A Randomized, Double-Blind Controlled Comparison of NRX-101 (D-cycloserine/lurasidone) to Lurasidone for Adults with Bipolar Depression and Subacute Suicidal Ideation or Behavior

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INTRODUCTION

Bipolar disorder affects approximately 8.5 million people in the United States.[1] The risk of suicidal ideation or behavior is uniquely high in patients during bipolar depressive episodes compared to those with major depressive disorder, thought disorders, and personality disorders. Lifetime suicide behavior occurs in 25% to 56% of people with bipolar disorder.[2,4] About 40% of the nearly 50,000 annual deaths from suicide in the United States are associated with bipolar disorder.[3] Thus, bipolar depression with suicidal ideation has uniquely lethal clinical characteristics.

Akathisia is the most common movement-related adverse effect of antipsychotics and is characterized by distressing feelings of restlessness or inner tension generally associated with the use of antipsychotics.[5] Akathisia has been identified as a principal cause of medication nonadherence in patients with schizophrenia and bipolar disorder and it is associated with treatment-emergent suicidality.[6] In prior nonclinical studies we have demonstrated that NMDA antagonists in general and D-cycloserine (DCS) in particular decreases akathisia in rodents.

In our prior phase 2 trial of DCS+lurasidone vs. lurasidone alone administered after ketamine in patients with bipolar depression and acute suicidality, we demonstrated a statistically-significant improvement in MADRS depression score (P=0.03), a reduction in suicidality (P=0.02) and a trend level of significance for reduction of akathisia favoring DCS+lurasidone (P=0.11).[7]

In this trial we attempted to demonstrate the benefit of DCS+lurasidone (NRX-101) vs. lurasidone alone without prior ketamine pretreatment in patients with bipolar depression and subacute levels of suicidality (C-SSRS=3 or 4)

STUDY DESIGN

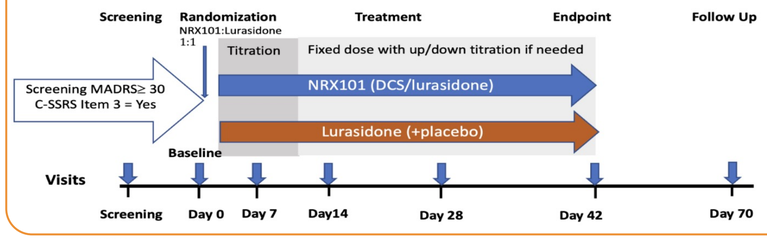
We conducted a multicenter, randomized, stratified, double-blind, parallel-group, two-arm outpatient study including 74 participants comparing NRX-101 to lurasidone in a 1:1 ratio for the treatment of bipolar depression (MADRS >30) in participants with subacute suicidal ideation or behavior and not requiring hospitalization (C-SSRS 3 or 4 screening).

Primary Efficacy Objective

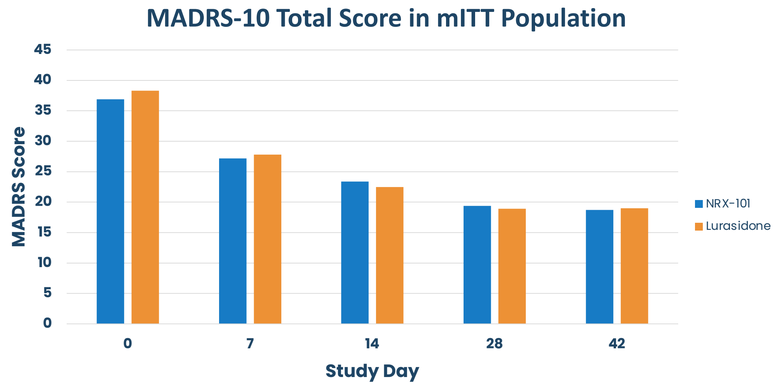
- To test the hypothesis that treatment with NRX-101 is superior to lurasidone (a standard of care medicine) in improving symptoms of depression as measured by the Montgomery Åsberg Depression Rating Scale (MADRS-10) total score in adults with severe bipolar depression and subacute suicidal ideation or behavior (SSIB).

Prospectively Defined Safety Objectives

- To test the hypothesis that treatment with NRX-101 is superior to lurasidone (a standard of care drug) in reducing suicidality in depressed bipolar patients with SSIB, as measured by the Columbia Suicide Severity Rating Scale (C-SSRS).
- To test the hypothesis that participants treated with NRX-101 are less likely to suffer from akathisia than those treated with lurasidone as measured by the Barnes Akathisia Rating Scale (BARS).
- To test the hypothesis that fewer participants treated with NRX-101 will be discontinued for lack of efficacy or exacerbation of suicidality than participants treated with lurasidone.



RESULTS



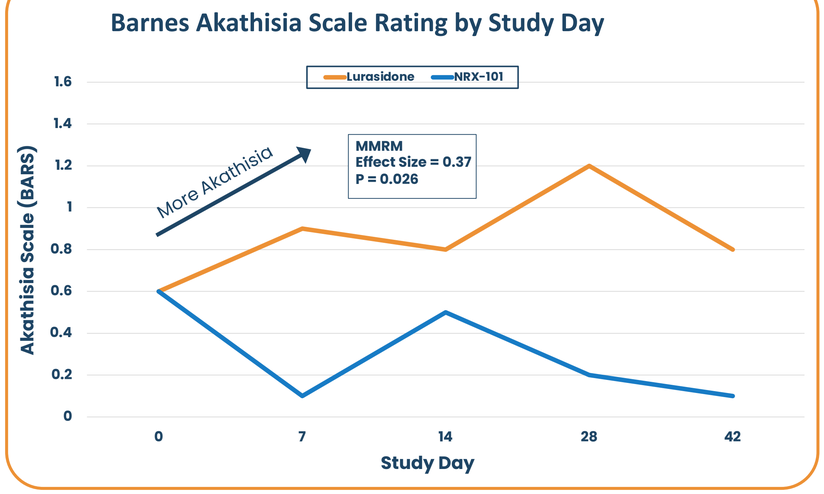
Time to Sustained Remission from Suicidality (C-SSRS≤3)

	NRX-101 (N=37)			Lurasidone (N=42)		
	Remission	At Risk	Cumulative Remission (95% CI)	Remission	At Risk	Cumulative Remission (95% CI)
Day 7	22	28	62.9 (47.3 - 78.4)	22	33	56.2 (41.5 - 71.9)
Day 14	26	9	74.3 (59.2 - 87.2)	26	12	66.7 (51.9 - 80.8)
Day 28	27	5	77.5 (62.6 - 89.6)	27	4	69.7 (54.9 - 83.3)
ET/Day 42	28	1	88.8 (66.4 - 98.7)	27	3	69.7 (54.9 - 83.3)

Stratified by Sex, Mood Stabilizer Use, Antipsychotic Use, Lifetime Suicide Event

Log Rank P-Value .05

A 58% relative reduction in Time to Remission is observed favoring NRX-101



CONCLUSIONS

- NRX-101 and lurasidone both demonstrated > 50% response for treating bipolar depression with no difference seen on primary efficacy endpoint (MADRS)
- A clinically meaningful difference was observed on both primary and secondary safety endpoints favoring NRX-101
  - NRX-101 was associated with more rapid sustained remission in suicidality as measured by time to C-SSRS <3 when controlling for Stratified by Sex, Mood Stabilizer Use, Antipsychotic Use, Lifetime Suicide Event (P=0.05). This represents a 58% relative reduction in suicidality
  - NRX-101 reduced symptoms of akathisia by a mean of 76% compared to lurasidone that was sustained over 42 days (Effect Size 0.37; P=0.03) on the Barnes Akathisia Rating Scale
- Akathisia was seen in 2% of participants treated with NRX-101 vs. 11% treated with lurasidone.
- NRX-101 showed superiority to lurasidone in akathisia starting at day 7 and continuing through day 42/ET.
- No treatment-related serious adverse event was observed in either group. No safety issues were detected except for MedDRA General disorders: NRX-101 18.2% vs lurasidone 0% (p=0.002).

KEY FINDINGS

1. This represents the second trial to demonstrate advantages of DCS+lurasidone vs lurasidone alone on akathisia and suicidality and clears the path for a registration trial of NRX-101 vs. placebo to treat bipolar depression together with earlier accelerated approval for those with akathisia
2. NRX-101 demonstrated comparable reduction in depression vs. SoC 5-HT_{2a} drug (lurasidone)in suicidal bipolar depression
3. NRX-101 is the first oral antidepressant to demonstrate more rapid sustained remission from suicidality compared to a standard of care antidepressant
4. NRX-101 is the first oral antidepressant to demonstrate reduction in akathisia (to placebo levels of akathisia) compared to a Standard of Care antidepressant

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CONFLICT STATEMENT

Drs. Sapko, Lothamer, and Javitt are employees of NRx Pharmaceuticals.

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