A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, THREE-PART SAFETY, PHARMACOKINETIC, AND PHARMACODYNAMIC STUDY OF CERC-301 IN HEALTHY SUBJECTS

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ABSTRACT

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.
Aim: The overall aim of this study was to conduct a thorough evaluation of the effects of single and repeated daily doses of CERC-301 on blood pressure (BP), safety, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy male and female subjects and in young, intermediate age, and elderly age subgroups.
Methods: The study was a randomized, double-blind, placebo-controlled parallel-group, three-part, repeated dose in-patient study investigating the safety, tolerability, PK, and PD of CERC-301 in healthy subjects dosed in the fed state. Young subjects received CERC-301 8, 12, 16 or 20 mg or matching placebo once daily for 7days. Intermediate age and elderly cohorts received 12 mg or matching placebo daily for 7 days.
Results: Overall, there were no clear-cut dose-related or age-related differences in treatment-emergent adverse events or related adverse events. There were no clinically significant adverse changes in vital signs, ECGs or physical examination that were attributable to CERC-301. The average 24-hour and daytime ambulatory systolic BP and diastolic BP increased with all CERC-301 doses compared to placebo, in a dose dependent fashion. The effects of CERC-301 on blood pressure appeared similar regardless of age subgroup. The effect of CERC-301 20 mg on SBP appeared slightly more pronounced in females compared to males on Day 7, however, overall, the BP effects of CERC-301 appeared similar in males and females. There was a high degree of variability in the plasma BDNF measurements in this study. However, there appeared to be a trend for an increase on average 7-day brain-derived neurotrophic factor (BDNF) values compared to placebo at the higher two doses of 16 and 20 mg. Following repeated daily doses of CERC-301, steady-state predose plasma CERC-301 concentrations were achieved by study day 5 or 6, and plasma CERC-301 concentrations increased in an approximately dose proportional manner from 8 to 20 mg on Days 1 and 7.
Conclusion: Repeated daily doses of CERC-301 8, 12, 16, and 20 mg for 7 days were generally well tolerated in these healthy subjects and there were no safety issues that would preclude intermittent dosing up to 20 mg. There were dose-related increases in blood pressure in the Young cohort. Clinically modest differences in PK parameters were observed in intermediate age and elderly subjects compared to young subjects, and in female subjects compared to male subjects.

BACKGROUND

Previous PK studies conducted with CERC-301 suggested a possible BP effect. The highest single dose of CERC-301 administered (20 mg fasted in young healthy males) led to maximum BP increases at 1 to 2 hours post-dose, which resolved by 4 to 6 hours post-dose. 20 mg fasted led to a mean maximum increase in systolic and diastolic BP of 32 mm Hg and 18 mm Hg, respectively.

Dosing in the fed state decreased Cmax by 56% without impacting AUC. PK modeling suggested that steady state exposure of 8 mg fed would be similar to that single-dose exposure of 20 mg fasted.

A repeated dose fed regimen of 8 mg CERC-301 in young healthy males led to a mean maximum increase in systolic and diastolic BP of 13 mm Hg and 9 mm Hg, respectively.

A single-dose study in elderly males and females suggested slightly higher drug exposure and BP effects in elderly females vs. elderly males.

To carefully characterize the potential BP effects of CERC-301, a well-controlled ambulatory blood pressure monitoring (ABPM) study was conducted to fully investigate the BP effects of multiple ascending doses of CERC-301 in healthy males and females (young to elderly).

OBJECTIVES

Primary Objective: To investigate the dose-response relationship between CERC-301 and PD effects (BP and BDNF) in healthy subjects.

Secondary Objectives: To investigate the safety and tolerability of CERC-301 over 7 days of once-daily administration. To investigate the single dose and 7-day repeated dose PK profiles of CERC-301.

Exploratory Objectives: To explore gender and age effects on PK and BP.

METHODS

This was a randomized, double-blind, placebo-controlled parallel-group, repeated dose study conducted in 48 healthy subjects. Young healthy subjects (18 to 45 years of age) were randomized to receive placebo (N=8) or 8, 12, 16, or 20 mg CERC-301 (N=6 per group). Intermediate age (46 to 64 years of age) healthy subjects were randomized to receive placebo (N=2) or 12 mg CERC-301 (N=6). Elderly (≥65 years of age) healthy subjects were randomized to receive placebo (N=2) or 12 mg CERC-301 (N=6). The groups were balanced for gender.

Subjects were domiciled in a clinical pharmacology research unit to undergo baseline ABPM (Day -1), 7 days of once daily dosing in the fed state (Days 1-7), 3 days of ABPM (Days 1, 4, and 7), 2 PK days (Days 1 and 7), with routine safety assessments throughout. Subjects were discharged on Day 8.

ABPM was conducted using fully automated recorders (Spacelabs 90207 monitors). 24-h ABPM was conducted on Day -1 (baseline) and Days 1, 4, and 7. BP was captured every 20 min from pre-dose to approximately 12 hours post-dose and every 1 hour from approximately 13 to 24-h post-dose. On each ABPM day, average BP was determined for the entire 24 h monitoring period, awake hours, and asleep hours (Biomedical Systems). Time-matched change from baseline was determined.

Blood samples for CERC-301 plasma concentration analyses (LC-MS/MS) were obtained on Days 1 and 7 (pre-dose, 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 h post-dose) with additional samples on Day 7 (48, 72, and 96 h post-dose). Plasma concentration-time profiles were analyzed via noncompartmental methods to calculate PK parameters.

Plasma BDNF was measured as a biomarker of drug activity. Blood samples were obtained for plasma BDNF determination at pre-dose and 4 hours post-dose on Days 1, 4 and 7.

Routine vital sign and adverse event (AE) monitoring were conducted throughout the study.

RESULTS

Demographic Characteristics of the Study Population

Characteristic / Statistic	Young 8 mg N = 6	Young 12 mg N = 6	Young 16 mg N = 6	Young 20 mg N = 6	Young PBO N = 8	Int. 12 mg N = 6	Int. PBO N = 2	Elder. 12 mg N = 6	Elder. PBO N = 2
Age (years) Mean (SD)	34.8 (10.3)	33.5 (6.7)	33.3 (9.0)	30.5 (8.6)	29.8 (8.1)	51.0 (4.5)	53.5 (3.5)	69.2 (3.3)	72.0 (8.5)
Gender, n (%)									
Male	3(50.0)	3(50.0)	3(50.0)	3(50.0)	4(50.0)	3(50.0)	1(50.0)	3(50.0)	1(50.0)
Female	3(50.0)	3(50.0)	3(50.0)	3(50.0)	4(50.0)	3(50.0)	1(50.0)	3(50.0)	1(50.0)
Race, n (%)									
Asian	0(0)	0(0)	1(16.7)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Black	2(33.3)	5(83.3)	3(50.0)	3(50.0)	3(37.5)	3(50.0)	0(0)	0(0)	0(0)
White	4(66.7)	1(16.7)	2(33.3)	1(16.7)	3(37.5)	3(50.0)	2(100)	6(100)	2(100)
Am Indian/ AK Native	0(0)	0(0)	0(0)	1(16.7)	1(12.5)	0(0)	0(0)	0(0)	0(0)
Other	0(0)	0(0)	0(0)	1(16.7)	1(12.5)	0(0)	0(0)	0(0)	0(0)
Body Mass Index (kg/m^2) Mean (SD)	22.3 (3.5)	28.4 (1.0)	25.5 (4.3)	25.9 (2.4)	25.1 (3.9)	25.9 (2.8)	25.7 (2.8)	25.5 (2.3)	24.7 (3.3)

RESULTS (continued)

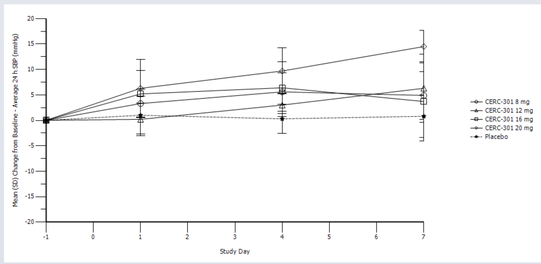
Select CERC-301 PK Parameters on Day 7

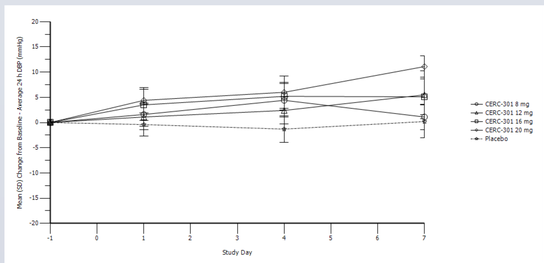
PK Parameter Statistic	Young Subjects 8 mg	12 mg	16 mg	20 mg	Int. 12 mg	Elder. 12 mg
C_{max} (ng/mL) Mean (SD)	224.00 (30.01)	273.50 (44.00)	412.75 (65.06)	534.33 (97.69)	257.00 (50.66)	228.83 (30.73)
t_{max} (h) Median min, max	3.00 2.00, 3.00	2.50 1.50, 3.00	1.75 1.50, 2.00	1.50 1.50, 2.00	1.50 1.00, 3.00	2.00 1.50, 3.03
AUC_{inf} (h*ng/mL) Mean (SD)	4109.8 (1398.1)	5933.1 (2133.5)	8023.5 (4985.1)	10468 (3506.7)	8104.1 (2270.0)	10304.0 (3904.9)
$t_{½}$ (h) Mean (SD)	17.22(6.20)	20.49(4.55)	20.00(10.22)	18.75(2.22)	26.09(2.78)	28.28(8.11)

AEs Reported by ≥ 2 Subjects Receiving CERC-301

Preferred Term	Young 8 mg N = 6	12 mg N = 6	16 mg N = 6	20 mg N = 6	Placebo N = 8	Intermediate 12 mg N = 6	Placebo N = 2	Elderly 12 mg N = 6	Placebo N = 2
Feeling abnormal	2(33.3)	2(33.3)	4(66.7)	4(66.7)	0	1(16.7)	1(50.0)	2(33.3)	0
Headache	4(66.7)	2(33.3)	1(16.7)	3(50.0)	1(12.5)	0	2(100.0)	0	0
Feeling of relaxation	1(16.7)	4(66.7)	4(66.7)	1(16.7)	0	4(66.7)	0	0	0
Elevated mood	1(16.7)	3(50.0)	1(16.7)	3(50.0)	0	1(16.7)	0	0	0
Dizziness	1(16.7)	2(33.3)	1(16.7)	3(50.0)	0	1(16.7)	0	1(16.7)	0
Logorrhea	1(16.7)	1(16.7)	1(16.7)	2(33.3)	0	0	0	2(33.3)	0
Sedation	1(16.7)	0	1(16.7)	2(33.3)	0	1(16.7)	1(50.0)	0	0
Visual impairment	0	0	2(33.3)	2(33.3)	0	0	0	1(16.7)	0
Energy increased	2(33.3)	0	1(16.7)	0	1(12.5)	1(16.7)	0	0	0
Balance Disorder	0	0	0	0	0	2(33.3)	0	0	0
Confusional state	0	0	0	2(33.3)	0	0	0	0	0
Disturbance in attention	0	0	2(33.3)	0	0	1(16.7)	0	1(16.7)	0
Hypervigilance	0	0	2(33.3)	0	0	0	0	0	0

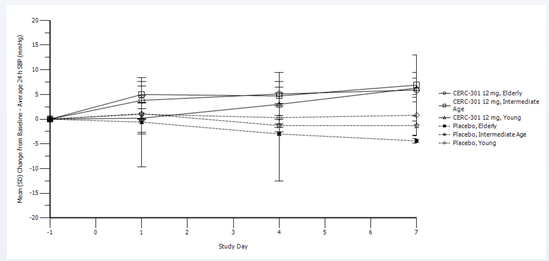
Mean (SD) Time-matched Change from Baseline in Average 24h ABPM Systolic BP and Diastolic BP (Young)

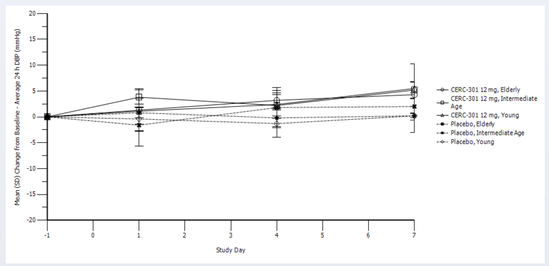




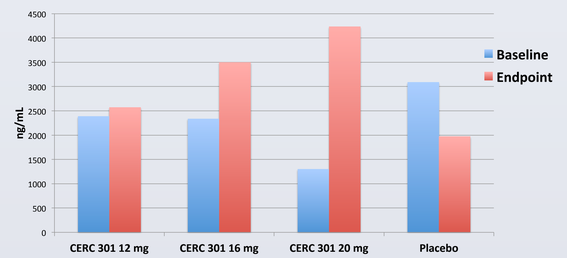
RESULTS (continued)

Mean (SD) Time-matched Change from Baseline in Average 24h ABPM Systolic BP and Diastolic BP (Young, Intermediate, and Elderly)





BDNF



CONCLUSIONS

- Clinically modest differences in PK parameters were observed in intermediate age and elderly subjects compared to young subjects
- Repeated daily doses of CERC-301 8, 12, 16, and 20 mg for 7 days were generally well tolerated in healthy subjects with similar AE reporting across the age groups. The most commonly reported AEs were feeling abnormal, feeling of relaxation, and headache
- There were dose-related increases in blood pressure in the young cohort, which was most pronounced at the 20-mg daily dose
- The effects of CERC-301 on ambulatory BP were similar regardless of age subgroup, with no age-dependent differences being observed at the 12 mg dose
- Overall, there were no safety issues that would preclude intermittent dosing up to 20 mg

ACKNOWLEDGEMENTS

Study Clin301-200-A was funded by Cerecor.