



Alto Neuroscience Announces Data from Presentations at the 62nd Annual Meeting of the American College of Neuropsychopharmacology

- New data support the development of ALTO-101, a novel brain-penetrant phosphodiesterase 4 inhibitor, for the treatment of cognitive impairment associated with schizophrenia –*
- Alto identified, and successfully replicated, clinically relevant biomarkers for ALTO-300 and ALTO-100 in independent patient groups within major depressive disorder (MDD) –*
- Large phase 2a studies of ALTO-300 and ALTO-100 demonstrated positive results; both product candidates are being evaluated in ongoing Phase 2b randomized placebo-controlled studies in MDD –*

LOS ALTOS, Calif., December 7, 2023 – Alto Neuroscience, Inc. today announced details from three presentations on clinical development programs presented at the 62nd annual meeting of the American College of Neuropsychopharmacology (ACNP) that took place in Tampa, Florida, from December 3-6, 2023.

Alto's data demonstrate advancements in biomarker identification for precision psychiatry and the potential to improve upon the trial-and-error approach to mental health treatment. The company's AI-enabled Precision Psychiatry Platform™ is designed to predict clinical response and match each patient to the right Alto product candidate through identifying, and prospectively replicating, brain biomarkers by analyzing data generated from EEG activity, neurocognitive task performance, wearable devices, and other measures.

“A precision approach could potentially address the treatment gap for patients living with depression and other difficult-to-treat mental health conditions,” said Maurizio Fava, MD, Psychiatrist-In-Chief, Massachusetts General Hospital, Executive Director, Clinical Trials Network and Institute, and Associate Dean for Clinical and Translational Research, Harvard Medical School. “Understanding the underlying biological mechanisms of psychiatric disease and associated brain biomarkers may finally enable quantifiable data to guide diagnoses and targeted treatments.”

The details of each presentation were as follows:

Presentation Title: Identification and prospective replication of brain/behavior-based pro-cognitive pharmacodynamic effects for ALTO-101: Results from a randomized, double-blind phase 1 study

Presenting Author: Amit Etkin, M.D., Ph.D., founder, president, and chief executive officer

Poster Authors: Akshay Ravindran, Guhan Sundar, Samantha Goncalves, Chao Wang, Li Shen, Maimon Rose, Joshua T. Jordan, Nicholas J. Cooper, Sebastian Marquez, Faizan Badami, Wei Wu, Amit Etkin, Adam J. Savitz

Presentation Highlights:

- 40 healthy adults completed multiple neurocognitive tests, electroencephalography (EEG) and event-related potential (ERP) measures in a cross-over placebo-controlled single-dose Phase 1 clinical trial to identify brain/behavior-based pharmacodynamic (PD) biomarkers for ALTO-101
- Analyses focused on PD markers relevant to schizophrenia and other cognitive disorders revealed clear and statistically significant effects of ALTO-101 in enhancing cognition and cognitive processing in a dose-dependent manner (all results are placebo-adjusted)
 - Resting EEG theta power, which is elevated in schizophrenia, was reduced by ALTO-101 (1.5mg: $d=-0.88$, $p=0.0003$; 0.5mg: $d=-0.51$, $p=0.02$)
 - Mismatch negativity, which is blunted in schizophrenia, was increased by ALTO-101 (1.5mg: $d=-0.53$, $p=0.02$; 0.5mg: $d=-0.38$, $p=0.07$)
 - Early gamma phase locking in response to auditory stimuli, which is reduced in schizophrenia, was increased by ALTO-101 (1.5mg: $d=0.68$, $p=0.003$; 0.5mg: $d=0.35$, $p=0.08$)
 - With respect to cognitive task performance, ALTO-101 also improved information processing speed, which is slowed in schizophrenia (1.5mg: $d=0.63$, $p=0.006$; 0.5mg: $d=0.32$, $p=0.16$)
- The data demonstrated strong PD effects of ALTO-101 in driving key brain processes important for cognition as measured by EEG and behavioral tasks.
- These findings validate the potential of ALTO-101, a novel brain-penetrant phosphodiesterase 4 inhibitor (PDE4i), to be developed for the treatment of cognitive impairment associated with schizophrenia

Presentation Title: Identification and prospective replication of an EEG biomarker for predicting the antidepressant effect of ALTO-300 in patients with Major Depression: Results from large Phase 2a studies

Presenting Author: Adam J. Savitz, M.D., Ph.D., chief medical officer

Poster Authors: Maimon Rose, Joshua T. Jordan, Chao Wang, Faizan Badami, Jessica Powell, Fadi Abdel, Wei Wu, Amit Etkin, Adam J. Savitz

Presentation Highlights:

- The study was an 8-week clinical trial to evaluate potential predictive biomarkers for efficacy and the safety of ALTO-300 as an add-on treatment in patients with MDD who experienced inadequate response to an antidepressant (site-based study: NCT05118750 and decentralized study: NCT05157945)
 - 239 patients were enrolled in the study, staying on their original antidepressant to which they had an inadequate response, while ALTO-300 was added as a new treatment
- Cross-validated machine learning analyses on the discovery set identified a resting state electroencephalography (rsEEG) biomarker that predicted the reduction in depressive symptoms with ALTO-300 (week 6 $d=0.60$, $p=0.004$)
- Results in the test data set indicated successful replication of the rsEEG biomarker-based treatment prediction
 - The week 6 test dataset effect size was $d=0.51$ ($p=0.03$) and week 8 effect size was $d=0.63$ ($p=0.03$)
- The rsEEG biomarker was also specific to ALTO-300 in that it did not predict response to placebo or to standard-of-care antidepressants



- ALTO-300 showed significantly enhanced MDD treatment response (as measured by MADRS) among MDD patients characterized by a machine learning-identified rsEEG biomarker than those who do not have the biomarker
 - For additional details and full dataset reported from the Phase 2a study of ALTO-300 presented at the 2023 ACNP annual meeting, read the full press release [here](#)

Presentation Title: Identification and prospective replication of a cognitive biomarker for predicting the antidepressant effect of ALTO-100, a novel pro-plasticity drug, in patients with Major Depression: Results from a large Phase 2a study

Presenting Author: Joshua T. Jordan, Ph.D., senior research scientist

Poster Authors: Joshua T. Jordan, Nicholas J. Cooper, Faizan Badami, Jessica Powell, Wei Wu, Amit Etkin, Adam J. Savitz

Presentation Highlights:

- The study was an 8-week clinical trial to evaluate potential predictive biomarkers for efficacy and the safety of ALTO-100 as either monotherapy or add-on treatment in patients with MDD who experienced inadequate response to an antidepressant (NCT05117632)
 - 243 patients with MDD and/or Post-Traumatic Stress Disorder (PTSD) were enrolled in the study
- Results from the discovery set demonstrated that patients with the cognitive biomarker experienced a greater reduction in depressive symptoms (as measured by MADRS) with ALTO-100 than participants without the biomarker (week 6 $d=0.96$, $p=0.01$)
- Results in the test data set indicated successful replication of the cognitive biomarker-based treatment prediction
 - The week 6 effect size was $d=0.58$ ($p=0.007$) and the week 8 effect size was $d=0.61$ ($p=0.007$)
 - The biomarker similarly predicted ALTO-100 response when given as monotherapy (week 6 $d=0.66$, $p=0.03$) or as adjunctive therapy (week 6 $d=0.56$, $p=0.01$)
- These data provide compelling evidence that ALTO-100, a compound that increases neuroplasticity, demonstrates a considerably greater effect on symptoms of depression (as measured by MADRS) among MDD patients with a poor cognition biomarker profile than those without

Alto is evaluating ALTO-100 and ALTO-300, stratified by their relevant biomarkers, in Phase 2b studies in MDD, with topline data expected in the second half of 2024 and first half of 2025, respectively. Additionally, Alto is advancing ALTO-101 into a Phase 2 proof of concept study in patients with cognitive impairment associated with schizophrenia, with topline data expected in 2025.

About Alto Neuroscience

Alto Neuroscience is a clinical-stage biopharmaceutical company with a mission to redefine psychiatry by leveraging neurobiology to develop personalized and highly effective treatment options. Alto's Precision Psychiatry Platform™ measures brain biomarkers by analyzing EEG activity, neurocognitive task performance, wearable data, and other factors to match each patient with the right Alto product candidate. The company's work in validating brain-based biomarkers has resulted in a multiple modality approach that supports robust drug-response predictions. Alto's clinical-stage pipeline includes novel



drug candidates in depression, PTSD, schizophrenia, and other mental health conditions. For more information, visit www.altoneuroscience.com or [follow Alto on X \(Twitter\)](#).

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