by DCS/lurasidone (NRX-101). A mixed model regression was conducted across all treatment weeks, followed by individual LOCF analyses by visit.

SUMMARY

Combined Oral D-Cycloserine + Lurasidone (NRX-101) is in late stage development for treatment of severe bipolar depression and ASIB and has received Breakthrough Therapy Designation by FDA.  Suicidality associated with bipolar depression is highly lethal. There are currently no approved treatments other than ECT.  Compared to other compounds in development for treatment of bipolar depression with suicidal ideation, NRX-101 is orally available, well tolerated, not hallucinogenic, and has no evidence of neurotoxicity or abuse liability.  The two components of NRX-101 have a longstanding track record of clinical safety.  The current findings support the efficacy and safety analyses used to power the ongoing phase III clinical trial, and provide both preclinical and clinical support for PB23 studies under an FDA Special Protocol Agreement.