Alto Neuroscience Announces Positive Results for ALTO-100 in Phase 2 Study Supporting Advancement of First-in-Class Mechanism for Treating Depression

– The primary objective of the study was achieved, with ALTO-100 demonstrating favorable safety and clear evidence of efficacy in patients with major depressive disorder (MDD) and replicating the effects in a holdout data set –

– Treatment with ALTO-100 led to a significantly greater improvement in MADRS in the biomarker-defined patient population at week 6 (-15.5 vs. -10.5; p=0.0001), with significantly more biomarker-defined patients achieving ≥ 50% improvement –

– Company to present data highlights at the 41st Annual J.P. Morgan Healthcare Conference at 8:00 p.m. ET/5:00 p.m. PT on January 11, 2023 –

LOS ALTOS, Calif., January 10, 2023 – Alto Neuroscience Inc. today reported results from its Phase 2a study of ALTO-100, demonstrating clear evidence of efficacy and favorable safety in patients with MDD. In the study, patients with a biomarker profile that ties back to a mechanistic understanding of ALTO-100 and depression exhibited a significantly greater change in Montgomery–Åsberg Depression Rating Scale (MADRS) scores and response rates than those without the biomarker profile. This first-of-its-kind Phase 2 study leveraged Alto's Precision Psychiatry Platform™ to identify likely drug responders based on an understanding of biological heterogeneity in depression and ALTO-100's novel mechanism. The results support the initiation of ALTO-100 into a large Phase 2b trial in patients with biomarker-defined MDD in January 2023. Topline data from the Phase 2b study is anticipated to readout in the first quarter of 2024.

Topline results from the ALTO-100 Phase 2a study include:

- The biomarker-defined MDD patient group (n=59) demonstrated a 15.5-point mean MADRS reduction compared to 10.6 points in the patient group without the biomarker profile (n=64) at week 6 (p=0.001, d=0.6).
    - In patients taking ALTO-100 as monotherapy (n=45), a 17.4-point change in MADRS was observed at week 6 in the biomarker-defined group compared to 11.8 points in the group without the biomarker (p=0.026, d=0.66).
    - In patients taking ALTO-100 in addition to another antidepressant (i.e., as adjunctive treatment) (n=78), a 14.4-point change in MADRS was observed at week 6 in the biomarker-defined group compared to 9.9 points in the group without the biomarker (p=0.013, d=0.56).

- 61% of biomarker-defined patients achieved clinical response (defined as ≥50% reduction in depression symptoms) compared to 33% of patients without the biomarker profile (p=0.004).
    - 81% of biomarker-defined patients taking ALTO-100 as monotherapy achieved clinical response compared to 38% of patients without the biomarker profile (p=0.01).
    - 50% of biomarker-defined patients taking ALTO-100 as adjunctive treatment, achieved clinical response compared to 31% of patients without the biomarker profile (p=0.07).

- On the Clinician Global Impression of Severity (CGI-S) scale, biomarker-defined patients demonstrated an improvement of 1.66 points (5-point scale) from baseline to week 8 compared to an improvement of 1.17 points in patients without the biomarker profile (p=0.02, d=0.41).

- ALTO-100 has now been studied in more than 395 subjects and has displayed a favorable tolerability profile. No new safety signals were observed in this study.

"The strength of these results demonstrates, for the first time, that we can prospectively identify likely responders to our novel drugs and apply data-driven measurement to the treatment of psychiatric and other central nervous system disorders," said Amit Etkin, M.D., Ph.D., founder and chief executive officer of Alto Neuroscience. "We are pleased to have finished this study ahead of schedule, and I am proud of our team for their relentless persistence and execution to reach this important milestone. As this provides a substantial level of de-risking, we are eager to move ALTO-100 into the Phase 2b study which will begin enrollment this month."

The study was an 8-week open-label, holdout dataset-controlled study to evaluate the efficacy and safety of ALTO-100 in patients with MDD or post-traumatic stress disorder (PTSD). 133 patients with primary MDD and 95 patients with primary PTSD were enrolled in the study. Alto utilizes a rigorous data science approach and prospective replication to predict clinical efficacy in holdout datasets and define reliable drug predictors while avoiding false discovery. The primary endpoint was change from baseline in MADRS score at week 6, with a replication threshold pre-specified as a Cohen's d effect of 0.5 or greater.

Adam Savitz, M.D., Ph.D., chief medical officer of Alto Neuroscience, added, "We are encouraged by the potential of these results to redefine the treatment paradigm in depression, which today is largely dependent upon trial-and-error. Using our biomarker platform and data analytic approach, we've demonstrated a clear clinical signal for ALTO-100 in a particularly underserved patient population. Stronger clinical signals in the MDD population defined by our biomarker profile support movement into a larger Phase 2b study in this population. Analyses are ongoing for the population with PTSD to inform potential future studies in that indication. We look forward to building on the learnings from this study for additional medications and patient subgroups as we continue to validate our precision psychiatry approach."

About Alto Neuroscience

Alto Neuroscience is pioneering precision psychiatry by developing targeted medicines to help patients get better faster. Differences in individuals' biology impact how they respond to treatment. Alto's Precision Psychiatry Platform™ measures brain biomarkers by analyzing EEG activity, behavioral task performance, wearable data, genetics, and other factors to match each patient with the right Alto drug. The company's work in identifying and categorizing core domains of mental function (cognition, emotion, and sleep processes) has resulted in a multiple modality approach that supports robust drug-response predictions. Alto's clinical-stage pipeline includes first- or best-in-class novel drug candidates in depression, PTSD, and other mental health conditions, resulting in the broadest and most-advanced precision psychiatry effort. For more information, visit https://www.altoneuroscience.com or follow us on Twitter.

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