W134

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 combination of DCS and 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 C57Bl6/J 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.

Results, Preclinical: DCS produced highly significant anti-depression like effects in the FST (p<.0001 vs. control), balanced effects in AMPH LMA (p<.0001 vs. both DCS and lurasidone alone), and anti-anxiety-like effects in the EPM (p<.0001 vs. control). During oral dosing, a linear dose-dependent effect was observed (p<.0001). Significant effects were observed at doses that produced peak plasma DCS levels >25 µg/mL. In safety assays, DCS showed no ability to support self-administration induced by ketamine (p<.0001 vs. ketamine, S-ketamine), and no evidence of neurotoxicity in "Olney lesion" studies.

Results, Clinical: NRX-101 was well-tolerated. During stage 1, all subjects showed significant remission of depression and suicidality symptoms. During stage 2, even though the study was not powered for efficacy, the difference between NRX-101 and lurasidone-alone across days 2-42 was p=.059. An LOCF analysis using day 14 data showed a significant, large effect size between-group difference (p=.014, d=1.6). "Stress tests" showed that results were not inordinately affected by individual patients. Suicidality improved acutely on ketamine in all subjects, and remained low throughout the remainder of the study.

Conclusions: During sequential ketamine/NRX-101 treatment, improvement in both depression and suicidality occurred within 24 hr of ketamine infusion and was maintained throughout the 6-week NRX-101 treatment period. No significant safety concerns were evident in either preclinical or clinical testing. These studies support the use of sequential treatment with ketamine followed by combined DCS+Lurasidone (NRX-101) in the treatment of ASIB.

CLINICAL STUDY DETAILS

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

Inclusion criteria:
- Age: 18-55; stable living situation; identified informant
- Bipolar depression based upon MINI 7.0.2
- BISS-derived MADRS score >20 (severe illness)
- C-SSRS score ≥4 (suicidal ideation + intent with or without specific plan)
- Concomitant psychotherapy allowed if stable for 3 months
- Concomitant benzodiazepines allowed if stable for ≥4

Exclusion criteria
- Severe substance abuse disorder within past 12 months
- Treatment with > 1 antidepressant at baseline (e.g. SSRI, SNRI, TeCA)
- Treatment with >1 mood stabilizer (e.g. lithium, valproic acid, carbamazepine)
- Pregnancy/unstable medical conditions

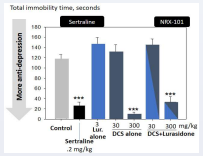
Concomitants medications
- Allowed to continue on prior anti-depressants/mood stabilizers
- Atypical antipsychotics discontinued at study initiation

Dosing:
- *Target dose*: 950 mg DCS/66 mg lurasidone
- *Start dose*: 375 mg DCS/33 mg lurasidone, 5 day upward titration
- *Up-titrations*: 950 mg DCS/99 mg lurasidone; 950 mg DCS/132 mg lurasidone for agitation/inadequate response
- *Down-titrations*: 826 mg DCS/49.5 mg lurasidone; 700 mg DCS/33 mg lurasidone for sedation/side effect

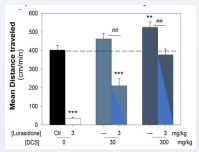
Preclinical efficacy assessment

"Efficacy" assessments evaluated NRX-101 in tests relevant to depression (FST), Psychosis (AMPH LMA) and anxiety/akathisia (EPM). N=10 animals were used per group.

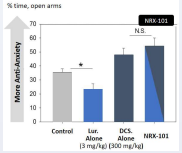
Forced swim test ("depression")



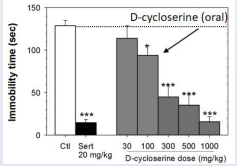
AMPH LMA ("psychosis")



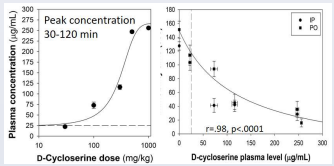
EPM ("anxiety")



"Efficacy" following oral administration

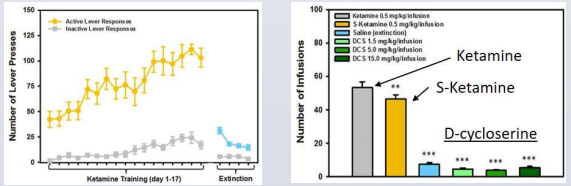


PK/PD relationships



Preclinical safety assessments

Abuse liability: A self-administration assay was used to evaluate potential abuse liability. Both ketamine and S-ketamine supported self-administration at doses relevant to their clinical effects. DCS did not maintain ketamine-induced self-stimulation at any dose tested.



Neurotoxicity: Liability to produce neuronal damage ("Olney lesions") was assessed in female Sprague-Dawley rats (n=106). DCS and lurasidone were administered at doses of up to 1600/100 mg/kg. Neurodegenerative lesions were assessed using H&E and Fluorojade stains. DCS did not induce neurodegeneration up to the maximum tolerated dose

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 assess prior to dosing on days 14 and 42
- As expected, peak levels at full-dose (day 42) were ~25 µg/mL
- Trough levels showed adequacy of BID dosing and did not change significantly (p=.2) from day 14 to 42
- These data support integrity of the formulation and dosing to be used for future studies

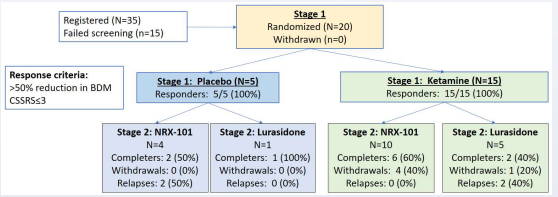
Peak levels (µg/mL)
Day 2: 7.99 ± 0.60
Day 42: 24.76 ± 2.09

Trough levels (µg/mL)
Day 14: 17.82 ± 2.26
Day 42: 13.37 ± 2.29

Clinical study: patient flow (CONSORT)

Stage 1: 20 subjects were randomized 3:1 to either ketamine or placebo

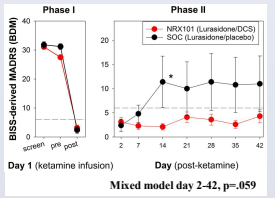
Stage 2: Ketamine responders (n=15) were randomized 2:1 to NRX-101 vs. lurasidone alone



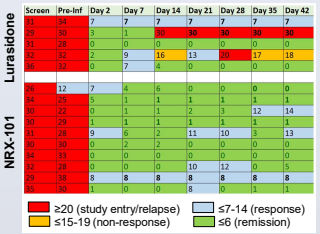
Clinical study: Results

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.

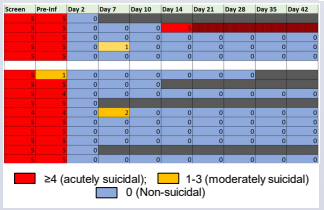
Mean depression score



Individual subject data



Suicidality scores (CSSRS)



"Stress test"

Day 14 LOCF	#subj	F	p	d
All subjects	15	8.34	0.014	1.60
Minus NRX-101 withdrawal patient	14	7.17	0.022	1.55
Minus Lurasidone relapse patient	14	5.19	0.044	1.32
Minus both	13	4.53	0.059	1.28

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 effect-size analyses used to power the ongoing phase III clinical trial, and provide both preclinical and clinical support for P2b/3 studies under an FDA Special Protocol Agreement.

Funded by NeuroRx, Inc.
Dr. Javitt did not participate in these studies as a faculty member at Columbia University