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A Phase 2, Double-Blind, Placebo-Controlled Study of NSI-189 Phosphate, a Neurogenic Compound, among Outpatients with Major Depressive Disorder

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ABSTRACT

Background: NSI-189 is a novel compound developed for the treatment of major depressive disorder (MDD), based on preclinical evidence of enhancing hippocampal neurogenesis, as well as encouraging results from a placebo-controlled, Phase Ib study in MDD inpatients. The present double-blind trial was performed to evaluate two doses of oral NSI-189 as monotherapy in outpatients with MDD. To improve signal detection, the sequential-parallel comparison design (SPCD) was chosen.
Methods: 220 subjects were randomized to: NSI-189 40mg daily (n=44), NSI-189 80mg daily (n=44), or placebo (n=132) for 6 weeks (Stage 1). At the end of 6 weeks, placebo-treated subjects who were non-responders (defined as less than 50% reduction in Montgomery-Asberg Depression Rating Scale (MADRS)) with a MADRS score greater than 15 were re-randomized to 6 weeks treatment with NSI-189 40 mg daily (n=22), NSI-189 80 mg daily (n=22), or placebo (n=22) (Stage 2). Patients on NSI-189 who completed Stage 1 continued the same dose for another 6 weeks. The primary outcome measure was the MADRS. Secondary outcome measures included the 17-item Hamilton Depression Rating (HAMD-17), the Symptoms of Depression Questionnaire (SDQ), the Cognitive and Physical Functioning Scale (CPFQ), the patient-rated version of the Quick Inventory of Depressive Symptomatology Scale (QIDS-SR), and CogScreen and CogState objective cognitive tests. Efficacy results concerning all patients randomized in Stage 1 were pooled (50:50 weighted average) with the Stage 2 results of all re-randomized patients who had been non-responders to placebo in Stage 1.
Results: Using the SPCD pooled analysis approach, MADRS score reduction from baseline with 40mg or 80mg NSI-189 versus placebo did not reach statistical significance (mean difference -1.8, p=0.22, mean difference -1.4, p=0.34, respectively). However, the 40 mg dose resulted in a greater reduction in SDQ (mean difference -8.2, p=0.04), and CPFQ scores (mean difference -1.9, p=0.03) versus placebo in the pooled SPCD analyses. There was also a statistically greater reduction in QIDS-SR scores versus placebo for patients treated with 40 mg of NSI-189 in Stage 2 (-2.5, p=0.04), but not Stage 1. Differences for the 80 mg dose versus placebo on these three self-report measures were not statistically significant. In addition, the 40mg dose also showed statistical advantages on objective cognitive measures of attention and memory as per the Cogscreen test, but not the Cogstate test. Both doses were well-tolerated.
Discussion: Although this exploratory study of NSI-189 did not reach a statistically significant advantage over placebo on the primary outcome measure, all three secondary self-rated measures of depressive symptoms showed significant advantages for NSI-189 as an antidepressant with cognitive benefits. Significant pro-cognitive effects were also shown on objective and subjective measures. These results replicate those from the previous MDD study, and warrant further evaluation of the antidepressant and pro-cognitive effects of this compound.

BACKGROUND

- NSI-189, a benzylpiperizine-aminiopyridine, is a novel compound that stimulates neurogenesis of human hippocampus-derived neural stem cells in vitro and stimulates neurogenesis in mouse hippocampus in vivo (Data on file, Neuralstem).
- It has shown behavioral efficacy at three different doses in a mouse model of depression (novelty suppressed feeding) after daily oral administration for 28 days (Data on file, Neuralstem).
- NSI-189 is believed to have a highly specific effect in the hippocampus and subventricular zone, two well-known neurogenic regions in the adult CNS, and nowhere else (Data on file, Neuralstem).
- The results of a small (n=24) Phase 1B, double-blind, randomized, placebo-controlled, multiple-dose study in MDD subjects demonstrated a promising greater reduction in depressive and cognitive symptoms for NSI-189 than placebo (Fava et al, 2016).
- The goal of the present study was to evaluate the efficacy, safety and tolerability of two different doses of oral NSI-189 as monotherapy in outpatients with MDD.
- To optimize signal detection (Fava et al, 2003; Papakostas et al, 2015), the sequential-parallel comparison design (SPCD) was chosen, which was masked for both subjects and raters.

METHODS

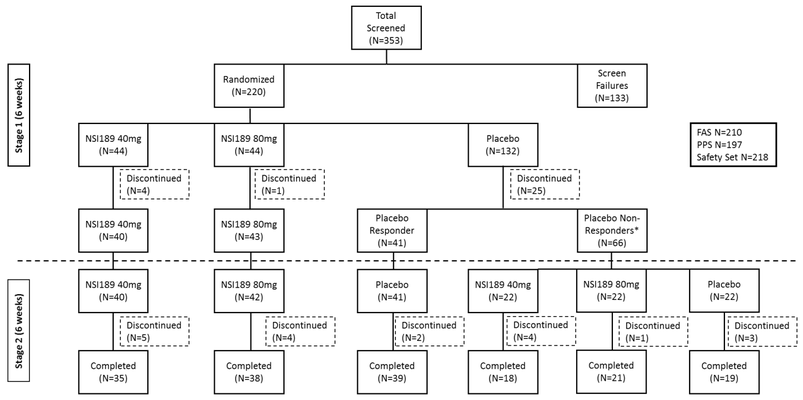
- This study was a multi-site, 12-week, randomized, double-blind, SPCD study.
- Inclusion Criteria:
  - Women and Men, 18-60.
  - MDD, current, 8+ weeks duration according to DSM-5 (assessed by SCID-CT)
  - MADRS>19 at screen (site), remote assessment (MGH CTNI), and baseline (site)
  - Passing MGH CTNI SAFER assessment (Freeman et al, 2017) during remote visit.
- Key Exclusion Criteria
  - Pregnant or breastfeeding women, women of childbearing potential not on contraception, or women with a positive pregnancy test.
  - Lifetime mania, hypomania, or psychosis.
  - Failure of more than 2 adequate antidepressant trials during the current depressive episode.
  - Treatment with ECT during the past 6 months.
  - Current OCD or PTSD, or a current Axis-I diagnosis deemed primary (other than MDD).
  - Active anorexia or bulimia nervosa within the past 5 years.
  - Active alcohol or drug use disorders in the past 12 months.
  - Patients on antidepressant, antipsychotics, lithium, buspirone – or patients on other psychotropics not stable in dose for at least 4 weeks prior to screen.
- Measures
  - Montgomery-Åsberg Depression Rating Scale (MADRS – primary outcome measure)
  - Hamilton Rating Scale for Depression, 17-item (HAMD-17)
  - Symptoms of depression questionnaire (SDQ, Pedrelli et al, 2014).
  - Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR)
  - Cognitive and Physical Functioning Questionnaire (CPFQ, Fava et al, 2009)
  - Cogstate and Cogscreen (objective cognitive testing – computer-based)
- SPCD Design and Analysis
  - Subjects were randomized in a 1:1:3 fashion to receive fixed-dose treatment with NSI-189 40 mg or 80mg daily during Stages 1 and 2, or to receive placebo during Stage 1.
  - Placebo-treated patients who completed Stage 1 with a MADRS score >15 and who also met criteria for non-response on the MADRS (less than 50% score reduction from baseline) were then re-randomized in a 1:1:1 fashion to receive either placebo, NSI-189 40 mg or 80 mg daily during Stage 2.
  - Each stage involved six weekly visits.
  - The protocol was masked for both subjects and raters.
  - Efficacy analyses: Stage 1 data are pooled with data from re-randomized patients in Stage 2.
  - Equal weights were given to data from Stages 1 and 2.
  - Safety analyses: data from subjects who received at least one study pill are included, regardless of whether they were re-randomized in stage 2.

RESULTS

Subject Disposition

- A total of 220 subjects were randomized to either receive treatment with NSI-189 40mg daily (n=44), or 80mg daily (n=44) during stages 1 and 2, or to receive placebo during Stage 1 (n=132).
- In the latter group, 107 (approximately 81%) subjects completed Stage 1, of which 66 were classified as placebo treatment non-responders.
- Placebo non-responders were then re-randomized in a 1:1:1 fashion to receive either placebo (n=22), NSI-189 40mg daily (n=22), or NSI-189 80mg daily (n=22).
- Baseline demographic/clinical variables for Stages 1 and 2 are presented in Tables 1 and 2, respectively.

Figure 1. CONSORT Diagram



*Placebo Non-Responders: <50% MADRS Reduction from Baseline and MADRS >15 at Week 7

Table 1. Demographics – Stage 1 Baseline Full Analysis Set (FAS*)

	NSI-189 40 mg/day (N=43)	NSI-189 80 mg/day (N=43)	Placebo (N=124)
Age (years)			
Mean (standard deviation)	38.0 (10.2)	42.3 (12.0)	42.3 (10.9)
Gender			
Women n (%)	27 (62.8%)	24 (55.8%)	78 (62.9%)
Race			
Caucasian	31 (72.1%)	32 (74.4%)	78 (62.9%)
African-American	11 (25.6%)	9 (20.9%)	38 (30.6%)
Asian	1 (2.3%)	1 (2.3%)	2 (1.6%)
Native American, Alaskan, Hawaiian, or Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
MADRS score			
Mean (standard deviation)	32.2 (5.5)	31.3 (5.6)	31.7 (5.0)

Full analysis set: randomized subjects who took at least one study pill and had at least one MADRS assessment after Stage 1 baseline).

Table 2. Demographics – Stage 2 Baseline Full Analysis Set (FAS*)

	NSI-189 40 mg/day (N=21)	NSI-189 80 mg/day (N=22)	Placebo (N=22)
Age (years)			
Mean (standard deviation)	45.3 (9.6)	42.9 (11.2)	43.3 (11.2)
Gender			
Women n (%)	14 (66.7%)	13 (59.1%)	14 (63.6%)
Race			
Caucasian	12 (57.1%)	17 (77.3%)	12 (54.5%)
African-American	7 (33.3%)	4 (18.2%)	5 (22.7%)
Asian	0 (0.0%)	0 (0.0%)	2 (9.1%)
Native American, Alaskan, Hawaiian, or Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
MADRS score			
Mean (standard deviation)	32.2 (4.6)	28.9 (4.6)	32.0 (5.4)

Full analysis set: Re-randomized subjects who took at least one study pill in Stage 2 and had at least one MADRS assessment after Stage 2 baseline).

Safety and Tolerability

Stage 1: 0, 0, and 7 subjects discontinued NSI-189 40mg, 80mg and placebo due to intolerance.
Stage 2: 1, 0, and 1 subjects discontinued NSI-189 40mg, 80mg and placebo due to intolerance.
No subjects treated with NSI-189 experienced a serious adverse event during the study.
Due to poster size limitations, the table summarizing spontaneously reported adverse events is not included but is available upon request.

Table 3. Efficacy: Primary Outcome Measure (FAS)

	NSI-189 40 mg/day (N=43)	NSI-189 80 mg/day (N=43)	Placebo (N=124)
MADRS			
Stage 1 (mean, sd)	-12.6 (11.2)	-11.7 (10.8)	-10.8 (11.1)
REML Estimate (95% CI), p-value	-1.8 (-5.6, 1.9), 0.342	-1.4 (-5.2, 2.3), 0.446	
Stage 2 (mean, sd)	-3.7 (7.5)	-3.0 (8.1)	-2.0 (6.8)
REML Estimate (95% CI), p-value	-1.8 (-6.4, 2.7), 0.432	-1.4 (-5.9, 3.2), 0.552	
Pooled SPCD			
REML Estimate (95% CI), p-value	-1.8 (-4.8, 1.1), 0.224	-1.4 (-4.4, 1.5), 0.344	
MADRS Responders			
Stage 1 (N, %)	16 (37.2)	14 (32.6)	41 (33.1)
p-value	0.646	0.962	
Stage 2	2 (9.5)	4 (18.2)	2 (9.1)
p-value	0.845	0.606	
SPCD p-value	0.738	0.643	
MADRS Remitters			
Stage 1 (N, %)	9 (20.9)	11 (25.6)	23 (18.5)
p-value	0.723	0.331	
Stage 2 (N, %)	3 (14.3)	4 (18.2)	1 (4.5)
p-value	0.145	0.272	
SPCD p-value	0.134	0.178	

Table 4. Efficacy: Secondary Outcome Measures (FAS)

	NSI-189 40 mg/day (N=43)	NSI-189 80 mg/day (N=43)	Placebo (N=124)
HAMD-17			
Stage 1 (mean, sd)	-8.5 (7.84)	-8.0 (6.93)	-7.4 (7.26)
REML Estimate (95% CI), p-value	-1.0 (-3.5, 1.5), 0.452	-0.9 (-3.4, 1.6), 0.482	
Stage 2 (mean, sd)	-3.4 (6.10)	-2.9 (5.94)	-0.8 (5.55)
REML Estimate (95% CI), p-value	-1.9 (-5.4, 1.6), 0.297	-2.2 (-5.6, 1.2), 0.212	
Pooled SPCD			
REML Estimate (95% CI), p-value	-1.4 (-3.6, 0.7), 0.195	-1.5 (-3.6, 0.6), 0.152	
SDQ			
Stage 1 (mean, sd)	-37.3 (33.56)	-31.3 (33.96)	-33.3 (27.63)
REML Estimate (95% CI), p-value	-3.0 (-12.4, 6.4), 0.532	-0.7 (-10.0, 8.5), 0.877	
Stage 2 (mean, sd)	-12.3 (24.73)	1.6 (23.75)	1.1 (19.18)
REML Estimate (95% CI), p-value	-13.4 (-26.3, -0.5), ***0.046***	-4.2 (-17.3, 8.8), 0.528	
Pooled SPCD			
REML Estimate (95% CI), p-value	-8.2 (-16.2, -0.2), ***0.044***	-2.5 (-10.5, 5.5), 0.543	
CPFQ			
Stage 1 (mean, sd)	-8.2 (7.61)	-7.0 (7.24)	-5.7 (6.48)
REML Estimate (95% CI), p-value	-1.7 (-3.8, 0.5), 0.133	-1.4 (-3.5, 0.7), 0.191	
Stage 2 (mean, sd)	-3.0 (5.66)	-0.5 (4.49)	-0.8 (4.57)
REML Estimate (95% CI), p-value	-2.1 (-4.9, 0.7), 0.139	-0.5 (-3.3, 2.4), 0.757	
Pooled SPCD			
REML Estimate (95% CI), p-value	-1.9 (-3.7, -0.1), ***0.035***	-0.9 (-2.7, 0.8), 0.302	
QIDS-SR (ANCOVA)			
Stage 1 (mean, sd)	-5.2 (5.50)	-4.7 (5.69)	-5.1 (4.90)
REML Estimate (95% CI), p-value	0.1 (-1.5, 1.8), 0.877	0.0 (-1.7, 1.6), 0.960	
Stage 2 (mean, sd)	-2.4 (3.17)	-1.1 (3.65)	0.2 (4.35)
REML Estimate (95% CI), p-value	-2.5 (-4.8, -0.2), ***0.040***	-1.4 (-3.7, 0.8), 0.210	
Pooled SPCD			
REML Estimate (95% CI), p-value	-1.2 (-2.6, 0.2), 0.105	-0.7 (-2.1, 0.6), 0.293	

Cogstate and Cogscreen (Pooled SPCD- FAS)

- **Cogstate Battery:** No statistically significant detectable signal between NSI-189 and placebo.
- **Cogscreen Battery (40mg)**: Statistical significance versus placebo was demonstrated for the following measures:
  - Simple attention (SATADRTC, p=0.034)
  - Complex attention (SATACACC, (p=0.048)
  - Memory (SDCDRACC, p=0.002)
- **Cogscreen Battery (80mg)**: Statistical significance versus placebo was demonstrated for the following measures:
  - Memory (SDCDRACC, p=0.015)
  - Impact of negative feedback on subsequent responses (SATINItol p<0.044)

CONCLUSIONS

- In this exploratory study, NSI-189 did not reach a statistically significant advantage over placebo on the primary outcome measure (MADRS).
- However, all three secondary self-rated measures of depressive and cognitive symptoms showed significant advantages for NSI-189 40mg as an antidepressant with cognitive benefits.
- These results replicate those from the previous MDD study.
- In addition, the 40mg dose showed statistical advantages on objective cognitive measures of attention and memory.
- These results warrant further evaluation of the antidepressant and pro-cognitive effects of this compound.

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Disclosures

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