Alto Neuroscience Announces Positive Results from Phase 2 Study of ALTO-300 in Major Depressive Disorder

– Treatment with ALTO-300 led to a significantly greater improvement in depression symptoms in a biomarker-characterized patient population –

– A machine learning-derived EEG biomarker predictive of likely response to ALTO-300 was identified –

– Significantly more patients with the EEG biomarker achieved clinical response (as defined by ≥50% improvement in depression symptoms) compared to patients without the biomarker profile –

– Outcome marks the third positive Phase 2 readout leveraging Alto's Precision Psychiatry Platform™, providing further validation of the biomarker-driven approach to matching the right patient with the right treatment –

LOS ALTOS, Calif., December 4, 2023 – Alto Neuroscience, Inc. today announced positive results from its Phase 2a study of ALTO-300 at the 62nd Annual Meeting of the American College of Neuropsychopharmacology (ACNP) demonstrating clinically meaningful improvements and favorable safety and tolerability in patients with major depressive disorder (MDD). Following administration of ALTO-300, patients characterized by an electroencephalogram (EEG) biomarker demonstrated robust clinical improvement in depression symptoms and higher response rates, as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS), compared to patients without the EEG biomarker. These results support the potential of ALTO-300 as a novel treatment for MDD. The company has initiated a Phase 2b study evaluating ALTO-300 in 200 patients with MDD, which is expected to read out in the first half of 2025.

"Our conviction in the promise of precision medicine for the brain is bolstered by these results," said Amit Etkin, M.D., Ph.D., founder, president, and chief executive officer of Alto Neuroscience. "Data from the ALTO-300 study showcase the potential of targeting patients' underlying neurobiology to achieve clear clinical benefit and further validate our precision drug development approach."

The study was an 8-week clinical trial to evaluate potential predictive biomarkers for efficacy and safety of ALTO-300 as an adjunctive treatment in patients with MDD who experienced inadequate response to an antidepressant. 239 patients between the ages of 18-74 years old were enrolled in the study, staying on a background antidepressant while ALTO-300 was added as a new treatment. 110 of these patients underwent an EEG at baseline. Alto used a rigorous machine learning-driven data science approach, which centrally requires prospective replication of a biomarker's ability to predict a drug's antidepressant clinical efficacy in an independent group of patients. Taking this approach, likely drug responders can be found while avoiding false discovery. The primary analysis was on prediction of change in depressive symptoms, as measured by the MADRS, at week 4.

Topline results from the ALTO-300 Phase 2a study include:

- A reproducible, readily scalable, and easily administered machine learning-derived EEG biomarker was identified. Alto is leveraging this biomarker and prospective patient identification with EEG in its ongoing Phase 2b trial of ALTO-300.
- Across the entire dataset, including the initial discovery data set and the independent test data set, the biomarker-characterized patients (n=55) demonstrated an 8.3-point mean MADRS reduction compared to 5.7 points in the patient group without the biomarker profile (n=48) starting at week 1 (p=0.03, d=0.37) and improved through week 8 of measurement (-17 vs. -12.3, p=0.002, d=0.59).
    - In the independent test data set, the biomarker-characterized MDD patient group (n=24) demonstrated an 11-point mean MADRS reduction compared to 7.8-points in the patient group without the biomarker profile (n=21) starting at week 4 (p=0.05, d=0.40), improving further through week 8 of measurement (-16.4 vs. -11.6; p=0.03, d=0.63).
- Significantly more biomarker-characterized patients (n=55) than patients without the biomarker (n=50) achieved clinical response (defined as ≥50% reduction in depression symptoms) at week 4 (47% vs. 27%) and week 6 of treatment (58% vs. 34%), with the trend continuing at week 8 (62% vs. 47%).
- The predictive biomarker is specific to patients receiving ALTO-300, as it is not predictive of response in patients taking either placebo or standard-of-care SSRI/SNRIs based on data from separate studies in which EEG measurements allowed Alto to differentiate between patients with or without this EEG biomarker.
- ALTO-300 demonstrated a favorable safety and tolerability profile with no unexpected adverse effects.

About Alto Neuroscience

Alto Neuroscience is pioneering precision psychiatry by developing targeted medicines designed to help patients get better faster. 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 us on X (Twitter).

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