A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SEQUENTIAL PARALLEL STUDY OF CERC-301 IN THE ADJUNCTIVE TREATMENT OF SUBJECTS WITH SEVERE DEPRESSION AND RECENT ACTIVE SUICIDAL IDEATION DESPITE ANTIDEPRESSANT TREATMENT

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ABSTRACT

Background: There is a significant unmet medical need for rapidly acting treatment of subjects with severe major depressive disorder (MDD) who have not adequately responded to antidepressant therapy. Considerable clinical and preclinical evidence suggests drugs that block the NMDA receptor complex, when administered intermittently, result in a rapid onset of antidepressant response in patients who are resistant to available antidepressants. CERC-301 is a highly selective, orally bioavailable, NMDA receptor subunit 2B (NR2B) antagonist with a safety and pharmacological profile suitable for daily dosing.

Methods: Clin301-201 was a Phase 2, randomized, double blind, placebo-controlled, 5 week study of 8mg of CERC-301 in the adjunctive treatment of subjects with severe depression and recent active suicidal ideation despite antidepressant treatment, using Sequential Parallel Comparison Design (SPCD) to evaluate the antidepressant effects of CERC-301. The study population was enriched for MDD subjects with recent active suicidal ideation. The sequential parallel comparison design (SPCD) included two study periods of different durations (Period 1 [7 days] and Period 2 [28 days]).

Results: CERC-301 was administered daily at a dose of 8mg for 28 days and did not meet its primary endpoint of a change in the HDRS-17 at day 7. CERC-301 was well tolerated. Fewer subjects on CERC-301 discontinued treatment due to adverse events than placebo treated subjects. The most commonly reported treatment emergent adverse events (≥ 5% incidence and reported at a higher incidence than placebo) included dizziness, headache, diarrhea, dry mouth, depression, nasopharyngitis, upper respiratory tract infection and blood pressure increased.

Conclusion: In this clinical study, CERC-301 8 mg/day as an adjunctive treatment to antidepressants was not an effective dose in a MDD patient population with a history of recent suicidal ideation. CERC-301 8 mg/day was safe and well tolerated in subjects with MDD.

BACKGROUND

CERC-301 (previously known as MK-0657) is an orally bioavailable N-methyl-D-aspartate (NMDA) receptor subunit 2B (NR2B) antagonist being developed for adjunct treatment of major depressive disorder

Clinical and preclinical evidence suggests that drugs that modulate the glutamatergic system, especially the NMDA receptor complex result in a more rapid onset of antidepressant response than existing antidepressants as well as potentially demonstrating efficacy in depressed patients who have had an inadequate response to antidepressant therapy

OBJECTIVES

Primary Objective:

- To evaluate the antidepressant effect of CERC-301 after 7 days of treatment assessed by the HDRS-17

Secondary Objective:

- To evaluate the antidepressant effect of CERC-301 as an adjunctive treatment of MDD over 28 days of treatment

METHODS

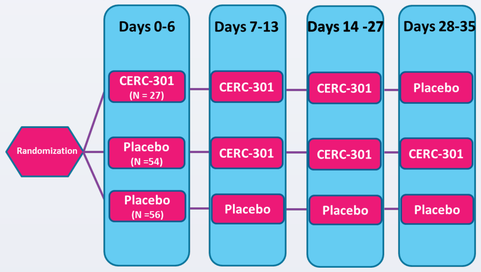
The study was a variation of the sequential parallel comparison design (SPCD) with two study periods of different durations (Period 1 [7 days] and Period 2 [28 days]). This study design enabled CERC-301 evaluation of (1) rapid onset of antidepressant effect, (2) maintenance effect of the study drug, and (3) effectiveness of a loading dose.

METHODS (Continued)

After a screening period of up to 14 days, subjects were randomly assigned to one of three treatment sequences with unequal distribution. One hundred thirty-five subjects with severe depression and recent active suicidal ideation were planned for randomization and participation in two treatment periods and a follow-up visit.

Twenty-seven subjects received a 12 mg loading dose followed by 8 mg daily, 54 subjects received placebo for seven days then received 8 mg daily, and 56 subjects received placebo for the whole study.

Statistical Analysis Schematic:



The 8 mg regimen was chosen based on efficacy and safety data from previous clinical studies. Two active treatment arms were included in this study such that active treatment was administered as (1) a 12-mg loading dose followed by an 8 mg stable dose or (2) an 8-mg stable dose.

CERC-301 has demonstrated an acceptable safety profile at the 8-mg dose in clinical pharmacology studies conducted to date. Preliminary evidence of CERC-301 antidepressant effects were observed in a depression study where dosing was titrated to 8 mg daily.

POPULATION

- Age 18-70
- Inadequate response to current stable (6 weeks) antidepressant
- Screening HAM-D 17 ≥ 21 (investigator)
- Enrollment HAM-D 17 ≥ 19 (MedAvante)
- CERC-301 added to stable current therapy (SSRI or SNRI)
  - Bupropion and tricyclics excluded
  - Exclude recent atypical antipsychotics, lithium
- Active suicidal ideation (C-SSRS 2) at baseline (previous 4 weeks) without suicidal behavior in past 6 months

RESULTS

DISPOSITION

	CERC-301/ CERC-301 (N=27)	Placebo/ CERC-301 (N=54)	Placebo/ Placebo (N=56)	Total (N=137)
Subjects who completed	22 (81.5)	42 (77.8)	37 (66.1)	101 (73.7)
Subjects who discontinued treatment	5 (18.5)	12 (22.2)	19 (33.9)	36 (26.3)
Blood pressure stopping criteria met	0 (0.0)	0 (0.0)	3 (5.4)	3 (2.2)
Suicidality	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.7)
Adverse event	1 (3.7)	4 (7.4)	3 (5.4)	8 (5.8)
Subject request	1 (3.7)	4 (7.4)	6 (10.7)	11 (8.0)
Lost to follow-up	2 (7.4)	1 (1.9)	5 (8.9)	8 (5.8)
Other	1 (3.7)	3 (5.6)	1 (1.8)	5 (3.6)

RESULTS (Continued)

BASELINE CHARACTERISTICS (mITT)

	CERC-301 / CERC-301 (N=26)	Placebo/ CERC-301 (N=52)	Placebo/ Placebo (N=51)	Total (N=129)
Number Female (%)	17 (65.4%)	30 (57.7%)	33 (64.7%)	80 (62.0%)
Number White (%)	13 (50.0)	34 (65.4)	29 (56.9)	76 (58.9)
Mean Age (yrs)	47.5 (11.6)	50.1 (10.5)	49.1 (10.4)	49.2 (10.7)
Mean Weight (kg)	90.75 (20.61)	90.24 (21.12)	92.20 (24.59)	91.12 (22.32)
Mean time since diagnosis (years)	15.16 (12.02)	13.64 (12.09)	15.69 (13.85)	14.76 (12.74)
Mean duration of current episode (months)	12.1 (15.9)	17.3 (26.7)	13.9 (24.4)	14.9 (23.9)
Median duration of current episode (months)	7.0	7.0	8.0	7.0
SSRI treatment [n (%)]	19 (73.1)	40 (76.9)	36 (70.6)	95 (73.6)
SNRI treatment [n (%)]	7 (26.9)	12 (23.1)	15 (29.4)	34 (26.4)

EFFICACY

HDRS-17 Score by 7 Day Treatment Period Primary Analysis (mITT Population)

Statistic	Period 1 CERC-301 (N=26)	Period 1 Placebo (N=103)	Period 2[a] CERC-301 (N=41)	Period 2[a] Placebo (N=33)
Change from baseline in HDRS-17				
N	25	101	39	30
Mean (SD)	-7.2 (5.98)	-6.5 (6.87)	-3.1 (5.74)	-2.8 (7.42)
Difference (CERC-301 – Placebo)[b]	-0.7		-0.2	
95% CI of difference	(-3.7, 2.2)		(-3.4, 2.9)	
Weighted average of difference (95% CI)[c]	**-0.4 (-2.7, 1.9)**			
P-value	**0.749**			

Note: Baseline is the last assessment prior to dosing in the corresponding period.
[a] Only data from Period 1 Placebo non-responders are included.
[b] Between treatment differences are estimated from an ANCOVA model including baseline HDRS-17 response as a covariate.
[c] The weighted average of the difference is calculated as 0.3*difference in Period 1 + 0.7*difference in Period 2.

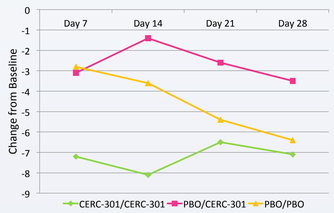
HDRS-17 Score by 28 Day Treatment Period Secondary Analysis (mITT Population)

	CERC-301/ CERC-301 (N = 26)	Placebo/ CERC-301[a] (N = 41)	Placebo/ Placebo (N = 33)
Mean HAMD-17 at Baseline	25.7 (3.24)	22.6 (4.95)	22.6 (4.65)
Least Squares Mean (SE)[b]	-6.5 (1.34)	-3.7 (1.07)	-6.3 (1.21)
95% CI	(-9.2, -3.9)	(-5.8, -1.5)	(-8.7, -3.9)
Difference in Least Squares Means (CERC-301-Placebo) (SE)[b]	1.2 (1.48)		
95% CI	(-1.8, 4.1)		

The baseline assessment is defined as the last assessment on or before Day 0, before dosing for subjects in the CERC-301CERC-301 arm and Day 7 for subjects in the Placebo/CERC-301 and Placebo/Placebo arms.
[a] Only Period 2 data from Period 1 Placebo non-responders are included.
[b] Least Squares (LS)
Means are from a repeated measures model for change from baseline in HDRS-17 response and includes treatment and time on study drug

RESULTS (Continued)

HDRS-17 Score by Day Treatment (mITT Population)



ADVERSE EVENTS

	CERC-301/ CERC-301 (N=27)	Placebo/ CERC-301 (N=52)	Placebo/ Placebo (N=49)
Any Adverse Event	16 (59)	37 (71.2)	36 (73.5)
Nervous system disorders	7 (25.9)	14 (26.9)	11 (22.4)
Dizziness	5 (18.5)	4 (7.7)	1 (2.0)
Headache	2 (7.4)	7 (13.5)	7 (14.3)
Gastrointestinal	6 (22.2)	19 (36.5)	14 (28.6)
Diarrhoea	5 (18.5)	5 (9.6)	4 (8.2)
Dry mouth	1 (3.7)	7 (13.5)	3 (6.1)
Abdominal pain	0	3 (5.8)	0
Psychiatric	5 (18.5)	9 (17.3)	8 (16.3)
Depression	1 (3.7)	3 (5.8)	0
Infections and Infestations			
Nasopharyngitis	2 (7.4)	3 (5.8)	2 (4.1)
Upper respiratory tract infection	2 (7.4)	3 (5.8)	1 (2.0)
Blood Pressure Increased	3 (11.1)	5 (9.6)	2 (4.1)
Hypertension	2 (7.4)	1 (1.9)	6 (12.2)

SAFETY ASSESSMENTS

Overall, CERC-301 had no clinically relevant effects on 12-lead ECG, physical examinations, or BPRS scores

There are no apparent differences in blood pressure effects between the treatment groups, and there was no indication of worsening blood pressure over time

CONCLUSIONS

- In this clinical study, CERC-301 8 mg/day as an adjunctive treatment to antidepressants was not an effective dose in a MDD patient population with a history of recent suicidal ideation
- The lack of efficacy in this trial may reflect the low dose that was given, daily dosing of an NR2B antagonist rather than intermittent dosing or the patient population (depressed patients with recent suicidal ideation) selected for the study
- CERC-301 8 mg/day was safe and well tolerated in subjects with MDD.

ACKNOWLEDGEMENTS

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