Alto Neuroscience Announces Positive Data from Phase 1 Study Evaluating Brain Effects of Novel Drug Combinations

– Results demonstrate robust therapeutic potential of proprietary drug combinations, validating the Company's method of identifying and targeting core pathways to improve brain function –

– EEG, behavioral, and patient-reported outcomes prospectively replicated in holdout data set for ALTO-103 and ALTO-104, with replication being a core tenet of Alto's approach to drug development –

– Alto plans to advance the development of these novel combinations for further mechanistic study and application to clinical populations –

LOS ALTOS, Calif., December 14, 2022 – Alto Neuroscience today announced top-line results from a Phase 1 human brain mechanism study of a series of novel combination drugs targeting the cyclic-AMP pathway, a key driver of cognition, memory, and mood in mental health conditions. Novel drug combinations, ALTO-103 and ALTO-104, exhibited significant pharmacodynamic effects compared to placebo on measures associated with therapeutic response in patients. The findings demonstrate clear pharmacological activity for these product candidates, provide justification for further evaluation in patients, and point toward disorders which may benefit the most from these drug candidates.

"We discovered these novel combinations based on the concept of synergistic pharmacology – drugs whose effects intersect on common signaling pathways in the brain. The robust pharmacodynamic effects exhibited provide strong validation of our approach, which leans heavily on conducting human mechanistic studies as early as possible rather than relying on preclinical models which have not translated to humans," said Amit Etkin, M.D., Ph.D., founder and chief executive officer of Alto Neuroscience. "Future clinical development of ALTO-103 and ALTO-104 as therapeutics for mental health conditions will be based on the specific pharmacodynamic profiles of these agents identified in our study. The potential of our novel combination approach for driving key brain circuitry more powerfully and specifically hits on a largely untapped therapeutic strategy."

Key findings prospectively replicated in the holdout data set included:

- ALTO-103 demonstrated broad pro-cognitive effects across measures of memory, attentional processing, executive functioning, motivational salience, and subjective alertness.
    - Behaviorally, ALTO-103 demonstrated improved memory recall (cohen's d effect size=0.43, p=0.04)
    - On event related potential (ERP) measures of neural information processing, ALTO-103 led to increases in:

        - mismatch negativity, a measure of attention (cohen's d effect size=0.83, p=0.001)
        - P300 in the flanker task, a measure of executive functioning (cohen's d effect size=0.61, p=0.02)
        - P300 in a reward-based learning task, a measure of motivational salience, (cohen's d effect size=0.63, p=0.009)
    - ALTO-103 also increased subjectively reported alertness (cohen's d effect size=0.23, p=0.15)

- ALTO-104 demonstrated positive pro-cognitive and subjective effects, specifically exhibited through information processing speed, alertness, and contentedness
    - Behaviorally, ALTO-104 demonstrated increased processing speed (cohen's d effect size=0.43, p=0.03)
    - ALTO-104 also increased subjectively reported alertness (cohen's d effect size=0.60, p=0.004) and contentedness (cohen's d effect size=0.31, p=0.08), suggesting a positive mood profile

- ALTO-103 and ALTO-104 were well-tolerated with no discontinuations related to adverse effects.
- ALTO-102 did not display effects on the behavioral, ERP, or subjective response pharmacodynamic markers.

The randomized, placebo-controlled, four-way cross-over design Phase 1 study investigated the effects within-subject of single doses of each of three different combination drugs targeting the cAMP pathway, compared to placebo. Outcomes were assessed on behavioral, ERP, and subjective measures. Tolerability profiles were also characterized. Within a combination, each drug was used at low doses in order to maximize sensitivity to their synergistic action and minimize side effects. A total of 41 healthy adult volunteers were studied. In evaluating the effects of the product candidates, the data was separated into a training and holdout data set to prospectively test and replicate observed effects. The training data set consisted of 30 subjects while the holdout data set consisted of 11 subjects. The holdout data set was not unlocked until test measures were finalized based on the analysis of the training set.

The results from this study provide validation of the mechanistic effects of two novel combination approaches tested, and also establish a generalizable biomarker-based drug development paradigm that can scale across a wide range of potential pharmacological synergy strategies.

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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