ALTO NEUROSCIENCE

NYSE: ANRO — July 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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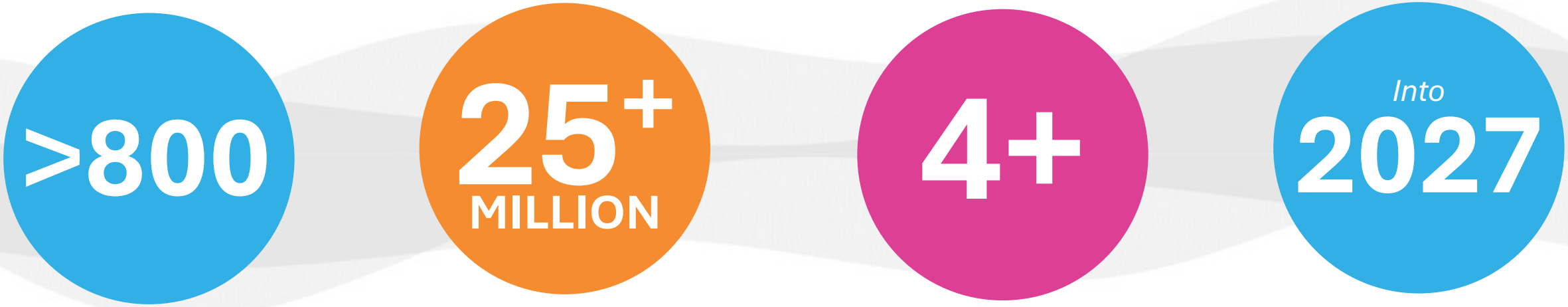
Alto by the numbers

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



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

Patient Impact
Opportunity across the portfolio

Phase 2 Data Read Outs
In next 2 years

Cash
Runway

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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 Biosciences · 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 to drive better clinical outcomes in CNS

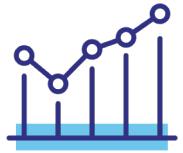
Alto Neuroscience

Targeting large high-need markets with little previous innovation

- Major depression (MDD)
- Schizophrenia
- Post-traumatic stress disorder (PTSD)
- Bipolar depression

Leveraging scalable responder biomarker platform to increase probability of clinical and commercial success

Team with deep CNS clinical expertise and demonstrated scientific leadership in precision psychiatry



Clinical-stage pipeline – key catalysts expected to be funded with current cash:

- ALTO-100 (MDD) PHASE 2B – 2H 2024
- ALTO-300 (MDD) PHASE 2B – 1H 2025
- ALTO-101 (SCHIZOPHRENIA (CIAS)) PHASE 2 – 2025
- ALTO-203 (MDD) PHASE 2 – 1H 2025

Perfect timing to transform mental health after a decade of development

2010

Etkin Lab

Stanford University

2017

NIH DIRECTOR'S PIONEER A·W·A·R·D

2019

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2022

First Alto precision psychiatry clinical outcomes

Alto's Foundational Science

nature biotechnology (2020)

nature human behaviour (2019)

nature biomedical engineering (2021)

JAMA Psychiatry (2020)

nature neuroscience (2021)

The American Journal of Psychiatry (2017a, 2017b, 2020, 2020)

Science Translational Medicine (2019)

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

A core problem in psychiatry: unguided treatments work poorly

Small effects on average… due to large heterogeneity in patients' biology

Current Approach

Trial-and-error, mostly failures

Precision Psychiatry

Differentiated drug profile

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

Ongoing Large Phase 2b Trials:

- ALTO-100: Oct. ‘24
- ALTO-300: 1H 2025

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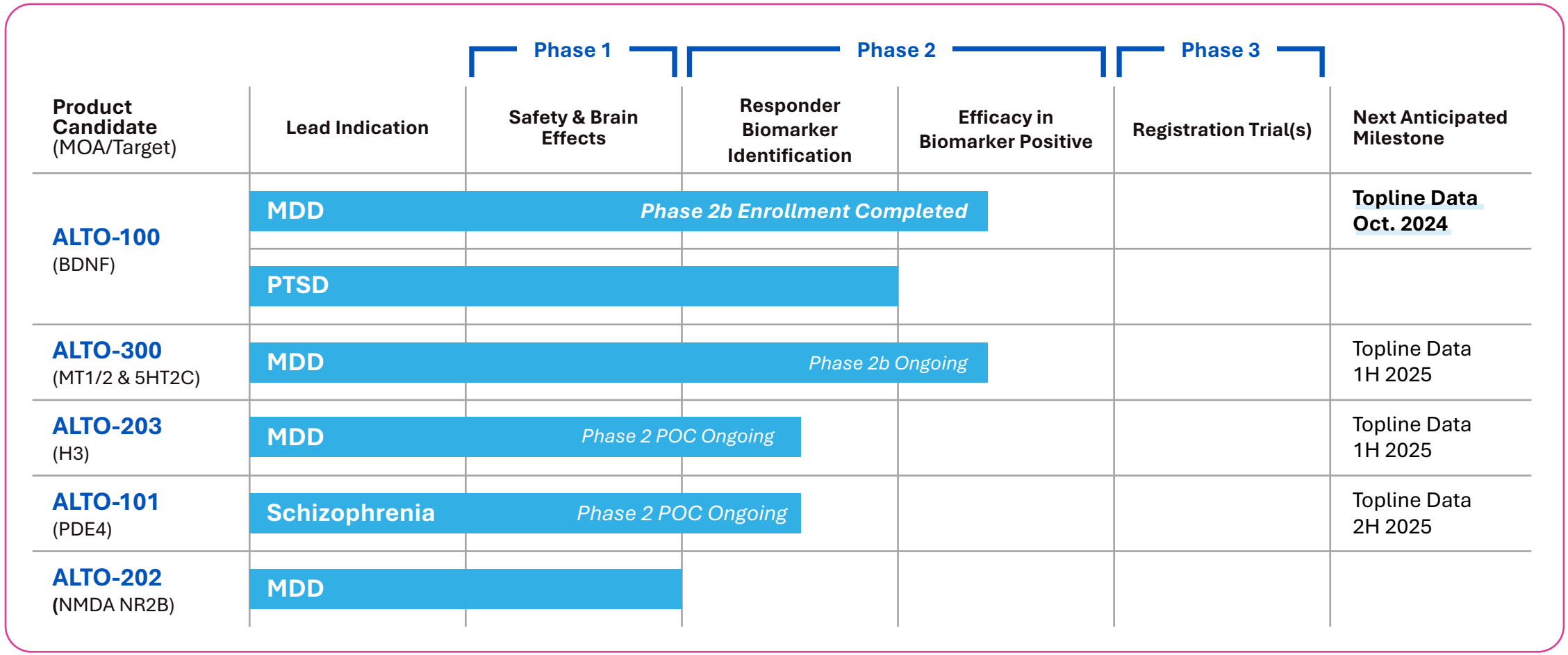
First biomarker-driven pipeline for mental health conditions

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



Targeting large patient populations with substantial unmet need

ALTO-100
(BDNF)

ALTO-300
(MT1/2 & 5HT2C)

ALTO-203
(H3)

ALTO-101
(PDE4)

ALTO-202
(NMDA NR2B)

21M
patients in US with MDD (50% not on therapy)[1]

9M
patients annually in US with PTSD[2]

2.8M
patients in US with Schizophrenia[3]

5.7M
patients in US with bipolar depression[4]

Estimated biomarker pop.

15M+
MDD with
memory or EEG Biomarker

5M+
PTSD with
Memory Biomarker

~2M
SZ with
cognitive impairment

~3M
BPD with memory biomarker

→ **~25M+**
Patient Opportunity

1 MDD is one of the most prevalent and incapacitating medical conditions, with ~21 million, or 8.3% of, adults experiencing at least one major depressive episode in 2021
2 PTSD is present in approximately 9 million individuals in any given year (3.6% of adults)
3 Schizophrenia is a life-long mental health disorder affecting approximately 2.8 million adults as of 2020
4 Bipolar depression affects 5.7 million adults, or about 2.6% of the population (NIMH)

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Alto’s strategy is purpose-built for speed & impact

Thoroughly characterizing drug activity and responsive patient populations before advancing

Typical failure point

No human target engagement

Uncontrolled and unmeasured patient heterogeneity

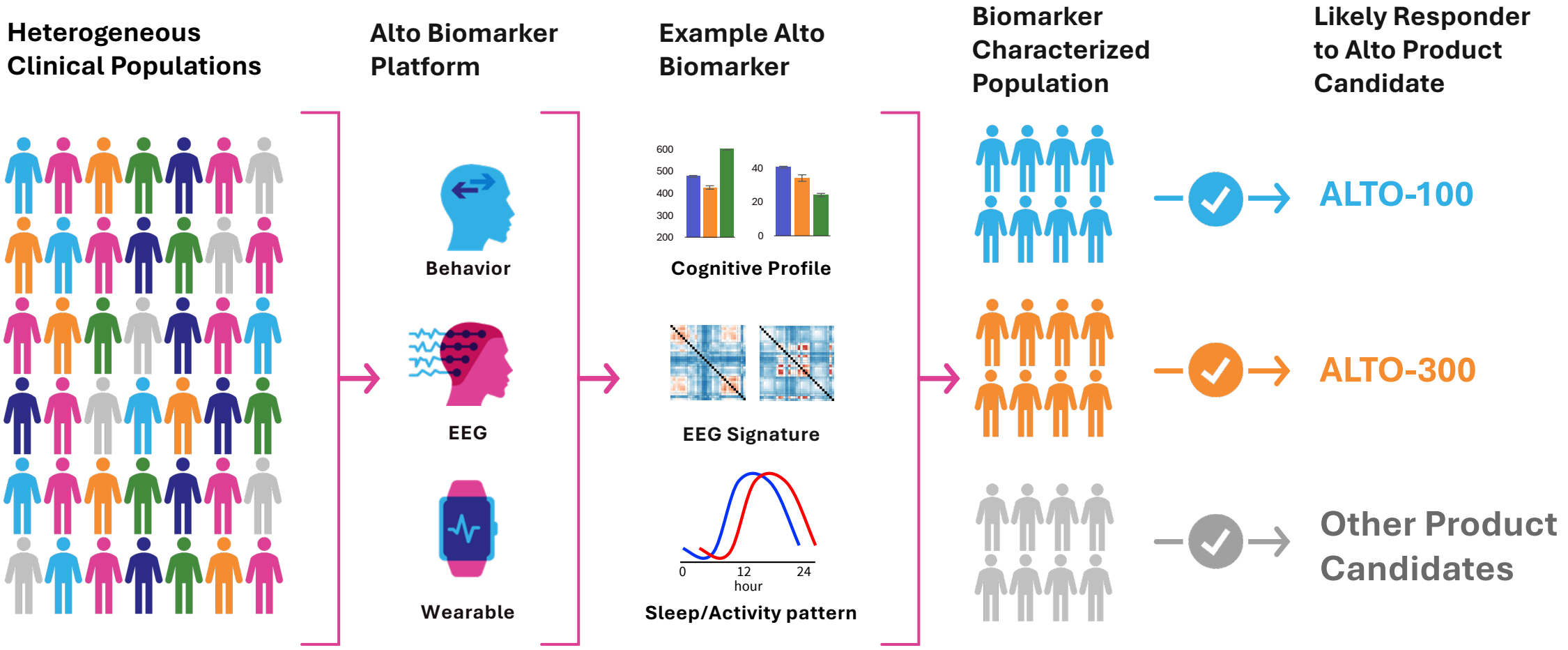
Alto approach

Broad utilization of pharmacodynamic biomarkers

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

Platform

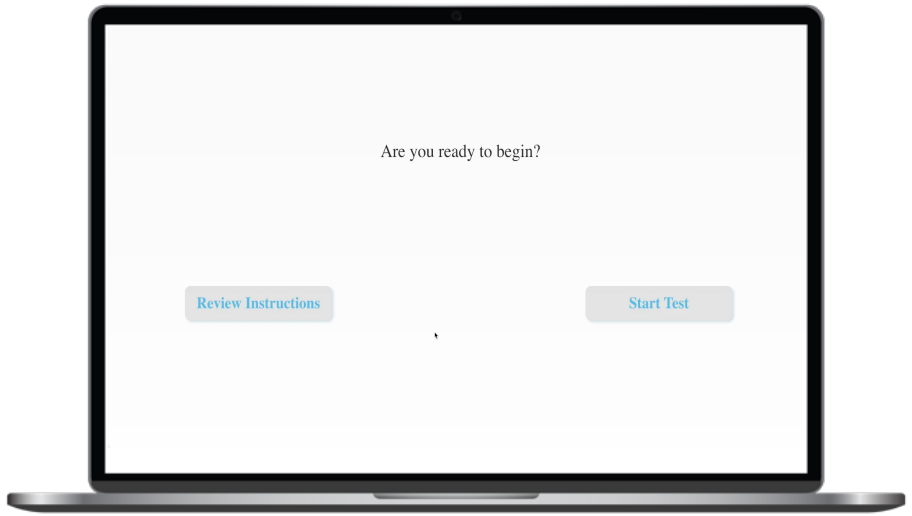
Alto's suite of biomarkers designed to segment patients to drive improved outcomes



Leveraging proprietary tools, anticipating commercial scale

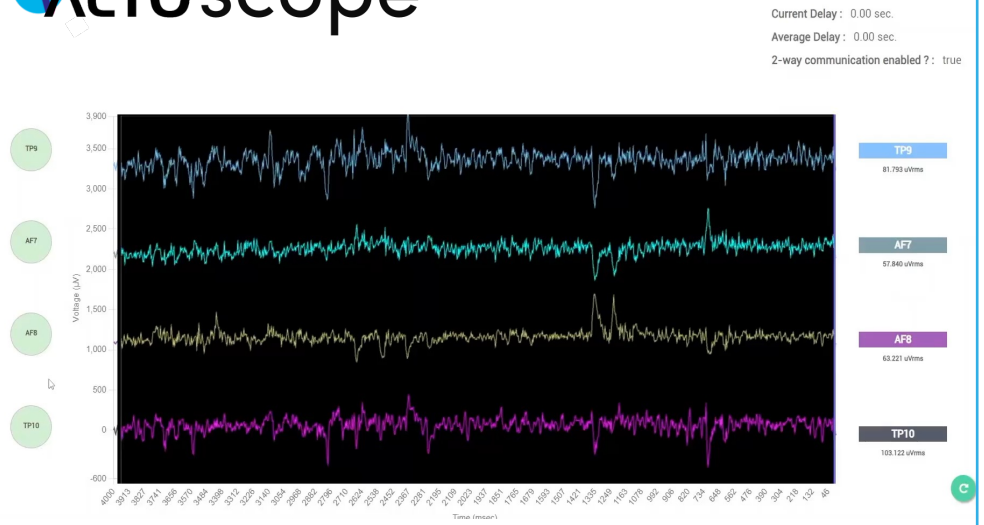
ALTO-100 biomarker is cognitive test-based

Spectra



ALTO-300 biomarker is EEG-based

ALTOscope



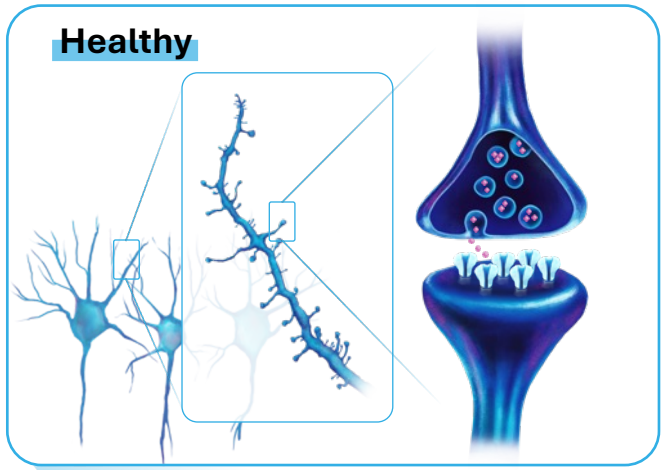
ALTO-100

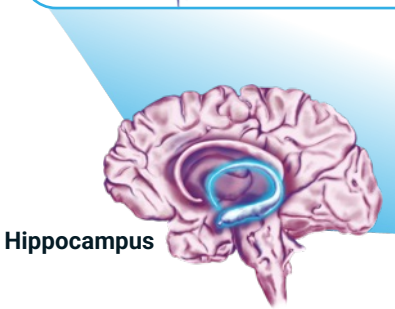
Phase 2B development for MDD

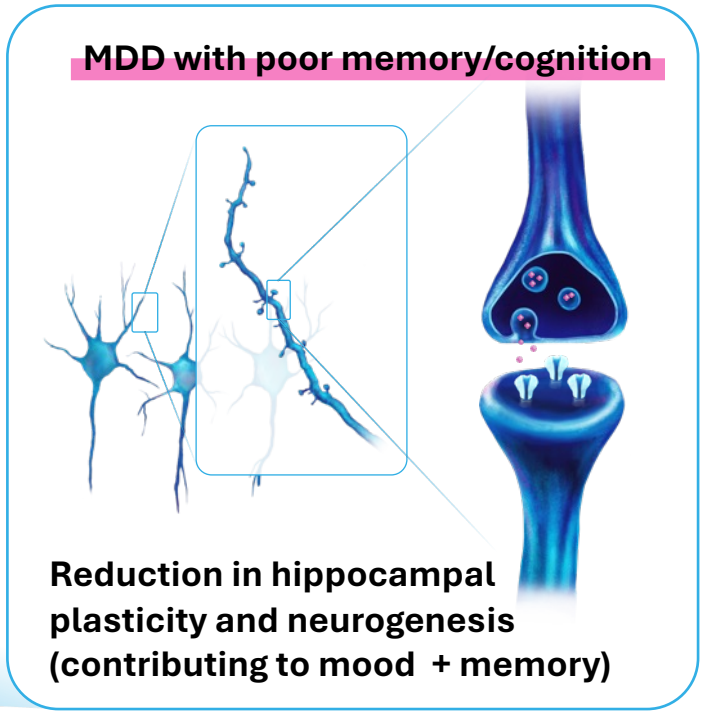
Depressed patients with poor memory/cognition reflect a specific mechanism of disease: a target for novel drug development

Poor memory/cognition in MDD – seen in 30-50% of patients

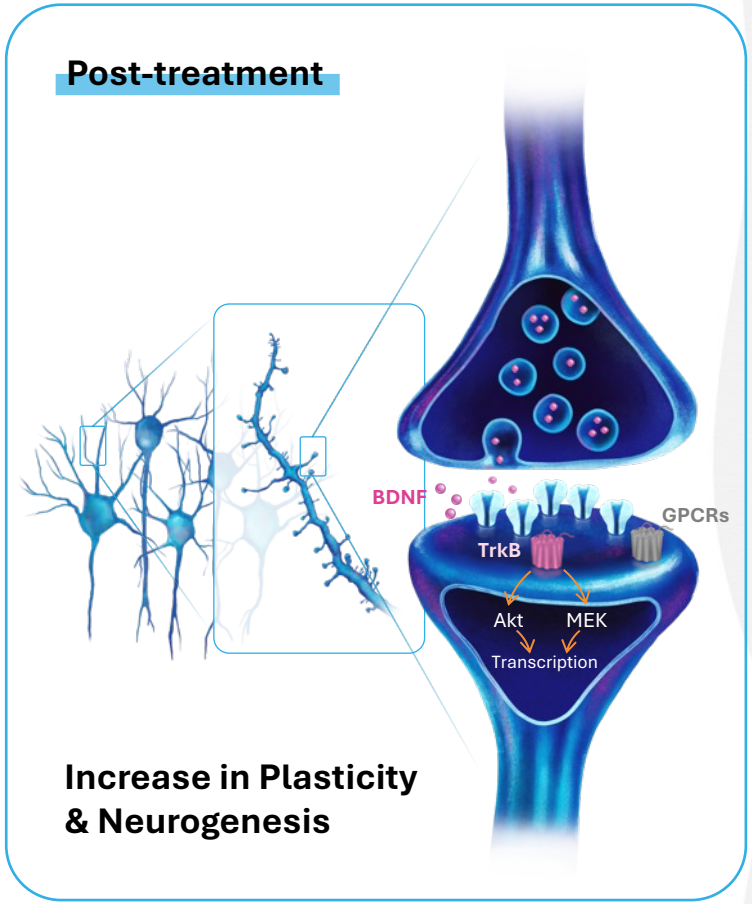
- Poor memory reflects reduced hippocampal plasticity, long implicated in MDD, but not previously used to identify which individual patients have the deficit
- Established role of the hippocampus in both mood and memory/cognition
- Worse response to standard-of-care treatments
  (poorer illness course, greater disability and recurrence; also reflects genetic risk)





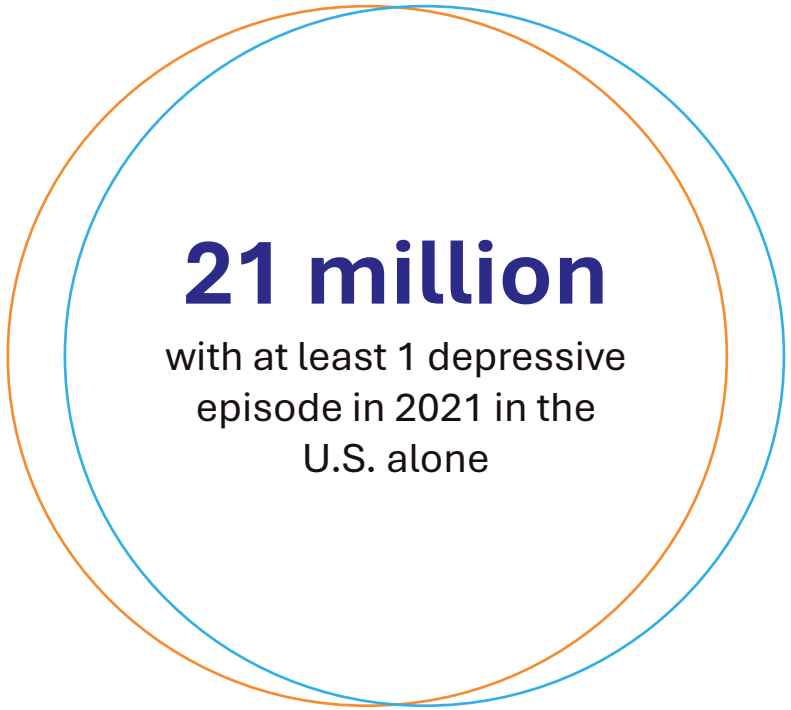


ALTO-100



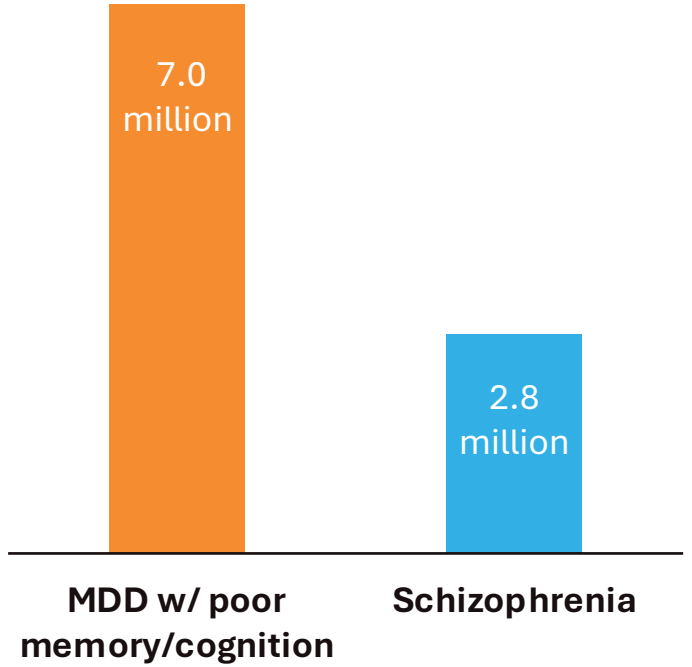
Cognitively impaired depression patients represent a very large and readily commercially addressable market

MDD population



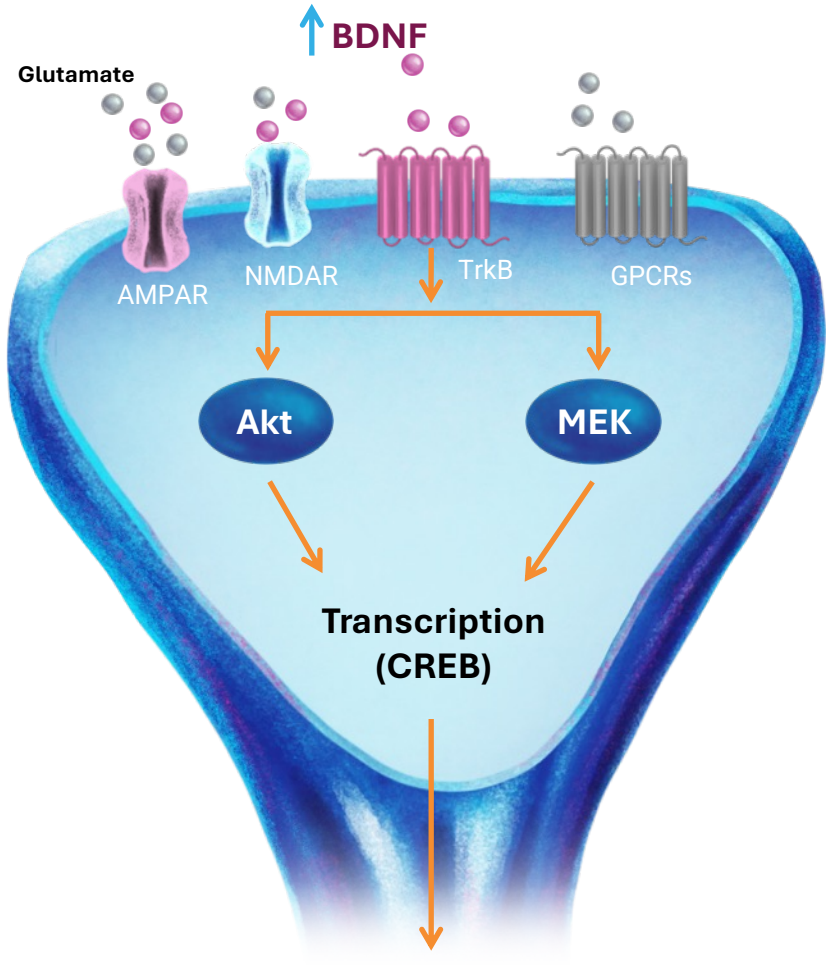
Even if only **1/3** have impaired cognition, population is **>2x** all of schizophrenia, and identifiable with minimal extra effort

Estimated U.S. population affected



A self-administered, 15–20-minute, web-based memory test (already in use in our studies) can identify target population – including via at-home testing

ALTO-100 – shown to drive key neuroplasticity mechanisms



Plasticity ↑ Neurogenesis ↑

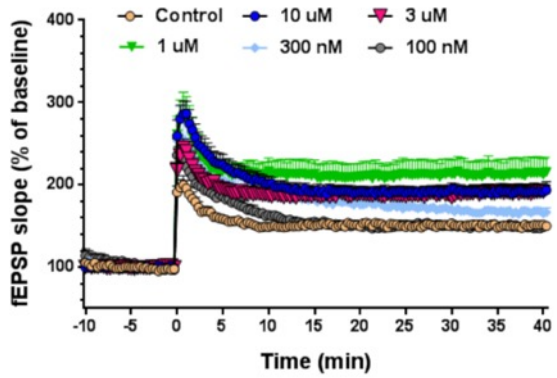
Identified based on a neurogenesis functional screen

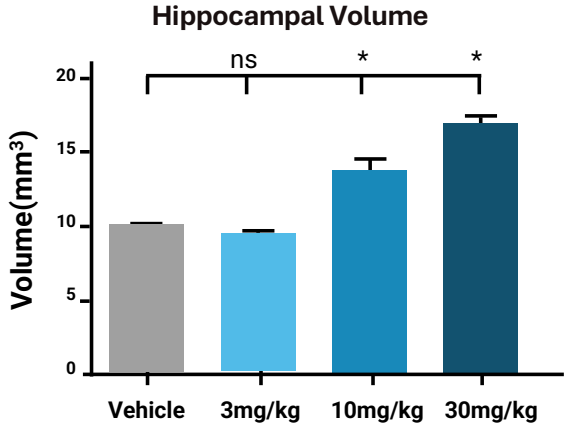
Preclinically, **increases** synaptic and cellular plasticity across multiple time scales, hippocampal volume

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

Novel, potentially first-in-class molecular mechanism

Increased hippocampal synaptic plasticity and volume preclinically





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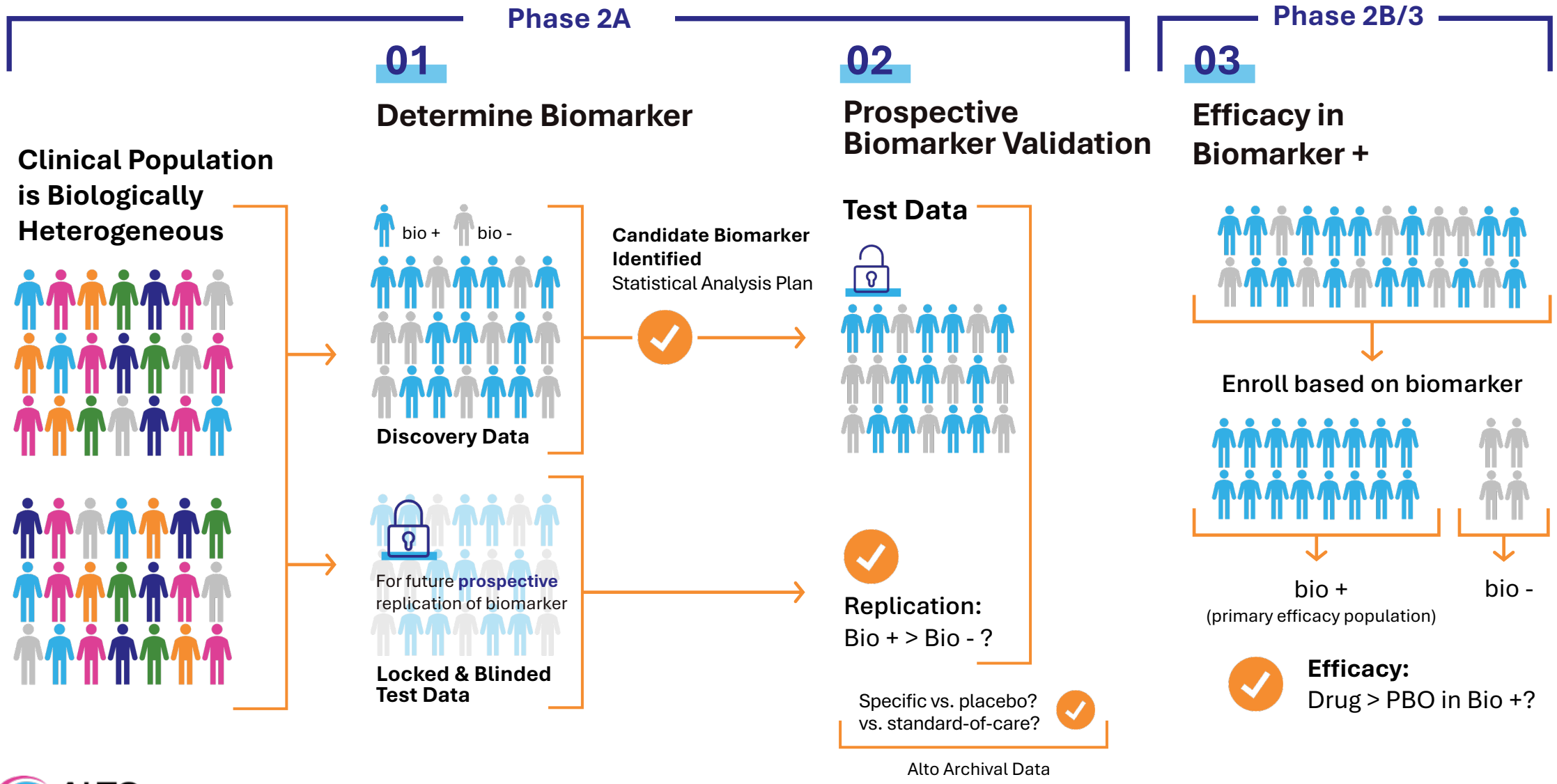
Alto's precision drug development approach



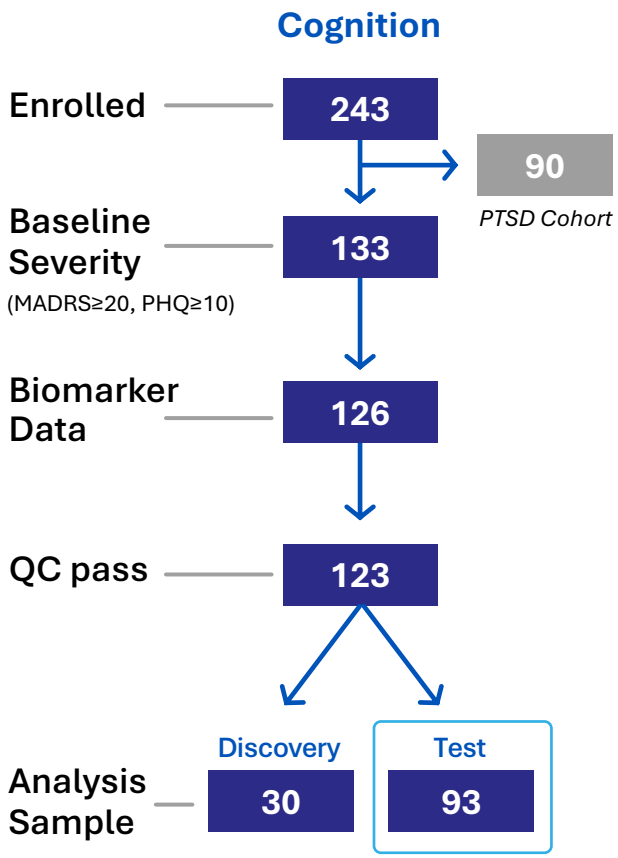
ALTO-100 Phase 2A study design and participant flow

Patient Population

- Adults 18- 65 years old
- Moderate to severe MDD and/or PTSD
- Monotherapy or adjunctive
- If adjunctive, <50% response to current drug

Treatment and Biomarkers

- 80 mg (as 40 mg BID) single-arm for 8 weeks
- ClinRO's at baseline, wks 2, 4, 6, 8
- Full Alto biomarkers at baseline, wks 2 & 8
- N=243 enrolled in 9 months (133 MDD) across 24 in-clinic sites
- Analyses focused on MADRS



MDD Cohort Baseline Demographics

	Discovery Data Set		Test Data Set	
	Bio-	Bio+	Bio-	Bio+
N	13	17	51	42
Age	40.2 (12.1)	45.8 (13.5)	40.3 (15.3)	45.0 (10.7)
Female	62%	82%	71%	71%
Edu (16+)	23%	29%	51%	29%
BMI	33.4 (8.4)	27.2 (6.4)	30.4 (7.0)	32.2 (10.7)
White	85%	88%	82%	71%
MADRS	31.5 (6.1)	33.4 (4.0)	27.9 (4.9)	31.0 (5.0)
HDRS	23.0 (5.1)	21.9 (3.7)	19.5 (4.0)	21.0 (4.0)
CGI-S	4.7 (1.0)	4.7 (0.8)	4.4 (0.6)	4.4 (0.5)
PHQ-9	17.4 (4.2)	16.2 (4.4)	15.9 (3.9)	15.7 (3.8)

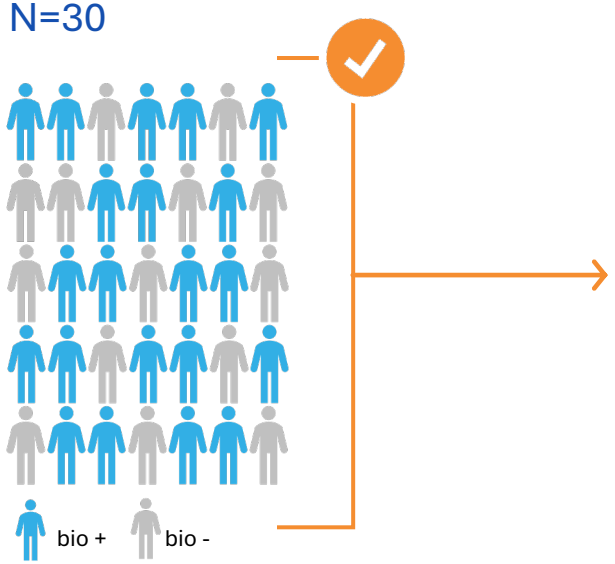
No baseline/clinical characteristics were shown to impact results of biomarker outcomes

ALTO-100 Phase 2A: prospective testing of memory/cognition biomarker as predictive of response

01

Determine Biomarker

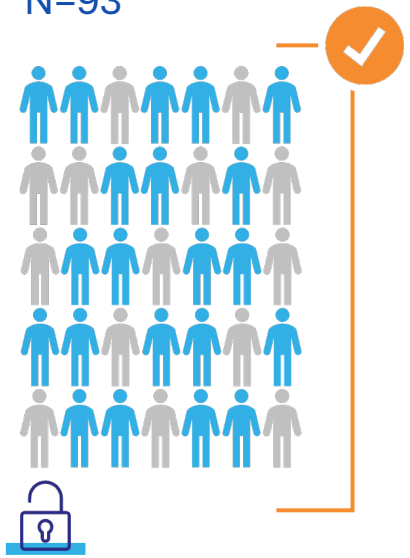
N=30



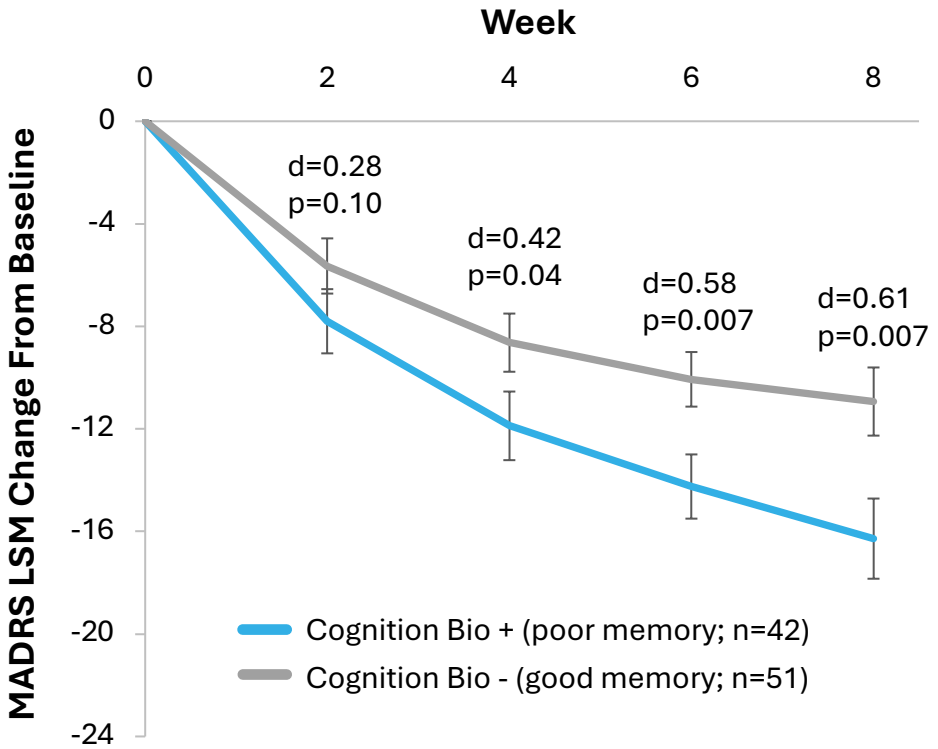
02

Prospective Biomarker Validation

N=93



Prospective Replication in Test Dataset



1. Poor verbal memory is the most predictive cognitive biomarker, consistent with role of hippocampal plasticity
2. Patients in test set **prospectively labeled as bio+/-**
3. High reliability of the memory test confirmed in independent data

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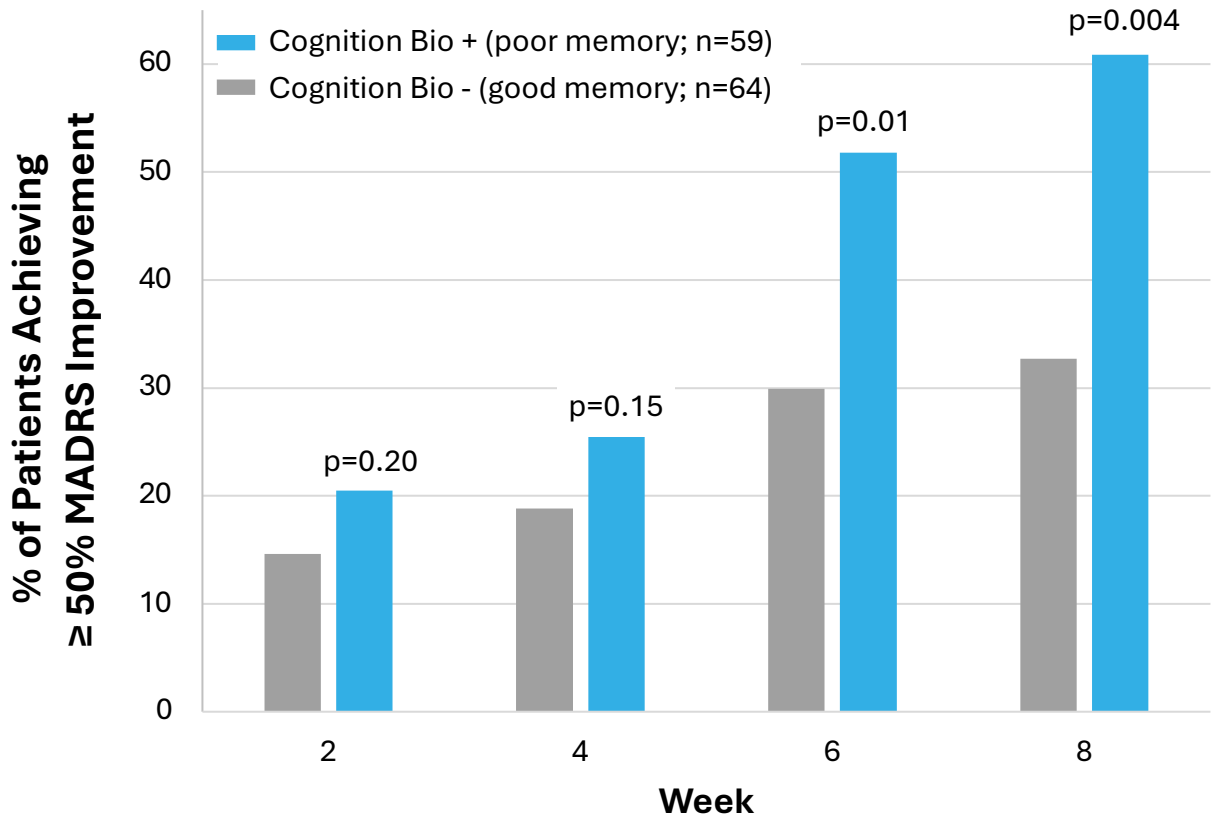
Poor memory/cognition patients derived greater benefit from ALTO-100

Clinical response to ALTO-100 observed to be more robust in patients with poor memory

- Poor memory/cognition response rates (MADRS reduction ≥50%) were roughly double vs. good cognition
- Response rates reached ~80% in monotherapy and ~50% in adjunctive
- Difference observed in CGI as well as symptoms



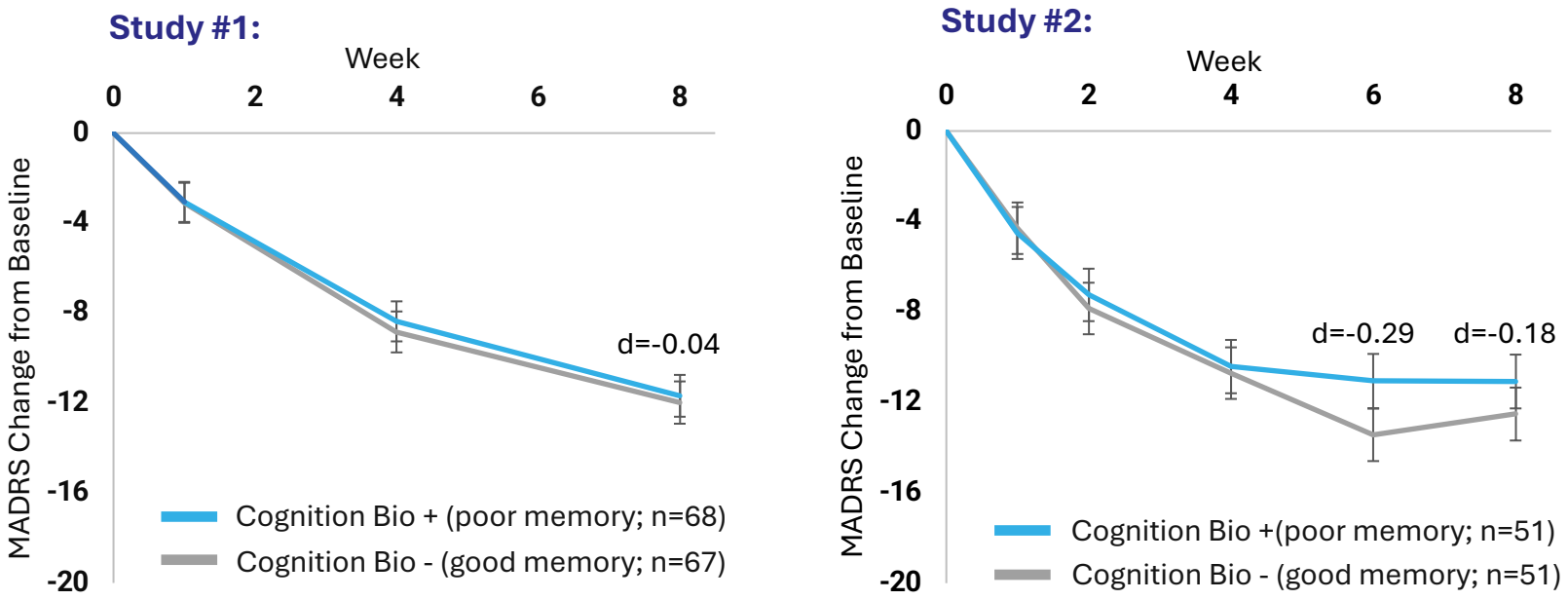
CGI – Clinician Global Impression of Severity

Poor memory did not predict higher placebo response

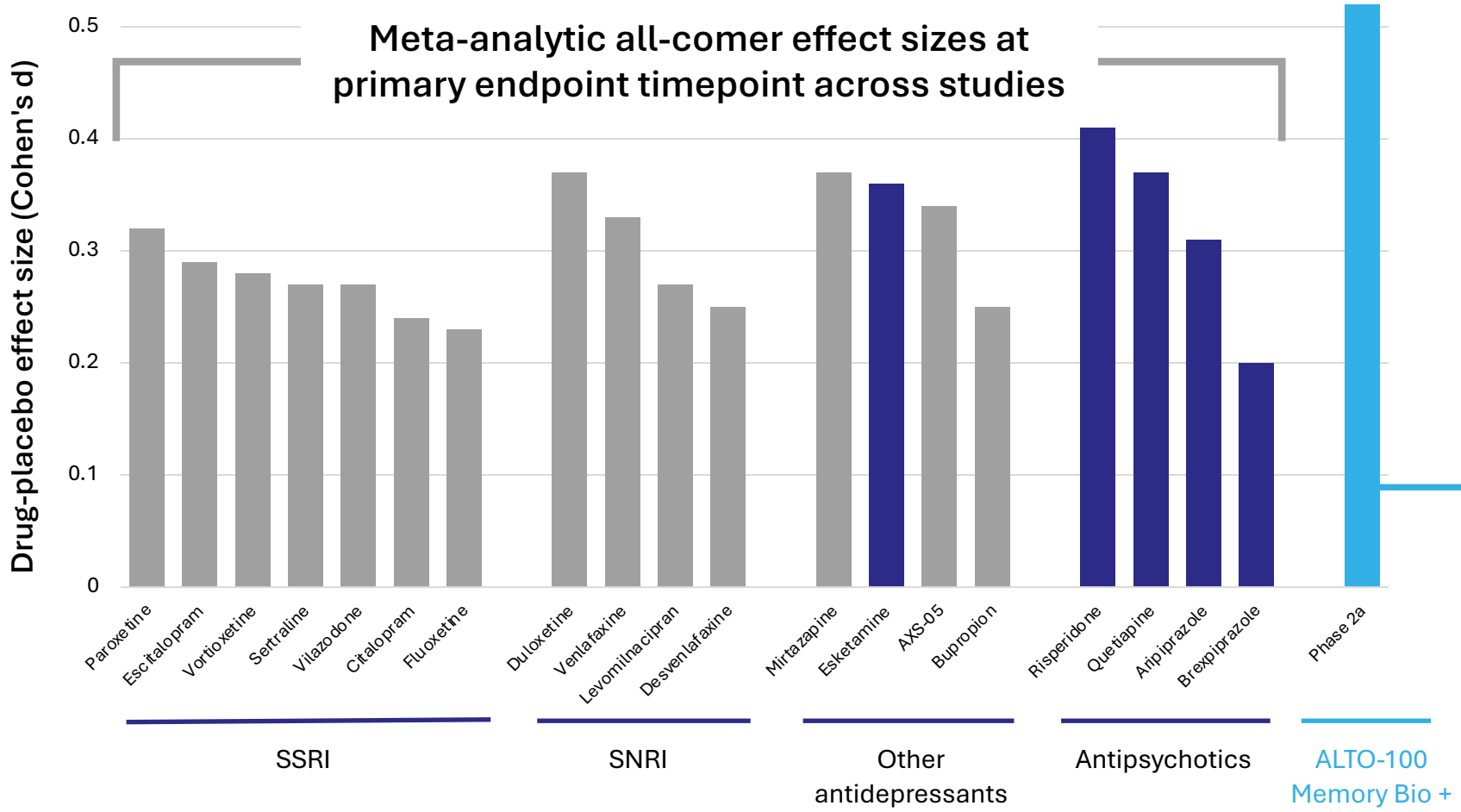
Tested poor memory and placebo response in 2 separate third-party MDD monotherapy trials, possible because they used **the same memory test**

On placebo, patients with poor memory did not show better response, suggesting better response is specific to ALTO-100

Placebo-treated Patients



ALTO-100 has potential to demonstrate greater efficacy in mechanistically-distinct and less-responsive population



Comparison all-comer effects:

- monotherapy
- adjunctive

Effect sizes: Cipriani et al, Lancet 2018; Zhou et al., Int J Neuropsych, 2015; Papakostas et al., J Clin Psych, 2020; Kishi, Int J Neuropsych, 2019; Iosifescu, J Clin Psych, 2022

→ ALTO-100 was **well tolerated**, unlike antipsychotics & esketamine

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.

ALTO-100 was well tolerated (Phase 2A study)

Overall Treatment Emergent Adverse Events (TEAEs)

Safety Analysis Set

	N (%)
Total Participants	243
At least one TEAE	146 (60.1)
No TEAE	97 (39.9)
SAEs (none related)	6 (2.5)
AEs leading to Discontinuation	14 (5.8)

	% of TEAEs
Related TEAEs (by TEAE)	40.2

Note: participants may have had more than one AE

TEAEs for ≥5% of the Population

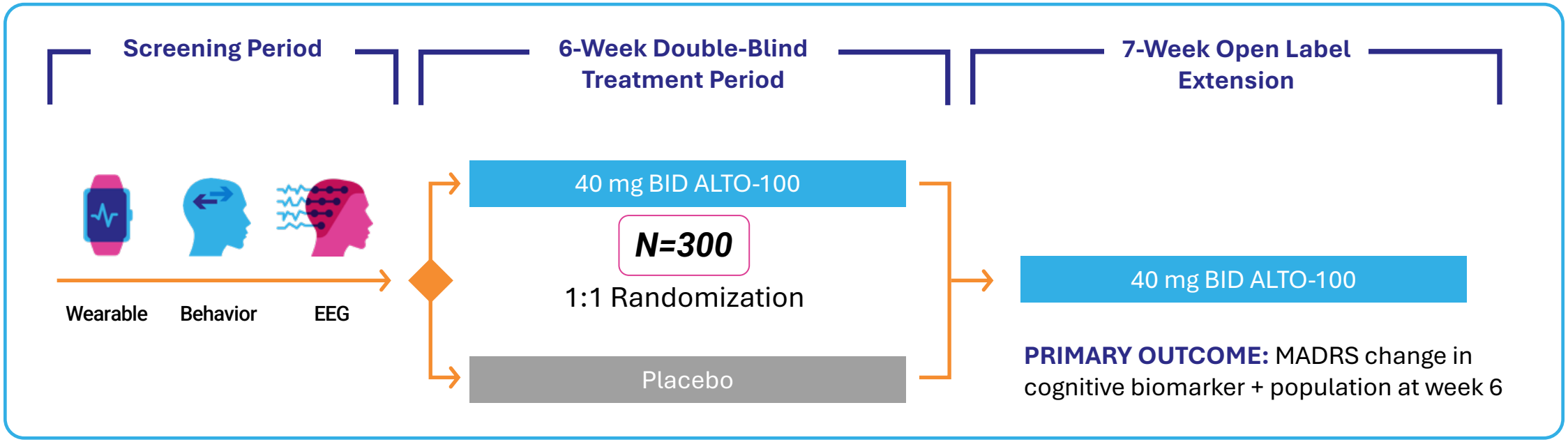
Safety Analysis Set

	N (%)
Headache	40 (16.5)
Abdominal discomfort	13 (5.4)

- TEAEs consistent with prior ALTO-100 studies
- Significantly fewer discontinuations in ALTO-100 group than placebo group in the prior Phase 2 RCT

ALTO-100 phase 2B biomarker-guided trial in MDD

Enrollment completed – topline data expected Oct. 2024



- 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

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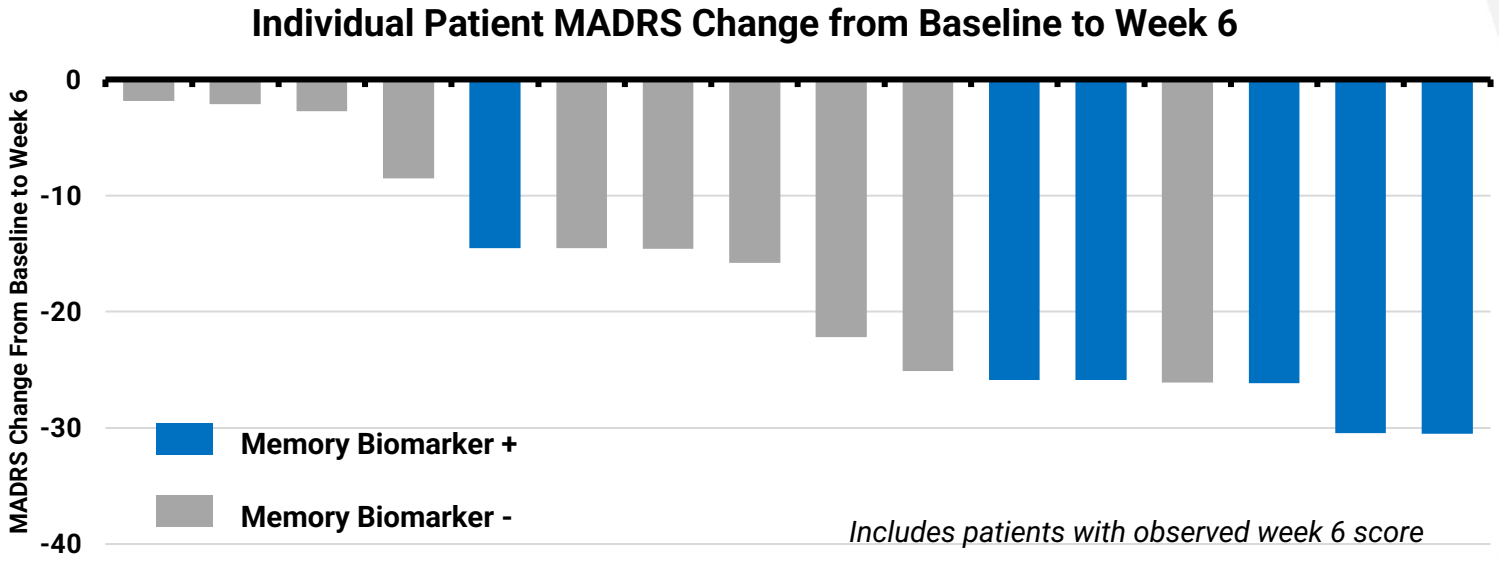
Pilot decentralized study of ALTO-100 in MDD demonstrates feasibility of at-home biomarker collection and consistency of biomarker results

Study Summary

- 20 adult moderate to severe MDD patients
- Single-arm trial including memory biomarker positive and negative patients
- All biomarker and clinical care done entirely remotely/virtual
- Memory test acquired on patients' own devices – much like ultimate clinical use context
- Biomarker status determined prior to data analysis

  (same memory biomarker as ongoing Ph. 2b)
- Analysis completed May 2024



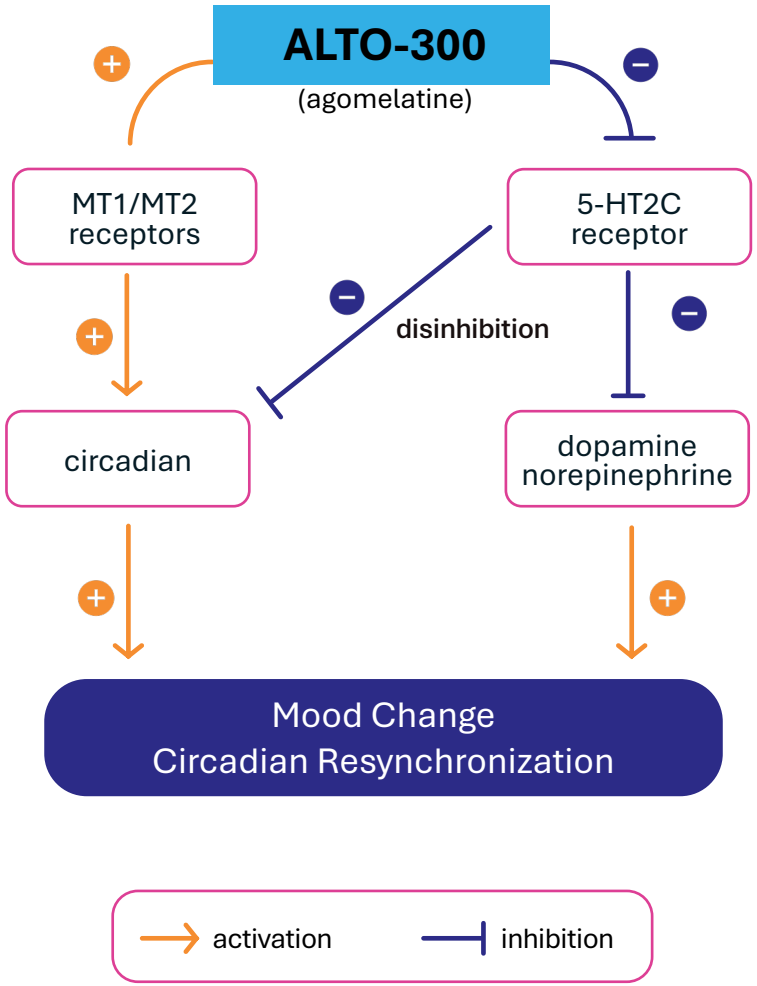
Key Takeaways

- **In-home biomarker collection provides consistent patient stratification**
- **ALTO-100 continues to be well-tolerated**
- **Memory-based biomarker enrichment consistent with Phase 2a results**

ALTO-300

Phase 2B development for MDD

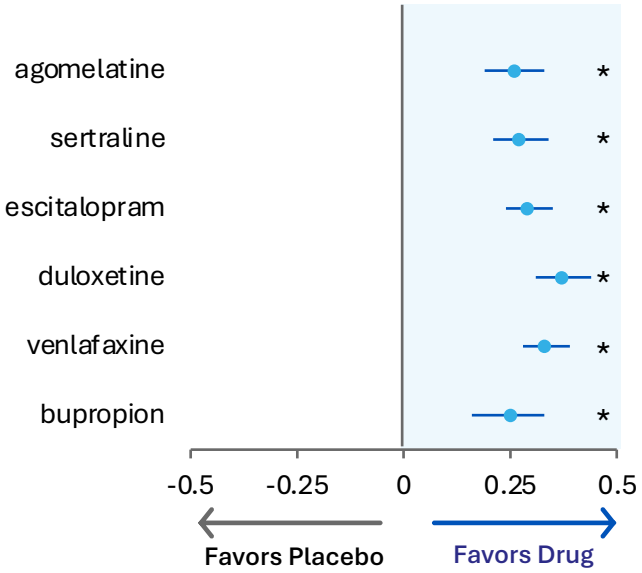
ALTO-300 proposed mechanism of action



Unique Opportunity:

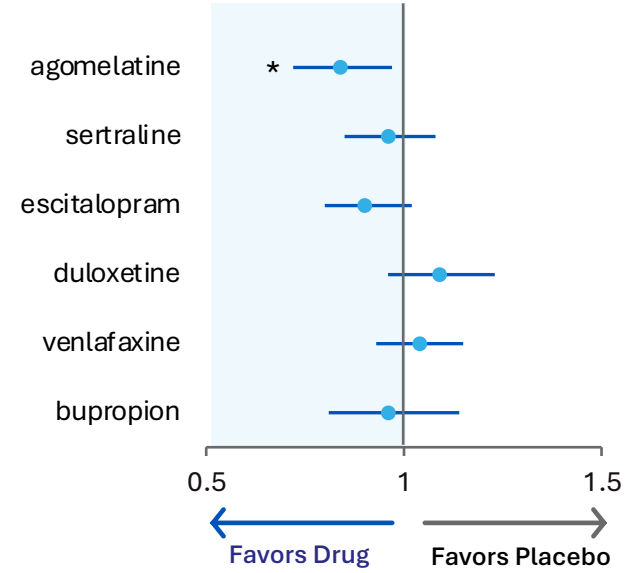
Well-tolerated antidepressant With Ex-U.S. Approval (NCE In U.S.)
Ready For Enhancement With A Biomarker

Efficacy



*shows effect sizes, * p<0.05*

Tolerability



*shows odds ratios, * p<0.05*

Plots from Cipriani et al., Lancet, 2018

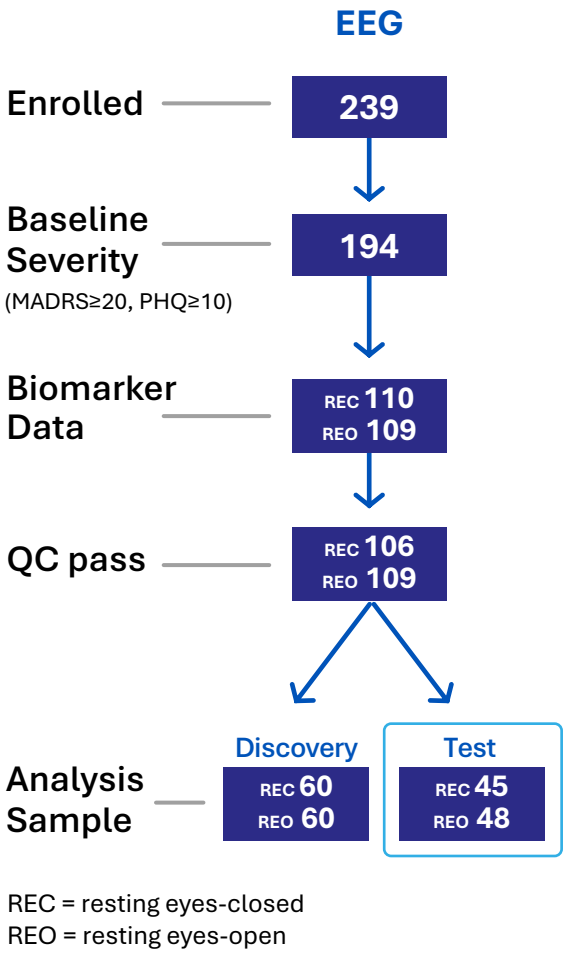
ALTO-300 Phase 2A study design and participant flow

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



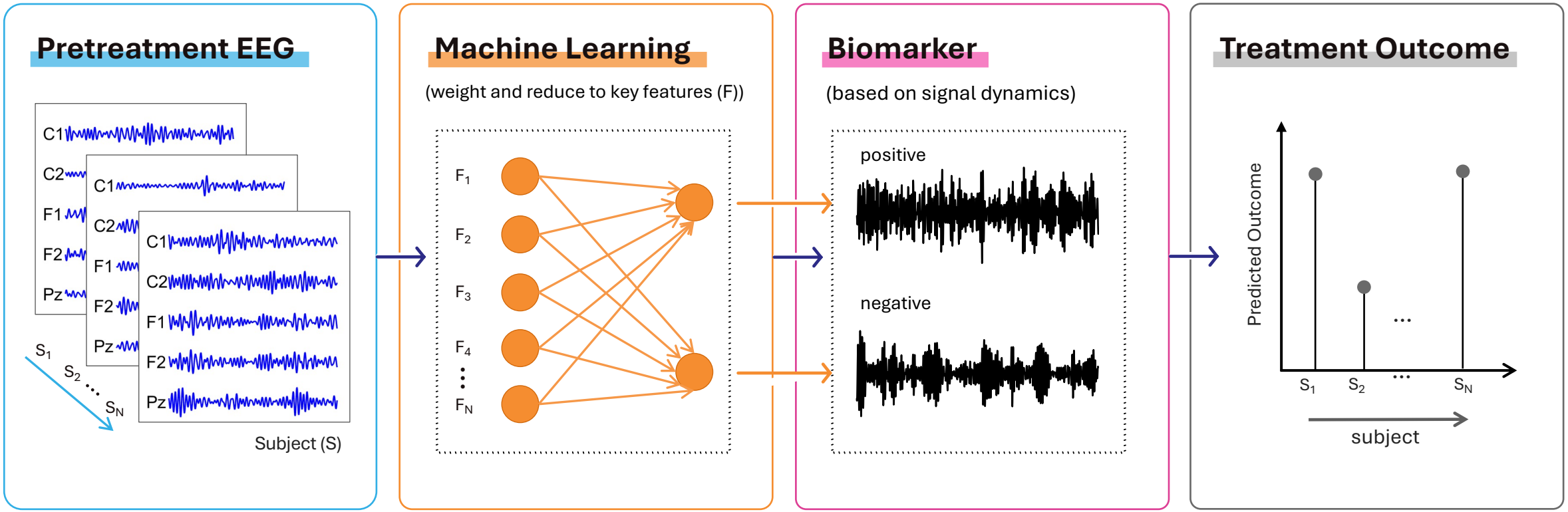
REC = resting eyes-closed
REO = resting eyes-open

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

EEG machine learning strategy

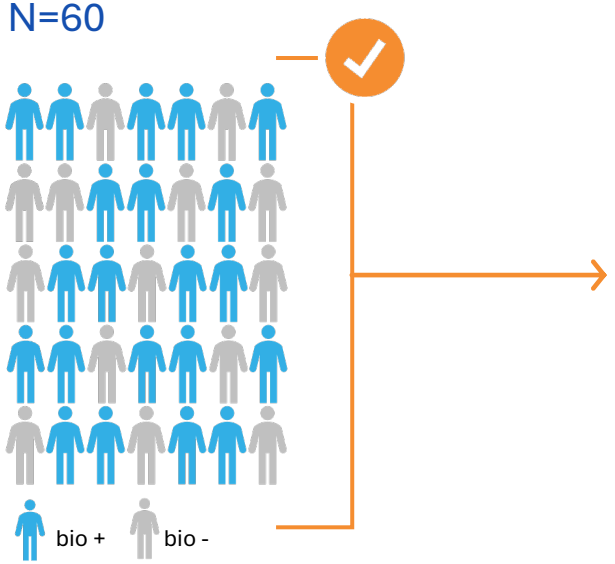


ALTO-300 Phase 2A: prospective testing of EEG biomarker as predictive of response

01

Determine Biomarker

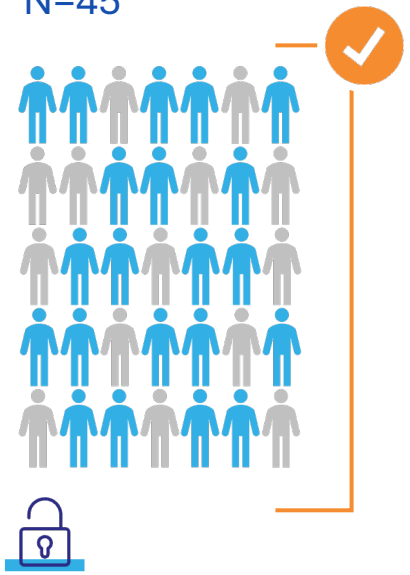
N=60



02

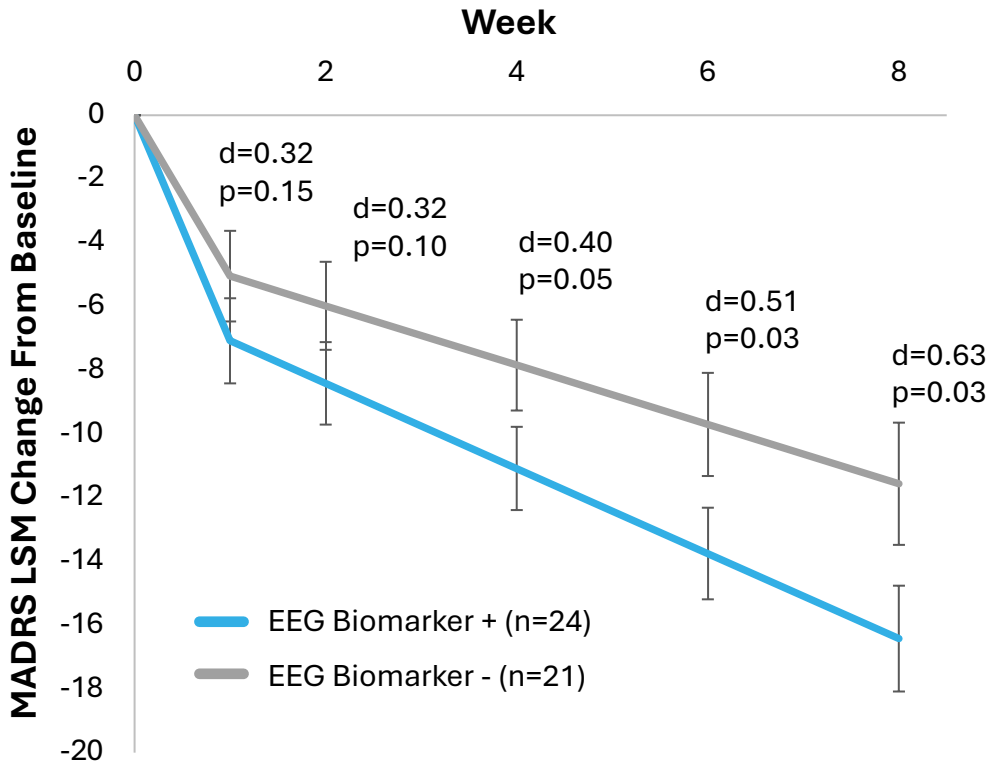
Prospective Biomarker Validation

N=45



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

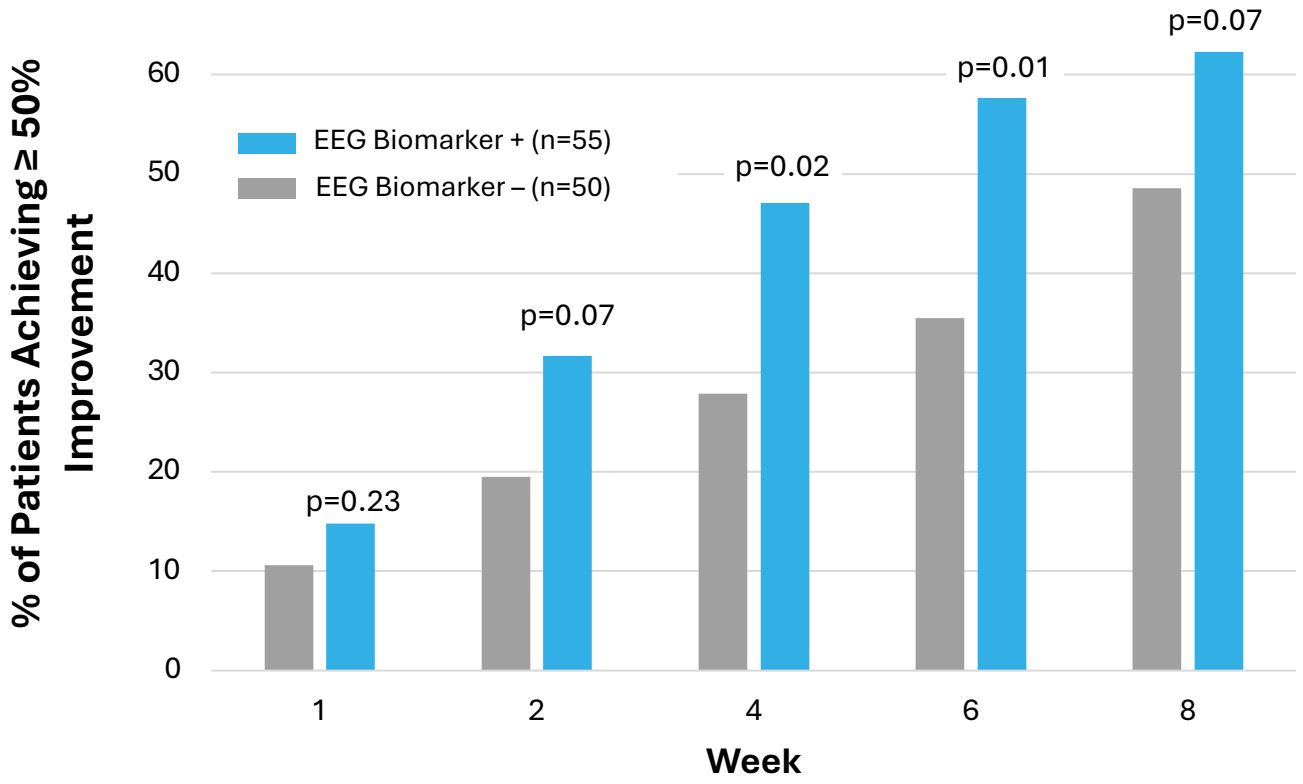
Prospective Replication in Test Dataset



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

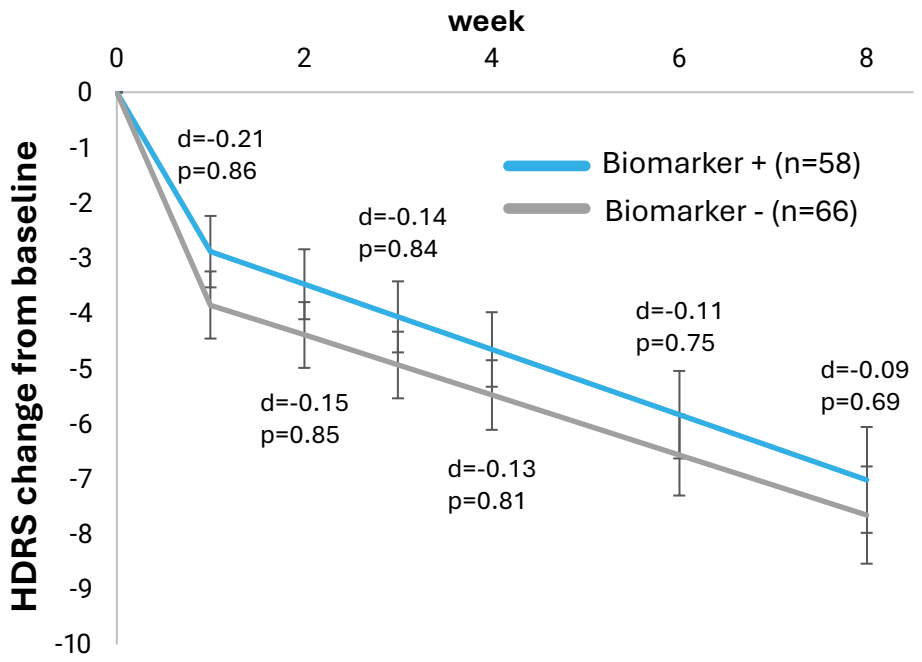


CGI – Clinician Global Impression of change
HAM-D – Hamilton Depression Rating Scale

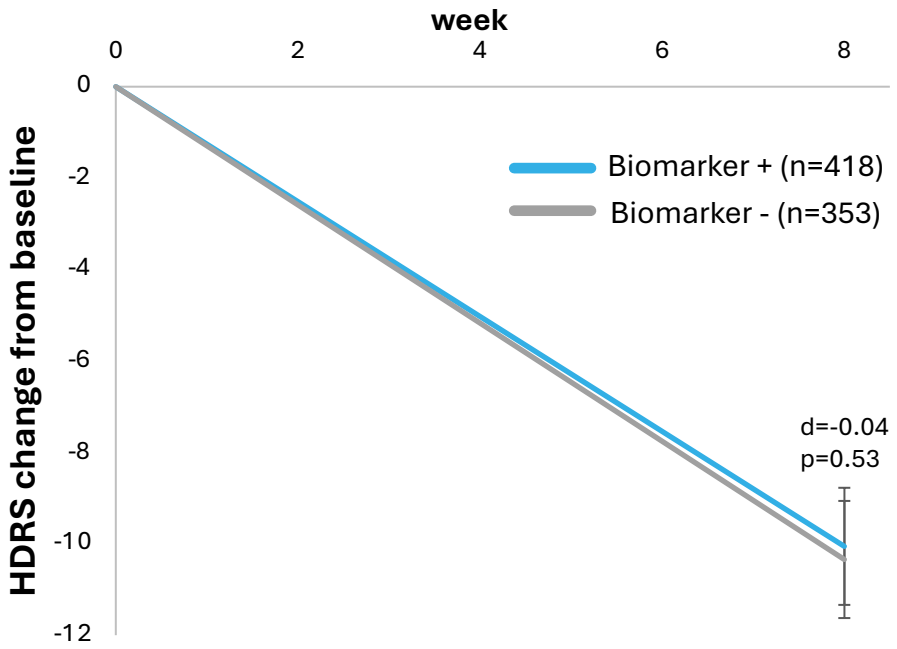
EEG model prediction is specific to ALTO-300

Apply the ALTO-300 EEG biomarker to:

Placebo-Treated Patients

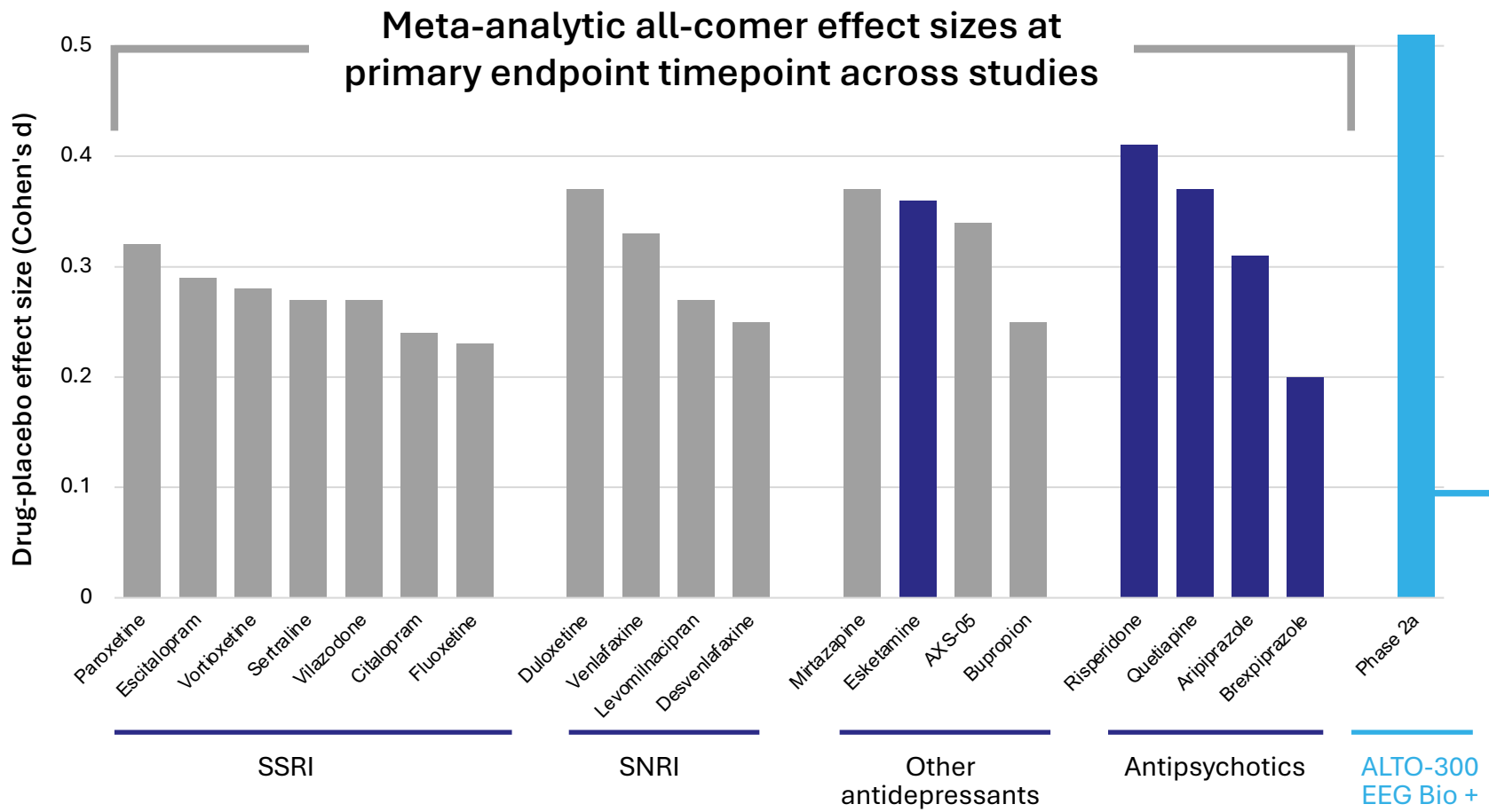


SSRI/SNRI-Treated Patients



ALTO-100 and 300 biomarkers are uncorrelated (r=-0.04) – ~three quarters of MDD population estimated to have one or both biomarkers

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



Comparison all-comer effects:

- monotherapy
- adjunctive

Effect sizes: Cipriani et al, Lancet 2018; Zhou et al., Int J Neuropsych, 2015; Papakostas et al., J Clin Psych, 2020; Kishi, Int J Neuropsych, 2019; Iosifescu, J Clin Psych, 2022

ALTO-300 **well tolerated**, unlike antipsychotics & esketamine

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.

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

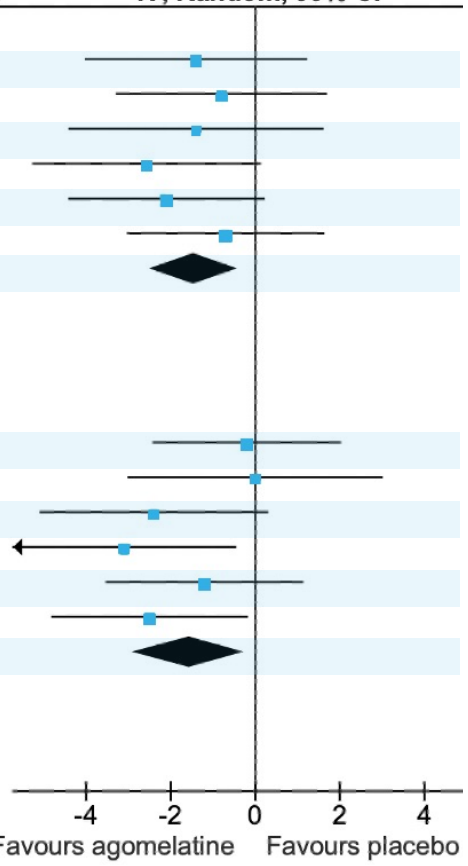
	N (%)
Headache	35 (14.6)
Nausea	18 (7.5)
Dyspepsia	15 (6.3)
Insomnia	15 (6.3)
COVID 19 Infection	14 (5.9)
Rash (10 from wearable)	12 (5.0)

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

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: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%								



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

Safety Goal:

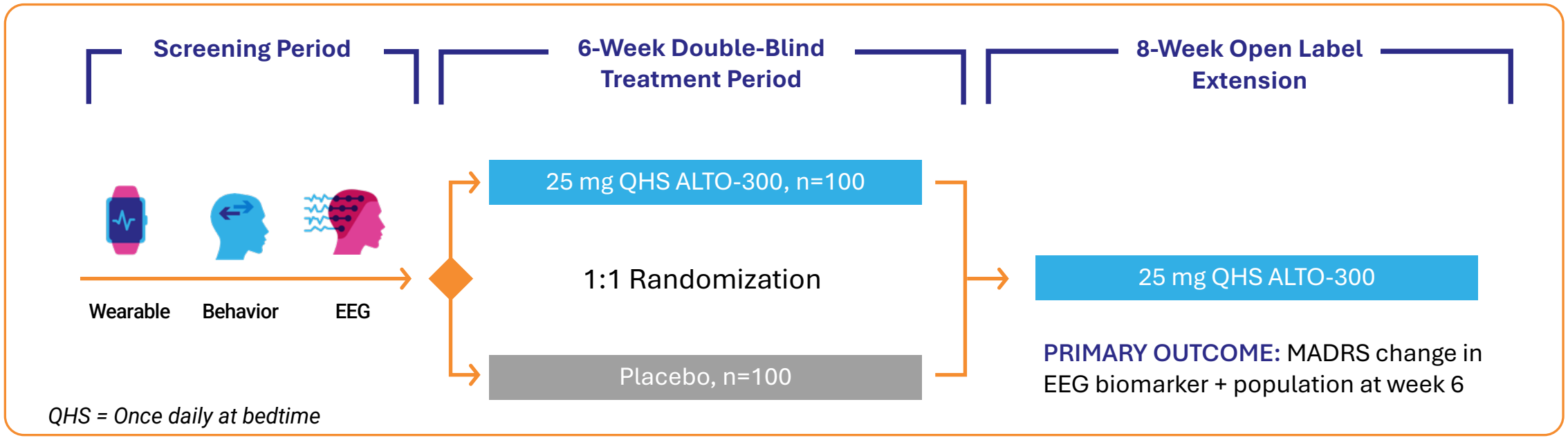
Placebo-like LFT Elevation Rate

- The 50 mg dose is associated with more LFT elevation than the 25 mg dose, all reversible
- Novartis US studies showed placebo-like LFT rate with 25 mg
  - 25mg: 0.3%
  - 50mg: 3.7%
  - Placebo: 0.3%

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

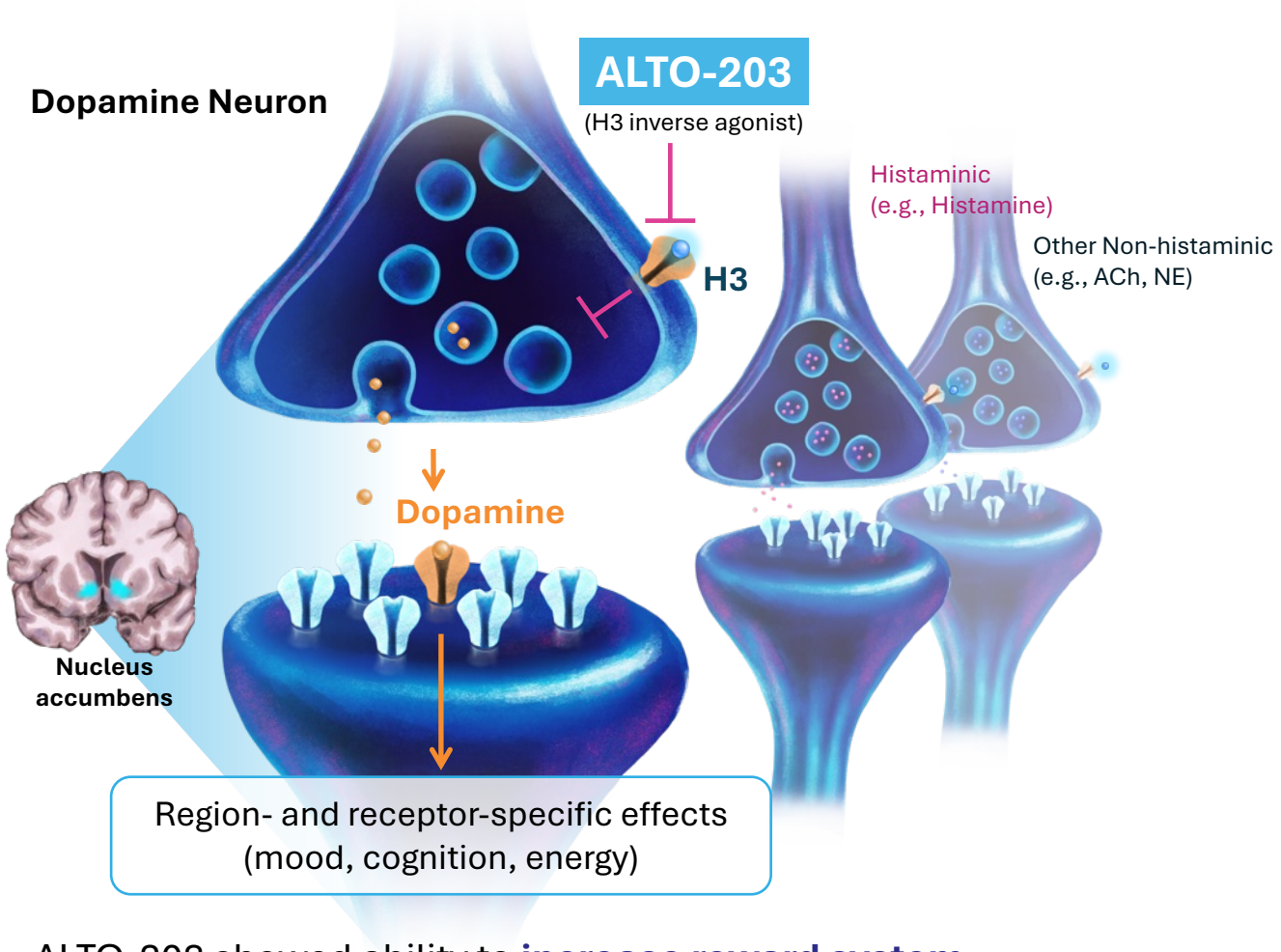


- Design follows **FDA's enrichment guidelines:** powered primary outcome in EEG biomarker positive patients
- **Adjunctive** treatment to an existing antidepressant with an insufficient response
- **Includes participants with and without the biomarker** and randomization stratified by biomarker status
- 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

ALTO-203

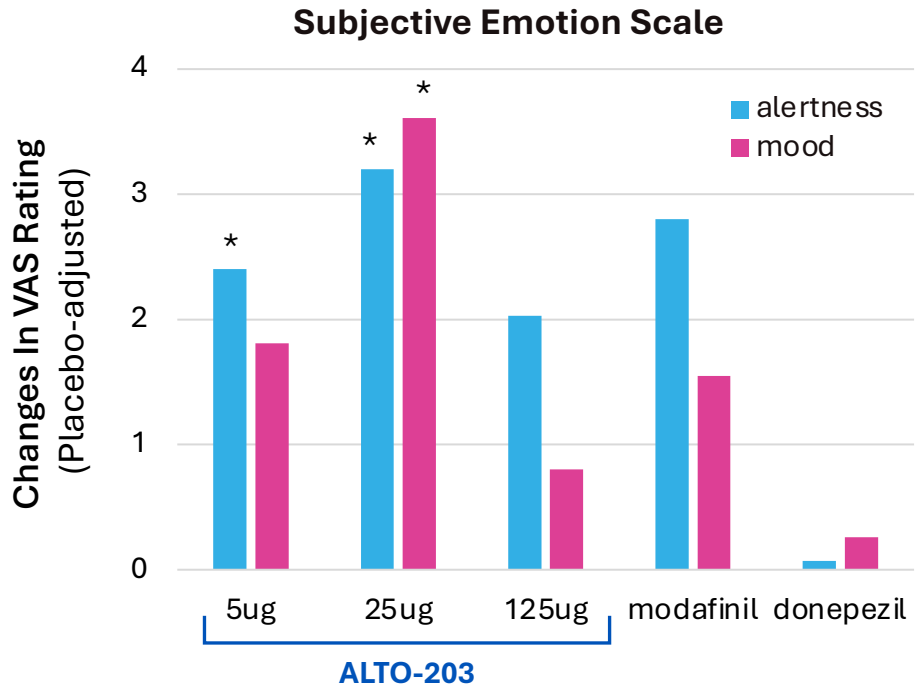
Development for MDD with anhedonia

An investigational H3 inverse agonist with demonstrated positive subjective emotional effects in humans



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

Phase 1 PD-focused dose-response study*
(N=40, crossover):



Phase 2 POC study in MDD with anhedonia launched and top-line data **1H 2025**

*Study conducted prior to Alto acquisition

Initiated proof-of-concept study in depression with Anhedonia

Study Population:

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

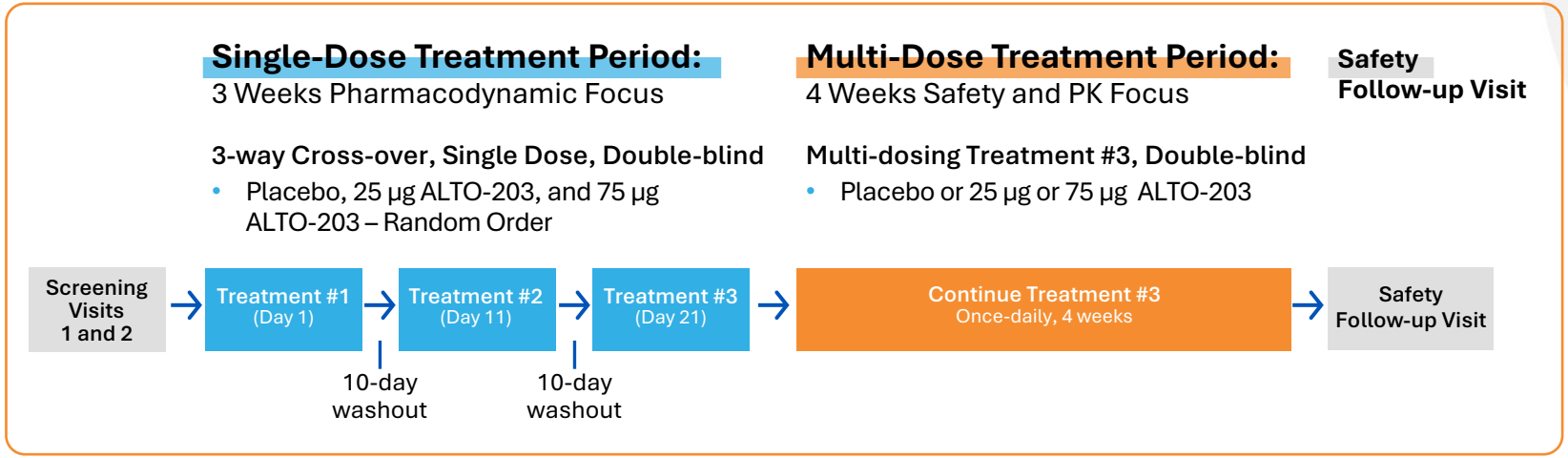
Design:

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

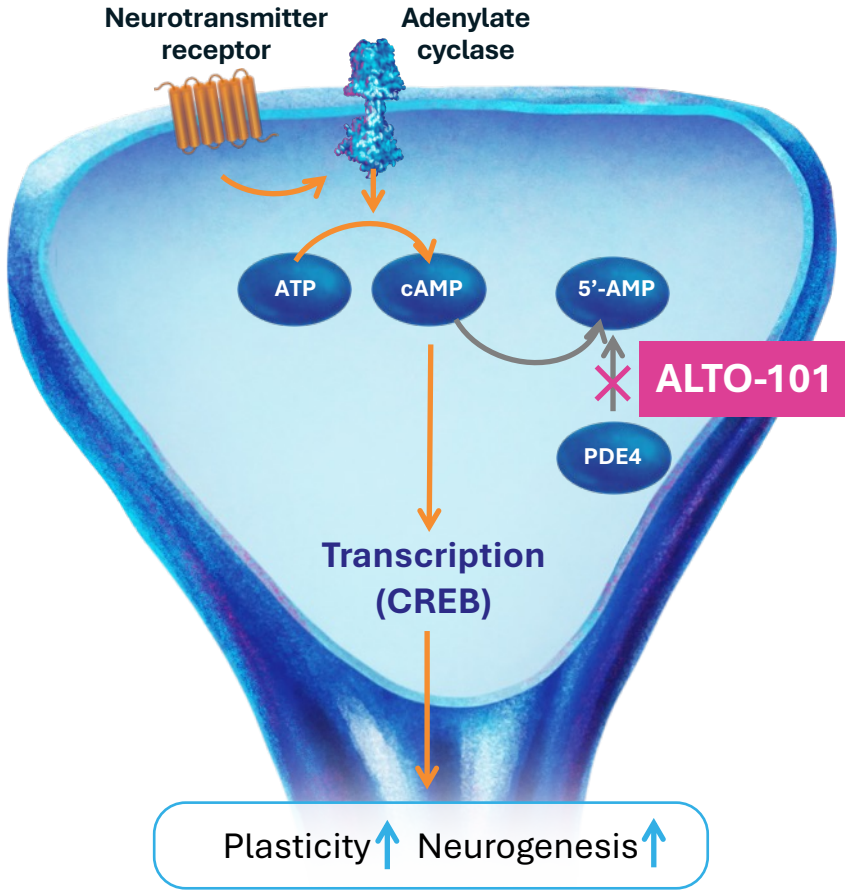
Exploratory outcomes: clinical depression, anhedonia, and other symptom scores in multi-dose period

Topline data readout expected 1H 2025

ALTO-101

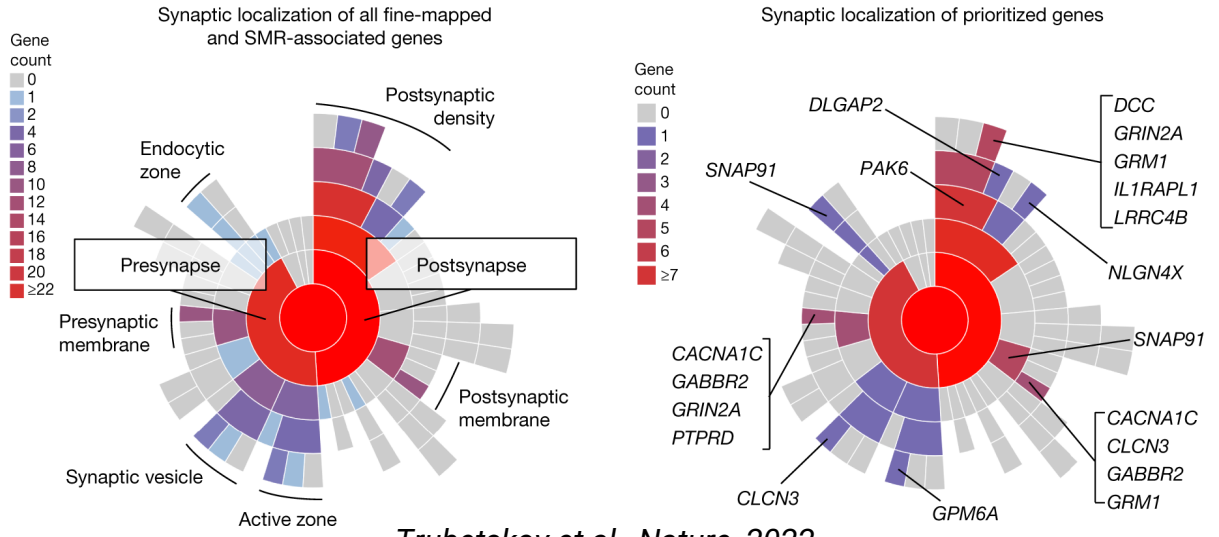
Development for CIAS

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

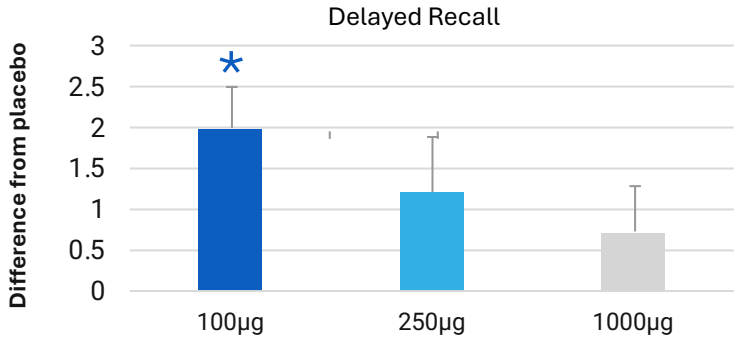


Trubetskoy et al., Nature, 2022

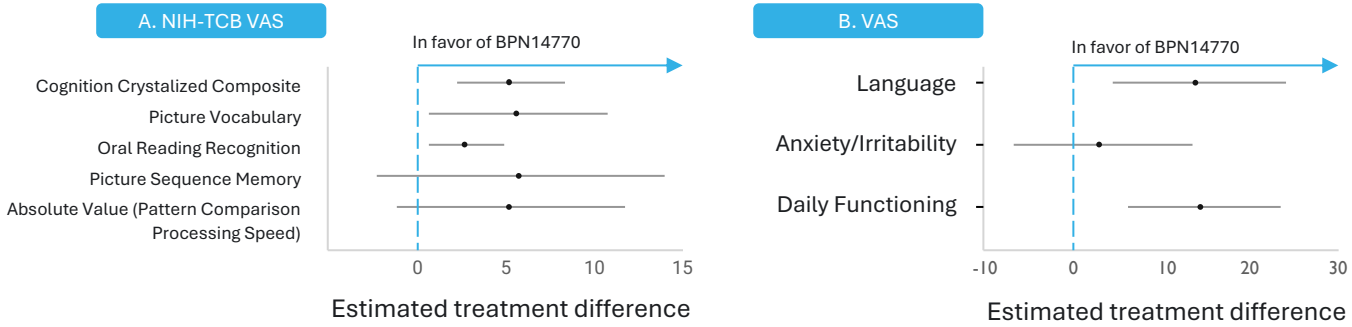
- Most CIAS drug targets have focused on ameliorating synaptic dysfunction (e.g., NMDA-R modulation)
- Directly enhancing downstream signaling represents a novel therapeutic approach

Human evidence for benefits of a PDE4 inhibitor

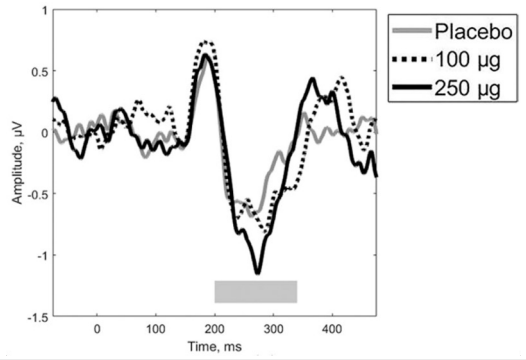
Memory in healthy elderly: roflumilast
(Blockland et al., Neurobiol Aging, 2019)



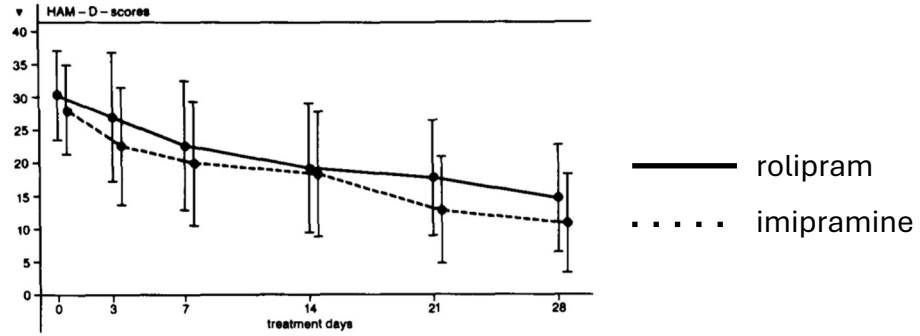
Cognition and function in Fragile X: BPN14770 (PDE4Di)
(Berry-Kravis et al., Nature Medicine, 2021)



Mismatch negativity in schizophrenia: roflumilast
(Gilleen et al., J Psychopharm, 2020)



Depression treatment comparison with imipramine: rolipram
(Hebenstreit et al., Pharmacopsychiatry, 1989)

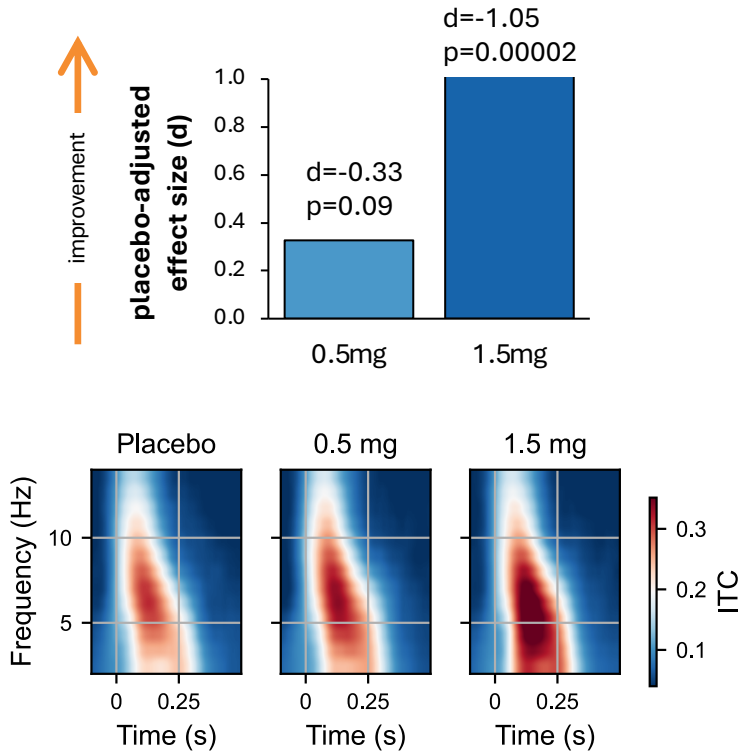


Main challenge with PDE4i's: balancing target occupancy for breadth of PD effect while minimizing intolerability

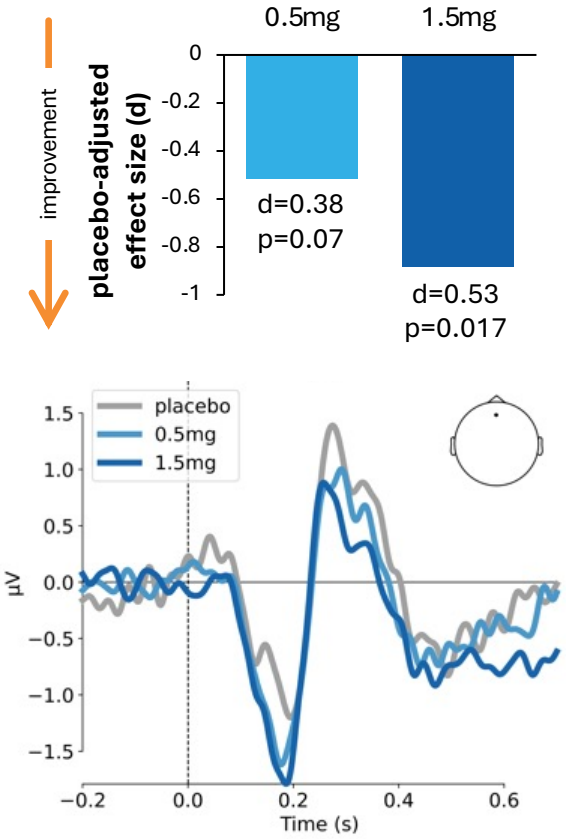
Novel investigational PDE4 inhibitor with broad pro-cognitive activity

Phase 1 PD-focused Dose-response Study (N=40, crossover):

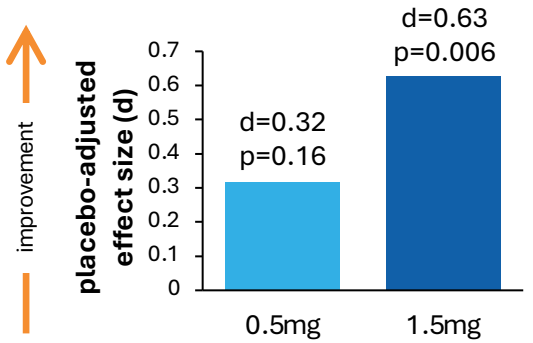
Increased theta band response *



Increased mismatch negativity



Improve processing speed



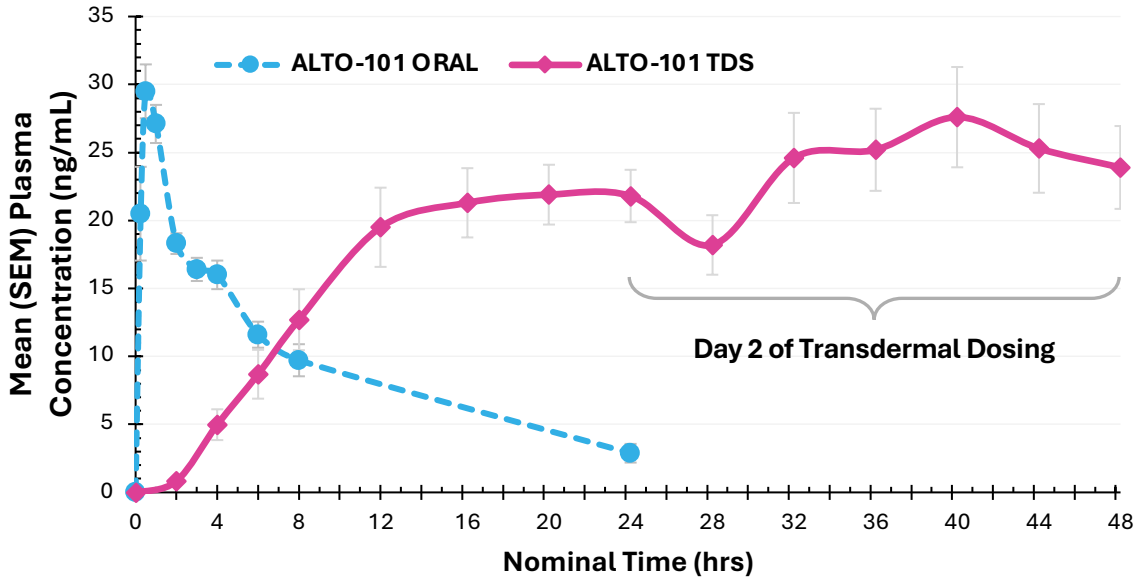
Improvement in processing speed correlated to increase in theta band response

POC study in schizophrenia (CIAS) planned to launch **1H 2024**

* Theta ITC found by Alto to have the best correlation with cognition and case-control sensitivity in patients with schizophrenia across previously characterized EEG disease biomarkers (Wang et al, SOBP 2024)

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:

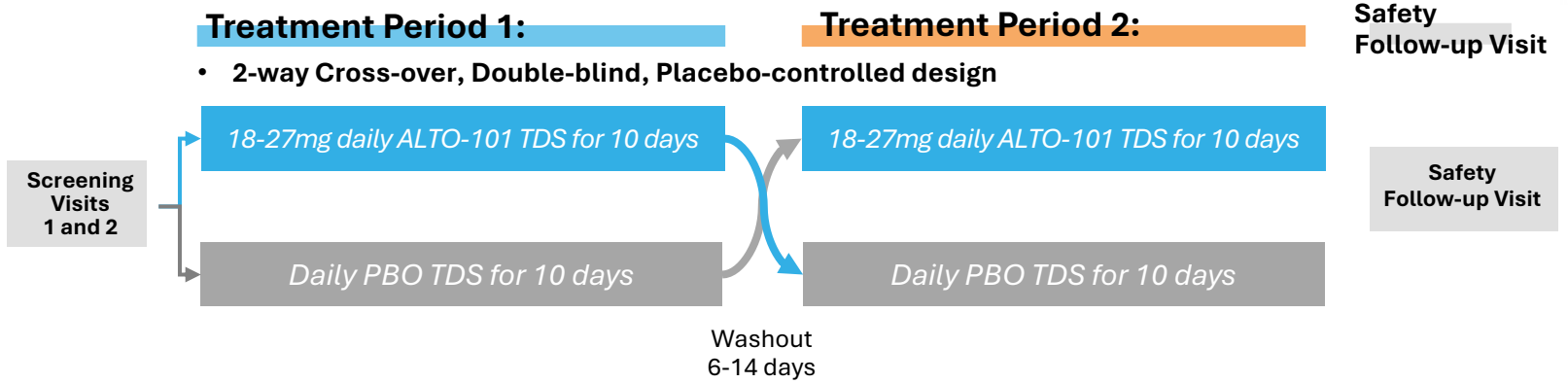
A two-way crossover, double-blind, placebo-controlled, dose-escalating study with ALTO-101 and placebo:

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

Our team has been involved in approval of 25 drugs and investigation of >100 product candidates

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
GC and Chief Administrative Officer

Fadi Abdel, MD
SVP, Innovation

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Akash Datwani, PhD
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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 value-creating milestones

Capitalized through at least 4 potentially value generating clinical milestones:

~$206MM (as of Mar. 31, 2024) → Cash runway into 2027

1H 2024

- ☑ Completed upsized Initial Public Offering (IPO) of $147MM
- ☑ Appointed to Board:
  Husseini Manji, MD
  Maha Radhakrishnan, MD
- ☑ Initiate ALTO-203 POC study in MDD
- ☑ **ALTO-101 transdermal PK/safety data**
- ☑ Initiate ALTO-101 POC study in CIAS

2H 2024

- ☑ Complete ALTO-100 Phase 2b enrollment
- ☐ **ALTO-100 Phase 2b MDD data (Oct.)**

2025

- ☐ **ALTO-300 Phase 2b MDD data (1H)**
- ☐ **ALTO-203 MDD POC data (1H)**
- ☐ **ALTO-101 CIAS POC Data (2H)**