ALTO NEUROSCIENCE

NYSE: ANRO — December 2024

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Precision Medicine for the Brain is Here.

OUR MISSION

Redefining psychiatry by leveraging individuals' neurobiology to develop personalized and highly effective medicines, helping patients get better faster.

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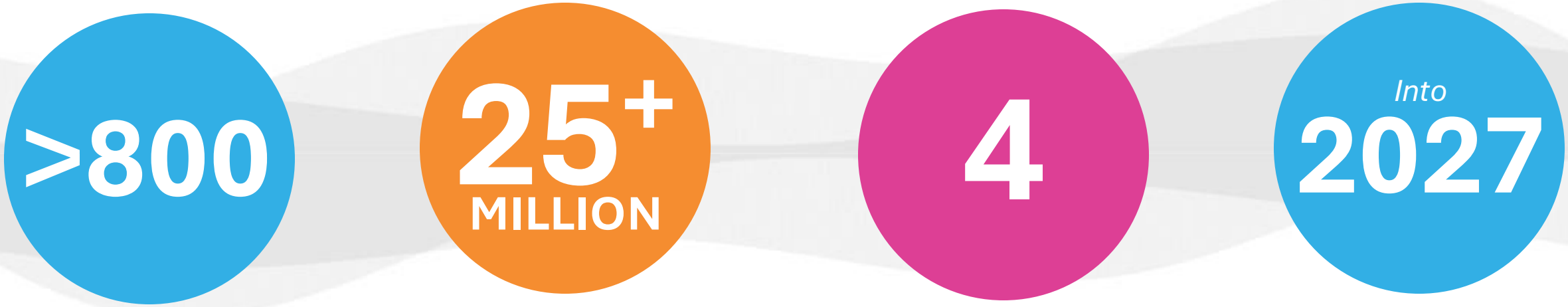
Alto by the numbers

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

CNS is the next frontier in precision medicine

Oncology

agios · Black Diamond Therapeutics · blueprint medicines · decīphera · Turning Point Therapeutics · Adaptive biotechnologies · PMVPharma · Prelude Therapeutics · Epizyme · IDEAYA · KURA ONCOLOGY · MIRATI THERAPEUTICS · REVOLUTION MEDICINES · KRONOS BIO · ORIC Pharmaceuticals · CODIAK · FOGHORN THERAPEUTICS

Cardiovascular

Bristol Myers Squibb / MYOKARDIA

CNS

predictive biomarkers

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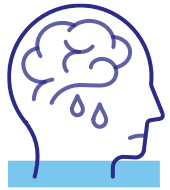
target specificity or genetics

BlackThorn Therapeutics · Prevail Therapeutics / Lilly · DENALI · PRAXIS · rapport therapeutics

Alto is the only company taking a precision biomarker-based approach to patient identification aiming to drive better clinical outcomes in CNS

Unmet needs pervade mental health disorders



Depression and schizophrenia are **leading causes of disability** worldwide

Lancet, 2017

13% of U.S. adults take antidepressants

Brody, 2020

$280B spent on mental health services in 2020

SAMHSA

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

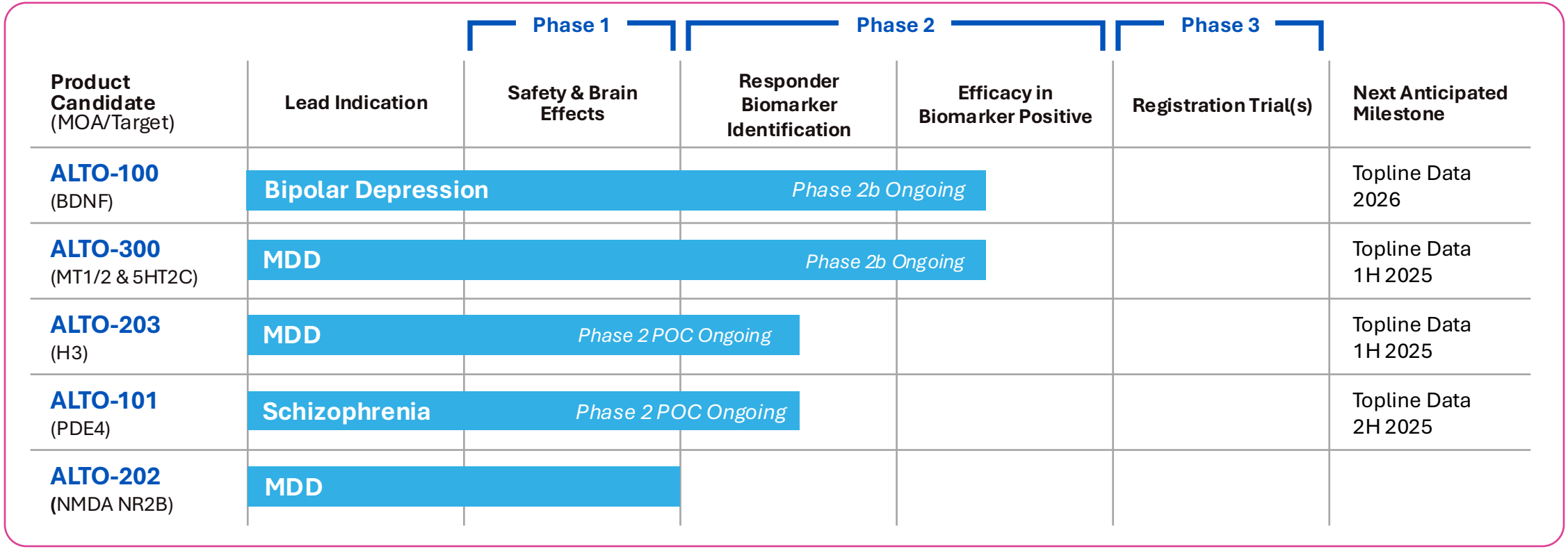
- Responder Biomarkers:
  - ALTO-100
  - ALTO-300
  - SSRI, ketamine, etc.

Biomarkers & phenotypes

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

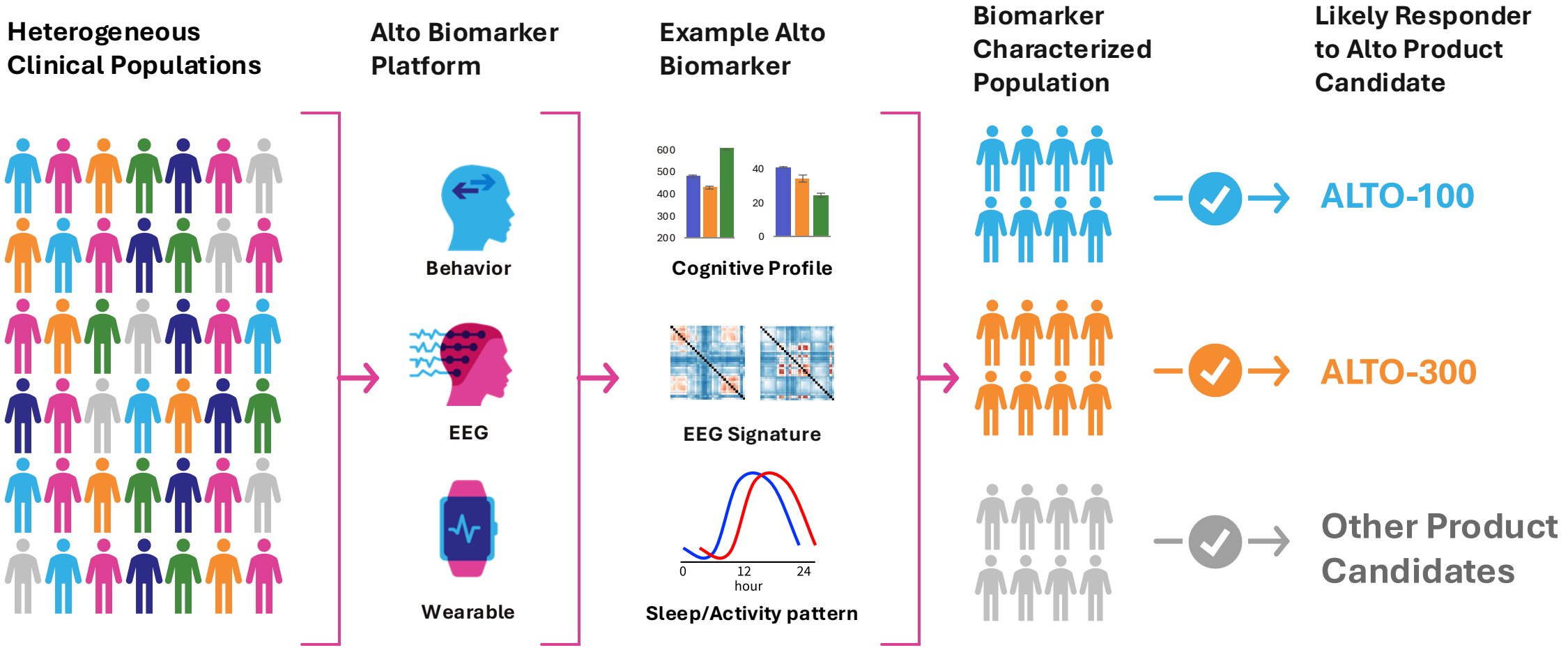
First biomarker-driven pipeline for mental health conditions

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



Platform

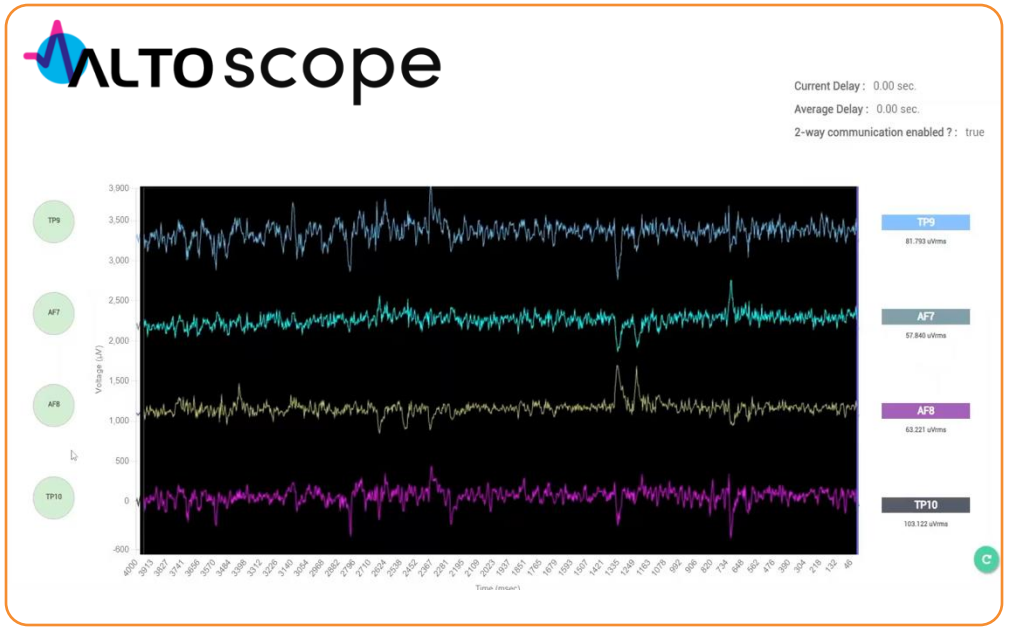
Alto's suite of biomarkers designed to segment patients to drive improved outcomes



Leveraging proprietary tools, anticipating commercial scale

ALTO-100 biomarker is cognitive test-based

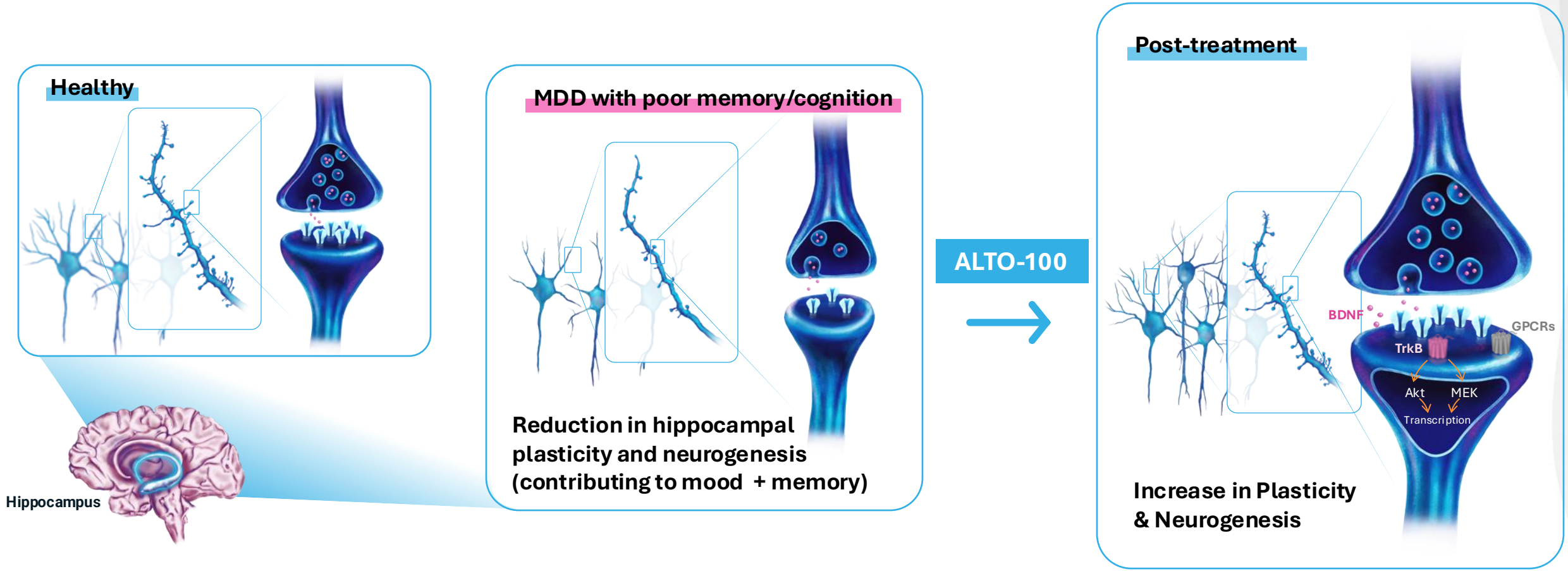
ALTO-300 biomarker is EEG-based



ALTO-100

MDD and Bipolar Depression

ALTO-100 offers a novel therapeutic option for depression with poor memory/cognition by enhancing hippocampal neuroplasticity



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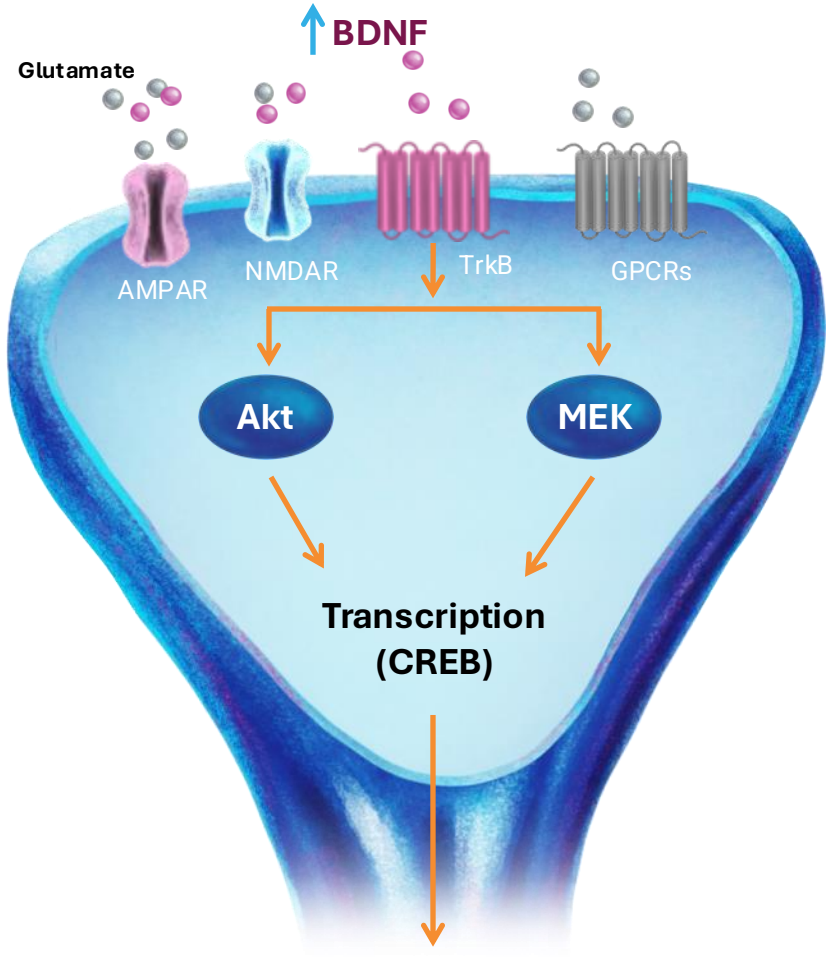
ALTO-100: developed to enhance hippocampal neuroplasticity, and improve cognition and mood



Plasticity ↑ Neurogenesis ↑

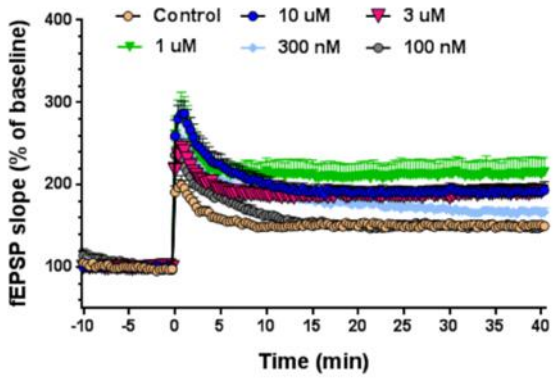
Identified based on a neurogenesis functional screen

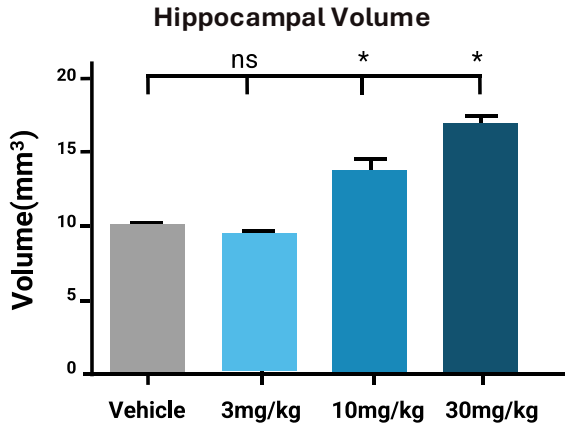
Preclinically, **increases** synaptic and cellular plasticity across multiple time scales, hippocampal volume

Evidence of working through BDNF, a core molecular mechanism important for hippocampal plasticity and mood

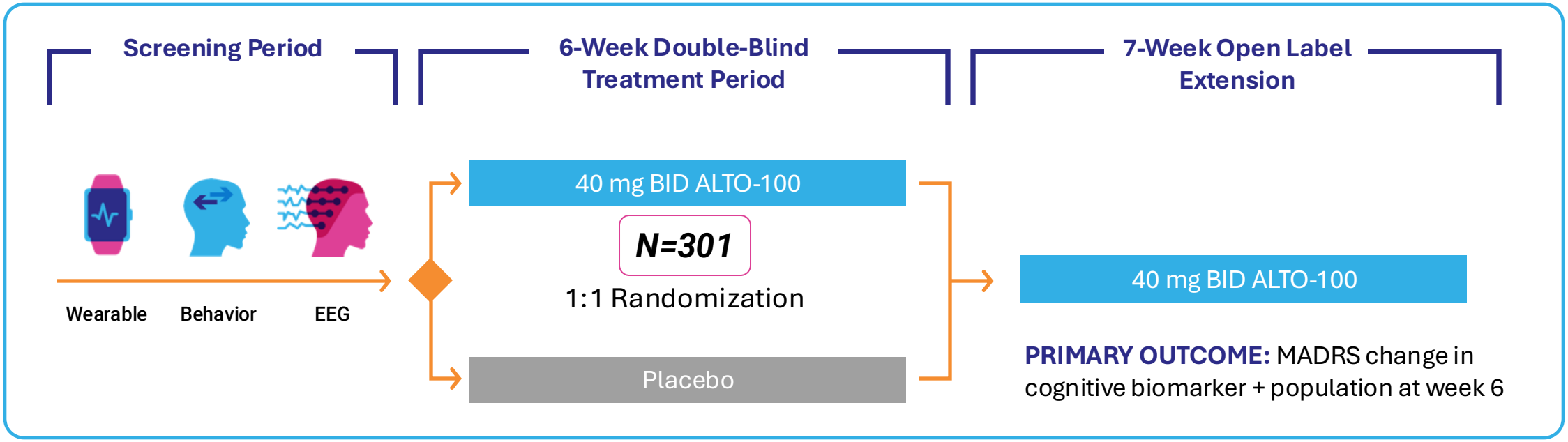
Novel, potentially first-in-class molecular mechanism (direct molecular target identified by Alto)

Increased hippocampal synaptic plasticity and volume preclinically



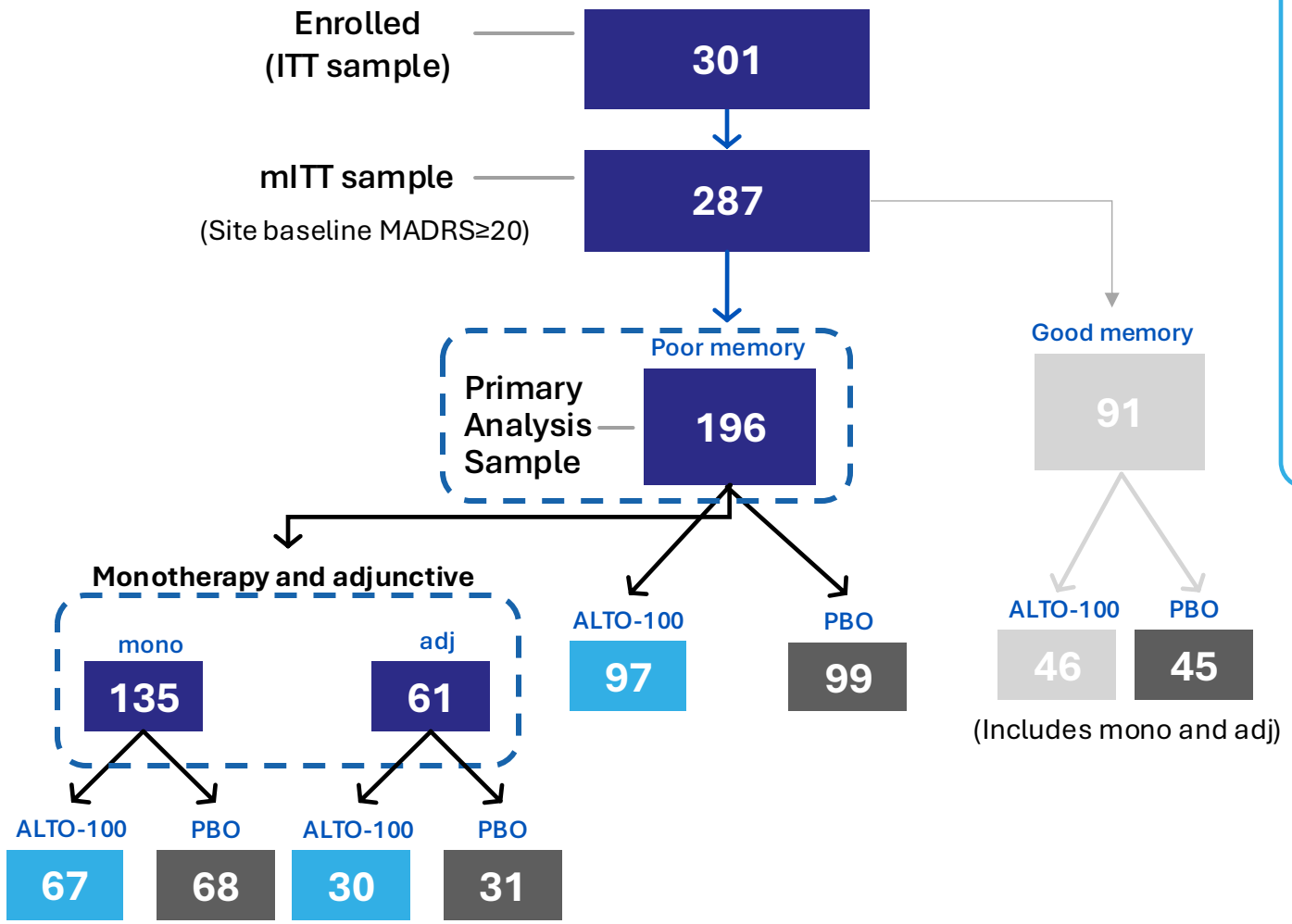


Completed ALTO-100 Phase 2b biomarker-guided trial in MDD



- 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
- **Monotherapy or adjunctive** treatment to an existing antidepressant with an insufficient response
- Site-based and decentralized – **sites, participants and Alto staff 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

Phase 2B study flow



Screening visit structure (key elements):

1. Visit 1:
   - Severity and diagnosis (at site), PHQ
   - SAFER including MADRS (MGH)**
2. Visit 2:
   - Biomarker baseline (at site), PHQ
3. Visit 3:
   - Clinical baseline MADRS (at site), PHQ

* Inclusion requires PHQ-9≥10 at visit 1 and 2 to ensure stability
** Inclusion requires SAFER MADRS ≥22

High rate of study-level QC pass:

- Biomarkers done after SAFER interview
- Broad set of biomarkers collected beyond memory as supports broader Alto platform

- Cognition: 95% all battery, 99% memory test
- EEG: 93%
- Wearables (7 days pre-baseline): 83%

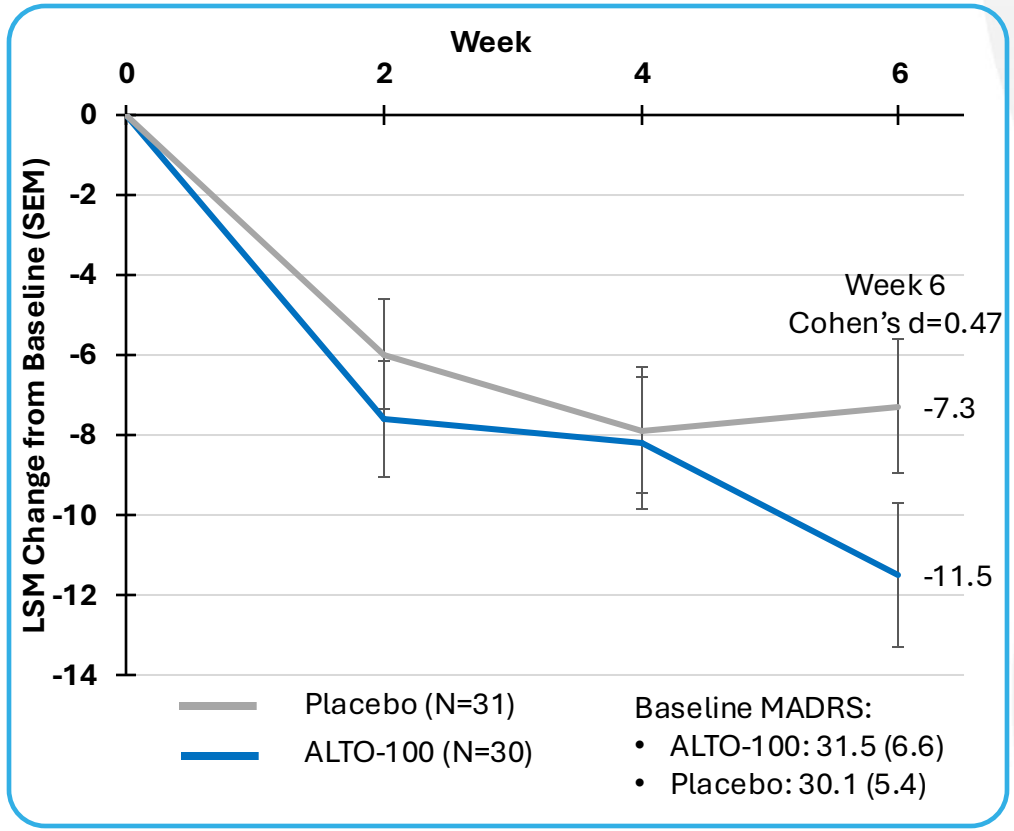
ITT = Intention-to-treat
mITT = modified intention-to-treat

Summary of ALTO-100 Phase 2b MDD results

Analysis Population	Sample Size (n)		Mean Baseline MADRS (SD)		Week 6 LSM MADRS Change (SE)		Cohen's d	p
	ALTO-100	Placebo	ALTO-100	Placebo	ALTO-100	Placebo		
All Bio + mITT *(Primary)*	97	99	31.2 (5.4)	31.5 (5.4)	-10.3 (1.0)	-9.8 (1.0)	0.05	> 0.1
Monotherapy Bio + mITT *(Key Secondary)*	67	68	31.0 (4.8)	32.2 (5.3)	-9.9 (1.2)	-11.1 (1.1)	-0.13	> 0.1
Adjunctive Bio + mITT *(pre-specified secondary, not powered)*	30	31	31.5 (6.6)	30.1 (5.4)	-11.5 (1.8)	-7.3 (1.7)	0.47	0.09

- Higher than anticipated non-compliance in monotherapy group → Adjunctive group demonstrated high compliance
  - Subset of patients had compliance evaluated through blood sample analysis
- Enrichment observed comparing biomarker positive vs. biomarker negative in patients with confirmed compliance

Pre-specified Adjunctive Bio + Subgroup



Clinically meaningful signal in the adjunctive subgroup provides confidence in continuing the Phase 2b study of ALTO-100 as an adjunctive treatment in bipolar depression; ALTO-300 is being studied as an adjunctive treatment in MDD

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ALTO-100 was well tolerated

Overall Treatment Emergent Adverse Events (TEAEs)

Safety Analysis Set

	ALTO-100 N (%)	Placebo N(%)
Total Participants	149	150
At least one TEAE	66 (44.3%)	61 (40.7%)
Related TEAE	38 (25.5%)	38 (25.3%)
AEs leading to discontinuation	6 (4%)	2 (1.3%)

Note: participants may have had more than one AE

**No related serious adverse events were observed*

TEAEs for ≥5% of the Population

Safety Analysis Set

	ALTO-100 (%)	Placebo (%)
Headache % (related %)	10% (6.7%)	12.7% (10%)

- TEAEs consistent with prior ALTO-100 studies

Rationale for ALTO-100 in poor memory/cognition patients with bipolar depression

- Bipolar disorder long thought to involve reduced neuroplasticity in the hippocampus, similar to MDD
  - Reduced hippocampal volume
  - Memory and broader cognitive deficits (as or more frequent than MDD)
  - Cellular and molecular evidence of neuroplasticity deficits
  - BDNF and related plasticity pathways implicated
- Much like MDD, poor memory/cognition patients have worse outcomes
  - Greater treatment resistance and disability, more likely to have future mood episodes, related to genetic risk, persists across disease phases
- Current treatment options are more limited than MDD as only approved therapies are antipsychotics
  - High side effect burden with limited efficacy
  - Patients spend more time depressed than manic, often needing chronic treatment
  - Mood stabilizers are not effective for bipolar depression
- Strong biological and clinical rationale for ALTO-100 as a putative pro-plasticity intervention for patients with reduced hippocampal plasticity (poor memory marker)

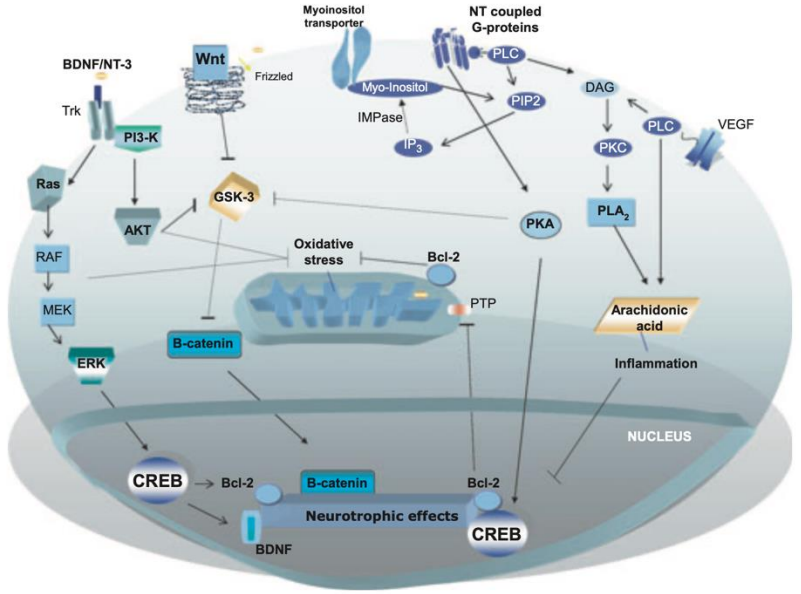
The role of hippocampus in the pathophysiology of bipolar disorder

Benicio N. Frey[a,e], Ana C. Andreazza[a,b], Fabiano G. Nery[c,f,g], Marcio R. Martins[d], João Quevedo[d], Jair C. Soares[h] and Flávio Kapczinski[a]

Behav Pharm, 2007

Clinical overview

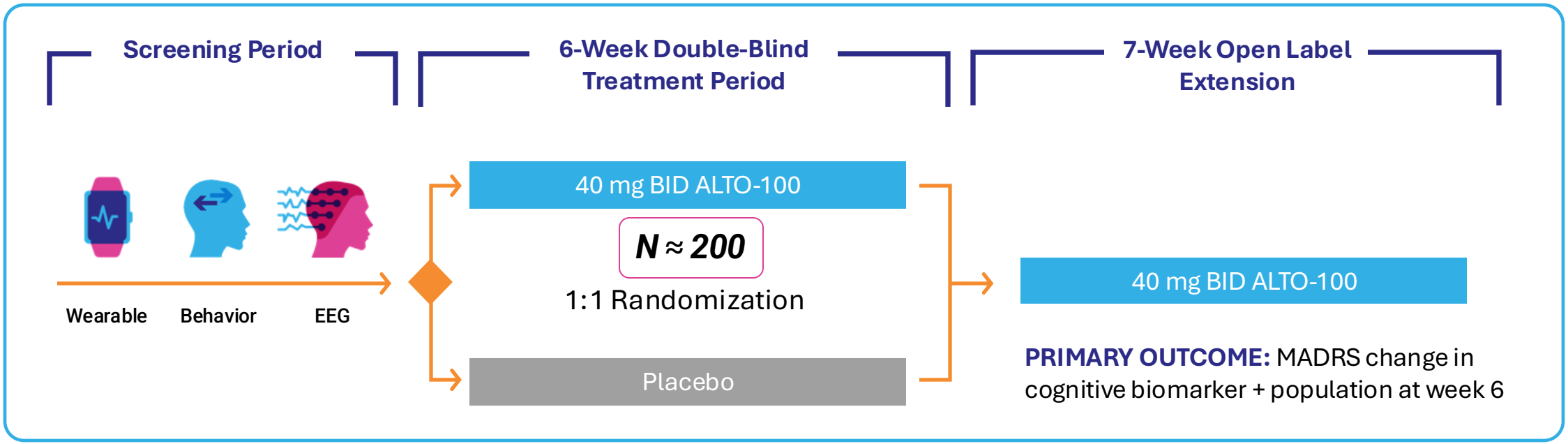
Translating neurotrophic and cellular plasticity: from pathophysiology to improved therapeutics for bipolar disorder



Soeiro-de-Souza et al, *Acta Psych Scan*, 2012

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

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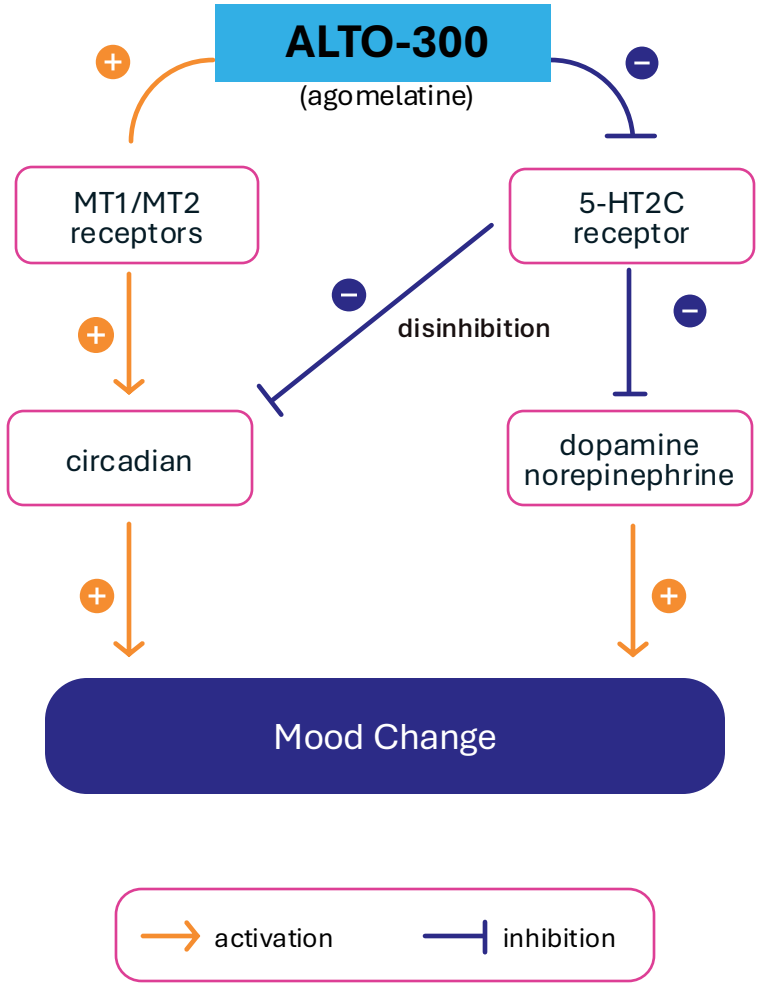
ALTO-300

Phase 2b development for MDD

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

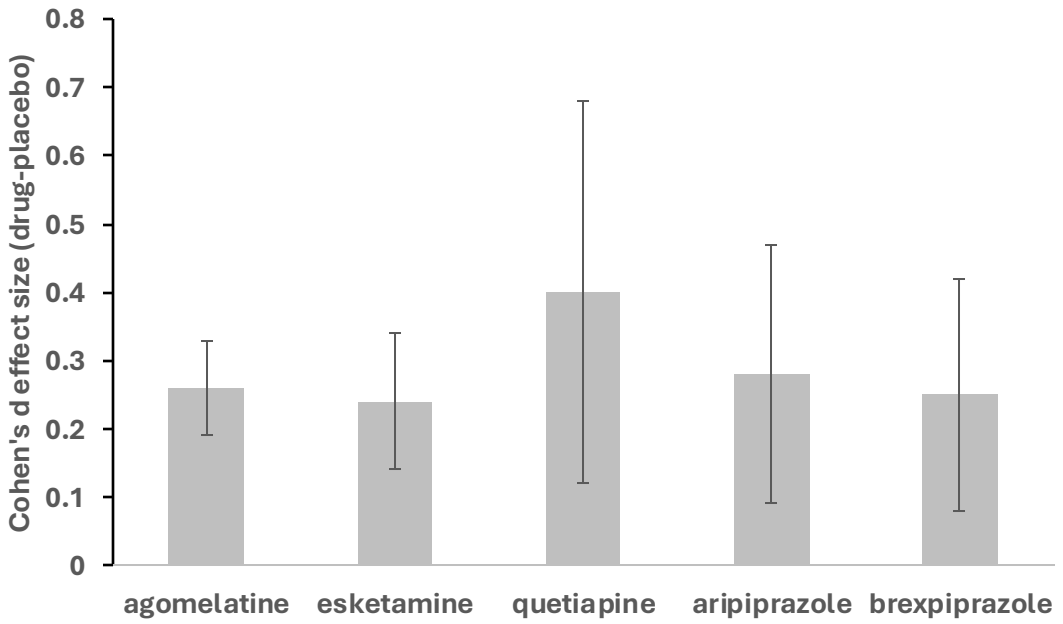
Antidepressant properties	Melatonergic (MT1 and MT2) Agonism	Serotonergic (5-HT2C) Antagonism
Enhancement of dopaminergic input to frontal cortex	+	+ +
Resynchronization of circadian rhythms	+ +	+
Anxiolysis	+	+
Improved sleep quality/patterns	+	+
Lack of weight gain and sexual dysfunction	+	+

Bodinat et al., Nature Reviews, 2010

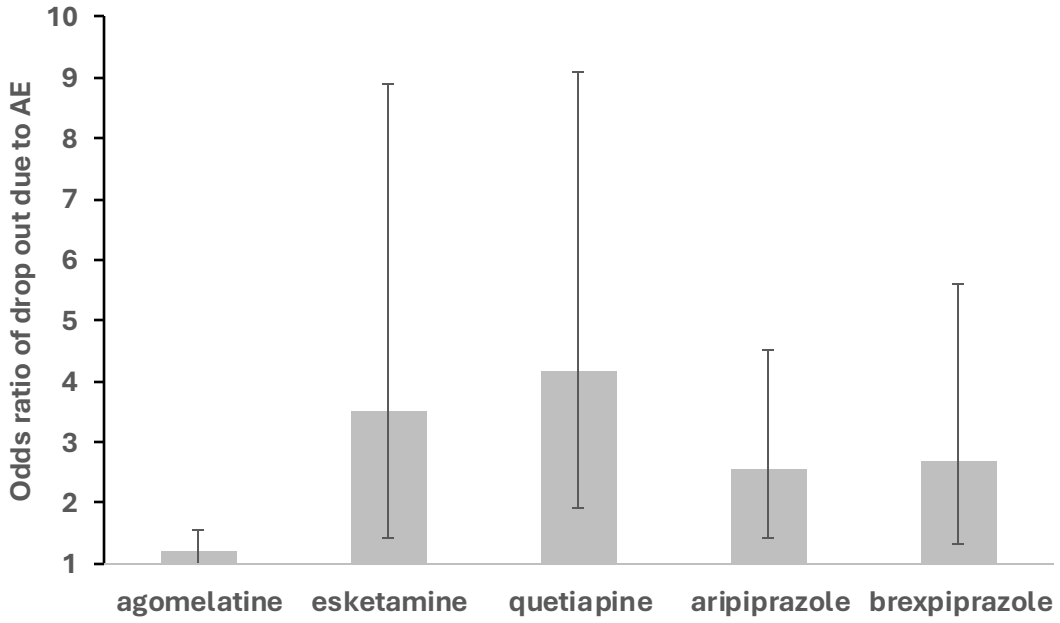
Unique Opportunity for ALTO-300 (agomelatine) as an adjunctive treatment in MDD

Well-tolerated and validated antidepressant with Ex-U.S. approval (NCE in U.S.) ready for enhancement with a biomarker

Similar all-comer efficacy as other adjunctive treatments



Favorable tolerability compared to other adjunctive treatments



No difference in dropout due to AE in agomelatine, unlike antipsychotics and esketamine

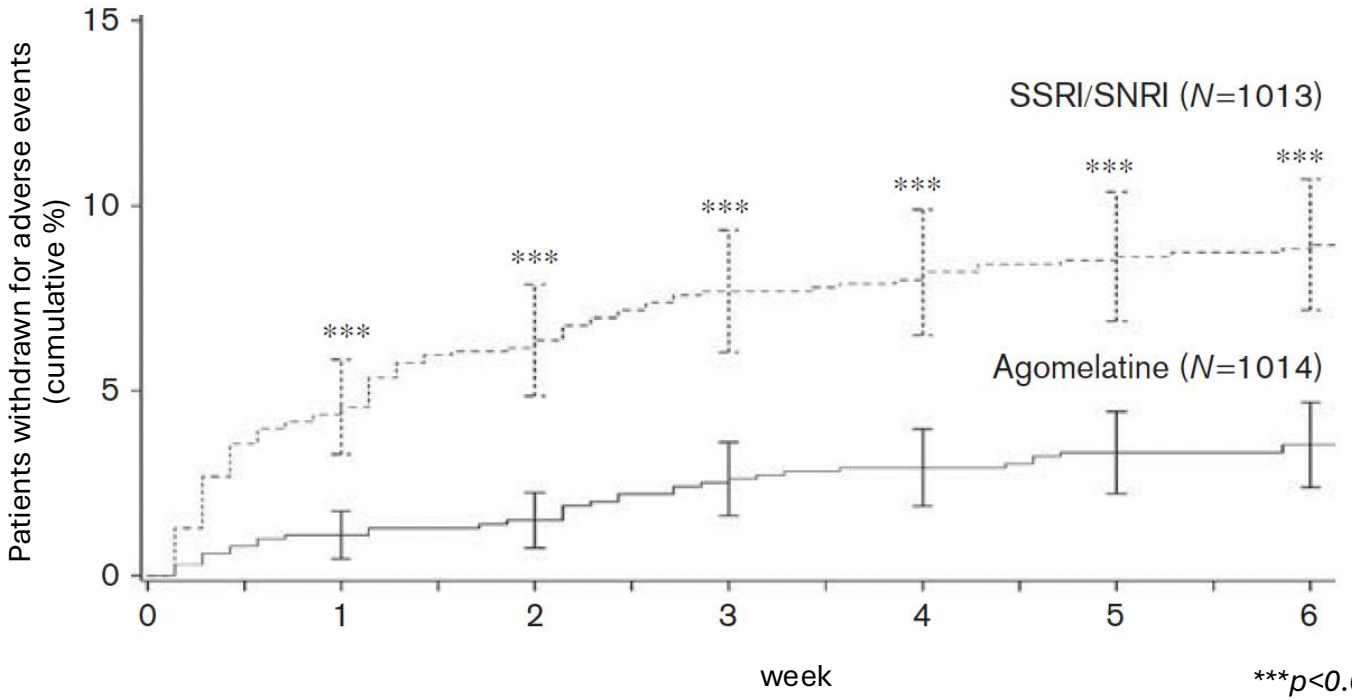
Meta-analytic values drawn from *Cipriani et al., Lancet, 2018; Wang et al., Medicine, 2023; Jawad et al., Exp Op Drug Saf, 2022; Wei et al, J Aff Dis, 2020;* Quetiapine, aripiprazole, and brexpiprazole are the atypical antipsychotics approved for MDD.

Head-to-head clinical trial data positions ALTO-300 favorably even against SSRI/SNRIs, setting up case for adjunctive use

ALTO-300 (agomelatine): superior efficacy and tolerability

- Greater efficacy (N=1014) vs SSRI/SNRIs (N=1013) in a pooled analysis on HDRS outcomes: p=0.013 (*Kasper, 2013)*
- Better treatment of anhedonia than venlafaxine XR on SHAPS (Martinotti, 2012)
- Lack of discontinuation symptoms following withdrawal vs. paroxetine *(Montgomery et al., 2004)*
- Fewer sexual side effects than venlafaxine XR *(Kennedy et al., 2008)*

ALTO-300 (agomelatine) consistently better-tolerated with fewer discontinuations versus SSRI/SSNRIs due to adverse events (pooled analysis of randomized trials)



****p<0.001*

Kasper et al., International Clinical Psychopharmacology, 2013

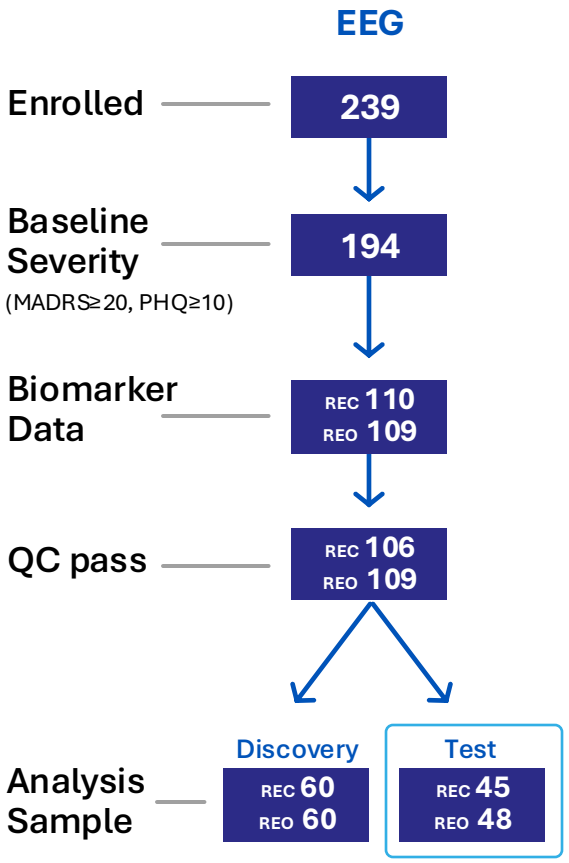
ALTO-300 Phase 2a study design and participant flow

Patient Population

- Adults 18-74 years old
- Moderate to severe MDD
- Adjunctive (<50% response to current drug)
- 45% of EEGs done at home

Treatment and Biomarkers

- 25 mg single-arm for 8 weeks
- ClinRO's at baseline, weeks 1, 2, 4, 6, 8
- Full Alto biomarkers at baseline, weeks 2 & 8
- N=239 enrolled in 14 months across 8 in-clinic sites and 2 decentralized sites
- Analyses focused on MADRS



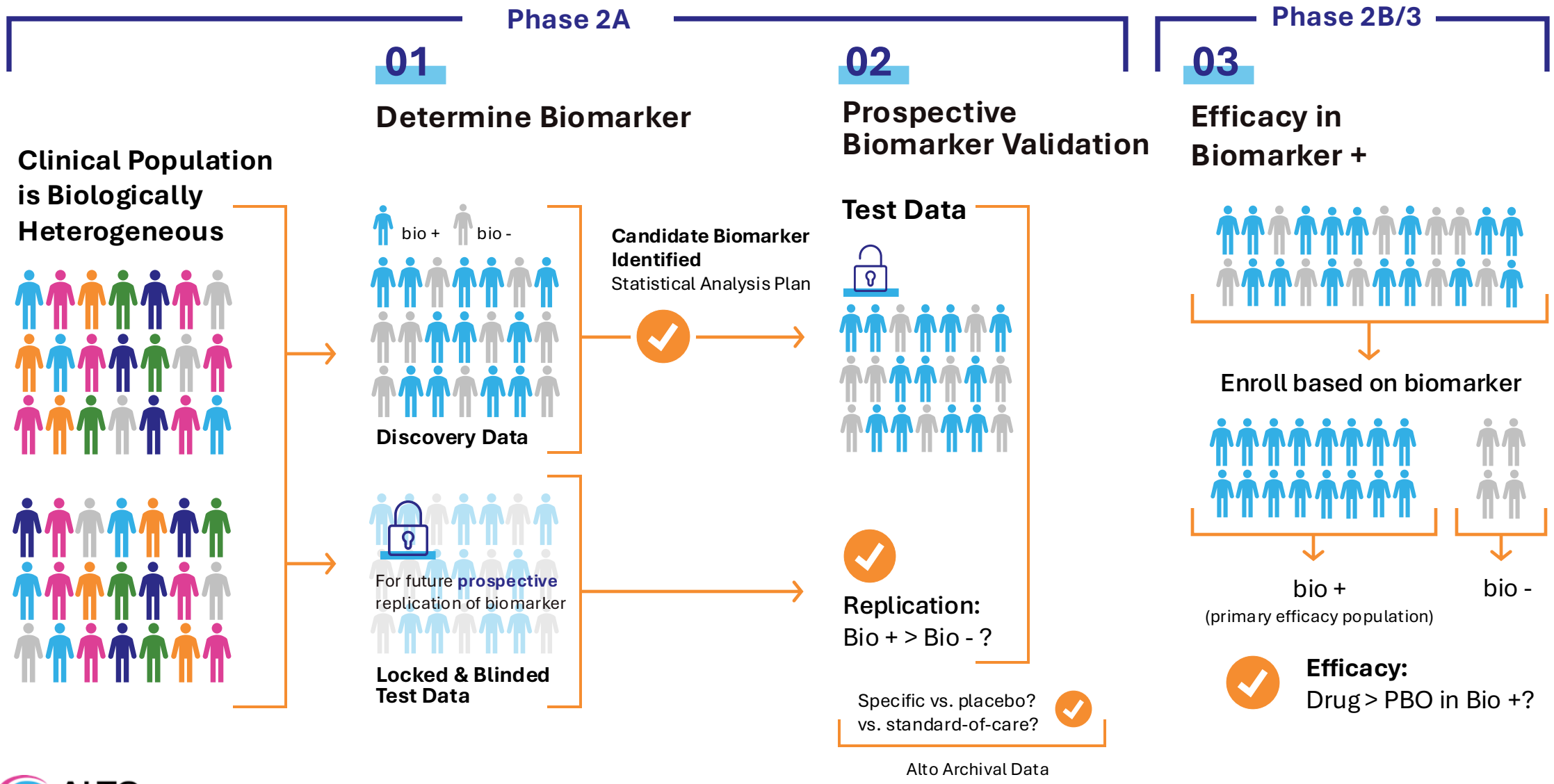
REC = resting eyes-closed
REO = resting eyes-open

Baseline Demographics

	Discovery data set		Test data set	
	Bio-	Bio+	Bio-	Bio+
N	29	31	21	24
Age	43.0 (16.2)	39.7 (14.9)	39.3 (14.3)	46.4 (14.4)
Female	66%	84%	71%	92%
Edu (16+)	55%	39%	29%	71%
BMI	31.9 (9.4)	34.4 (8.7)	29.7 (8.0)	31.4 (7.6)
White	69%	77%	76%	88%
MADRS	26.7 (4.3)	29.5 (5.4)	28.4 (5.7)	27.0 (4.7)
HDRS	19.0 (3.8)	19.6 (4.8)	20.0 (6.2)	18.6 (5.6)
CGI-S	4.4 (0.6)	4.5 (0.6)	4.7 (0.8)	4.3 (0.8)
PHQ-9	14.9 (3.3)	17.3 (4.6)	16.4 (3.3)	14.8 (3.4)

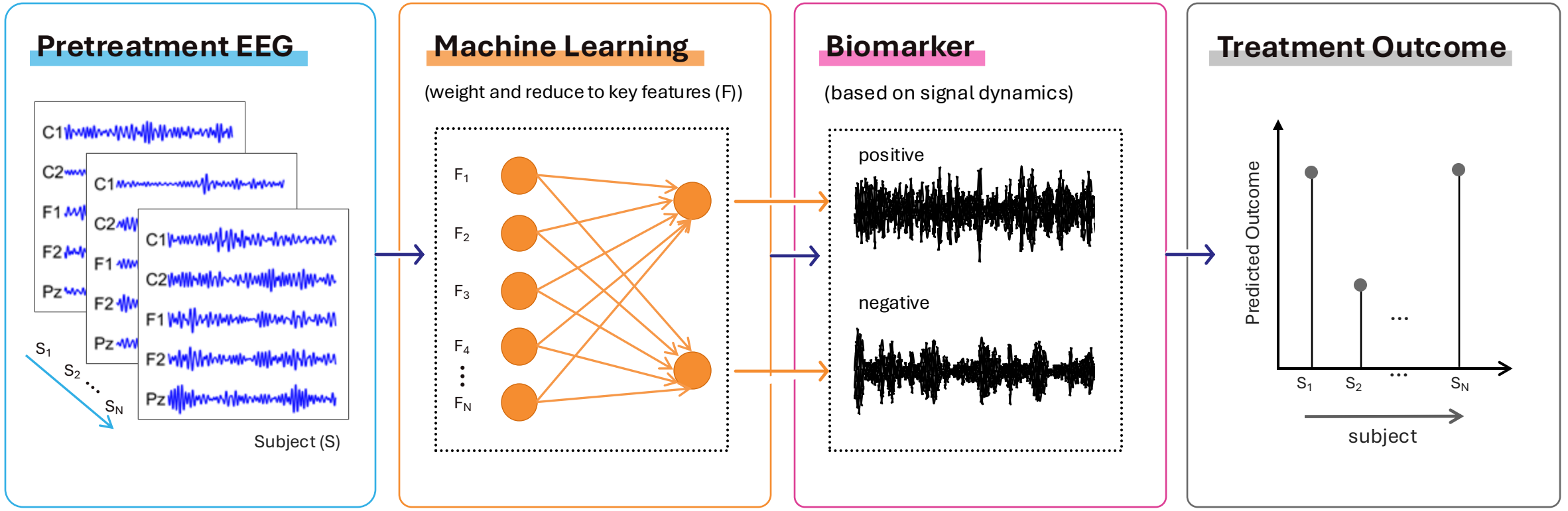
No baseline/clinical characteristics were shown to impact results of biomarker outcomes

Alto's precision drug development approach



Identified a unique and scalable biomarker for ALTO-300

Using an EEG machine learning strategy validated for other treatment biomarkers (e.g., SSRIs), a unique resting-state EEG signal from a single electrode was identified and prospectively replicated as a predictor of ALTO-300 response



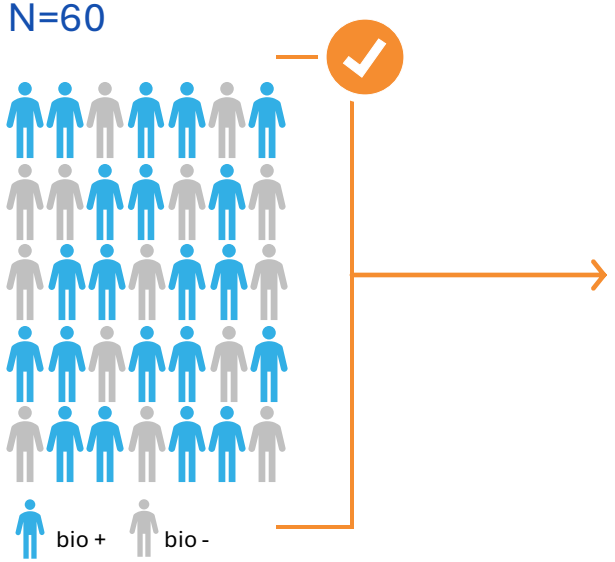
The biomarker is calculated from a single electrode and automatically scored, facilitating scalability

ALTO-300 Phase 2a: prospective replication of EEG biomarker as predictive of response

01

Determine Biomarker

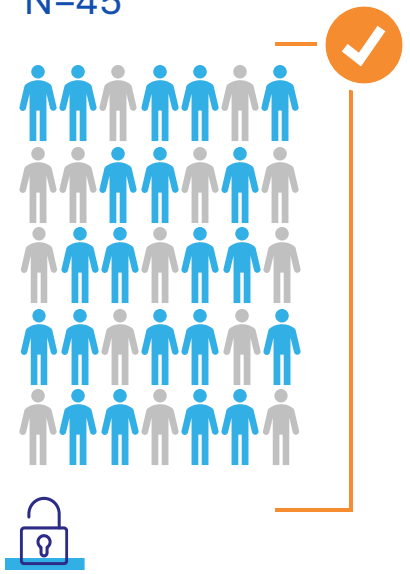
N=60



02

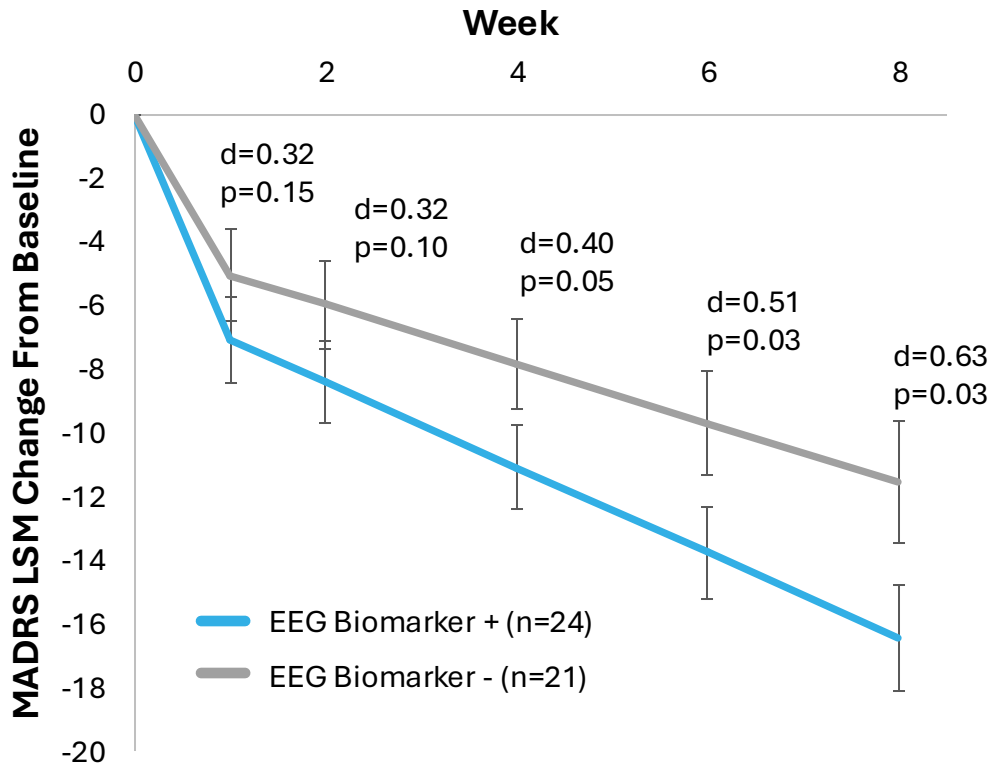
Prospective Biomarker Validation

N=45



1. Identified EEG signature as predictive
2. Prospectively label patients as bio+/-

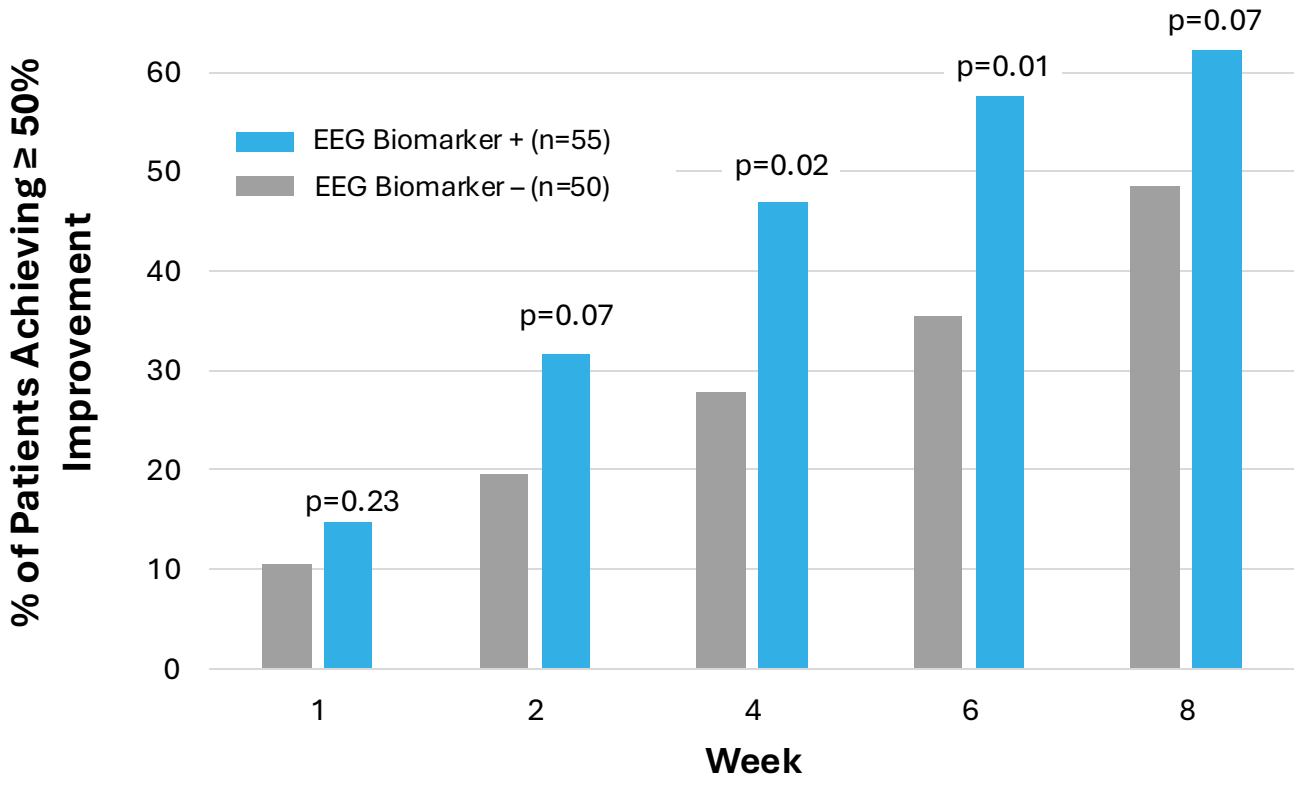
Prospective Replication in Test Dataset



Biomarker positive patients derived greater benefit from ALTO-300

EEG biomarker positive patients observed to achieve more robust clinical response to ALTO-300

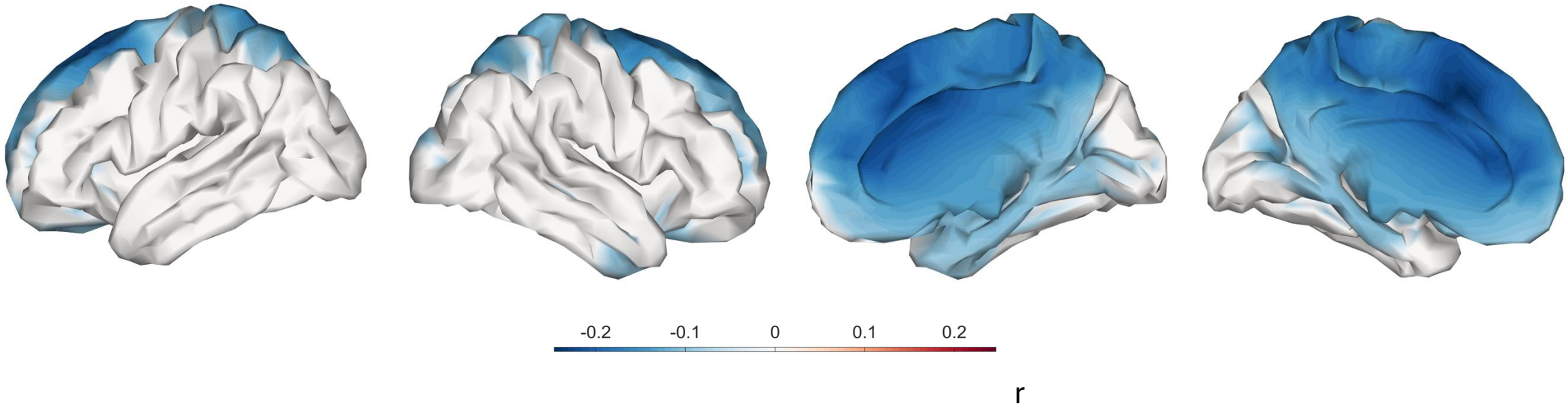
- Response rates (MADRS reduction ≥50%) were higher in Bio +
- Positive effects observed across CGI and HAM-D



CGI – Clinician Global Impression of change
HAM-D – Hamilton Depression Rating Scale

ALTO-300 biomarker: a measure of reduced neural signaling stability

- Greater EEG irregularity (i.e., biomarker positivity) is associated with decreased neural connectivity
- Across multiple independent datasets (N=784), biomarker positive patients demonstrated reduced medial prefrontal neural connectivity, an area important for MDD



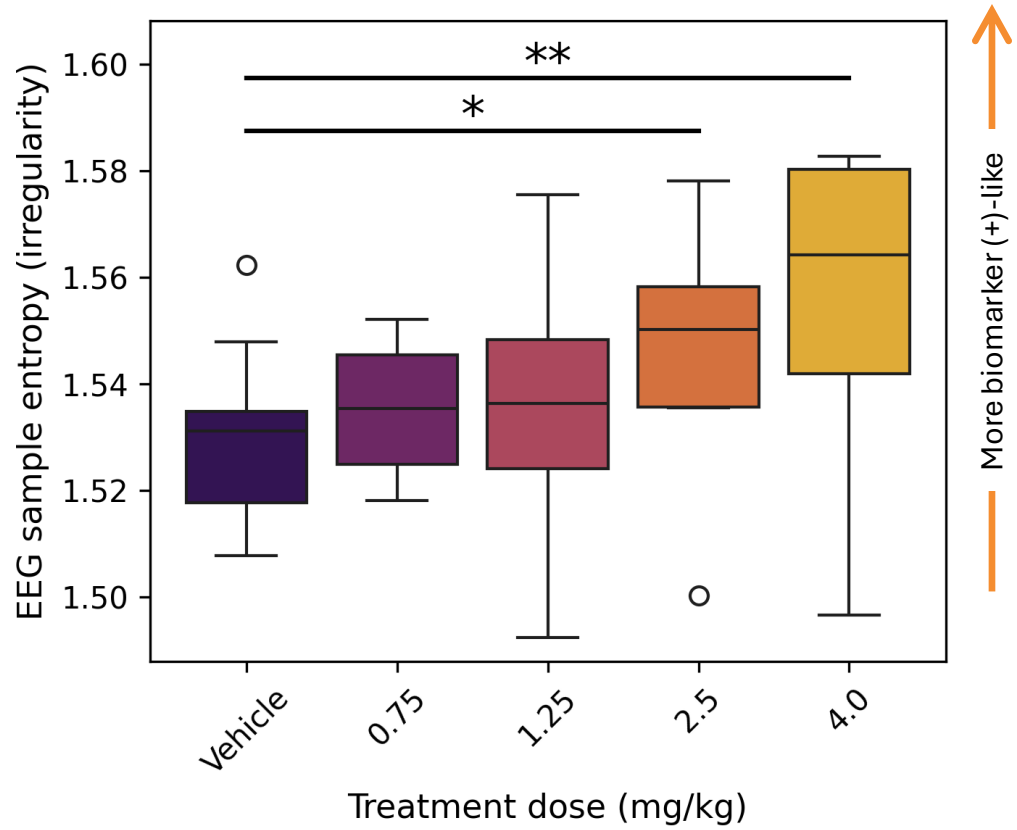
Ravindran et al, ACNP 2024

Preclinical data demonstrates the link between the mechanism of ALTO-300 and its EEG biomarker

ALTO-300 biomarker was induced by activating the 5-HT2C receptor in a reverse translation study

- ALTO-300 MOA: MT 1/2 agonist and 5-HT2C antagonist
  - ALTO-300 blocks the 5-HT2C serotonin receptor which has been shown to increase dopamine release, stabilizing neural signaling
  - Activating 5-HT2C receptors leads to a depression-like phenotype
- Administration of a 5-HT2C agonist (R0-0175) led to a dose-related increase in EEG irregularity using the same measure as the human biomarker

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

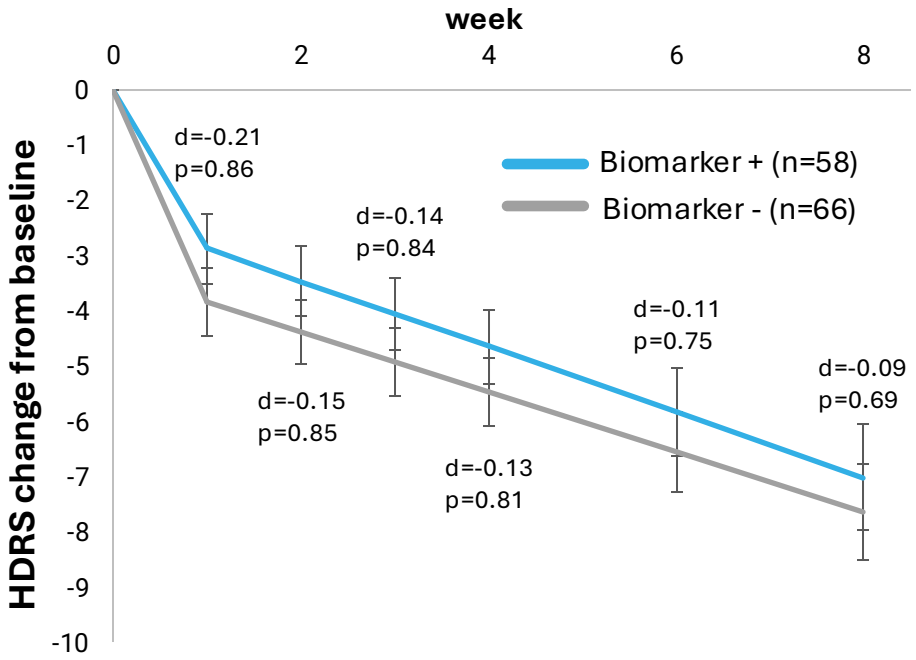


Ravindran et al, ACNP 2024

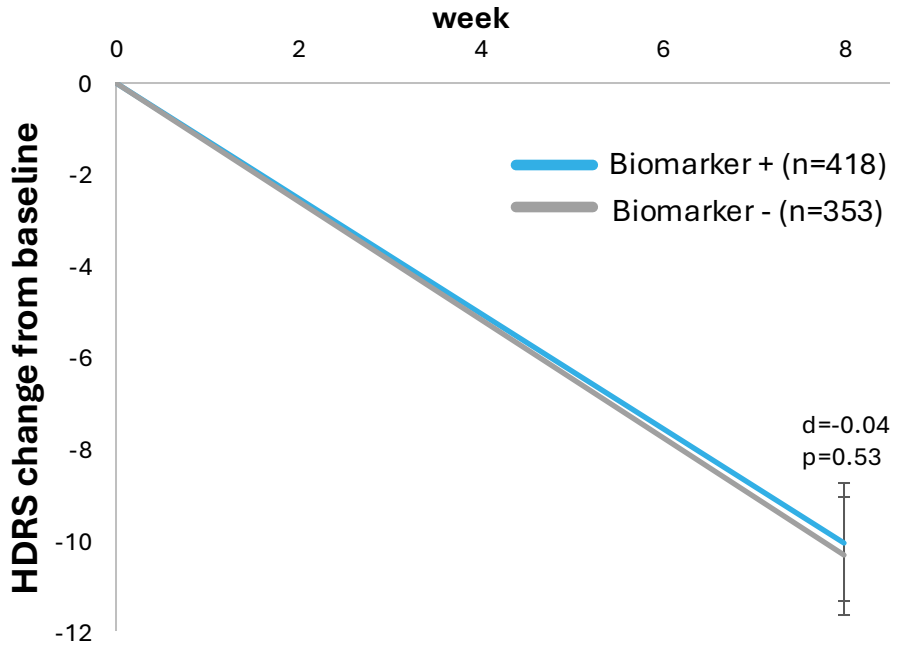
EEG model prediction is specific to ALTO-300 as it does not predict greater placebo or SSRI/SNRI response

Apply the ALTO-300 EEG biomarker to:

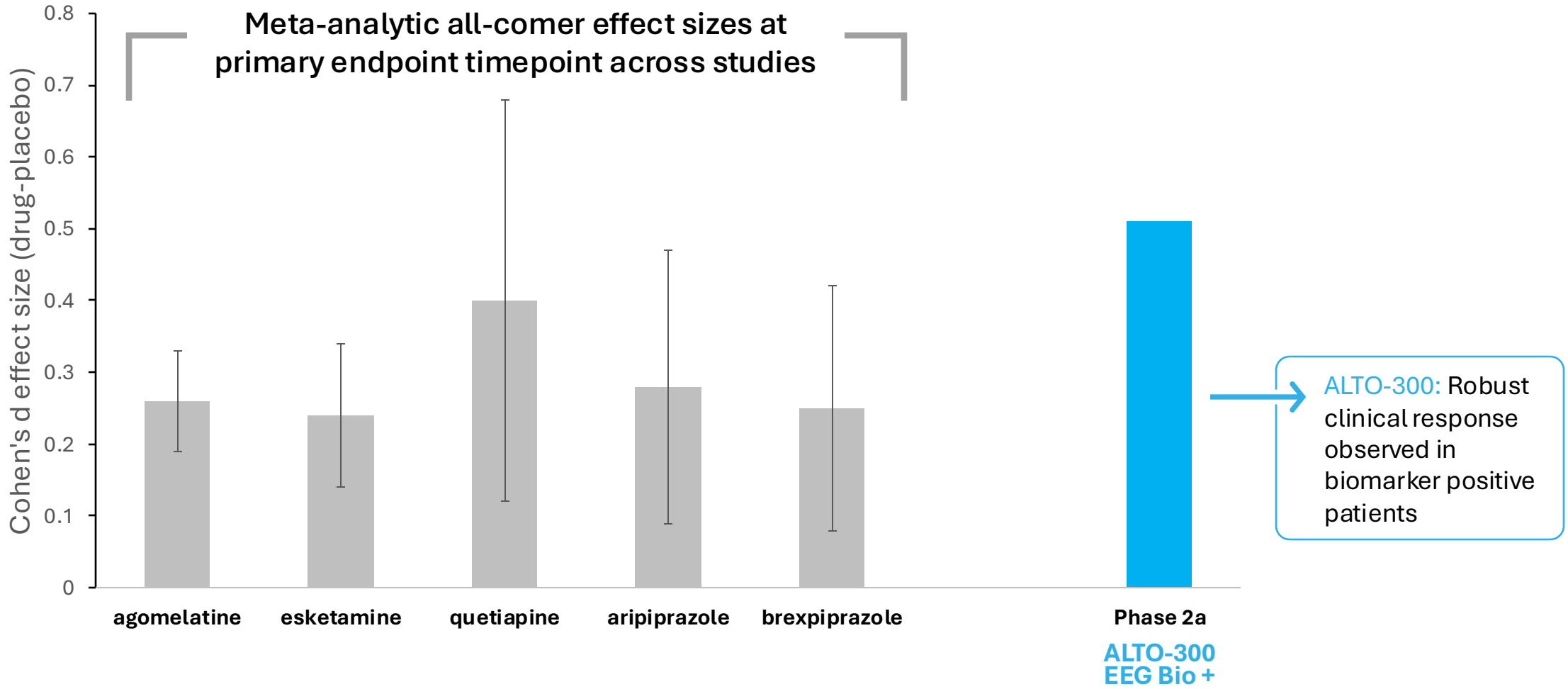
Placebo-Treated Patients



SSRI/SNRI-Treated Patients



Estimated placebo-adjusted ALTO-300 response: biomarker positive patients



The results shown above are not based on head-to-head trials between the products or product candidates . Study designs and protocols differed, and results may not be comparable. Meta-analytic values drawn from *Cipriani et al., Lancet, 2018; Wang et al., Medicine, 2023; Jawad et al., Exp Op Drug Saf, 2022*
Quetiapine, aripiprazole, and brexpiprazole are atypical antipsychotics approved in MDD.

Agomelatine has a favorable established tolerability profile

No unexpected AEs in the completed ALTO-300 study

Overall Treatment Emergent Adverse Events (TEAEs)

Safety Analysis Set

	N (%)
Total Participants	239
At least one TEAE	172 (72.0)
No TEAE	67 (28.0)
SAEs (none related)	6 (2.5)
AEs leading to Discontinuation	12 (5.0)
	% of TEAEs
Related TEAEs (by TEAE)	35.7

Note: participants may have had more than one AE

TEAEs for ≥5% of the Population

Safety Analysis Set

	N (%)
Headache	35 (14.6)
Nausea	18 (7.5)
Dyspepsia	15 (6.3)
Insomnia	15 (6.3)
COVID 19 Infection	14 (5.9)
Rash (10 from wearable)	12 (5.0)

TEAEs consistent with prior agomelatine studies

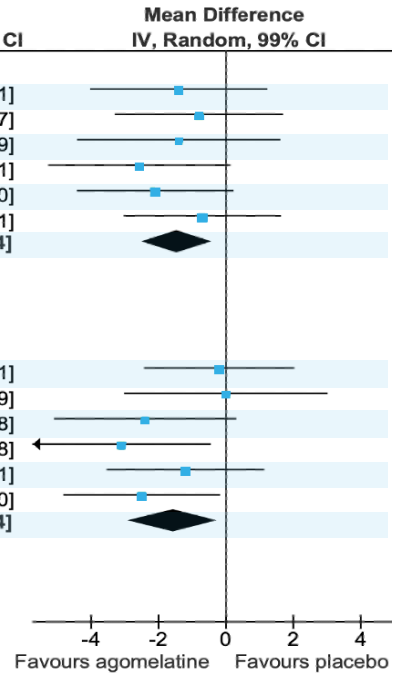
No LFT elevation with ALTO-300, validating choice of 25mg dose

- 25mg and 50mg approved in EU/Australia
- Meta-analyses show similar clinical efficacy for 25mg and 50mg
- The 50mg dose is associated with reversible LFT elevation (25mg is placebo-like)

25mg dose maintains efficacy while avoiding LFT elevation risk with 50mg

25mg leads to similar efficacy as 50mg:

Study or Subgroup	Agomelatine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 99% CI
1.11.1 25mg								
CL3-022	14.5	8.2	129	15.9	8.6	147	15.7%	-1.40 [-4.01, 1.21]
CL3-023	13	8	141	13.8	8	137	17.4%	-0.80 [-3.27, 1.67]
CL3-024	12	8.2	148	13.4	8.4	79	11.9%	-1.40 [-4.39, 1.59]
Loo 2002	12.77	8.23	135	15.34	8.87	136	14.9%	-2.57 [-5.25, 0.11]
Stahl 2010	15	8.04	158	17.1	7.92	163	20.2%	-2.10 [-4.40, 0.20]
Zajecka 2010	15.9	7.74	156	16.6	8.4	167	19.9%	-0.70 [-3.01, 1.61]
Subtotal (99% CI)			**867**			**829**	**100.0%**	**-1.47 [-2.50, -0.44]**
Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 5 (P = 0.72); I² = 0%								
Test for overall effect: Z = 3.67 (P = 0.0002)								
1.11.2 >25mg								
CAGO2303	17.1	7.38	162	17.3	7.92	158	19.2%	-0.20 [-2.41, 2.01]
CL3-024	13.4	8.2	147	13.4	8.4	79	13.3%	0.00 [-2.99, 2.99]
Kennedy 2006	14.1	7.7	106	16.5	7.4	105	15.3%	-2.40 [-5.08, 0.28]
Olie 2007	13.9	7.7	116	17	7.9	119	15.7%	-3.10 [-5.72, -0.48]
Stahl 2010	15.9	8.25	161	17.1	7.92	163	18.2%	-1.20 [-3.51, 1.11]
Zajecka 2010	14.1	7.74	161	16.6	8.4	167	18.3%	-2.50 [-4.80, -0.20]
Subtotal (99% CI)			**853**			**791**	**100.0%**	**-1.57 [-2.90, -0.24]**
Heterogeneity: Tau² = 0.66; Chi² = 8.54, df = 5 (P = 0.13); I² = 41%								
Test for overall effect: Z = 3.04 (P = 0.002)								
Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.88), $I^2 = 0\%$								



Plot from Koesters et al., Br J Psych, 2013

Safety Goal:

Placebo-like LFT Elevation Rate

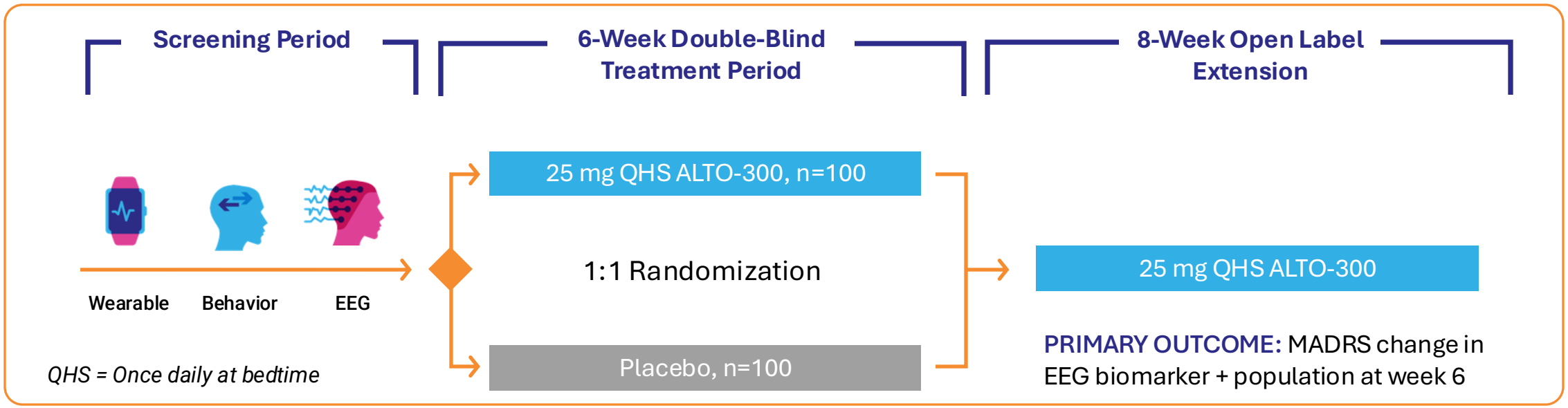
- Novartis US studies showed placebo-like LFT rate with 25 mg
  - 25mg: 0.3%
  - 50mg: 3.7%
  - Placebo: 0.3%
- Antipsychotics lead to LFT elevation at similar or greater rates as 50mg dose (Marwick et al., Clin Neuropharm, 2012) thus agomelatine concerns are more historical/contextual than of relevant absolute level

ALTO-300 Phase 2a:
no patients AST or ALT > 3xULN

LFT – Liver Function Test
AST – Aspartate Aminotransferase
ALT – Alanine Transaminase
ULN – Upper Limit of Normal

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
- **Planned interim analysis** expected to inform the final sample size needed to achieve adequate powering; expected 1Q 2025

ALTO-203

Development for MDD with anhedonia

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

Reduction in reward system dopaminergic function in depression has broad effects on symptoms

Dopamine system
↓ Receptors
↓ Synthesis
↓ Availability

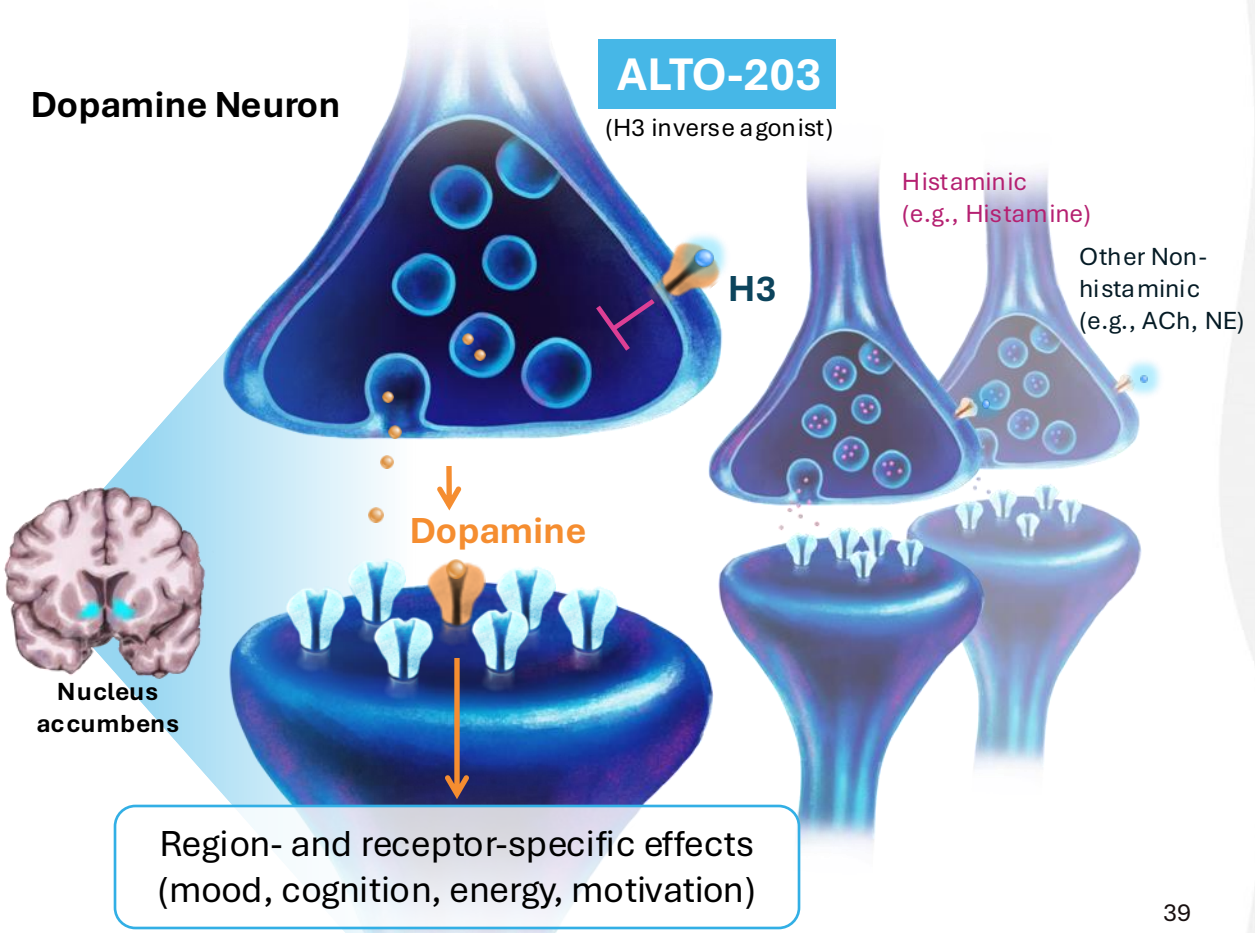
↓ **Dopamine function**

Cognitive
↓ Processing speed
↓ Cognitive control
↓ Learning

Positive valence
↓ Motivation
↓ Energy
↑ Effort cost

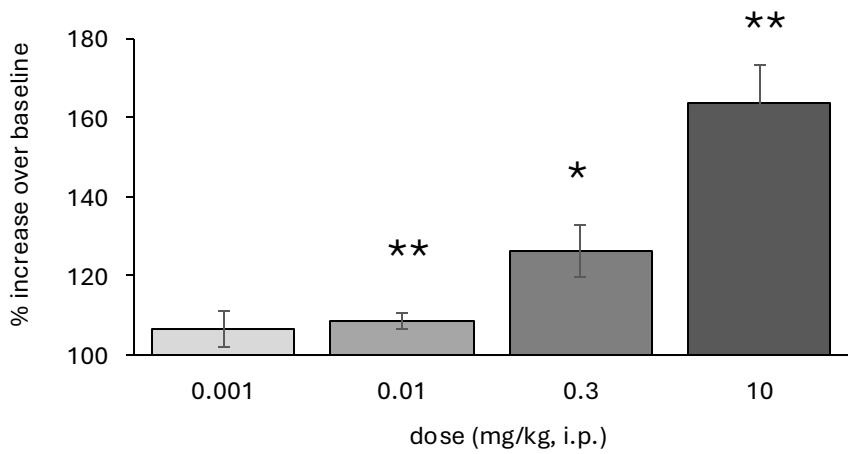
Motor
↑ Psychomotor slowing

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



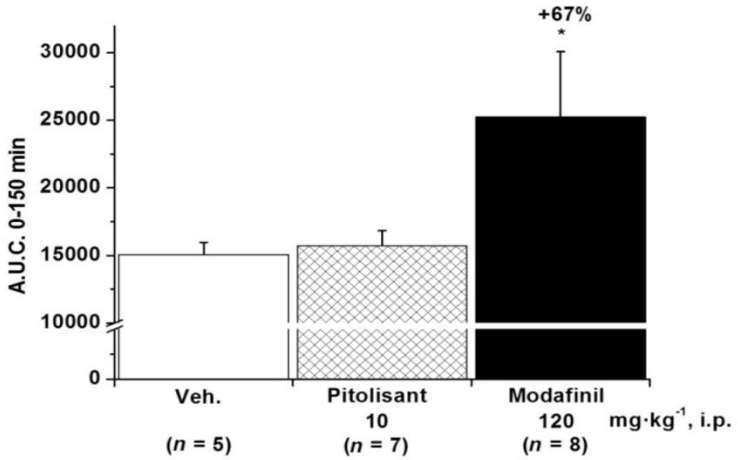
ALTO-203 showed ability to increase reward system dopamine, unlike the only approved H3 (pitolisant)*

ALTO-203 increases dopamine release in the reward system (nucleus accumbens) in a dose-related manner



ALTO-203 results plotted as percent increase over baseline from 0-150min post-dose, to compare to timing of pitolisant/modafinil study outcome (* p<0.05; ** p<0.01)

Pitolisant does not increase reward system dopamine (modafinil used as a comparator)

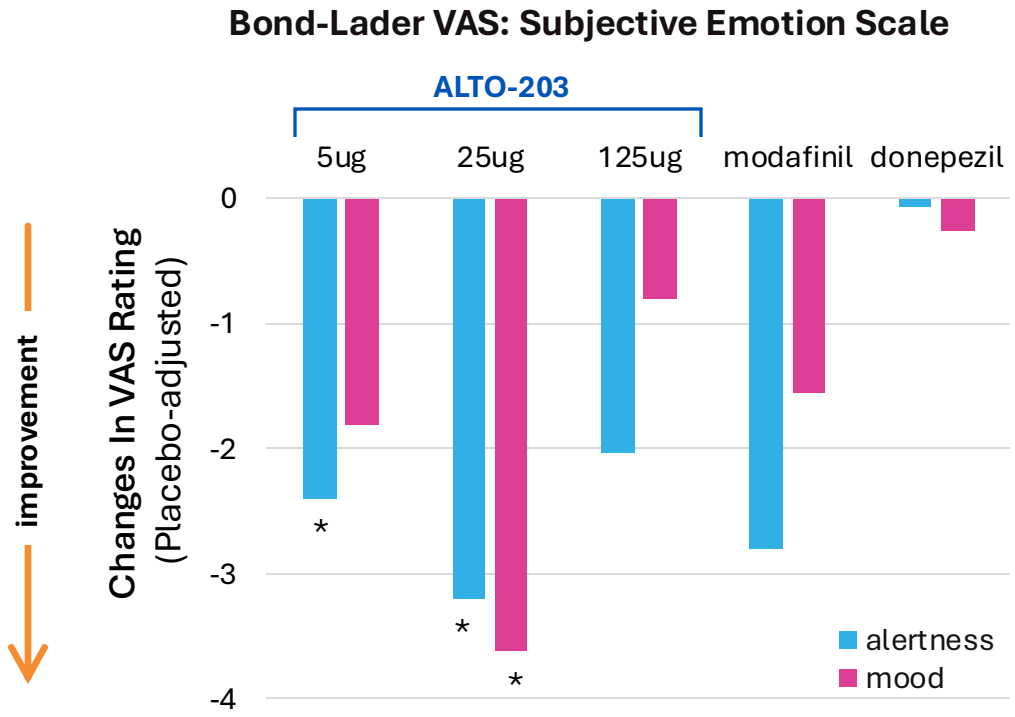


Uguen et al., BJP, 2013

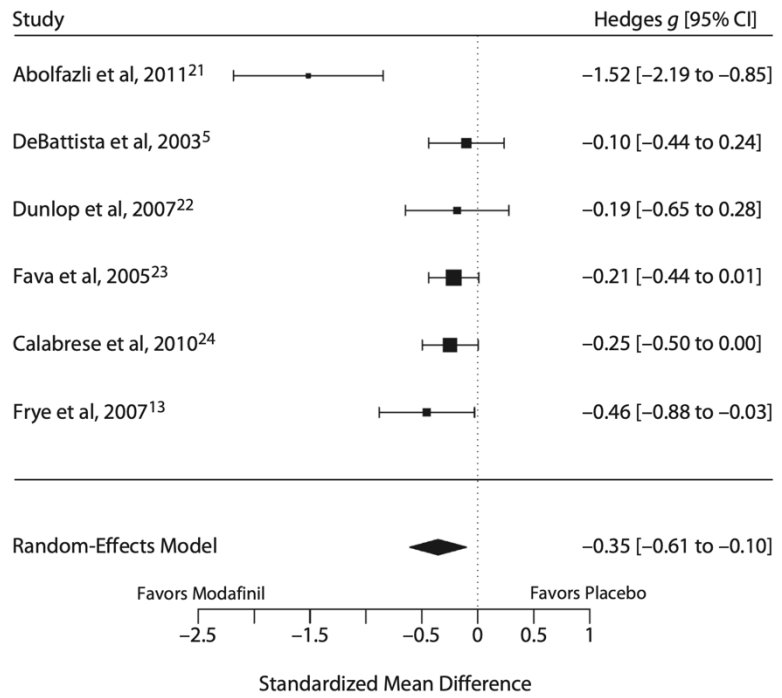
*Study conducted prior to Alto acquisition

Evidence of clinical relevance of acutely increasing reward system dopamine release

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



Clinical trials show antidepressant efficacy of adjunctive modafinil in MDD and bipolar disorder



Goss et al., JCP, 2013

Phase 2 POC study in MDD with anhedonia enrolling → top-line data expected 1H 2025

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

Initiated proof-of-concept study in depression with anhedonia

Study Population:

Patients with MDD with anhedonia and who are not on an antidepressant (monotherapy)

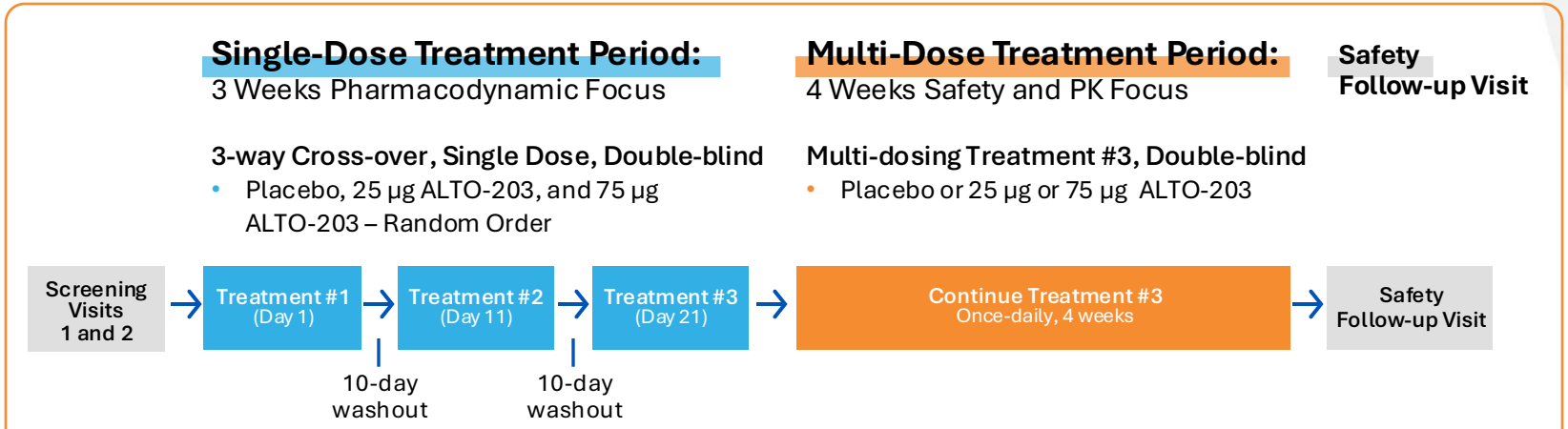
Design:

Two sequential double-blind, placebo-controlled treatment periods:

- **Single-dose:** randomized, 3-way crossover. Evaluation of PD measures (positive emotion, cognition, reward processing tests)
- **Multi-dose:** Participant continues to take Tx #3 dose once daily for 28 days. Focus on safety and PK but will also measure MDD and anhedonia symptoms

Number of participants:

60 completers of 3-way crossover (single dose period)



Primary outcome: Alertness & Mood Components of Bond-Lader Visual Analog Scale (BL-VAS) in single dose period, safety in multiple dose period

Exploratory outcomes: clinical depression, anhedonia, and other symptom scores in multi-dose period

Topline data readout expected 1H 2025

ALTO-203 Phase 2 POC primary outcome scale provides a measure of momentary emotion that correlates with depression

Bond-Lader subjective emotion visual analog scale (BL-VAS) used in the ALTO-203 studies. Items are scored into alertness (9 items), mood/contentedness (5 items) and calmness subscales (2 items)

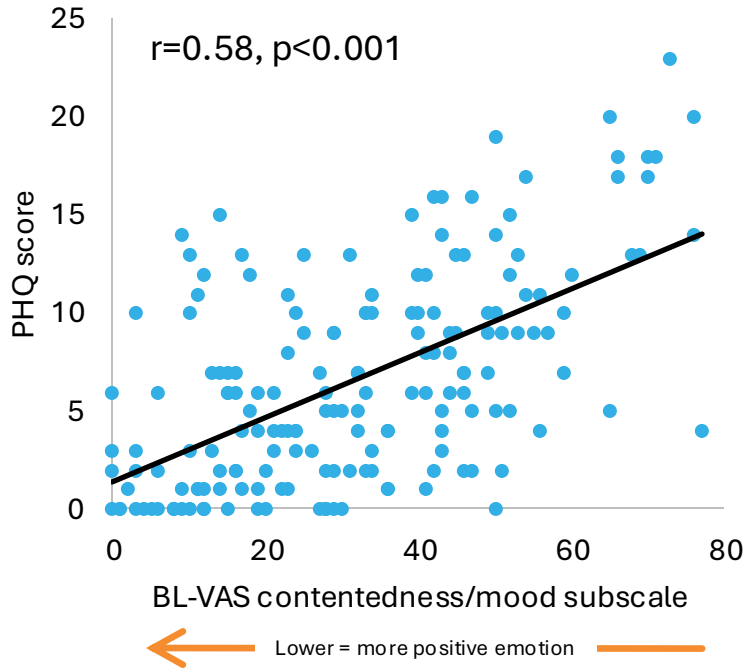
Instructions:

1. Please rate the way you feel in terms of the dimensions given below
2. Regard the line as representing the full range of each dimension
3. Rate your feelings as they are at the moment

Alert	Drowsy
Calm	Excited
Strong	Feeble
Muzzy	Clear-headed
Well- coordinated	Clumsy
Lethargic	Energetic
Contended	Discontented
Troubled	Tranquil
Mentally Slow	Quick-witted
Tense	Relaxed
Attentive	Dreamy
Incompetent	Proficient
Happy	Sad
Antagonistic	Amicable
Interested	Bored
Withdrawn	Gregarious

Bond & Lader, *Br J Med Psychol*, 1974

Despite measuring momentary emotion, BL-VAS scores correlate with longer-term measures of depression symptoms



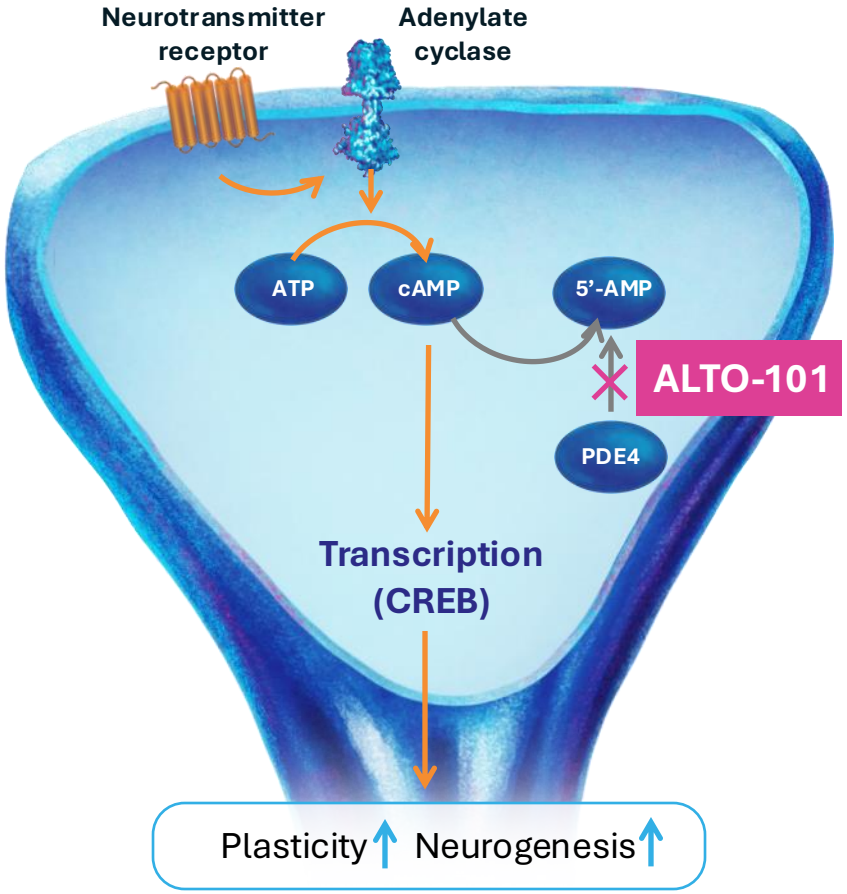
Other BL-VAS subscales also correlate with PHQ scores:

- Alertness: r=0.45, p<0.001
- Calmness: r=0.40, p<0.001

ALTO-101

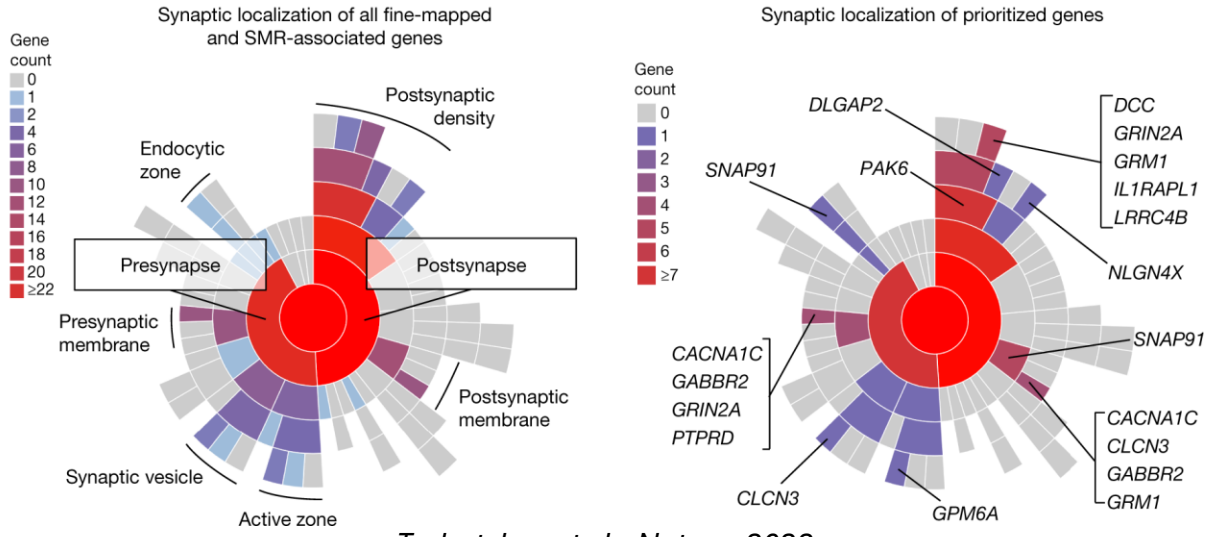
Development for CIAS

Novel investigational PDE4 inhibitor with broad pro-cognitive activity



PDE4 inhibition has been of **long-term interest** as a potential pro-cognitive and antidepressant MOA

Schizophrenia genetics has implicated abnormalities in synaptic function

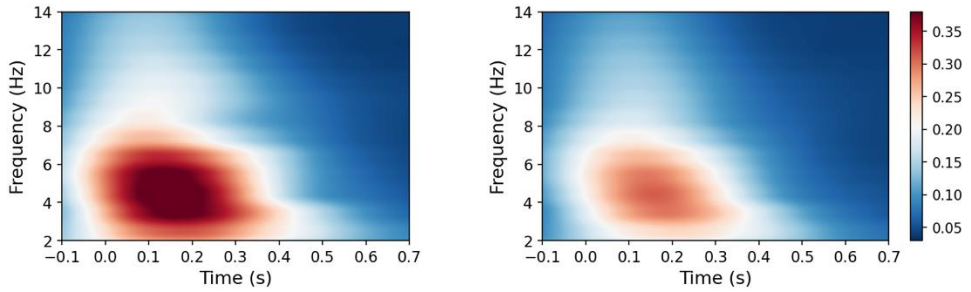


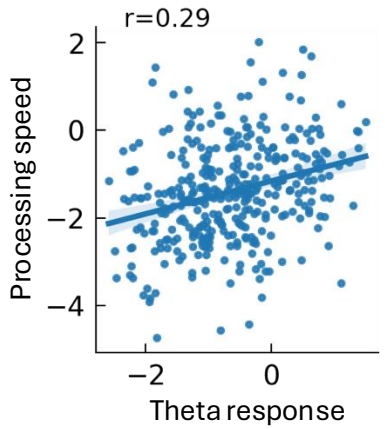
Trubetskoy et al., Nature, 2022

- Most CIAS drug targets have focused on ameliorating synaptic dysfunction (e.g., NMDA-R modulation)
- Directly enhancing downstream signaling represents a novel therapeutic approach

Theta EEG response to auditory stimuli links CIAS pathophysiology and drug PD activity

Robust and prospectively replicated reduction in theta response in patients with schizophrenia linked to CIAS phenotype (n=625)*

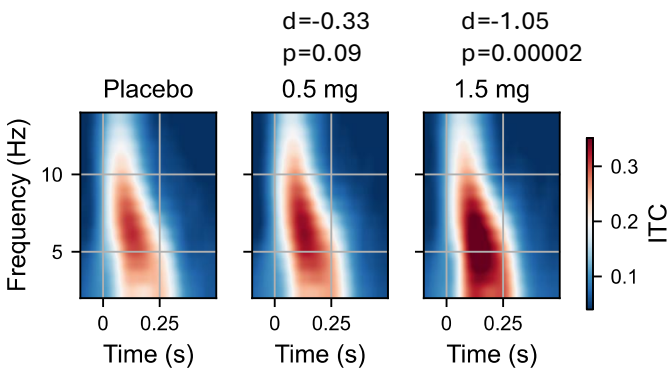


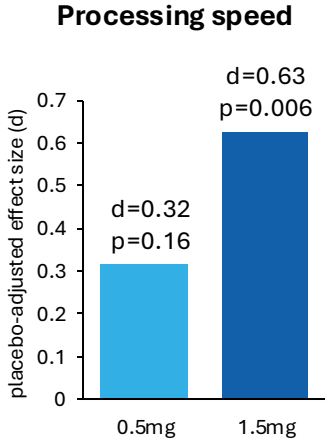


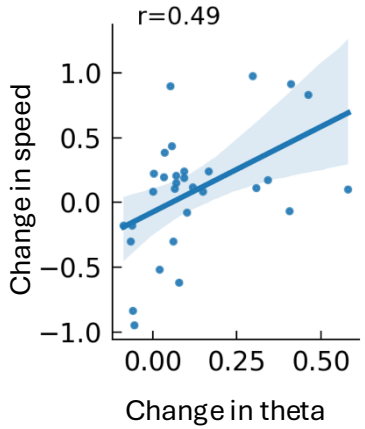
Reduced theta response correlates with poor cognition and worse processing speed

*Wang et al, SOBP 2024

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



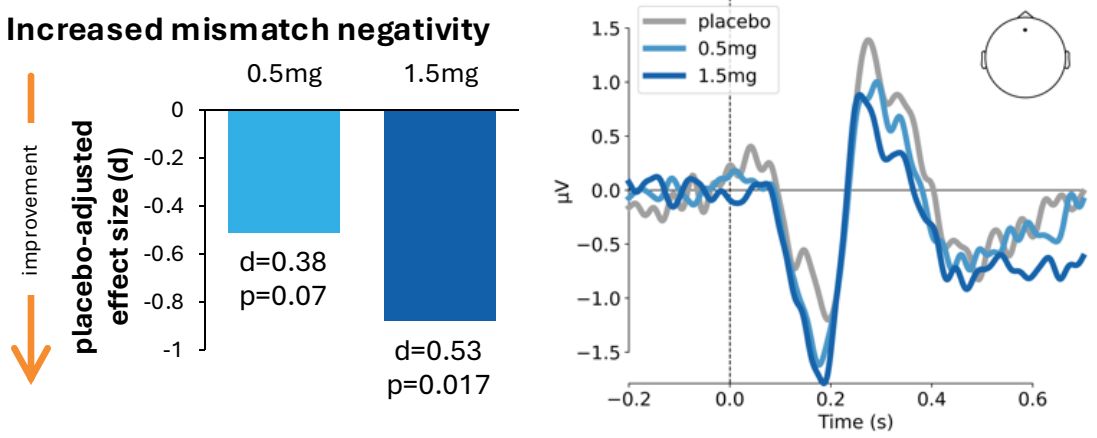




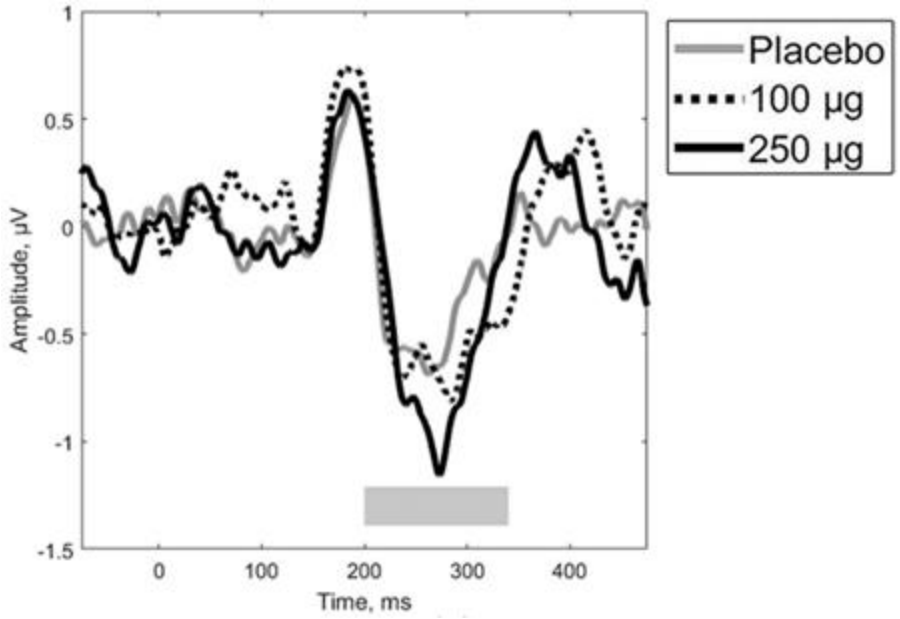
Greater increase in theta response by ALTO-101 correlates with greater improvements in processing speed

EEG effects of ALTO-101 replicate previously reported PDE4i effects in schizophrenia using a similar study design

ALTO-101 increases mismatch negativity amplitude, a frequently studied schizophrenia biomarker



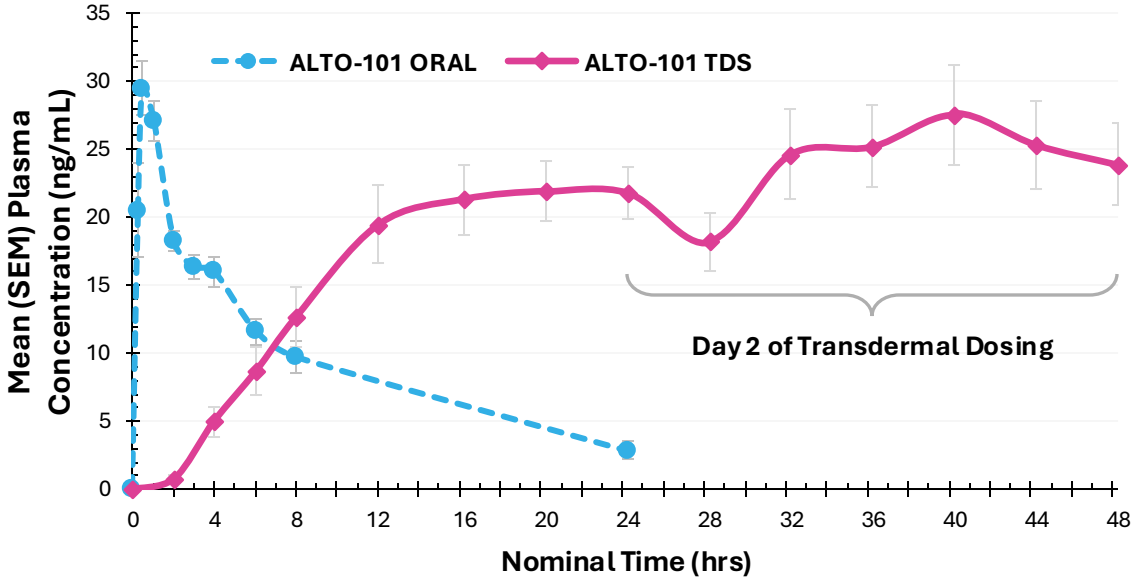
Similar effect demonstrated in an 8-day cross-over treatment study in schizophrenia with the PDE4i roflumilast



Gilleen et al., J Psychopharm, 2020

Transdermal formulation: greater drug exposure and improved tolerability profile

- Goal of TDS formulation: Eliminate rapid C_{max} related AEs and **maintain steady exposure**
- Healthy Volunteer (age 40-64) PK and Tolerability Study. **15 participants** (1 did not complete TDS period due to positive urine drug screen).
- TDS achieved similar C_{max} as oral, but for **longer** and **more consistently**
- AUC 62% and 170% **greater for TDS** on day 1 and 2 respectively (day 1 p=0.01; day 2 p<0.001) vs. oral
- Even with higher AUC, TDS **reduced typical AEs**
- Overall **well-tolerated** with no discontinuations. All AEs were mild, no SAEs reported
- TDS showed **favorable** adhesion properties. No application site reactions that led to patch removal or intolerance.
- **Allows** QD dosing in trials (vs. BID or TID for oral)



Related Adverse Events >5%	ALTO-101 Oral Formulation (N = 15)	ALTO-101 TDS Formulation (N = 14)
PDE-4i Class-Related AEs		
Dizziness, n (%)	6 (40.0)	1 (7.1)
Nausea, n (%)	3 (20.0)	0
Diarrhea, n (%)	1 (6.7)	0
Dyspepsia, n (%)	1 (6.7)	0
Vertigo, n (%)	1 (6.7)	0
Other AEs		
Headache, n (%)	2 (13.3)	5 (35.7)
Administration site pruritus, n (%)	0	2 (14.3)
Asthenia, n (%)	1 (6.7)	0

ALTO NEUROSCIENCE

Phase 2 POC study in cognitive impairment in schizophrenia

Study Population:

Adults 21-55 years old with a diagnosis of schizophrenia for > 1 year and sufficient cognitive impairment

Design:

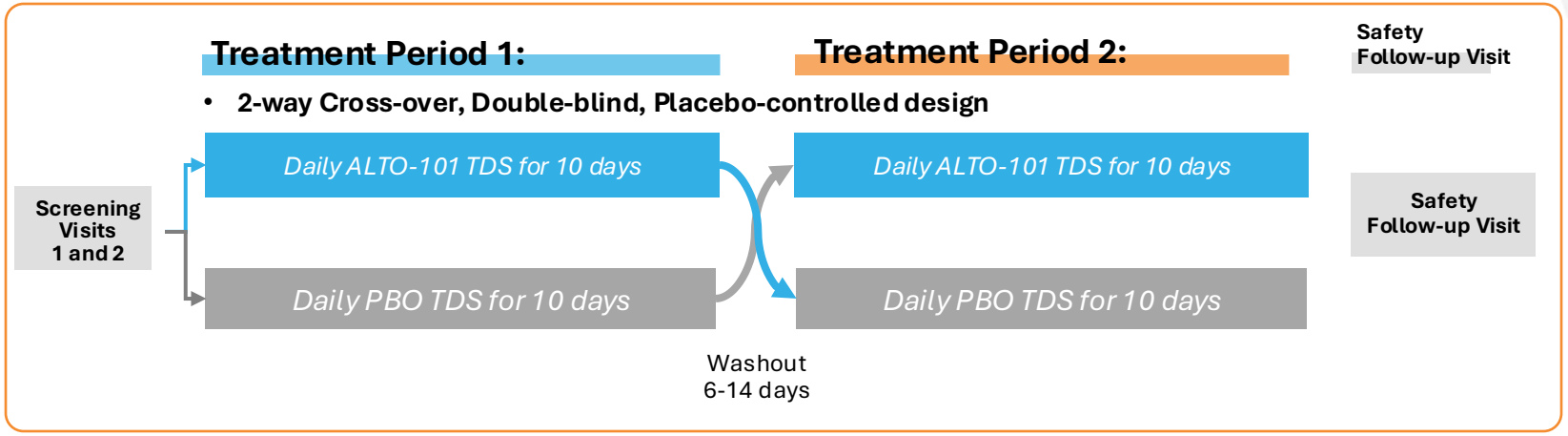
A two-way crossover, double-blind, placebo-controlled study with ALTO-101 and placebo:

Treatment Periods 1 + 2:

- Randomized, 2-way crossover, washout separates the two periods
- Evaluation of EEG and cognitive markers

Number of participants:

70 completers
(two dosing periods each)



Primary outcome: Effects of ALTO-101 on theta band activity, an EEG-based measure of PD activity correlating to cognitive function, after 5 and 10 days of dosing of ALTO-101 compared to placebo in two treatment periods

Other outcome measures: Cognitive function, PK, safety and tolerability

Topline data readout expected 2H 2025

PDE4 inhibition is relevant across numerous high-need therapeutic areas

Available medications are non-brain penetrant and only approved outside CNS – both come with substantial tolerability and dosing limitations

$2.2bn

2022 SALES

Otezla® (apremilast) 30mg tablets

$0.3bn

2021 SALES

Daliresp® (roflumilast) tablets

NON - CNS INDICATIONS

- **Plaque Psoriasis**
- **Psoriatic Arthritis**
- **COPD**
- Asthma
- Atopic Dermatitis
- Psoriasis & Eczema
- Rosacea
- Palmoplantar Pustulosis
- Nummular Eczema
- Pruritus
- Rheumatoid Arthritis
- Lupus (SLE)
- Crohn's
- Idiopathic Pulmonary Fibrosis

Bold denotes approved indications

ALTO-101

ALTO NEUROSCIENCE

CNS

- Schizophrenia
- Bipolar
- PTSD
- Depression
- Substance Dependence
- Multiple Sclerosis
- Fragile X
- Allergic Encephalomyelitis
- ALS
- Migraine
- Glioblastoma
- Alzheimer's
- Huntington Disease
- Anxiety Disorders
- Dementia
- Cerebrovascular Disorder
- Mild Cognitive Impairment
- ADHD
- Parkinson's Disease
- Autism Spectrum Disorders
- Frontotemporal Dementia
- Developmental Delay
- Learning Disabilities

Biotech leadership team with extensive late-stage precision psychiatry experience

Executive management team

Amit Etkin, MD PhD
Chief Executive Officer

Michael Hanley
Chief Operating Officer

Adam Savitz, MD PhD
Chief Medical Officer

Jessica Powell
Chief Development Officer

Nick Smith
Chief Financial Officer

Erin McQuade
General Counsel and Chief Administrative Officer

Melissa Berman
VP, Finance & Accounting and Controller

Michelle Moran
VP, Quality Assurance

Patricio O'Donnell, MD PhD
VP, Translational Medicine

Akash Datwani, PhD
VP, Business Development & Strategic Alliances

Board of directors

Jeff Chen, PhD
Managing Director, Alkeon Capital

Christopher Nixon Cox
CEO, Lightswitch Capital

Andrew Dreyfus
Former President and CEO, Blue Cross Blue Shield of MA

Husseini Manji, MD
Former Global Head of Neuroscience JNJ

Maha Radhakrishnan, MD
Former Group SVP & CMO, Biogen

Gwill York
Founding Managing Director, Lighthouse Capital Partners

Amit Etkin, MD, PhD
CEO, Alto Neuroscience

Multiple near-term clinical milestones expected

Capitalized through multiple value generating clinical milestones:
~$182MM* (as of Sept. 30, 2024) → Expected cash runway into 2027

1H 2025

- ☐ **ALTO-300 Phase 2b MDD data**
- ☐ **ALTO-203 MDD POC data**

2H 2025

- ☐ **ALTO-101 CIAS POC Data**

2026

- ☐ **ALTO-100 Phase 2b Bipolar Depression data**

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

Bold denotes clinical data readout

**includes cash, cash equivalents, and restricted cash balance as of Sept. 30, 2024*