TD Cowen 45th Annual Health Care Conference

Founder & CEO – Amit Etkin, M.D., Ph.D.

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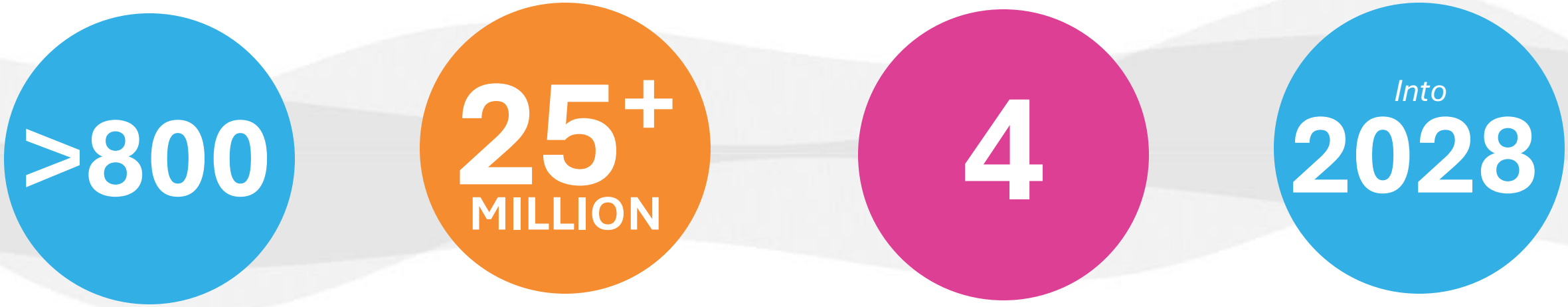
Alto by the numbers

Advancing
a leading, clinical-stage precision medicine portfolio for the brain



Patients Dosed
Across studies with Alto's novel product candidates and precision approach

Patient Impact
Opportunity across the portfolio

Phase 2 Data Readouts
In next 2 years

Expected **Cash** Runway

Alto's strategy addresses a core problem in psychiatry

Characterizing drug activity and identifying responsive patient populations before advancing

Current approach

Unguided trial-and-error treatments in heterogeneous populations work poorly

No human target engagement

Uncontrolled and unmeasured patient heterogeneity

Alto precision approach

Differentiated drug profile in stratified patient populations

Broad utilization of pharmacodynamic biomarkers

Discover and **prospectively replicate** objective biomarkers for patient selection

Alto’s flywheel goes beyond binary drug outcomes

Biomarker-based clinical data

- Large Phase 2a Biomarker Studies
- Decentralized Trial Infrastructure

Predictive algorithms

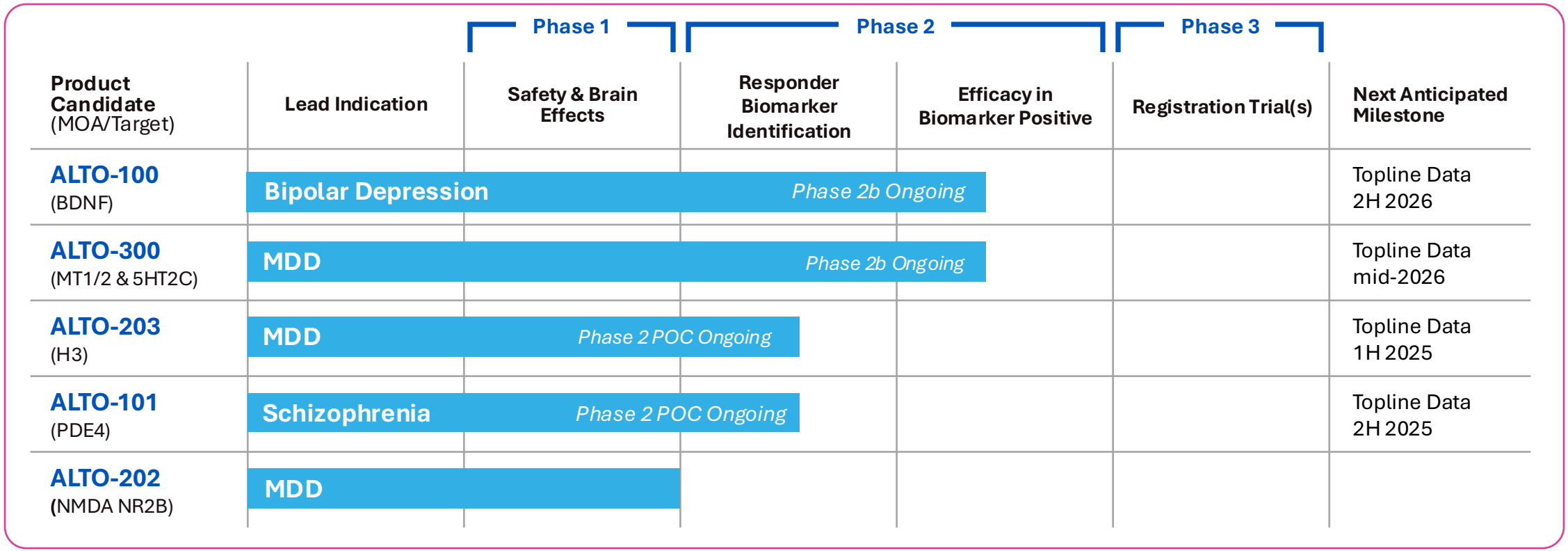
- Responder Biomarkers:
  - ALTO-100
  - ALTO-300
  - SSRI, ketamine, etc.

Biomarkers & phenotypes

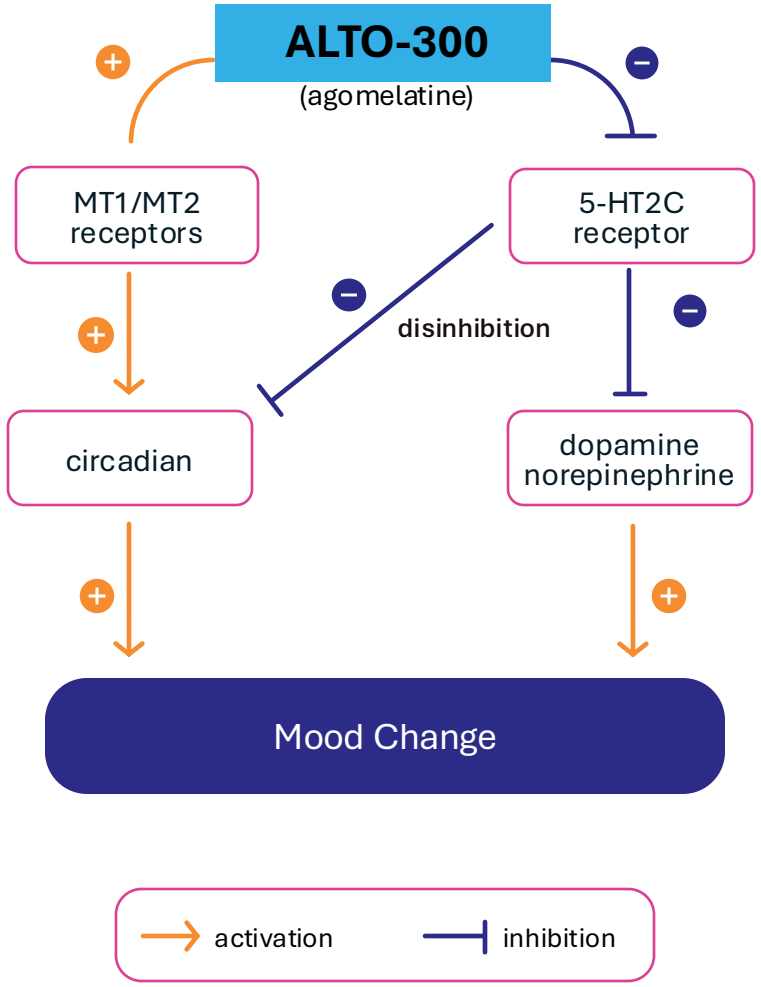
- Target Engagement By Drug Candidates (ALTO-101)
- Placebo-Controlled Trials in Biomarker Population

First biomarker-driven pipeline for mental health conditions

Multiple independent programs leveraging our biomarker strategy to systematically reduce development risk



ALTO-300 proposed mechanism of action: synergy between melatonergic agonism and 5-HT2C antagonism



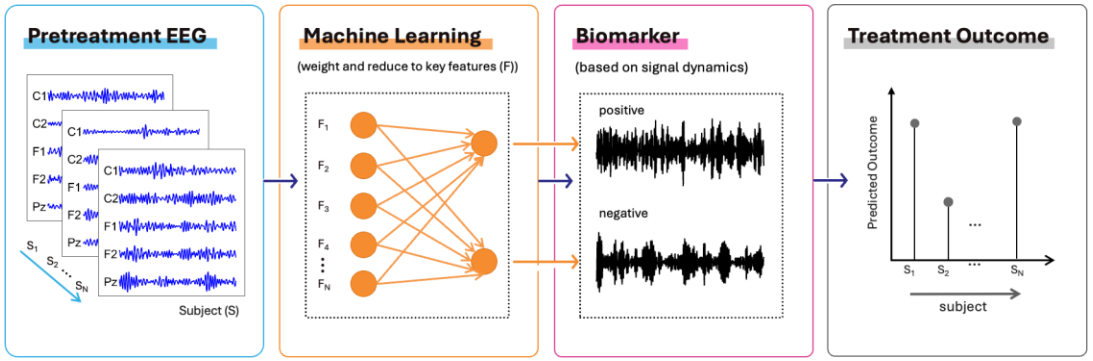
ALTO-300 is a multi-modal antidepressant with a broad range of **synergistic neurobiological effects** that lead to antidepressant activity and favorable tolerability

Antidepressant properties	Melatonergic (MT1 and MT2) Agonism	Serotonergic (5-HT2C) Antagonism
Enhancement of dopaminergic input to frontal cortex	+	+ +
Resynchronization of circadian rhythms	+ +	+
Anxiolysis	+	+
Improved sleep quality/patterns	+	+
Lack of weight gain and sexual dysfunction	+	+

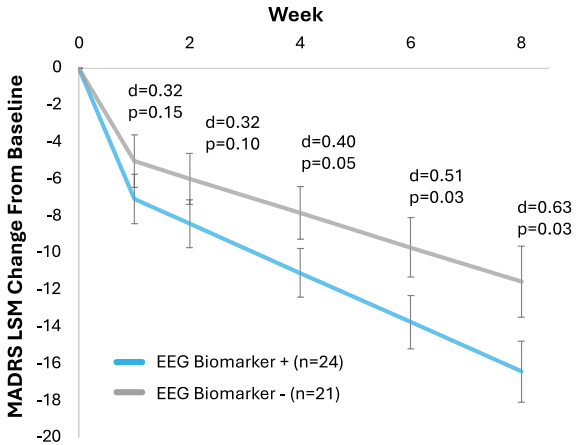
Bodinat et al., Nature Reviews, 2010

ALTO-300 EEG biomarker has been replicated and reverse translated with clear biologic link to MoA

1 Machine-learning discovered EEG biomarker

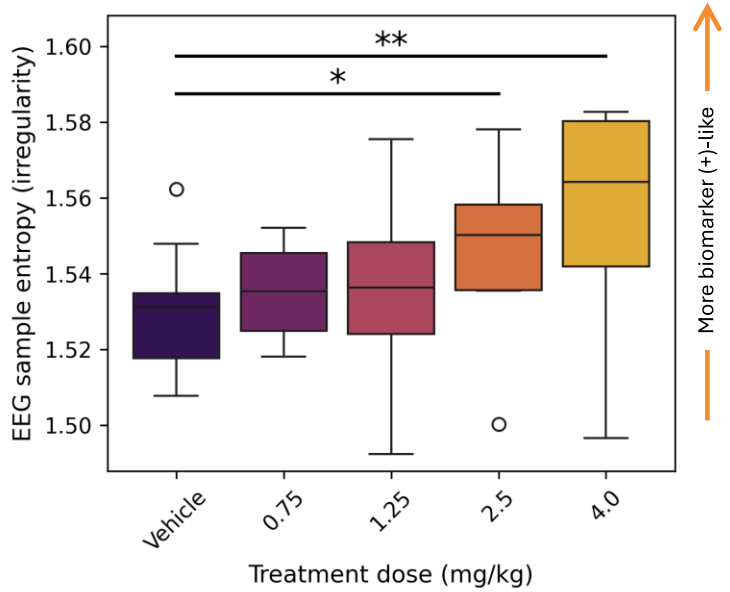


2 Biomarker effect prospectively replicated



3 Reverse translated biomarker in animals

N=13, cross-over with 5-HT2C agonist R0 60-0175 or vehicle:

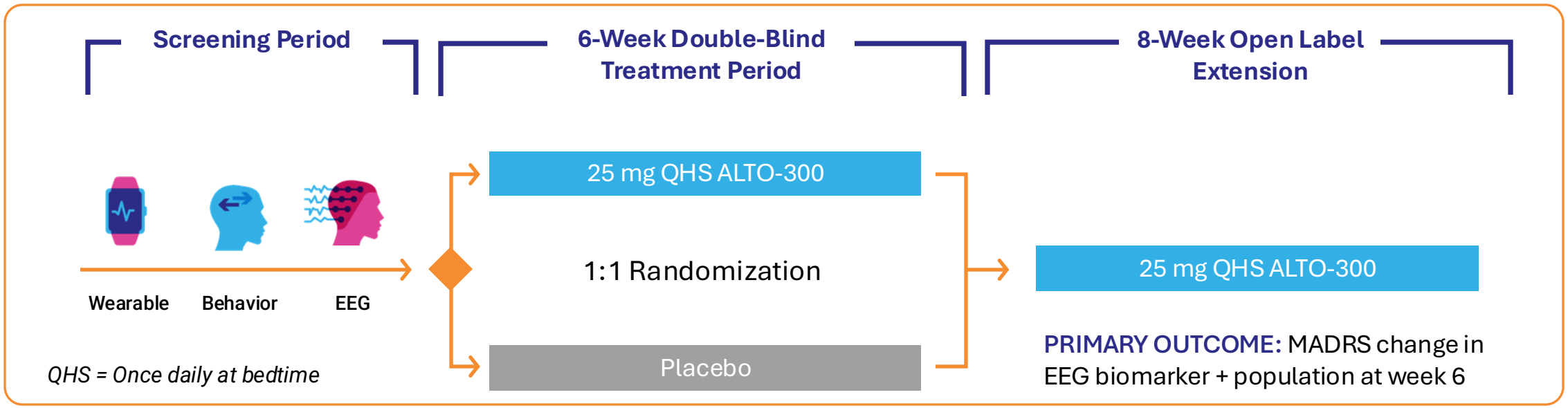


Dose-dependent response on EEG biomarker establishes this as the first machine-learning discovered biomarker that has been reverse-translated to animals to elucidate mechanistic link

ALTO NEUROSCIENCE

ALTO-300 Phase 2b biomarker-guided trial in MDD

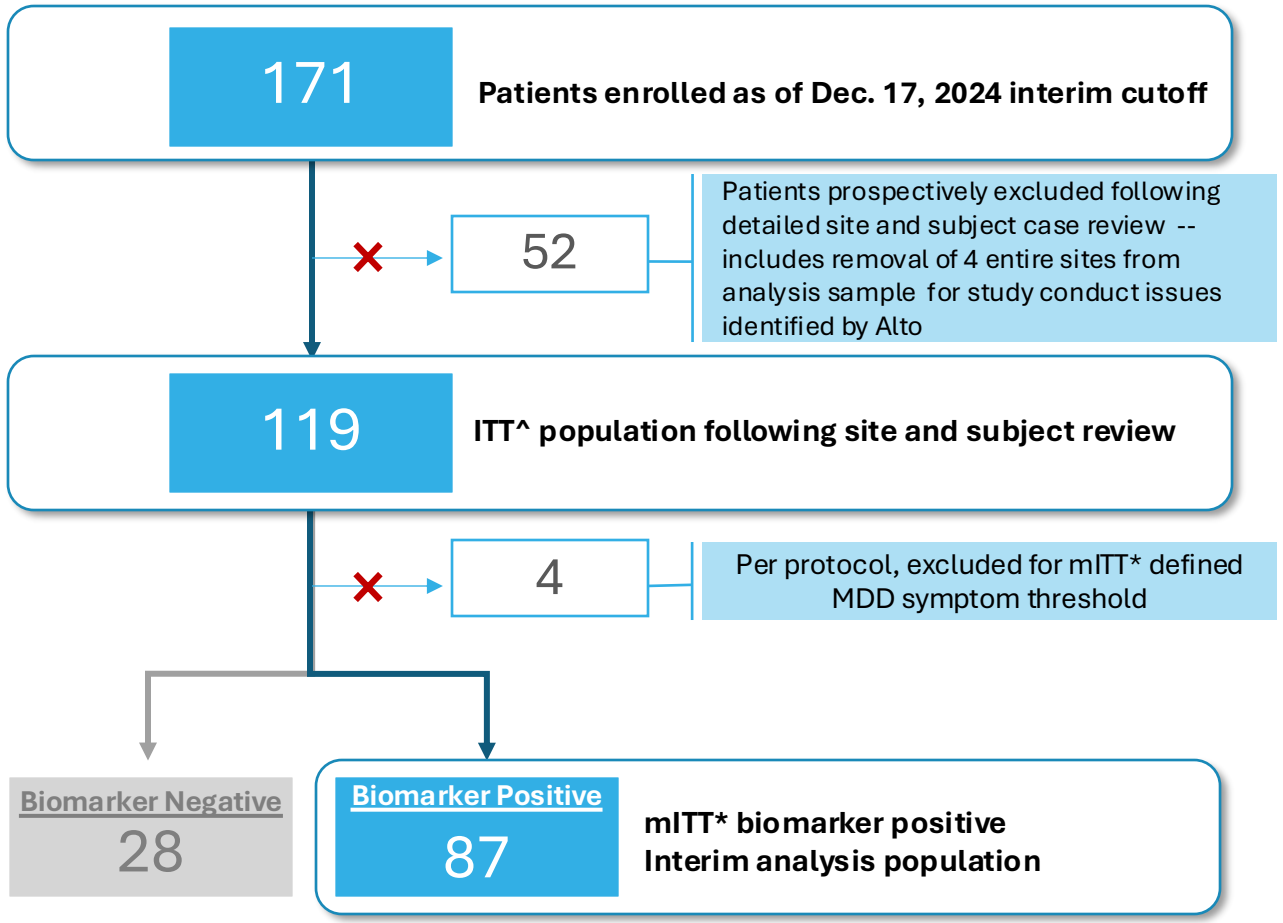
Evaluating ALTO-300 as an ***adjunctive to an existing antidepressant*** with an insufficient response



- Design follows **FDA's enrichment guidelines:** powered primary outcome in EEG biomarker positive patients
- **Includes participants with and without the biomarker** and randomization stratified by biomarker status
- Site-based and decentralized – **sites and participants blinded to biomarker status**
- Primary MDD but allows co-morbid anxiety disorders and PTSD
- **Central review (MGH-CTNI SAFER interview)** of all participants before randomization
- **Favorable outcome from interim analysis** informs final sample size; ~200 biomarker positive patients targeted for the final analysis sample to achieve adequate powering

ALTO NEUROSCIENCE

Interim analysis on ALTO-300 Phase 2b informs final sample size



Note: Site and patient exclusions prospectively determined by a blinded review committee

Outcome

✚ **Continue study with sample re-estimation: Enroll Bio + target N of ~200 patients in final analysis sample**

✚✚ **Stop early for success:** If interim analysis achieves p-value <0.005

− **Futility:** Non-binding futility recommendation based on effect size threshold of Cohen's d < 0.20

According to standard α spend calculation for a study with 1 interim analysis, conservative success stopping criterial of p≤~0.005 results in final analysis success threshold of p<0.049

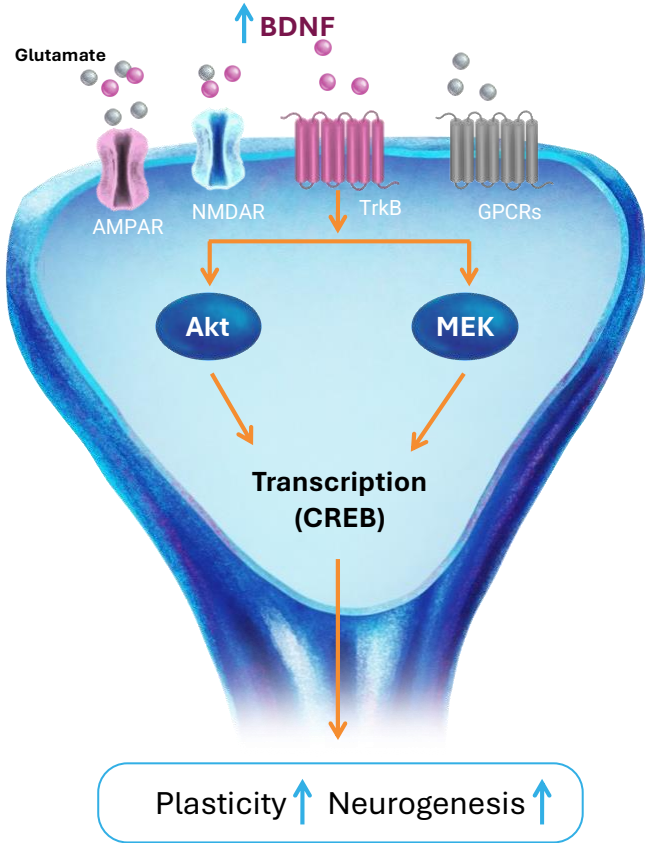
ALTO NEUROSCIENCE

^ITT = Intention to Treat
**mITT = Modified Intention to Treat*

ALTO-100: Novel product candidate enhancing neuroplasticity to address depression symptoms

Enhancing neuroplasticity to address depression

Targeting pathways abnormal in MDD and bipolar depression



Clinical data indicate potential in bipolar depression

239-patient Phase 2a study

- Clear antidepressant activity
- Robust separation between biomarker positive and negative population

301-patient Phase 2b study*

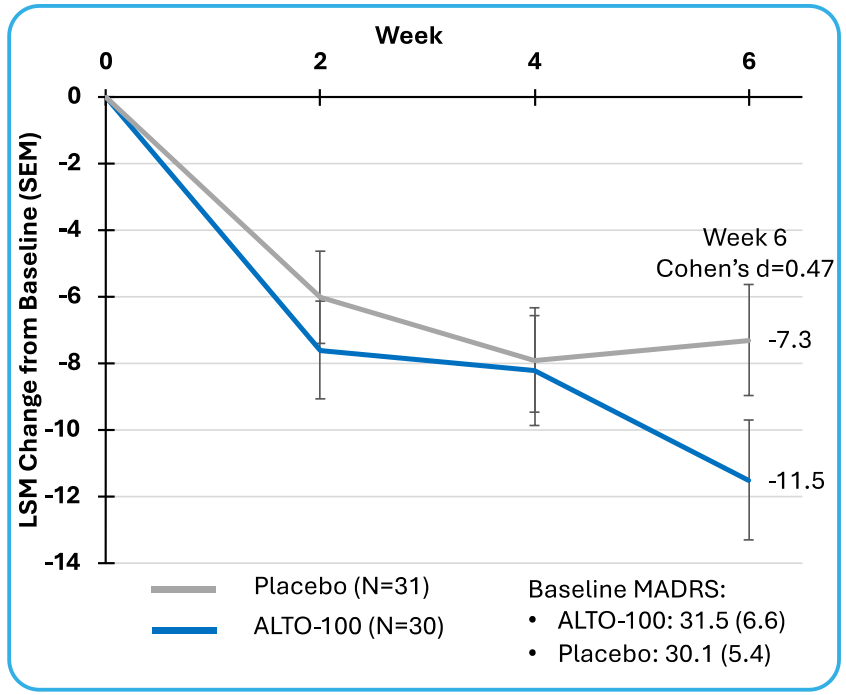
- Evidence of effect in prespecified analysis of adjunctive population
- Evidence of effect in population shown to be compliant with medication
- Evidence of effect in analysis excluding sites with objective data quality issues

**ALTO-100 did not meet primary endpoint in Phase 2b MDD study*

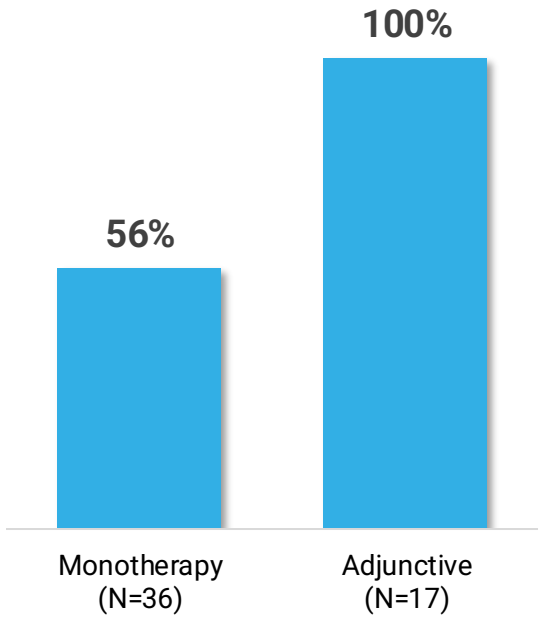
Adjunctive population demonstrated clinically meaningful response to ALTO-100 and had significantly higher compliance

The study included Bio+ patients taking ALTO-100 as monotherapy (69%) and those taking it adjunctive to an antidepressant (31%)

Clear drug effect in prespecified adjunctive population



Compliance rate among monotherapy and adjunctive patients in PK sample*



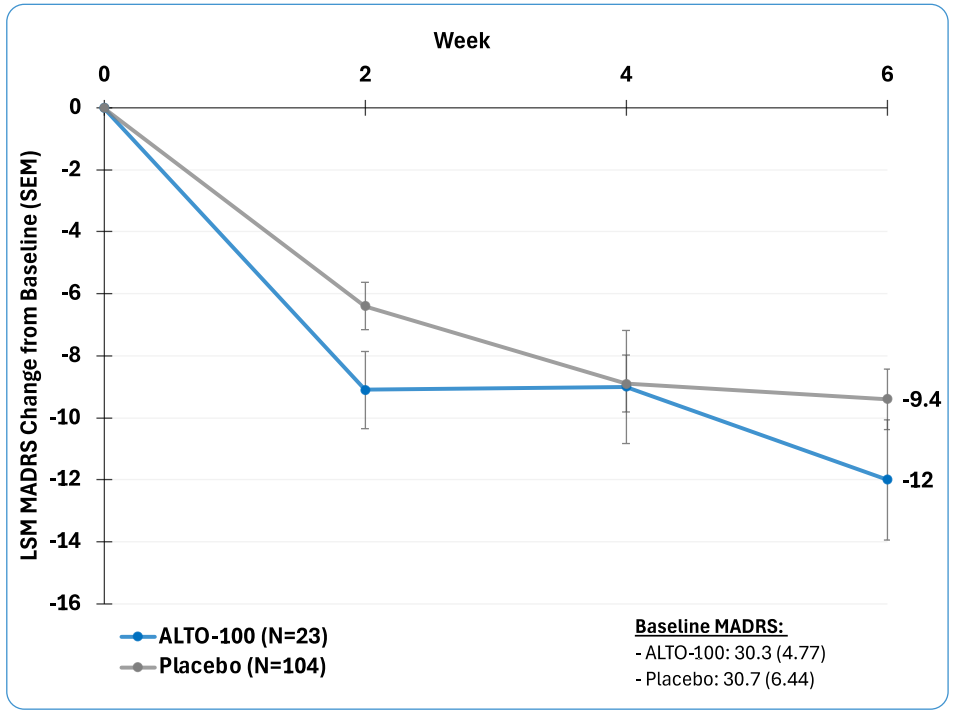
Only a subset of sites within the study were setup to evaluate PK levels

We believe the adjunctive signal is the most indicative of the ALTO-100 effect based on the clinically meaningful signal & high compliance rate

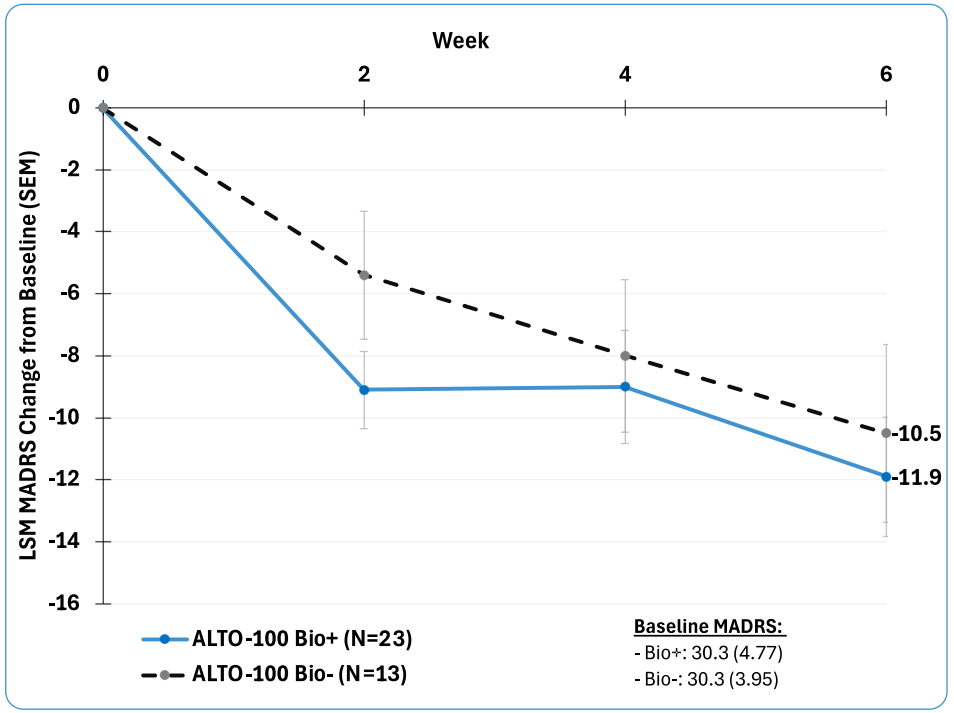
PK Sample: Sample of patients from overall study who had blood draws to evaluate pharmacokinetic levels

Evidence of drug effect & biomarker enrichment observed in the compliant population in additional analyses

Bio + confirmed compliant patients vs. all placebo



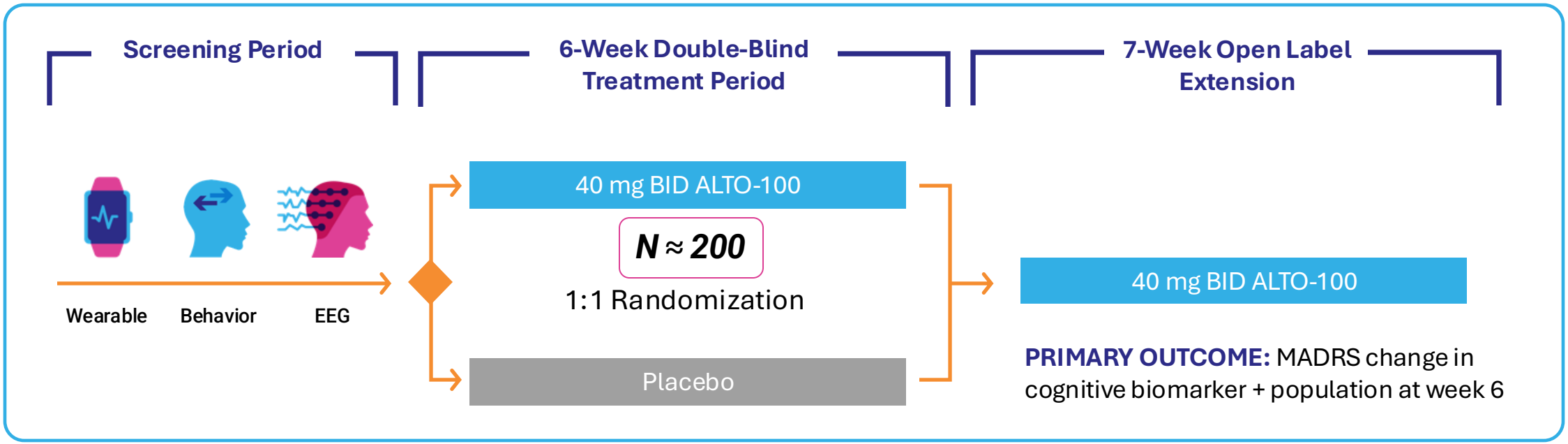
Bio + vs. bio – in confirmed compliant patients



Retrospective analyses conducted within population with measurable PK levels of ALTO-100, including monotherapy and adjunctive use

ALTO-100 Phase 2b biomarker-guided trial in bipolar depression

Evaluating ALTO-100 as an ***adjunctive treatment*** to an existing mood stabilizer (no antipsychotics)



- Design follows **FDA's enrichment guidelines:** powered primary outcome in memory biomarker positive patients
- **Includes participants with and without the biomarker** and randomization stratified by biomarker status
- **Sites, participants and Alto staff blinded to biomarker status**
- **Central review** (MGH-CTNI SAFER interview) of all participants before randomization

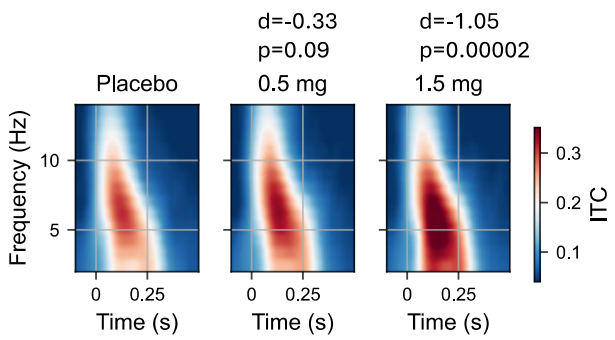
Alto received $11.7 M funding award from Wellcome Trust to support study

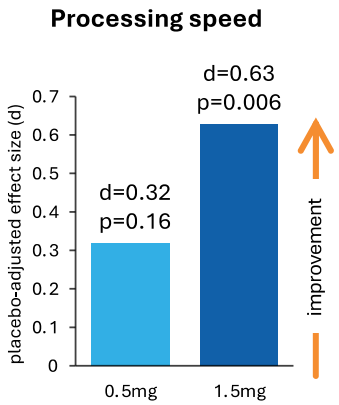
ALTO NEUROSCIENCE

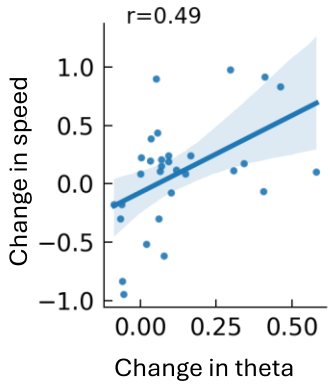
ALTO-101 positioned as a novel transdermal PDE4 inhibitor with broad pro-cognitive activity

EEG response links CIAS and PD activity

Dose-dependent increase in theta EEG activity and improvement in processing speed by ALTO-101 (N=40, crossover)

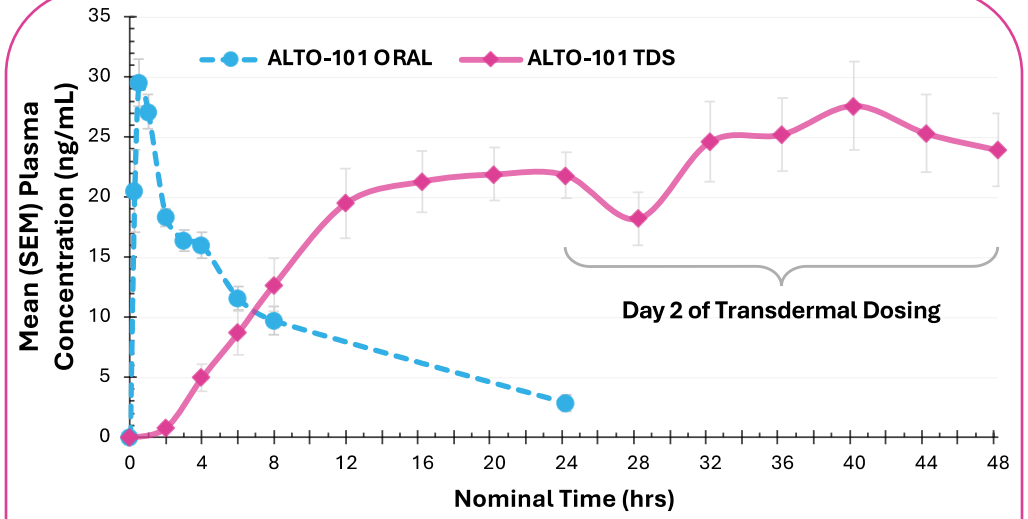






Greater increase in theta response by ALTO-101 correlates with greater improvements in processing speed

Greater drug exposure and improved tolerability



Transdermal formulation (TDS) eliminated rapid C_{max} related AEs and maintained steady exposure

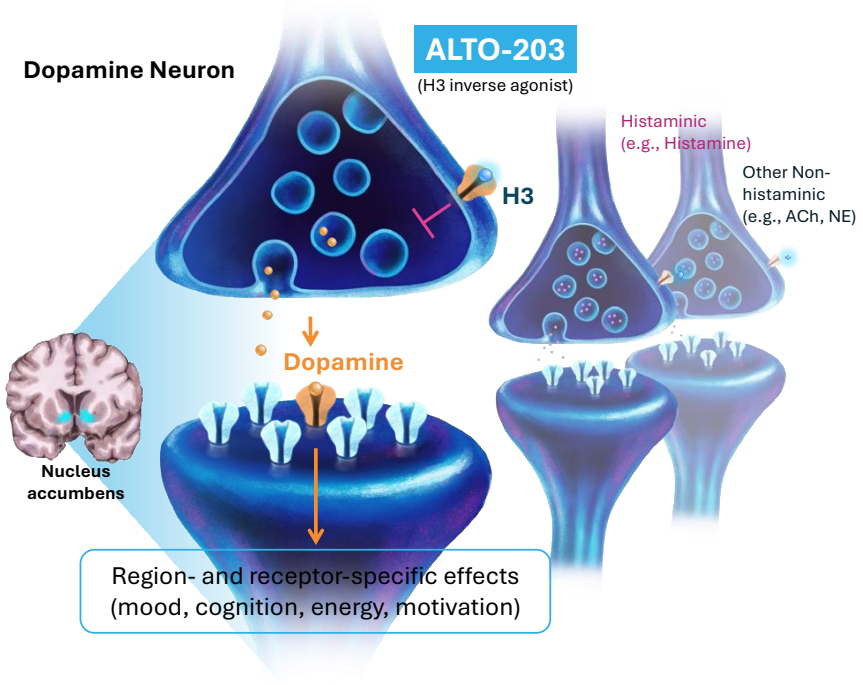
AUC 170% **greater for TDS** by day 2 vs. oral ($p<0.001$)

Well-tolerated with no discontinuations

Proof-of-concept study in CIAS is designed to provide clear understanding of effects on well characterized EEG markers and cognitive performance**; on track to report data 2H 2025**

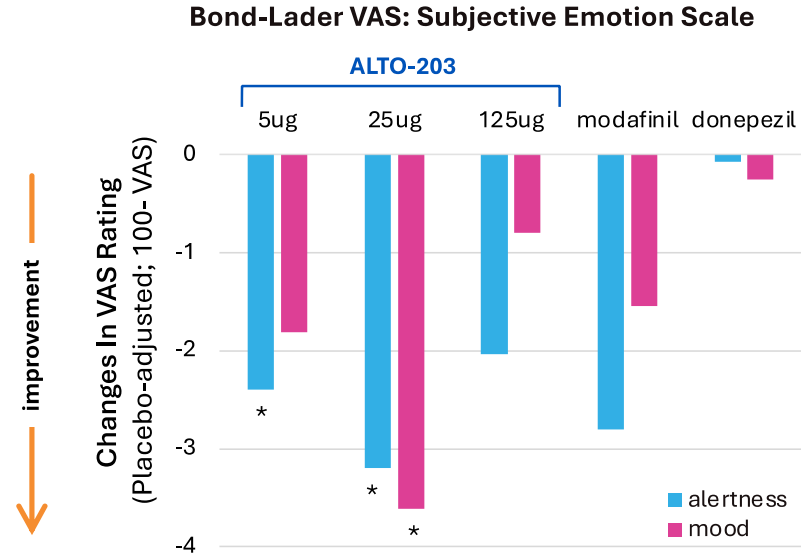
ALTO-203: An investigational H3 inverse agonist with demonstrated positive subjective emotional and cognitive effects in humans

ALTO-203 represents a unique approach at enhancing the function and control of dopamine in the reward system



Demonstrated acute subjective effects in Phase 1

ALTO-203 led to an acute **single-dose** improvement in a PD-focused Phase 1 study (N=40, crossover)*



**Study conducted prior to Alto acquisition*
VAS= visual analog scale; higher score on the scales shown (plotted as 100-VAS) denotes lower alertness or mood

Proof-of-concept study will provide understanding of subjective and objective effects in depression population**; on track to report data 1H 2025**

Multiple near-term clinical milestones expected

Capitalized through multiple value generating clinical milestones:
~$168MM* (as of Dec. 31, 2024) → Expected cash runway into 2028

2025

- **ALTO-203 MDD POC data (1H 2025)**
- **ALTO-101 CIAS POC data (2H 2025)**

2026

- **ALTO-300 Phase 2b MDD data (mid-2026)**
- **ALTO-100 Phase 2b Bipolar Depression data (2H 2026)**

Positive results from any of these ongoing clinical trials has the potential to support moving into registrational trials

Bold denotes clinical data readout

**includes unaudited approximate cash and cash equivalents balance as of Dec. 31, 2024*