Cognitive Performance After Repeated Administration of the NMDA Positive Allosteric Modulator SAGE-718 in Healthy Volunteers

Aaron Koenig, MD, Jason Berlin, MS, Yingzhen Luo, PhD, Sigal Li, MS, Lu Liu were employed to develop the study procedures and provided statistical programming (MRC) support. A number of healthy volunteers received double-blind, first oral doses of either SAGE-718 1.0 mg or placebo, with daily dosing through Day 11.

**Methods**
- Healthy volunteers, ages 18-65, body weight 55-80 kg, and a body mass index of 18.5-30.0 kg/m², who were willing to comply with all study procedures and the clinical assessment of safety and efficacy, and had a stable medical condition, were included.
- Cognitive testing was performed on Days 2, 4, 6, 8, and 10 when no ketamine was being administered.
- Exclusion criteria included clinically significant findings during physical examination, heart rate >50 or <60 beats per minute, systolic blood pressure <90 or >140 mmHg, or diastolic blood pressure <60 or >90 mmHg.
- Plasma samples were used to calculate Cₘₕ (the minimum effective concentration) as well as other pharmacokinetic (PK) parameters.
- Primary endpoints were related to auditory evoked potential deficits.

**Results**

**COGNITIVE TESTS**

**Two Back Test**
- In the Two-Back test, the SAGE-718 group demonstrated numerically better performance and made fewer errors in paired associative learning than placebo, from Days 2 through 10.

**Groton Maze Learning Test (Spatial Learning/Recall)**
- Healthy volunteers in the SAGE-718 group demonstrated numerically better performance and made fewer errors in paired associative learning than placebo on Day 6 (6.797 vs. 8.621, 15.62 diff, 95% CI 29.88 to -2.170, p=0.024).

**Continuous Paired Associative Learning (Spatial Learning/Recall)**
- No clinically relevant changes from baseline were observed in any cognitive test score as the response variable, and the Bonferroni adjustment (see Table).

**TREATMENT EMERGENT ADVERSE EVENTS (TEAEs)**

Subjects with any TEAE: 7/18 (38.9%) vs. 6/19 (31.6%).
- Most treatment-emergent adverse events were mild in severity; no serious or severe AE were reported.
- No TEAEs resulted in study withdrawal or discontinuation or dose reduction.
- No clinically relevant mean changes from baseline were observed in clinical laboratory parameters, vital signs, ECGs, or safety EEG results.

**RELATIONSHIP BETWEEN COGNITIVE PERFORMANCE AND CMAX AT DAY 10**

**Two-Back Test** performed showed a positive correlation with SAGE-718 plasma concentration at Day 10 (n=20; R²=0.024).

**GROTON MAZE LEARNING TEST**

A negative correlation was observed between SAGE-718 plasma level and number of errors in the Groton Maze Learning test at Day 10 (n=21; R²=0.061).

**EFFECTS ON COGNITIVE PERFORMANCE**

Healthy volunteers in the SAGE-718 group demonstrated numerically better performance and made fewer errors in paired associative learning than placebo, from Days 2 through 10.