



ALTO
NEUROSCIENCE

NYSE: ANRO — Nov. 2025

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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.

Alto by the numbers

Advancing

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

>800

Patients Dosed

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

25+
MILLION

Patient Impact

Opportunity across the portfolio

4

Mid- to Late-Stage Data Readouts

In next ~2 years

Into
2028

Expected Cash Runway

CNS is the next frontier in precision medicine



Oncology



Cardiovascular



CNS

predictive biomarkers



target specificity or genetics



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 and ALTO-207)
- ☐ Placebo-Controlled Trials in Biomarker Population

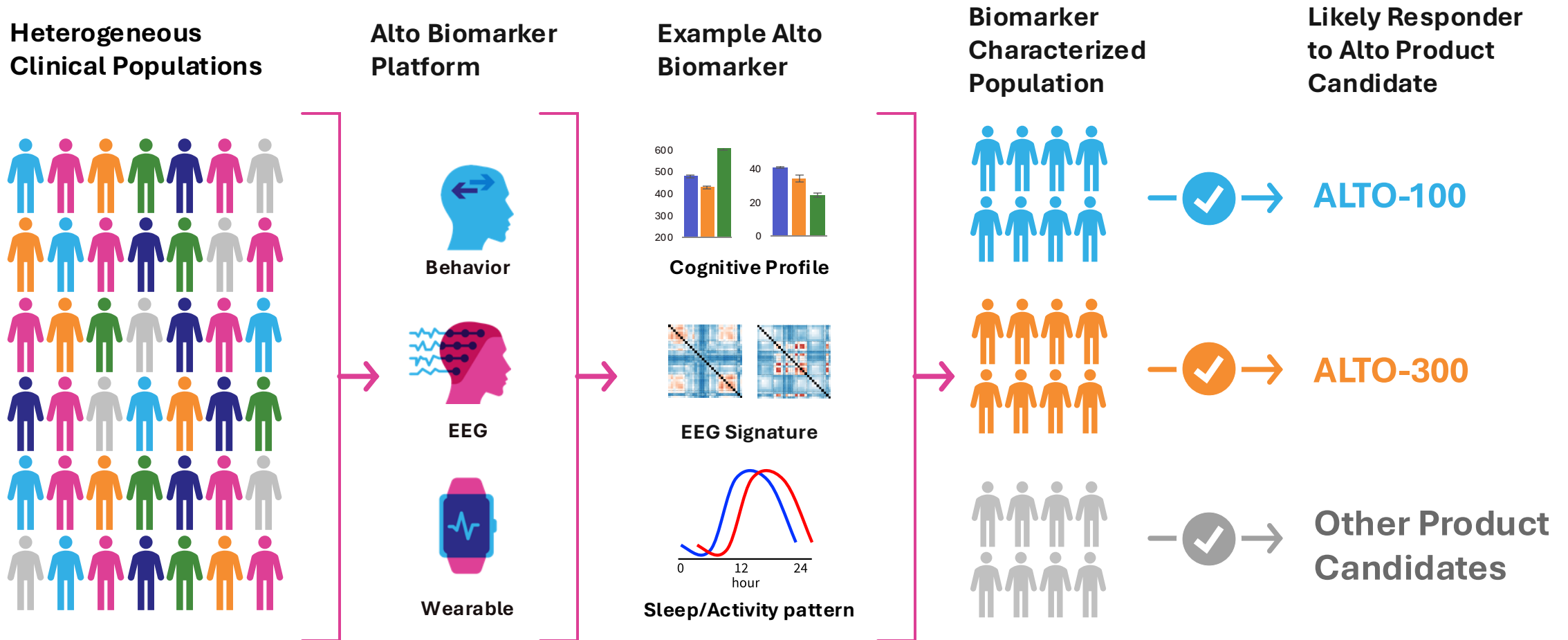
First biomarker-driven pipeline for mental health conditions

Multiple independent programs leveraging our biomarker strategy to systematically reduce development risk; all programs remain on track to achieve upcoming milestones

Product Candidate (MOA/Target)	Lead Indication	Phase 1		Phase 2		Phase 3		Next Anticipated Milestone
		Safety & Brain Effects	Clinical Effect in Biomarker Positive	Registration Trial(s)				
ALTO-207 (D3/D2 & 5-HT3)	TRD	Potentially Pivotal Study*/Phase 2b & Ph. 3 Planned						Ph. 2b Initiation 1H 2026 (Topline 2027) Ph. 3 Initiation planned by early '27
ALTO-300 (MT1/2 & 5HT2C)	MDD	Phase 2b Ongoing						Topline Data mid-2026
ALTO-100 (BDNF)	Bipolar Depression	Phase 2b Ongoing						Topline Data 2H 2026
ALTO-101 (PDE4)	Schizophrenia (CIAS)^	Phase 2 POC Ongoing						Topline Data 1Q 2026
ALTO-203 (H3)	MDD	Phase 2 POC Completed						
ALTO-202 (NMDA NR2B)	MDD							
ALTO-208 (D3/D2 & NK-1)	Parkinson's Disease							

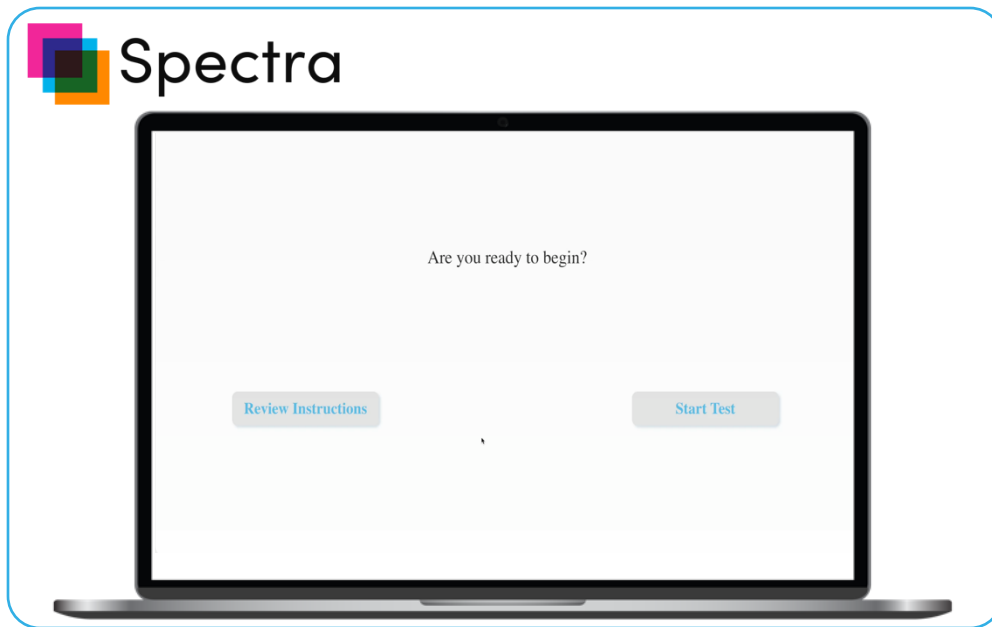
Platform

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

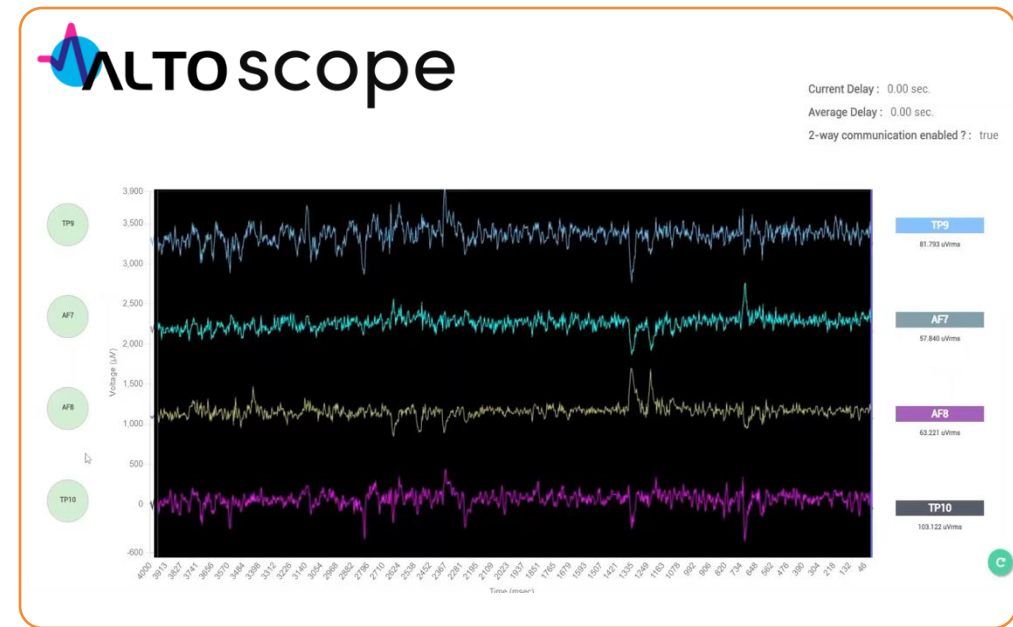


Leveraging proprietary tools, anticipating commercial scale

ALTO-100 biomarker is cognitive test-based



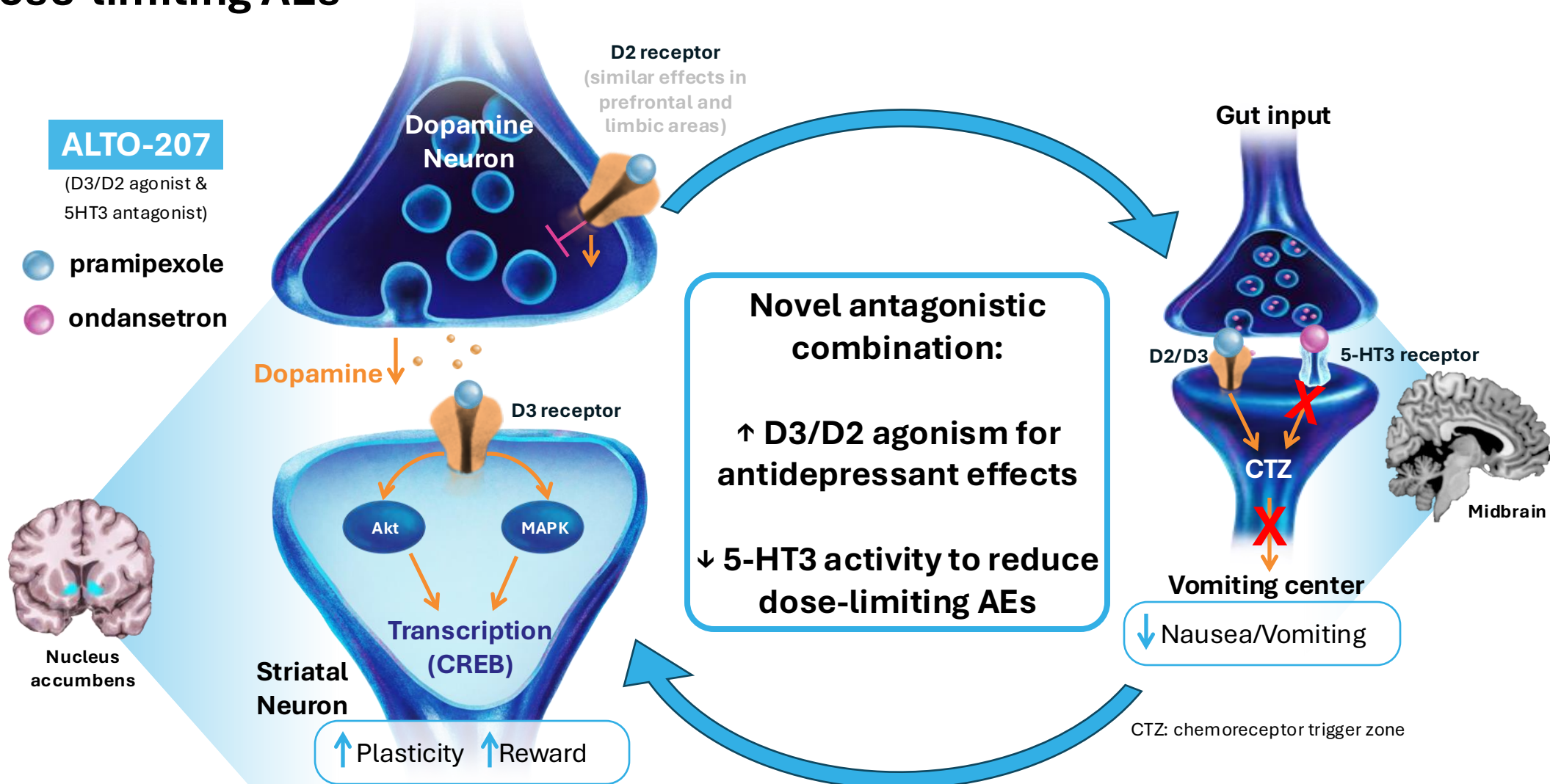
ALTO-300 biomarker is EEG-based



ALTO-207

Development for TRD

ALTO-207: combining a dopamine D3-preferring D3/D2 agonist with demonstrated antidepressant effects and 5-HT3 antagonist designed to reduce dose-limiting AEs



ALTO-207 (fka CTC-501) is a novel, clinically validated product candidate for a high need patient population



Pramipexole has shown robust antidepressant effects but is limited by significant tolerability issues



CTC-501 demonstrated clear safety benefits over pramipexole alone, achieving higher doses in Phase 1, with 5x faster titration – a Phase 2a placebo-controlled study then showed robust clinical effects



Findings enable acceleration: a potentially pivotal* / planned Phase 2b TRD trial (topline data 2027) and planned Phase 3 trial start in early 2027



Efficient and straightforward 505(b)(2) regulatory pathway provides a potentially shorter time to market



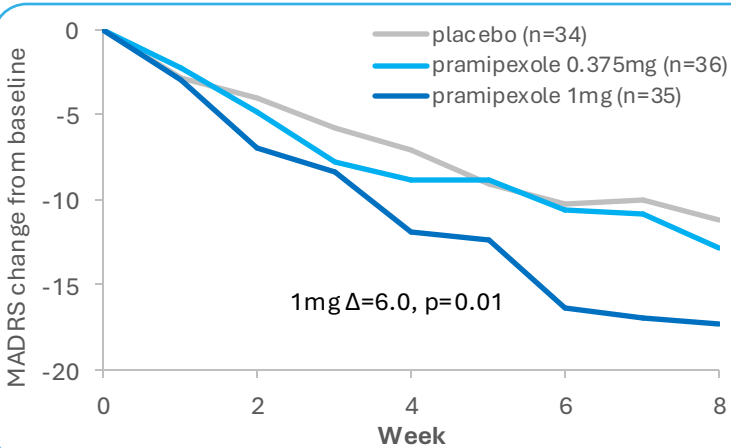
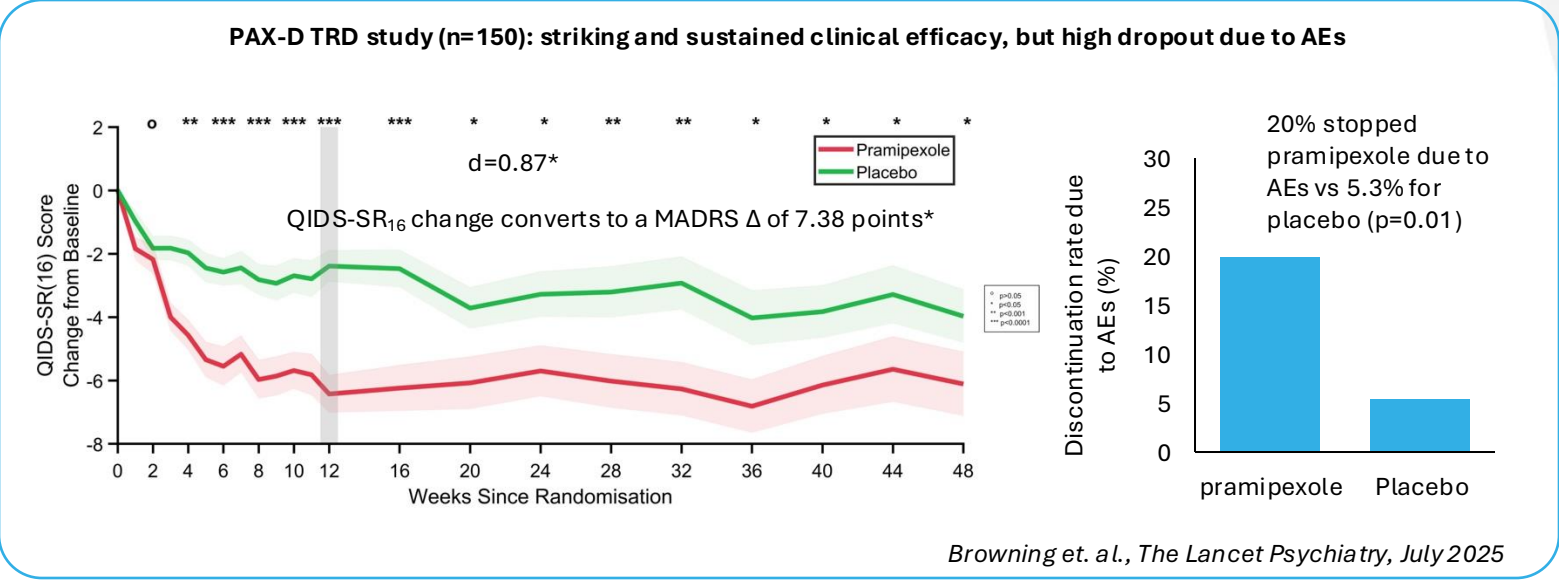
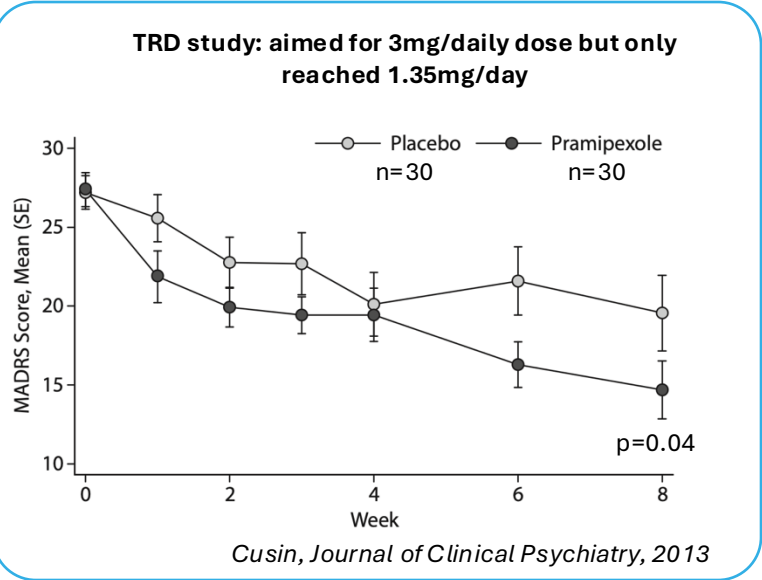
Strong patent protection; validated commercial approach on combination products in psychiatry; compelling commercial case with substantial need in TRD

Pramipexole augmentation for the acute phase of treatment-resistant, unipolar depression: a placebo-controlled, double-blind, randomised trial in the UK



- PAX-D TRD study (n=150) with a target dose of 2.5mg:
 - Demonstrated a large (Cohen's $d=0.87$) reduction in symptoms relative to placebo at 12 weeks
 - High drop-out rate due to AEs

Pramipexole trials showed antidepressant effect, but speed of titration and max dosage limited by nausea/vomiting



MDD study: efficacy at 1mg, and bigger effect at 5mg but dramatic drop-out due to AEs

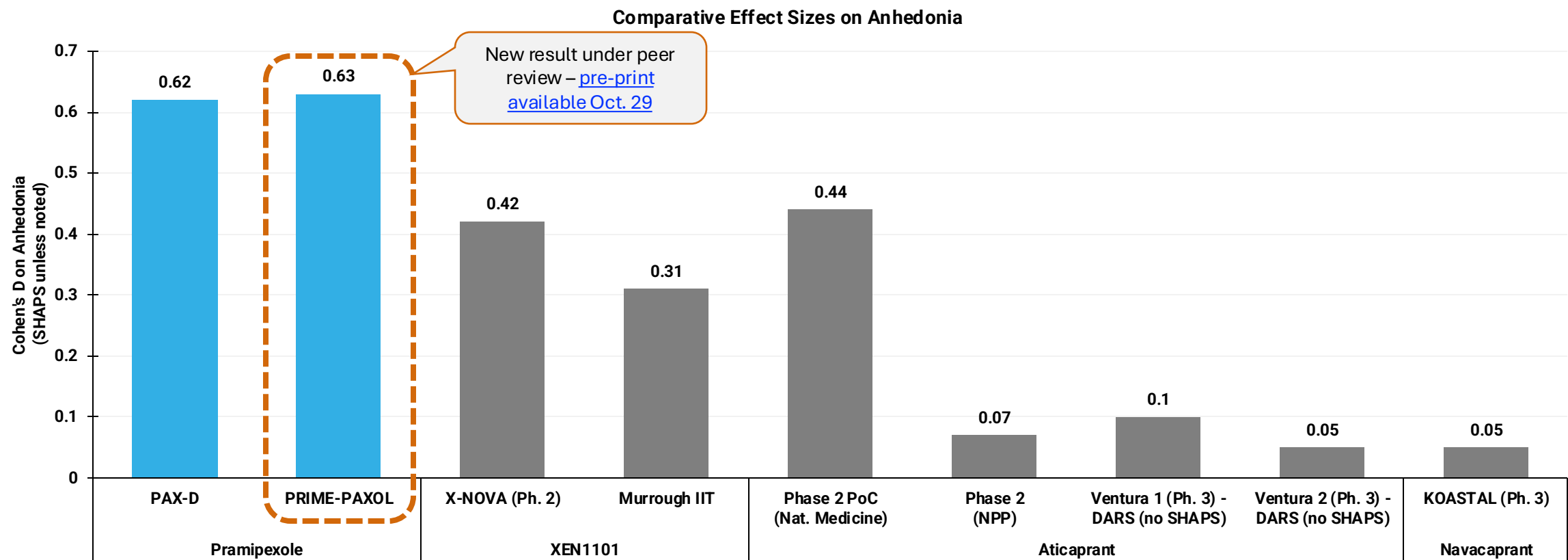
5mg* Δ =7.4

*5mg arm not shown due to 23+% greater dropout than placebo by week 8

Category	Placebo	Pramipexole 0.375 mg	Pramipexole 1 mg	Pramipexole 5 mg
Total number of patients	34 (100)	36 (100)	35 (100)	33 (100)
Number of patients with AEs	28 (82.4)	34 (94.4)	30 (85.7)	31 (93.9)
Nausea	7 (20.6)	9 (25.0)	16 (45.7)	25 (75.8)
Vomiting	2 (5.9)	0	4 (11.4)	13 (39.4)

Adapted from Corrigan, Depression and Anxiety, 2000

Pramipexole has exhibited field-leading effects on anhedonia measures, demonstrating potential to address a critical need in the treatment of depression

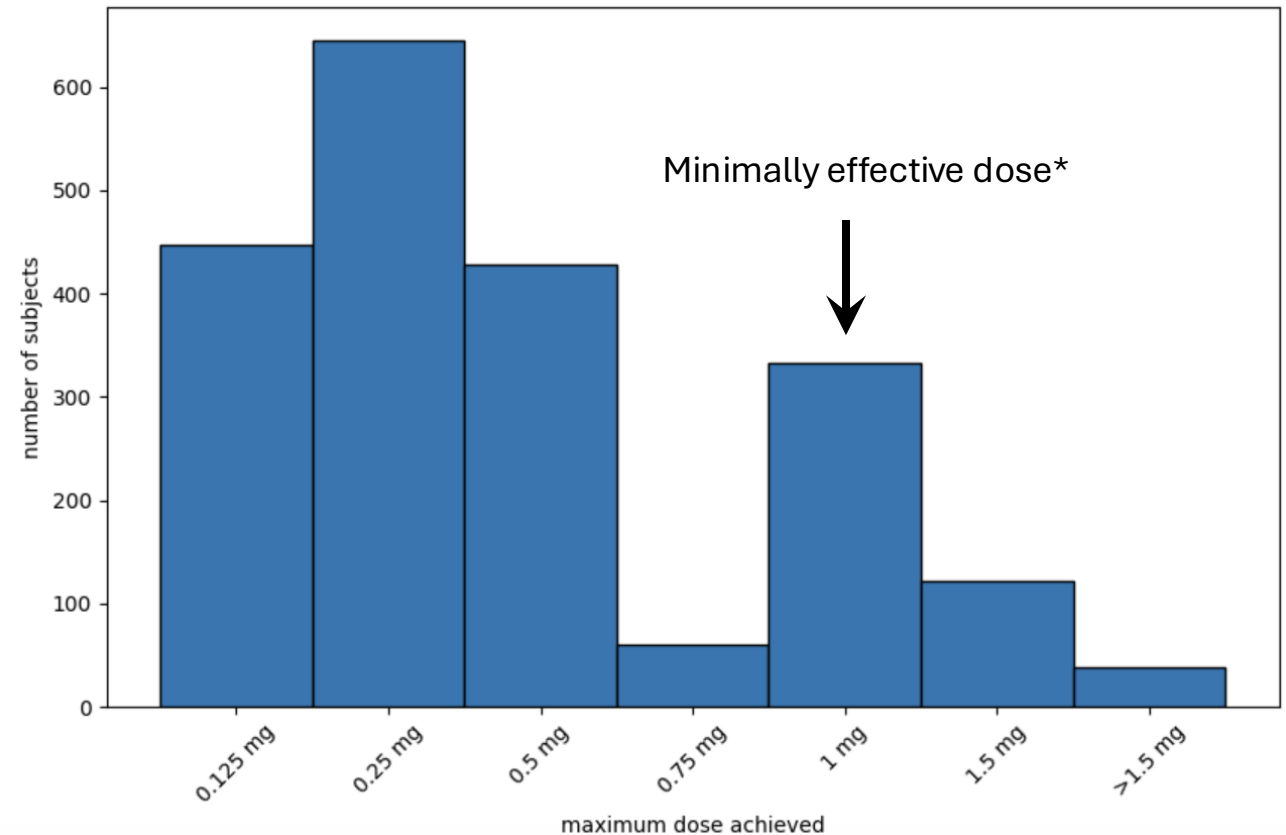


Clear & consistent effects on anhedonia provide strong differentiation and support for ALTO-207

Real world prescribing of pramipexole in MDD shows very slow titration and few get to a therapeutic dose level, limiting use

Data drawn from NIH's *All of Us* dataset (N=633,547), focusing on those with MDD (N=113,666)

- 1.8% treated with pramipexole (N=2,093)
 - 23.7% achieved $\geq 1\text{mg/day}$
 - 1.5% achieved $> 1.5\text{mg/day}$
- Suggests the vast majority of patients are treated with sub-therapeutic doses and very few achieve TRD-level dose targets
- Likely limited by AEs and practical difficulty of titration in clinical practice
- Average time between dose escalation: **273 days**

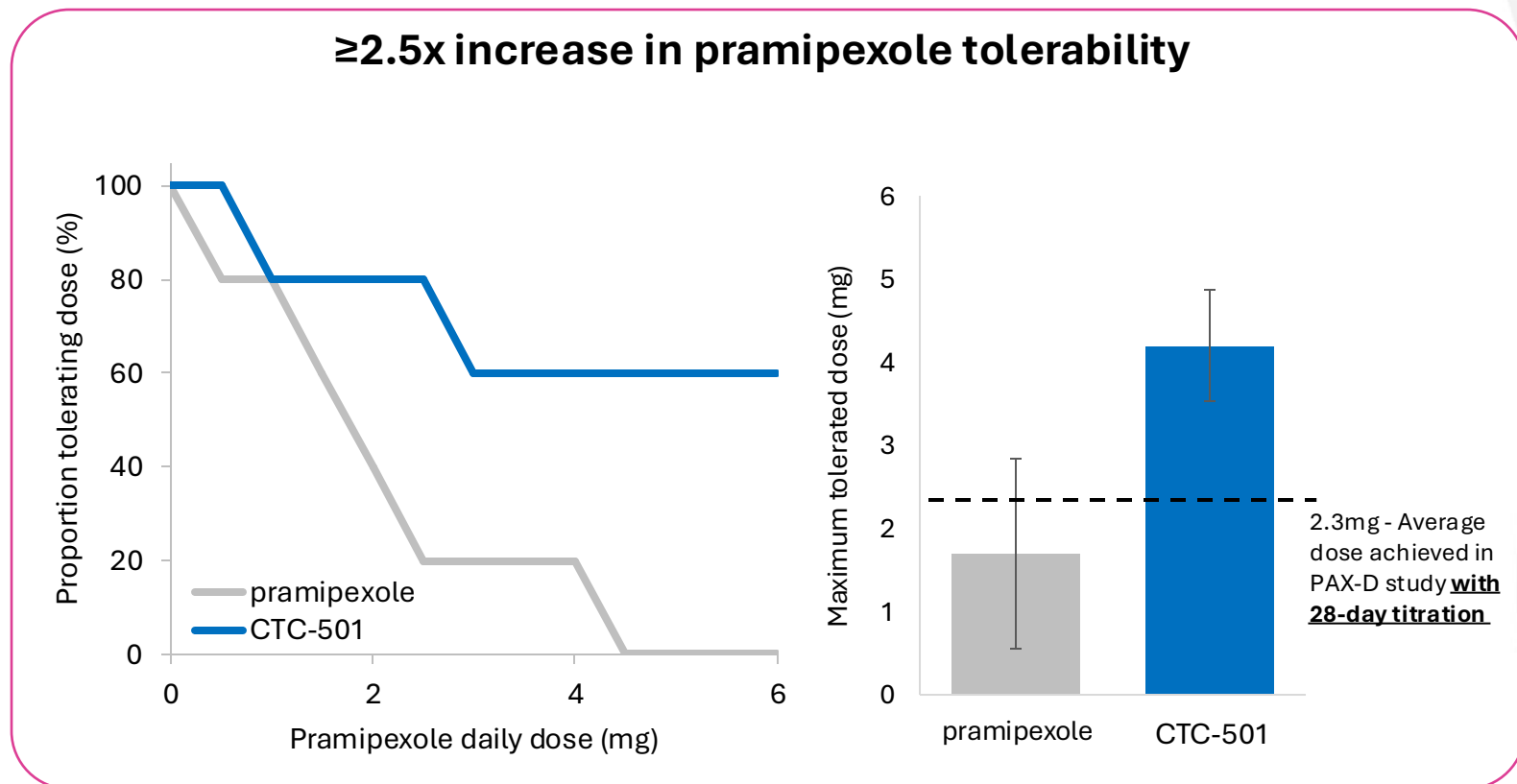


*Cusin et al and Corrigan et al suggest 1-1.5mg is minimally effective dose

CTC-501 (n.k.a. ALTO-207) combination approach achieved higher pramipexole doses faster and more consistently

Novel combination supported by Phase 1* safety data

- Achieved a **2.5-fold or greater increase** in the pramipexole max tolerated dose with addition of ondansetron vs. pramipexole alone
- **60% tolerated max dose of CTC-501** (6mg pramipexole), in 12 days
- Supports more rapid titration to a higher and more consistent dose



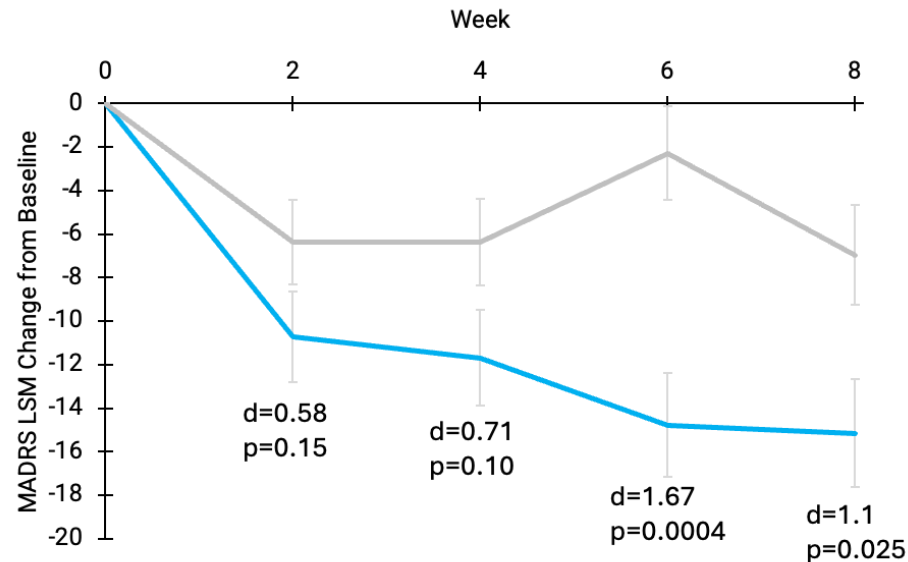
CTC-501 (n.k.a. ALTO-207) development builds on strong clinical evidence of antidepressant effects

Phase 2a: MDD randomized, placebo-controlled trial (N=32)

- Rapid titration to avg of 4.1mg/d pramipexole in 8 days (77% reached max 5mg/d after initial dosing schedule change)
- Moderate-severe MDD (baseline MADRS CTC-501: 28.8; placebo: 28.2)

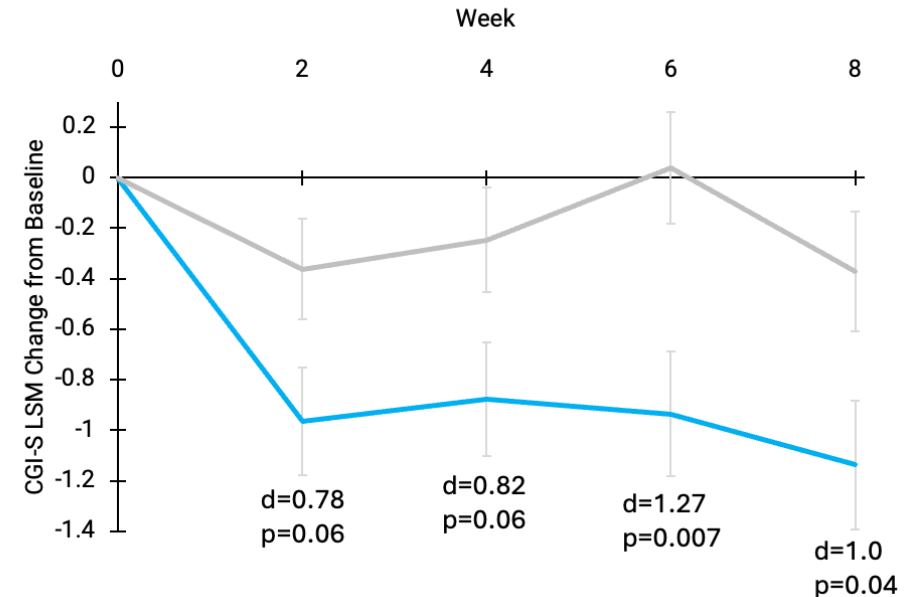
1 CTC-501 demonstrated significantly greater reduction in depressive symptoms compared to placebo

MADRS – Change from Baseline



2 CTC-501 demonstrated significantly greater reduction in illness severity compared to placebo

CGI-S – Change from Baseline



Phase 2a trial of CTC-501 (n.k.a. ALTO-207) in MDD confirmed favorable safety and tolerability profile

Nausea and vomiting were the most common AEs – all were mild to moderate

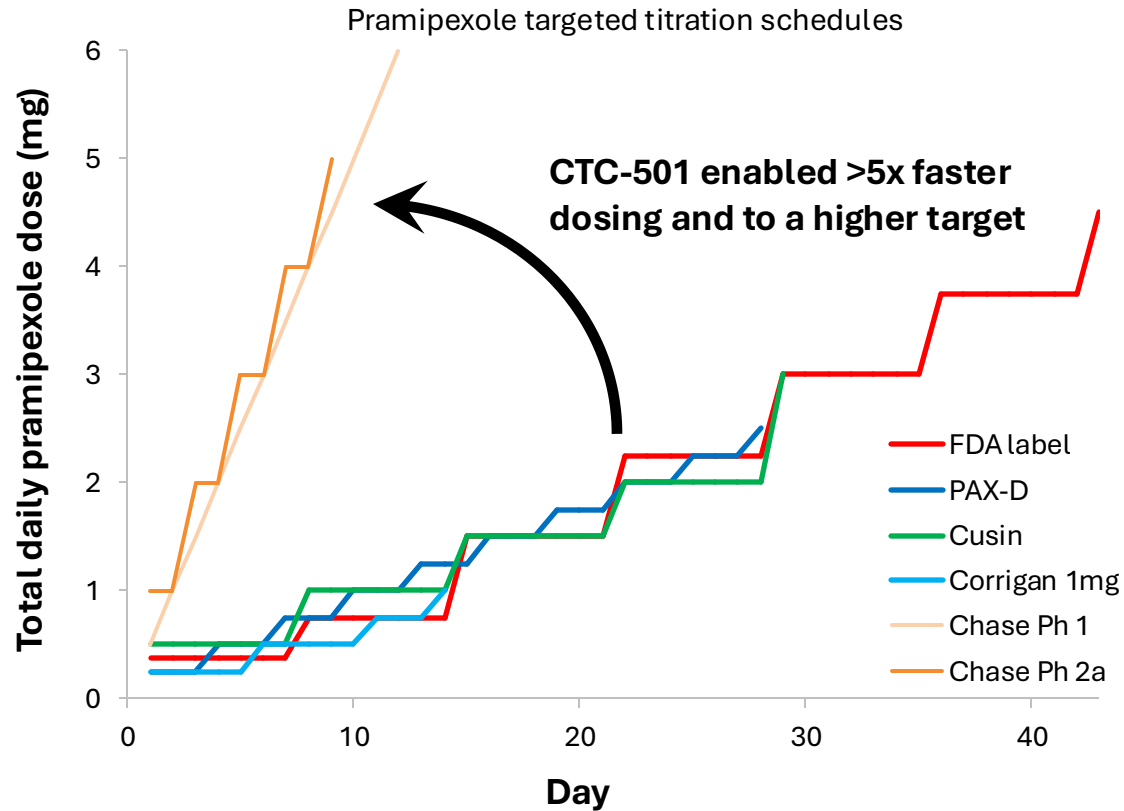
Post-titration AEs*

	CTC-501 (N=13)		Placebo (N=15)	
	Related	Unrelated	Related	Unrelated
Nausea	2 (15%)	2 (15%)	0 (0%)	2 (13%)
Vomiting	1 (8%)	3 (23%)	0 (0%)	2 (13%)
Headache	1 (8%)	0 (0%)	0 (0%)	0 (0%)
Sleepiness	0 (0%)	0 (0%)	0 (0%)	0 (0%)

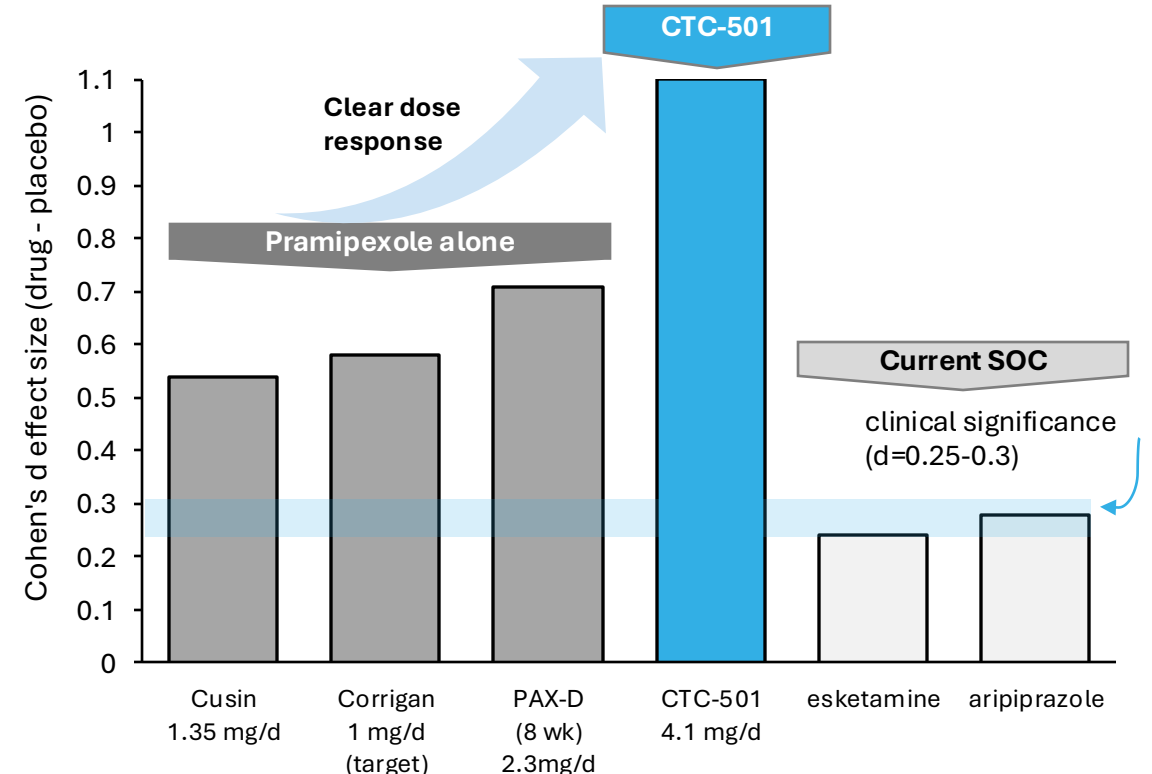
Titration AEs are related to Chase's maximum tolerated dose-based titration schedule, which Alto aims to further optimize in planned future trials

ALTO-207 designed to achieve rapid antidepressant effect

Until CTC-501, all pramipexole depression trials followed the FDA-approved titration schedule



CTC-501 showed the largest clinical effect, with rapid onset due to faster titration with good tolerability



Note: 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-207 positioned for potential Phase 2b/pivotal* success

- ✓ Highly compelling evidence for the clinical effect of pramipexole in TRD, with principal limitation being dose-related intolerability (which motivated development of CTC-501)
- ✓ Completed Phase 1 study demonstrated significantly improved tolerability with 5x faster dose escalation
- ✓ Phase 2a placebo-controlled study met its primary and secondary endpoints, showing large clinical effect sizes
- ✓ Planned collaboration with PAX-D sites, building on their highly successful trial outcome

Alto expects to initiate a Phase 2b (potentially pivotal design*) trial in TRD in 1H 2026 with TLD in 2027

Alto expects to initiate a Phase 3 trial by early 2027

Intended regulatory strategy makes use of biomarkers

Dopamine-related biomarker strategy

- Will focus on both clinical effect and tolerability
- Biomarkers will be pre-specified key secondary measures for the Phase 2b trial and verified in Phase 3 as complementary enrichment markers
- Leverage Alto's dopamine-related EEG and behavioral assessments already employed across studies

Regulatory considerations

- Anticipate a regulatory path with broad TRD approval as well as potential for an enrichment marker to identify patients with even greater effect⁽¹⁾
- Biomarker strategy builds on Alto's FDA interactions on enrichment markers in the ALTO-100 program
- 505(b)(2) regulatory path enables streamlined development and potentially shorter time to commercialization

Novel ALTO-207 product attributes and substantial patient risk deters off-label generic substitution

Key attributes of ALTO-207 that mitigate likelihood of generic substitution

- Strong IP portfolio covering formulation and use protects from generic combination
- Simple dosing & titration regimen
- Single pill/capsule for ease of administration
- Clear evidence of effect of combined product, if approved
- Commercial strategies can mitigate patient out-of-pocket costs and improve access

Prescribing generic components introduces substantial patient & prescriber risk

- Complex regimen of pill combo likely to lead to dosing errors & severe adverse events
- Unproven dose levels with non-standard combinations
- Lack of formulation consistency/quality
- Off-label prescribing creates liability for physicians
- Lack of payer coverage for off-label Rx

Real-world treatment demonstrates lack of generic substitution

Auvelity (combination of bupropion and dextromethorphan) provides clear evidence that off-label combination generic substitution does not impede significant commercial success



Recent success in psychiatry strongly supports combination approach and novel mechanism

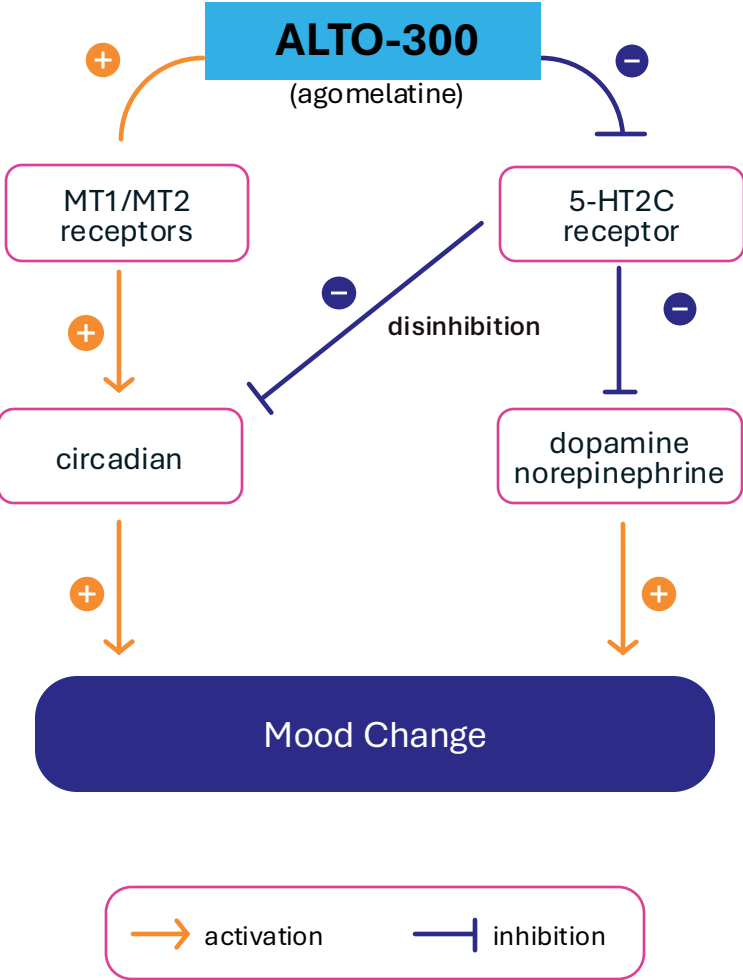
	 COBENFY™ (xanomeline and trospium chloride) capsules 50mg/20mg, 100mg/20mg, 125mg/30mg	 Auvelity™ (dextromethorphan HBr and bupropion HCl) extended-release tablets 45mg/105mg	
Innovation	Antagonistic combination to mitigate AEs in schizophrenia (SZ)	Synergistic combination of two generic medications	Recent combination analogs demonstrate...
Clinical Benefit	Novel MoA in SZ with Cohen's D > 0.5	Novel combination in MDD with similar effect size to existing Tx (d=0.35)	• improved tolerability, • larger effect size, • more convenient dosing, • and novel MoA in disease...
Projected/Est. Peak Revenue*	\$3bn - \$6bn	\$1bn - \$3bn	can result in significant adoption by physicians and substantial commercial success

If clinical effects and tolerability profile remain consistent with observed data, we expect ALTO-207, as a novel combination with a differentiated mechanism in depression, has blockbuster potential

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

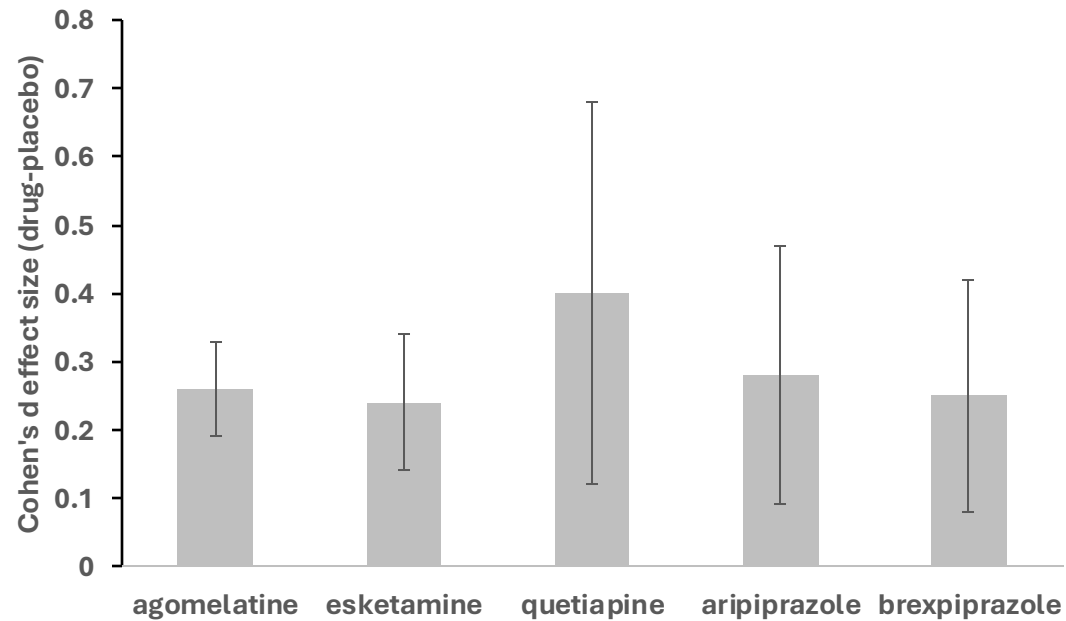
Antidepressant properties	Melatonergic (MT1 and MT2) Agonism	Serotonergic (5-HT2C) Antagonism
Enhancement of dopaminergic input to frontal cortex	+	+ +
Resynchronization of circadian rhythms	+ +	+
Anxiolysis	+	+
Improved sleep quality/patterns	+	+
Lack of weight gain and sexual dysfunction	+	+

Bodinat et al., Nature Reviews, 2010

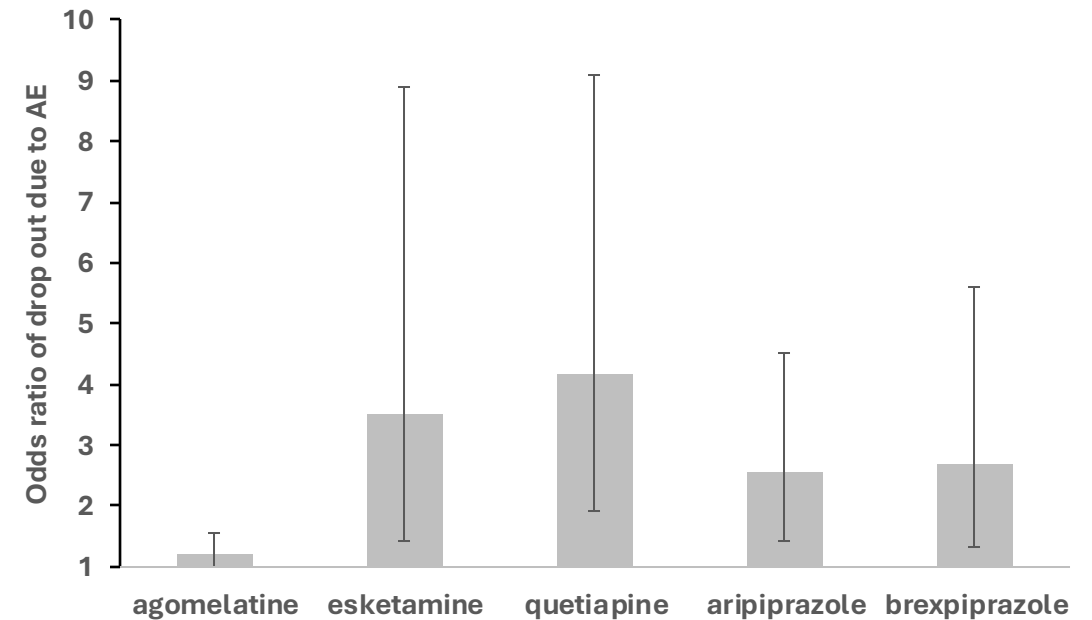
Unique opportunity for ALTO-300 (agomelatine) as an adjunctive treatment in MDD

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



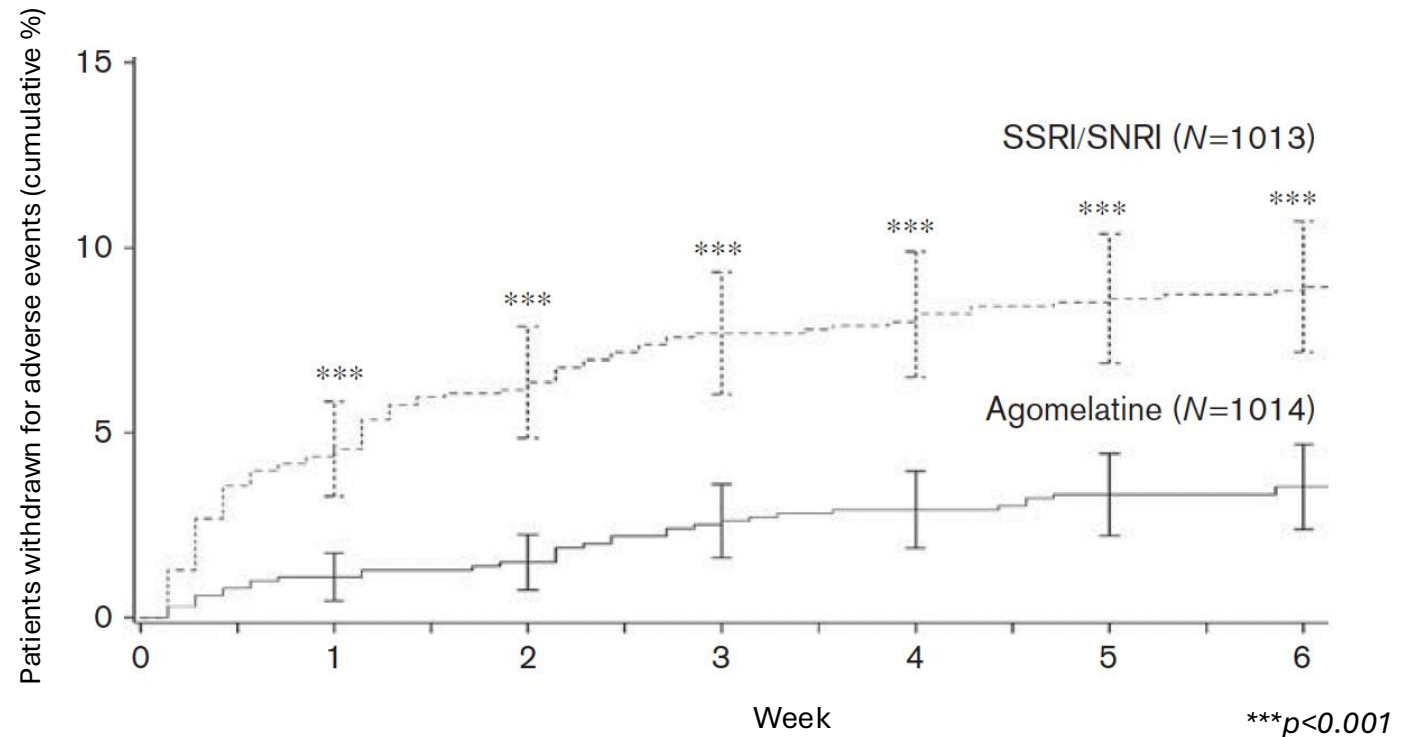
No difference in dropout due to AE in agomelatine, unlike antipsychotics and esketamine

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/SNRIs due to adverse events (pooled analysis of randomized trials)



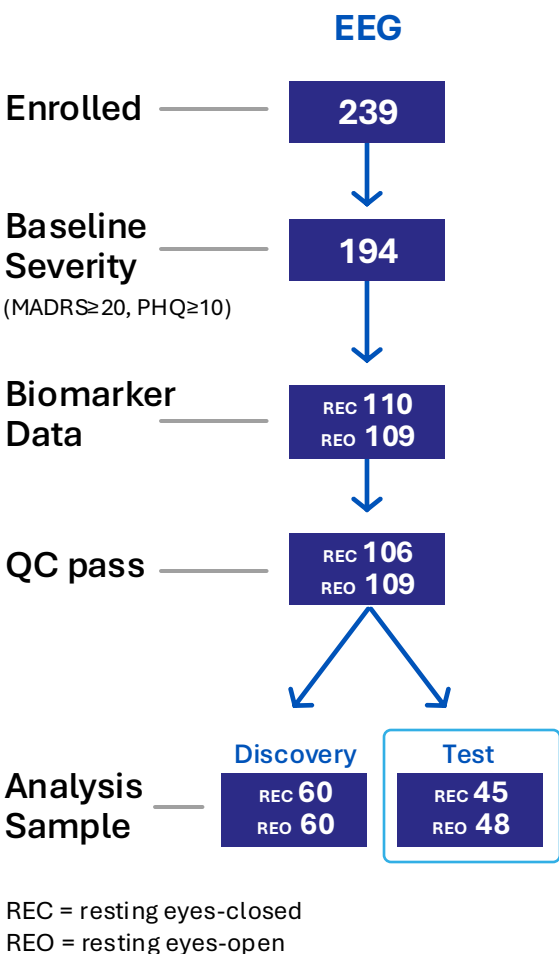
ALTO-300 Phase 2a study design and participant flow

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



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

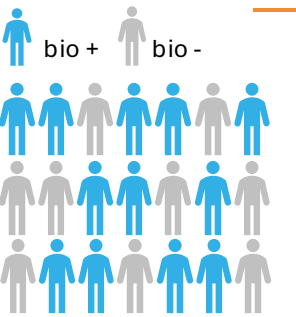
Phase 2A

Phase 2B/3

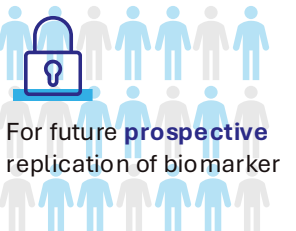
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Determine Biomarker

Clinical Population
is Biologically
Heterogeneous



Discovery Data



Locked & Blinded
Test Data

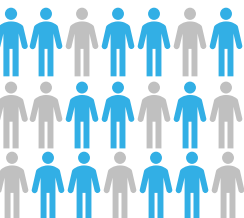
Candidate Biomarker
Identified
Statistical Analysis Plan



02

Prospective
Biomarker Validation

Test Data



Replication:
Bio + > Bio - ?

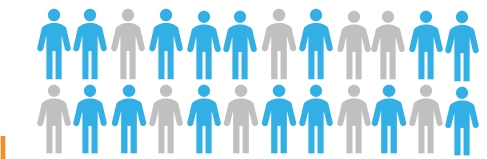
Specific vs. placebo?
vs. standard-of-care?



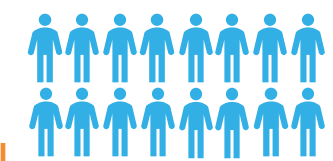
Alto Archival Data

03

Efficacy in
Biomarker +



Enroll based on biomarker



bio +
(primary efficacy population)



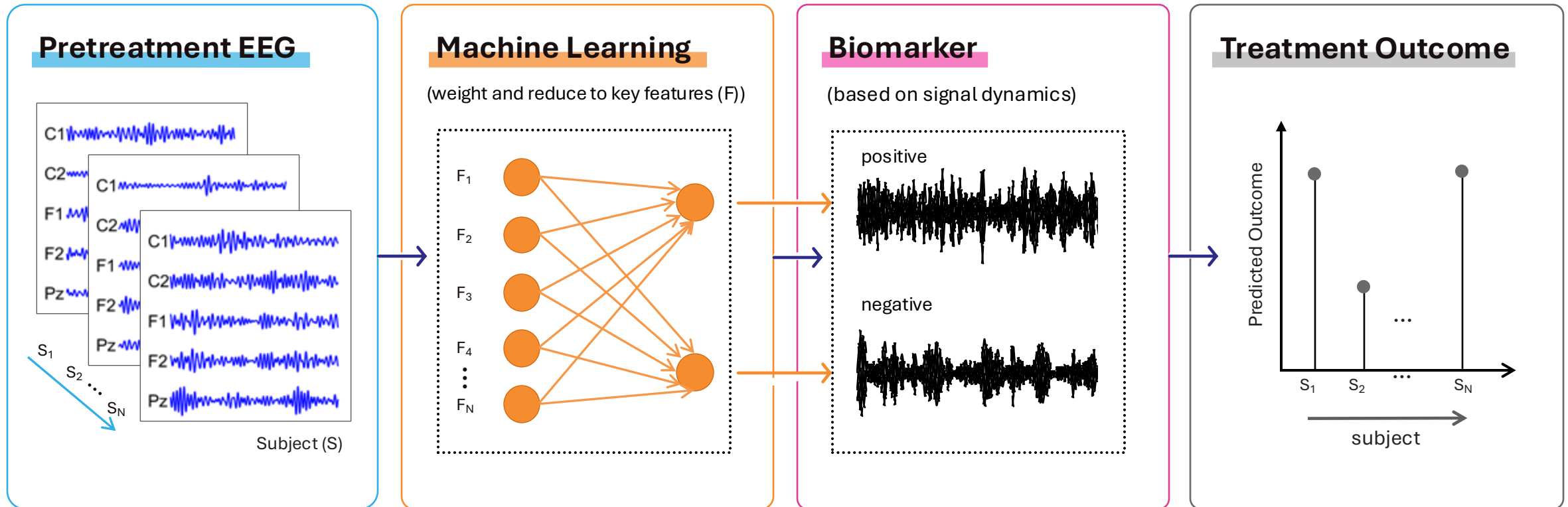
bio -



Efficacy:
Drug > PBO in Bio +?

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



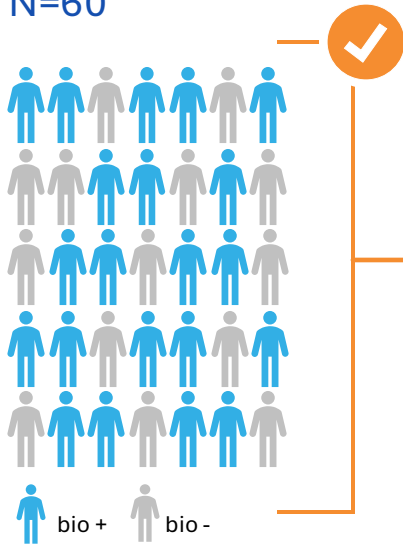
The biomarker is calculated from a single electrode and automatically scored, facilitating scalability

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

01

Determine Biomarker

N=60



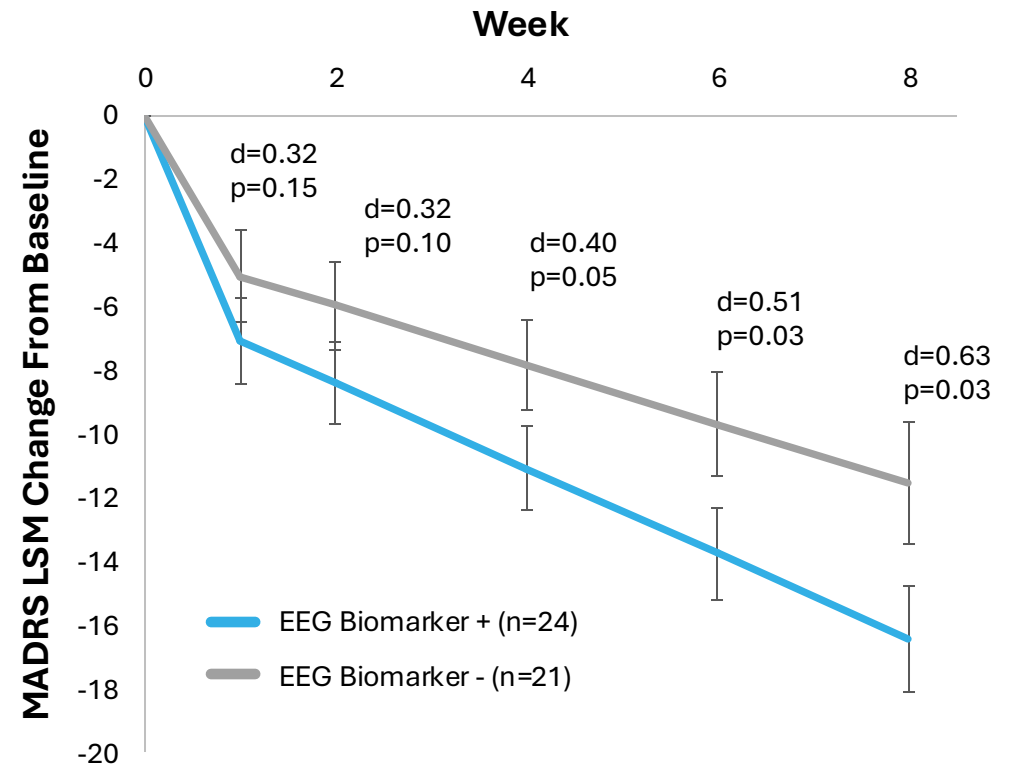
02

Prospective Biomarker Validation

N=45



Prospective Replication in Test Dataset

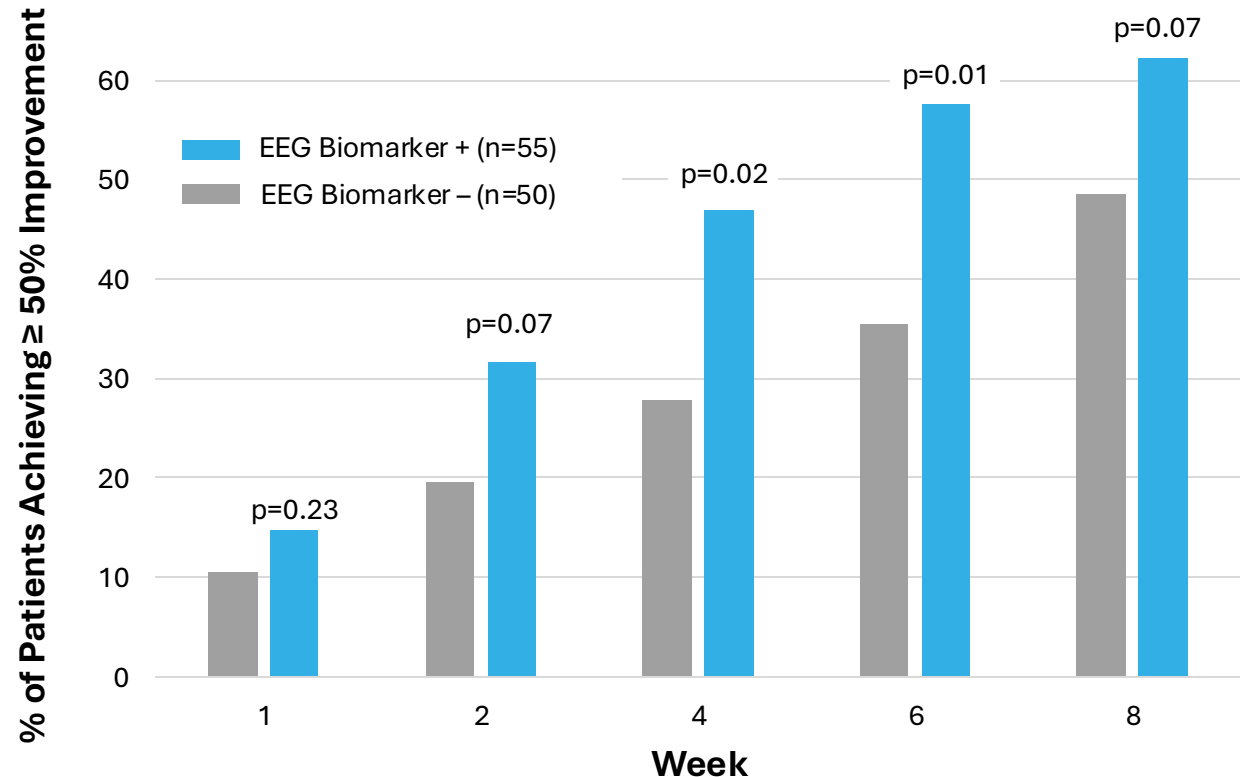


1. Identified EEG signature as predictive
2. Prospectively label patients as bio+/-

Biomarker positive patients derived greater benefit from ALTO-300

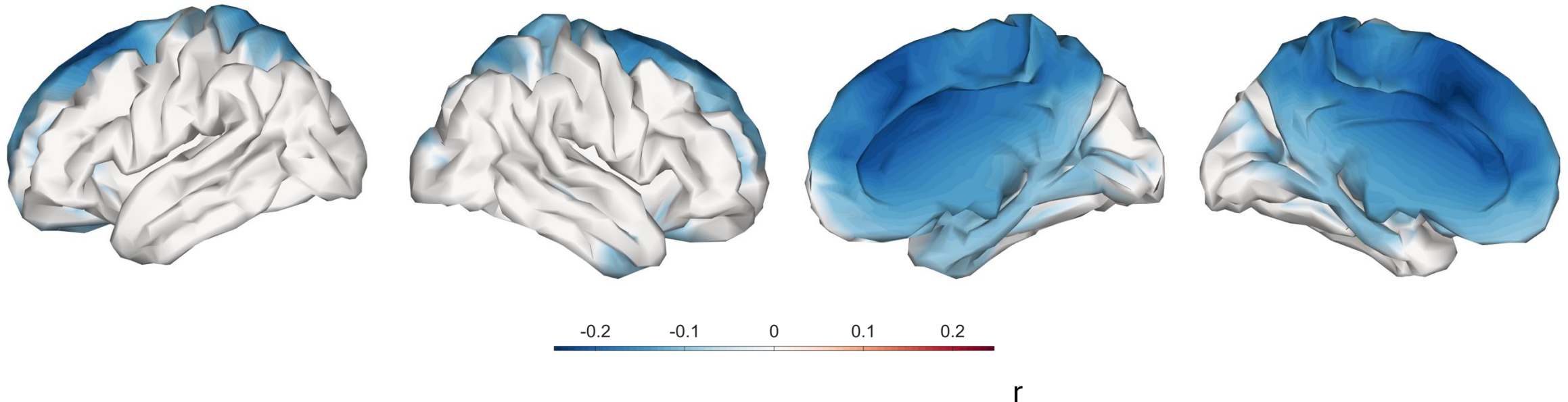
EEG biomarker positive patients observed to achieve more robust clinical response to ALTO-300

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



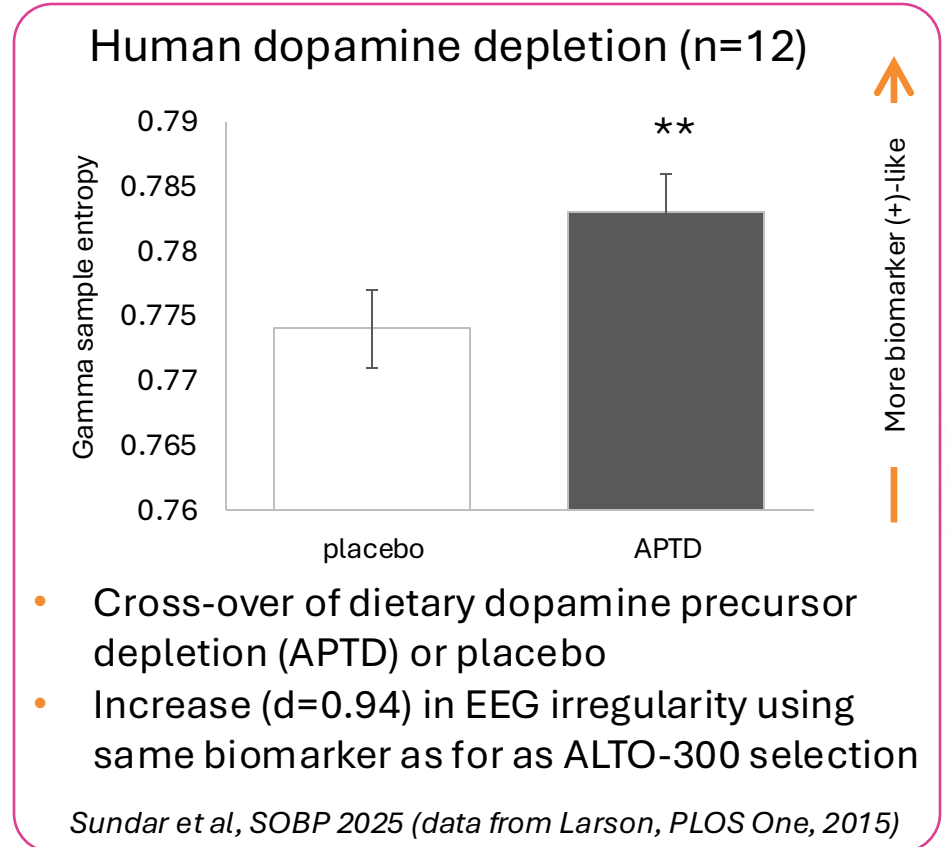
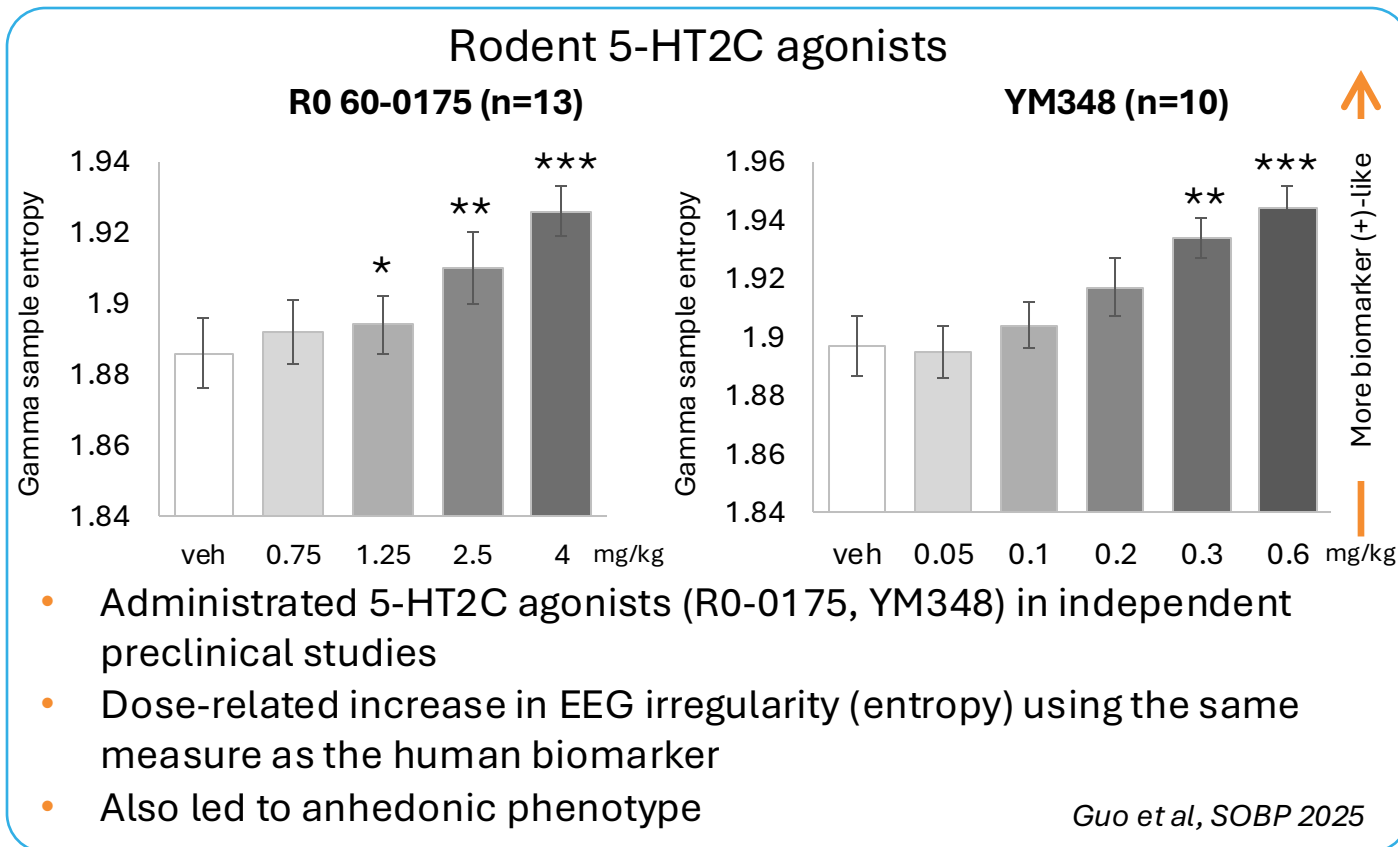
ALTO-300 biomarker: a measure of reduced neural signaling stability

- 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



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

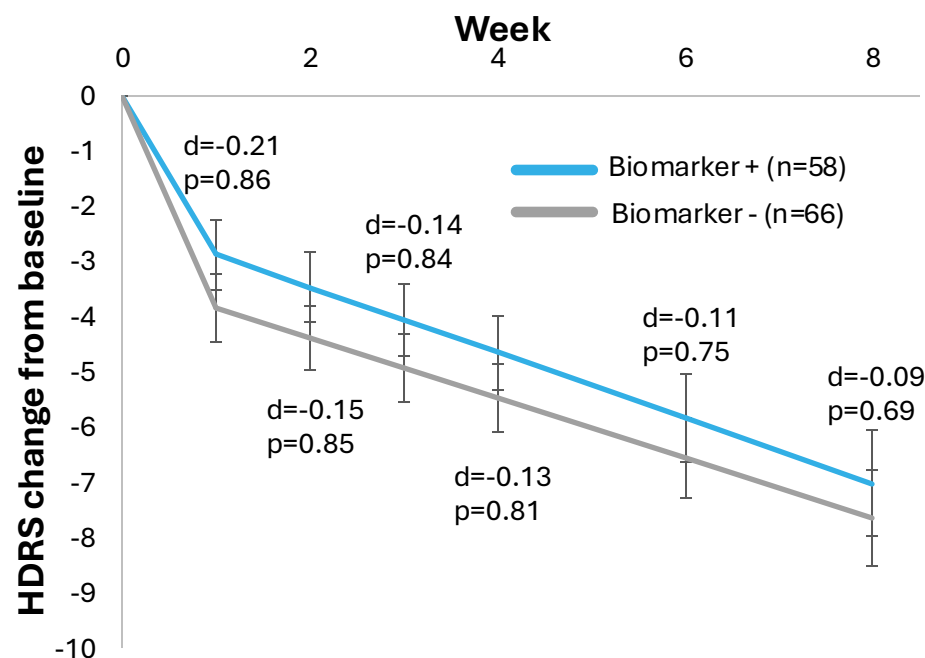
- The biomarker signal reflects increased neural variability, which dopamine acts to reduce
- ALTO-300's MOA includes 5-HT_{2C} antagonism and leads to an increase in dopamine
- Studies test mechanistic link between ALTO-300's EEG biomarker and 5-HT_{2C}/dopamine activity: **increased 5-HT_{2C} activity (which reduces dopamine) or directly depleting dopamine drives the ALTO-300 response biomarker**



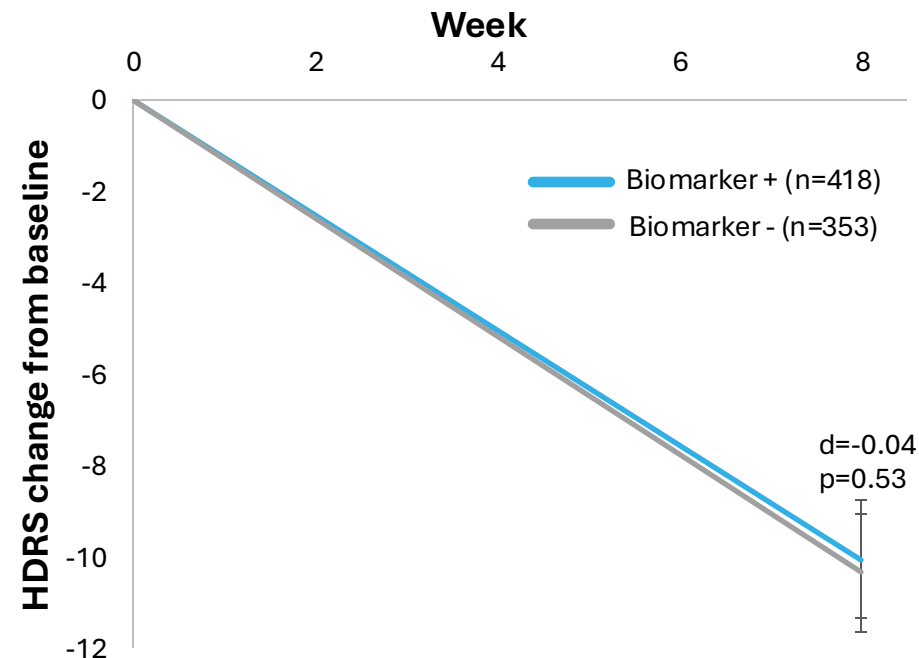
EEG model prediction is specific to ALTO-300 as it does not predict greater placebo or SSRI/SNRI response

Apply the ALTO-300 EEG biomarker to:

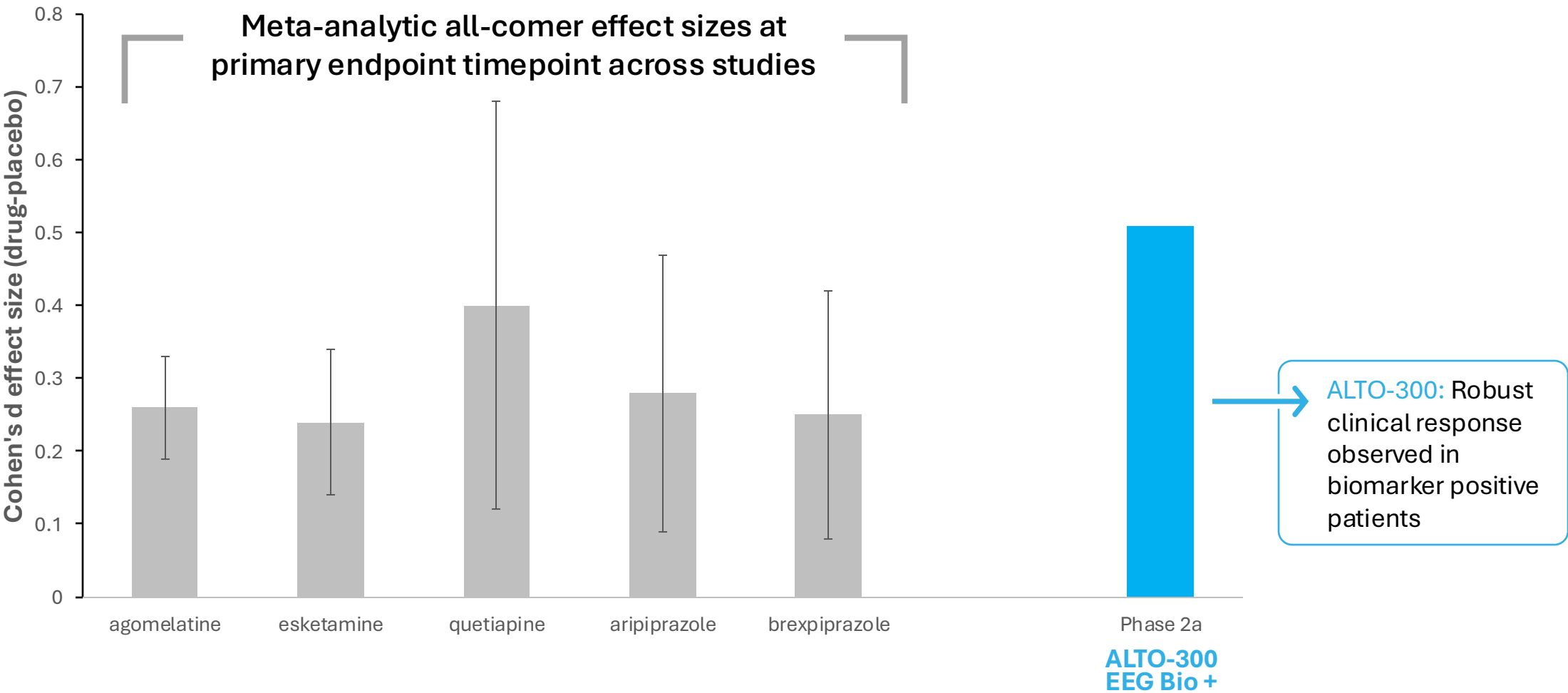
Placebo-Treated Patients



SSRI/SNRI-Treated Patients



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



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

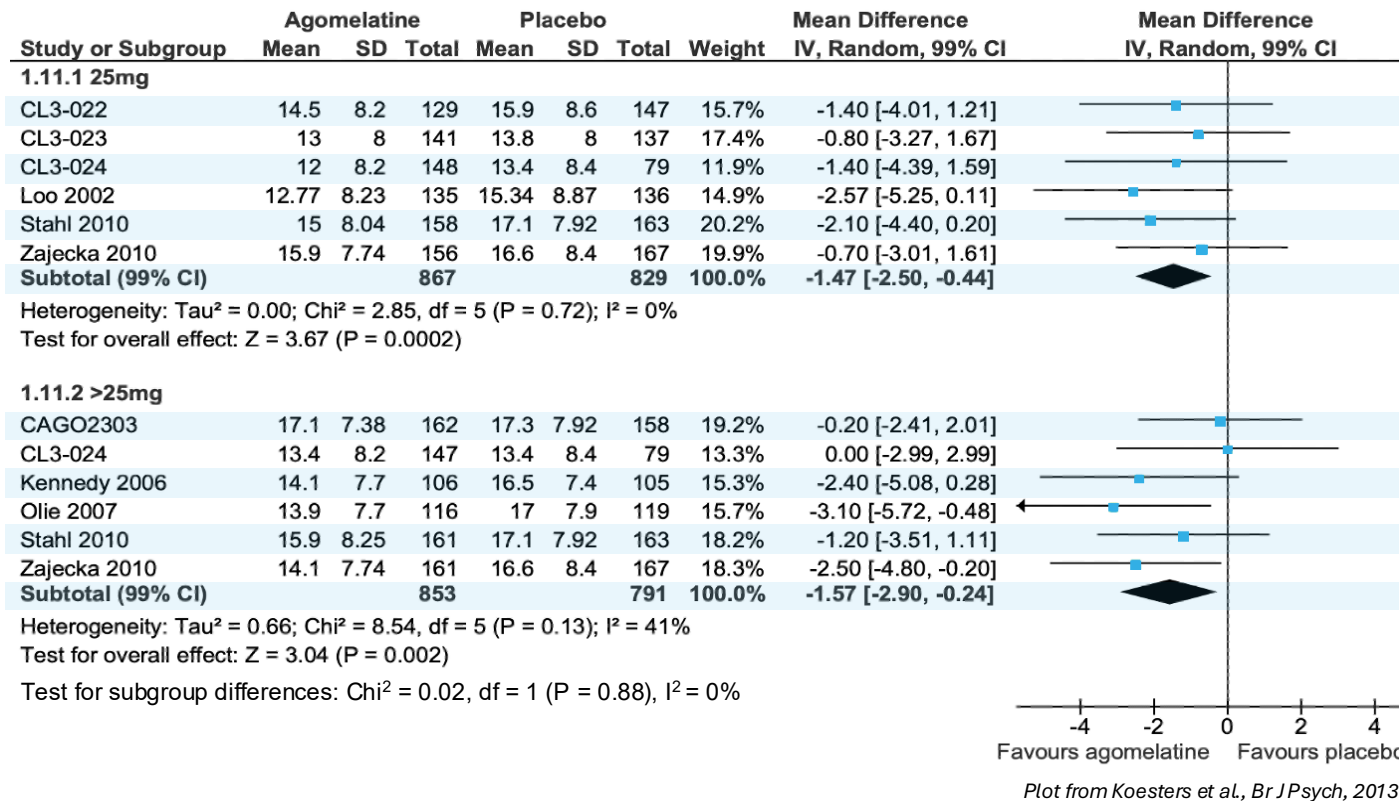
	N (%)
Headache	35 (14.6)
Nausea	18 (7.5)
Dyspepsia	15 (6.3)
Insomnia	15 (6.3)
COVID 19 Infection	14 (5.9)
Rash (10 from wearable)	12 (5.0)

TEAEs consistent with prior agomelatine studies

ALTO-300 at 25mg maintains efficacy while avoiding LFT elevation

We selected the 25mg dose as meta-analyses show similar efficacy as 50mg

25mg and 50mg approved in EU/Australia



Placebo-like LFT rate for 25mg

✓ Novartis US studies showed placebo-like LFT rate with 25 mg:

- **25mg:** 0.3%
- **Placebo:** 0.3%
- **50mg:** 3.7%

✓ Alto's Phase 2a showed no LFT elevation (>3x ULN)

✓ Even when LFTs increase (mainly 50mg), they are reversible and do not result in liver failure

Agomelatine concerns are more historical/contextual, not clinically meaningful, and less frequent than with antipsychotics (adjunctive MDD comparator drugs)

Large-scale and real-world use demonstrates agomelatine-induced LFT elevation is low and adaptive

Acute studies using the 25mg dose (n=4,957) shows placebo-like LFT rate consistent with Alto's Phase 2a results where no patient exceeded >3x ULN (even with baseline allowance of up to 2x ULN)

Agomelatine safety supported by low LFT elevation rate following long-term use

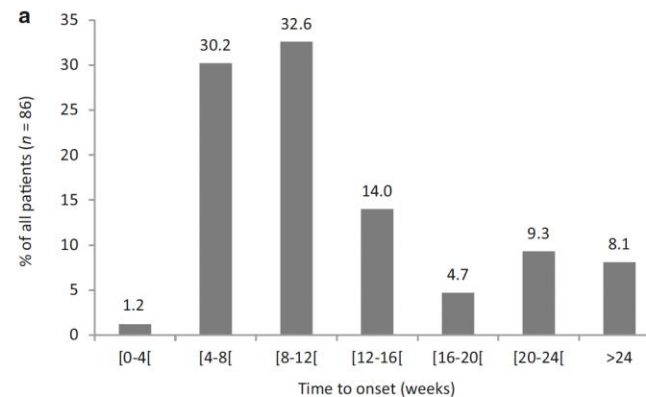
- VIVALDI real-world evidence: Patients (n=3,317) treated with 25-50mg agomelatine over 12 weeks demonstrated very low rates of LFT elevation (~0.2%; *Laux et al., Pharmacopsychiatry, 2012*)

No difference in the rate of acute liver injury in agomelatine patients (n=74,440) versus conventional SSRI citalopram (n=782,812), following long-term use

- Even observed a trend in the dataset that suggests less of a risk of acute liver injury with agomelatine vs. citalopram as comparator antidepressant (*Pladevall-Vila et al., CNS drugs, 2019*)

Analysis of patients treated with agomelatine (25 or 50mg/day) demonstrated effects of LFTs are adaptative (n=7,605)

- Onset of LFT elevation at any dose (mainly driven by 50mg) occurred early, before 12 weeks in 64 % of patients and was not cumulative
- Withdrawal of agomelatine led to rapid recovery. The median time to recovery (to $\leq 2x$ ULN) was 14 days following treatment withdrawal
- Liver function tests recovered in 36 % of patients despite continuation of agomelatine
- No cases of acute liver failure or fatal outcome occurred



Perlemuter et al., CNS Drugs, 2016

LFT monitoring not expected for ALTO-300 label

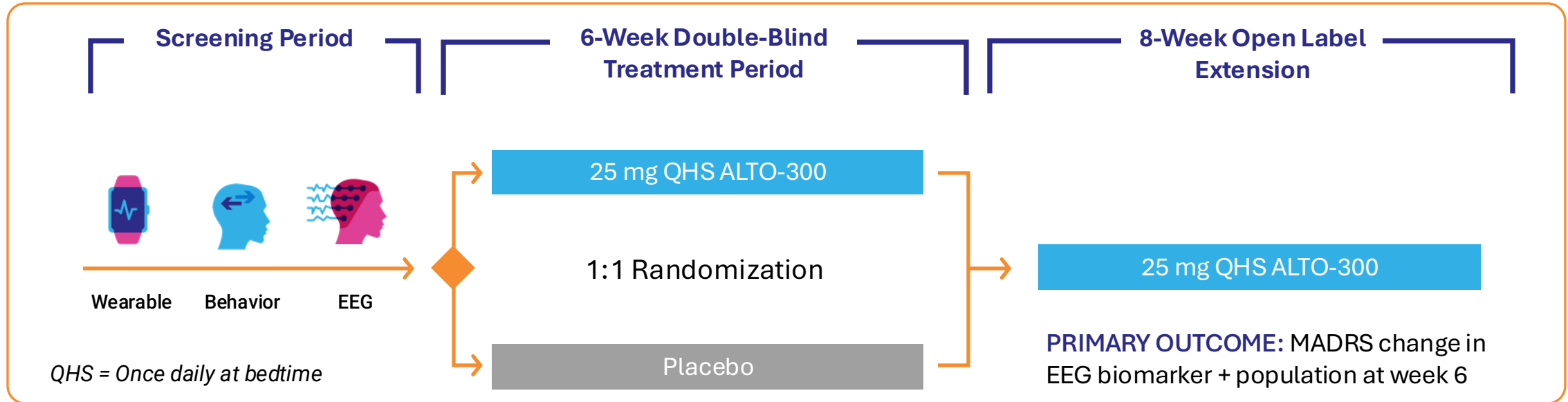
LFT monitoring not required for approved antipsychotics despite higher rate of LFT elevation, which is expected to guide the label for ALTO-300

- Approved antipsychotics shown to induce LFT elevation at greater rates (comparable or higher than 50mg agomelatine) and occasionally result in severe or fatal hepatic injury (*Marwick et al., Clin Neuropharm, 2012*)

Extensive long-term safety and real-world evidence builds **confidence** in lack of liver signal for selected 25mg dose of ALTO-300

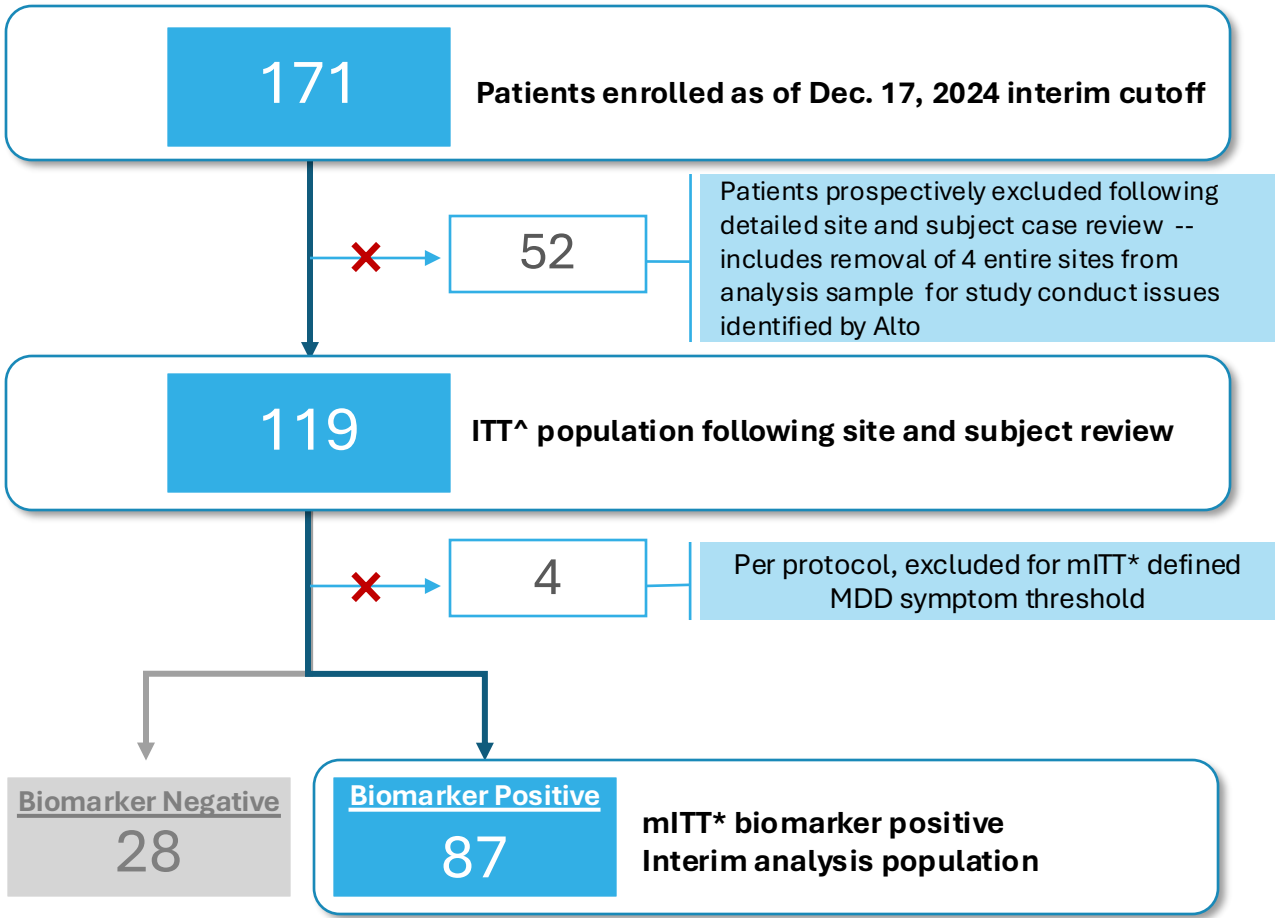
ALTO-300 Phase 2b biomarker-guided trial in MDD

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

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



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 $p \leq 0.005$ results in final analysis success threshold of $p < 0.049$

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



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

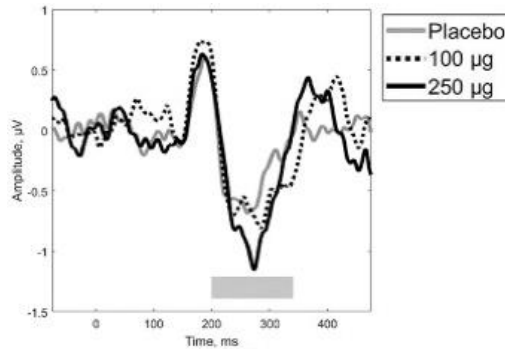
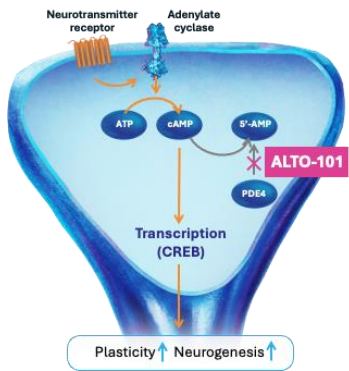
ALTO-101

Development for CIAS

ALTO-101, a novel PDE4 inhibitor, in development for CIAS with a validated mechanism and demonstrated pro-cognitive activity

1 PDE4i represents a historically validated mechanism to address cognition

PDE4 inhibition has shown clear pro-cognitive effects in humans (including CIAS)

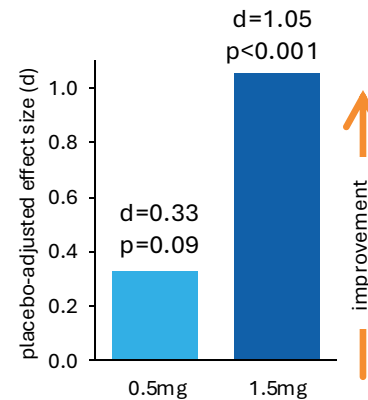


Gilleen et al., J Psychopharm, 2020

Historical roflumilast studies provide external support for ALTO-101 in cognition and EEG

2 Direct effects on best EEG biomarker of CIAS

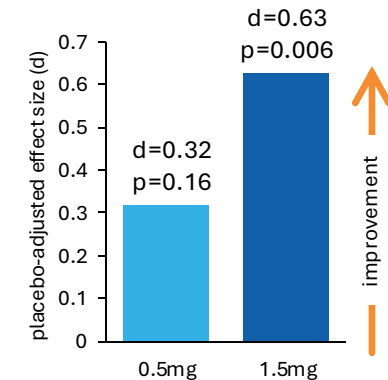
Theta response (placebo adjusted)



ALTO-101 has demonstrated statistically significant effects vs. placebo on Theta response in Phase 1

3 ALTO-101 has demonstrated clear pro-cognitive effects in humans

Processing speed (placebo-adjusted)



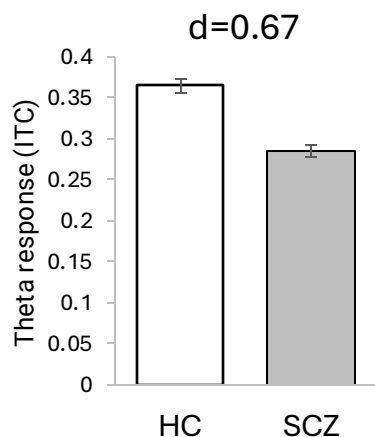
Good correlation between theta response & cognition, supported by ALTO-101 effects on cognition in human Phase 1 study

Ongoing POC study: theta response EEG (primary) and cognition (secondary)

Theta EEG response is the best index of CIAS pathophysiology

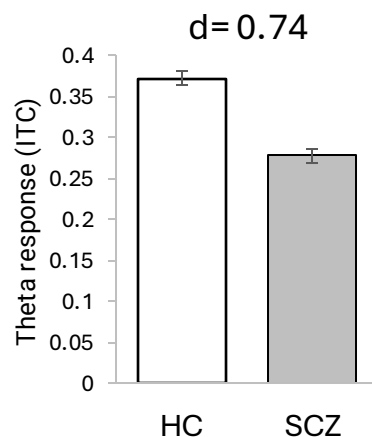
- **EEG biomarkers indexing cognition-relevant neural circuitry** have been extensively studied in schizophrenia
- They provide a biological measure of the processes accounting for disorder pathophysiology
- Alto put all established biomarkers head-to-head

Discovery dataset



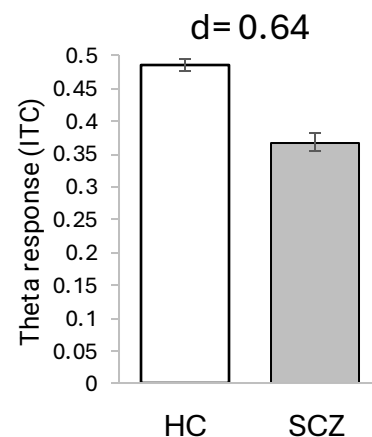
Schizophrenia (SCZ) N=257; Healthy (HC) N=251

Replication dataset #1



Schizophrenia (SCZ) N=251; Healthy (HC) N=236

Replication dataset #2



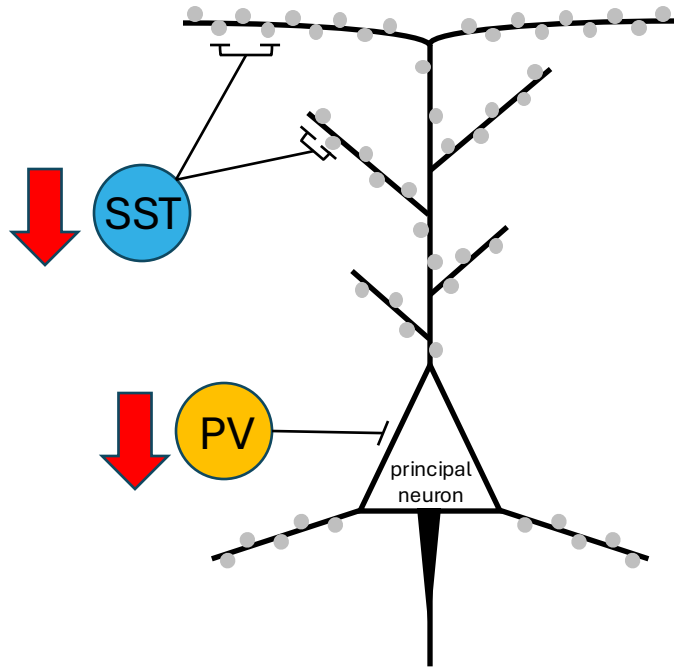
Schizophrenia (SCZ) N=128; Healthy (HC) N=241

In each dataset:

- **Theta response was more sensitive than all other EEG biomarkers**, including the most commonly-used; mismatch negativity (MMN)
- Largest **case-control** difference
- Strongest **correlation with cognitive deficit**

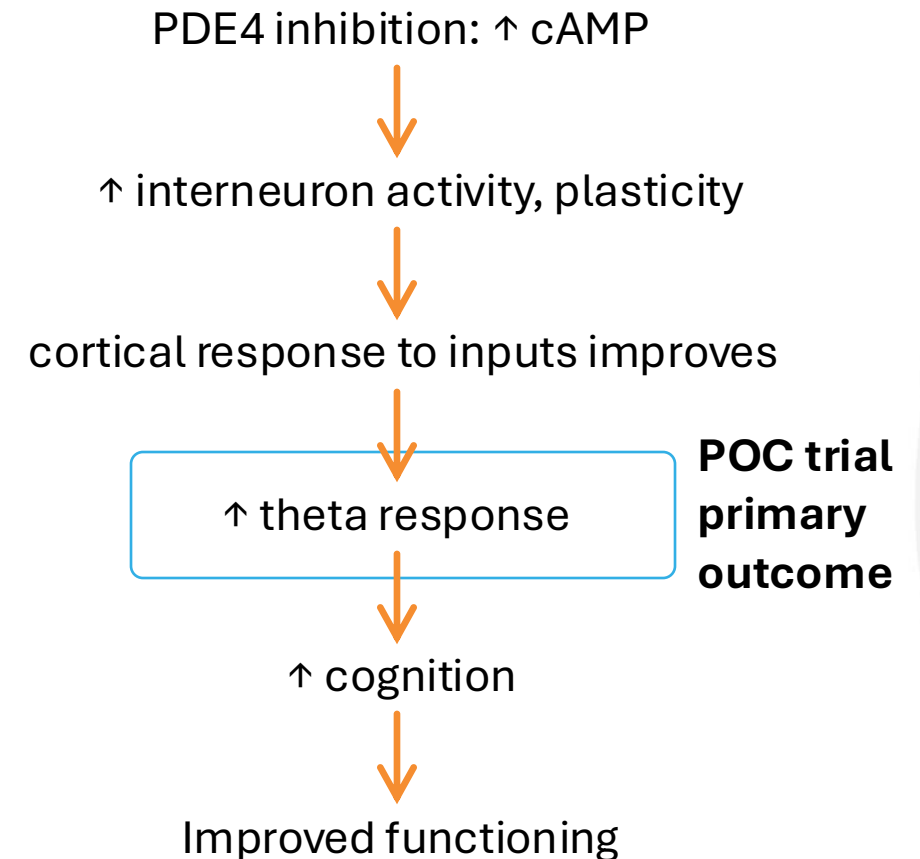
Theta response in the ALTO-101 POC study: linking biology of CIAS to drug mechanism and clinical meaningfulness

Cortical circuit disruptions in schizophrenia



- Post-mortem data in schizophrenia consistently shows a reduction in cortical inhibitory interneurons (especially somatostatin [SST] and parvalbumin [PV] types)
- SST generate theta; PV generate gamma (both reduced in patients)
- Reduction in SST or PV neurons leads to cognitive deficits
- **EEG theta response is an index of interneuron functioning**

ALTO-101 impacts key cognitive circuitry

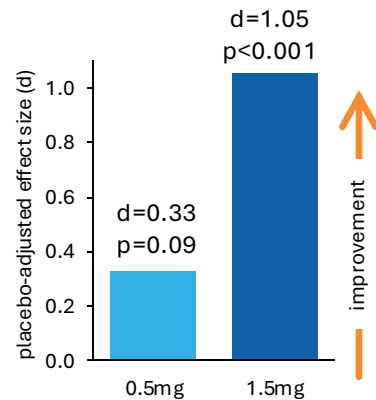


ALTO-101 improves theta response, and with it, cognition

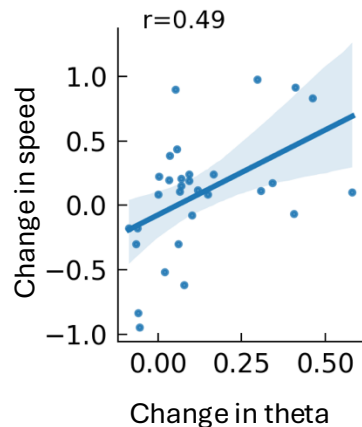
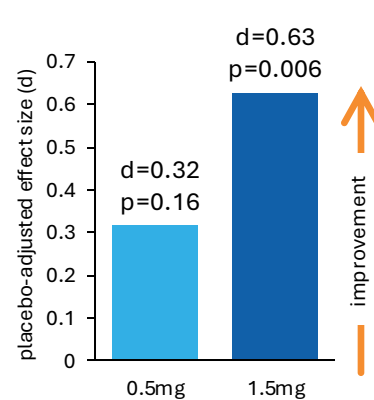
ALTO-101 Phase 1 data (N=40, healthy volunteer, crossover)

Dose-dependent increase in theta response and processing speed

Theta response (placebo adjusted)



Processing speed (placebo-adjusted)

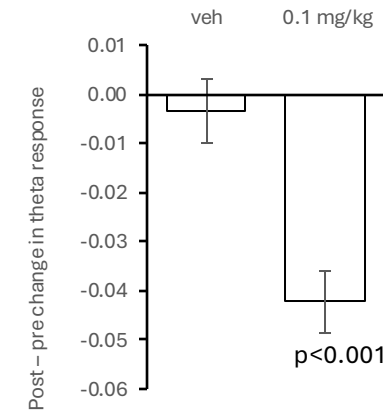


Greater increase in theta response by ALTO-101 correlates with greater improvements in processing speed

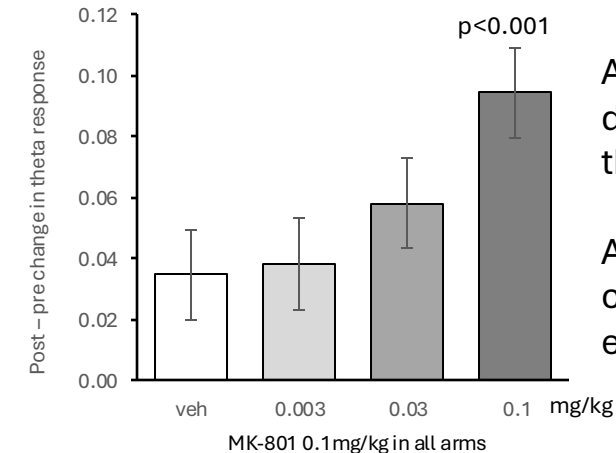
Processing speed is the most impaired cognitive domain in CIAS and is associated with disability

ALTO-101 preclinical data

Dose-dependent increase in theta response mirrors humans



MK-801, an NMDA antagonist used to model schizophrenia, reduces theta EEG response



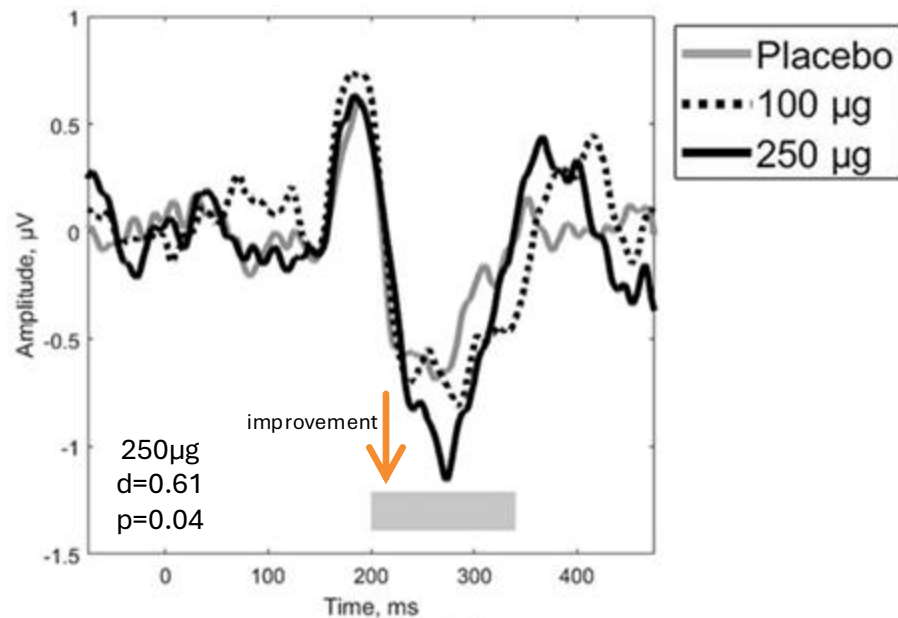
ALTO-101 dose-dependently rescues the MK-801 deficit

ALTO-101 improves cognition in separate experiments

Additional evidence for PDE4 inhibition targeting of cognition and its neural circuitry in humans (including CIAS)

8-day crossover in 18 patients w/ CIAS using roflumilast (PDE4i)

Demonstrated significant improvement in the mismatch negativity, a commonly-used EEG biomarker reduced in patients



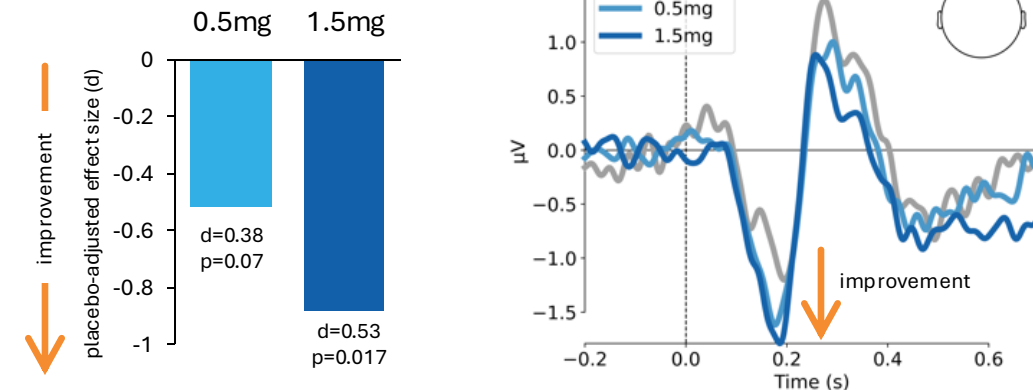
Gilleen et al., *J Psychopharm*, 2020

Significant improvement in verbal memory with 250µg roflumilast as well (d=0.77, p=0.044; Gilleen et al, *Psychopharm*, 2018)

ALTO-101 Phase 1 data (N=40, healthy volunteer, crossover)

Dose-dependent increase in mismatch negativity

Mismatch negativity (placebo-adjusted)

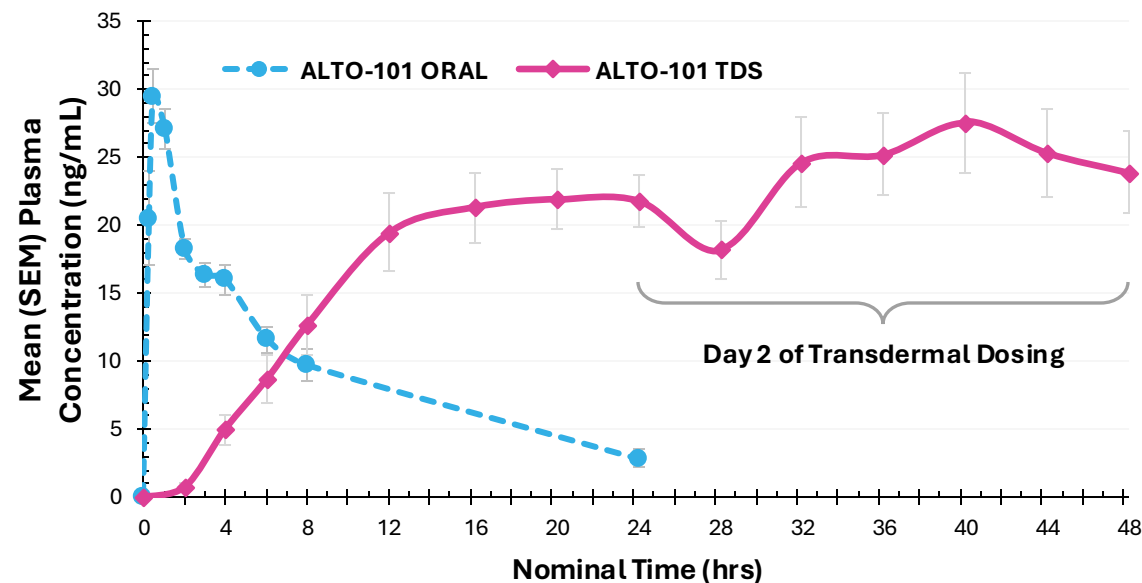


Roflumilast also improves memory in:

- Older healthy volunteers (Blokland et al, *Neurobiol of Aging*, 2019)
- Younger healthy volunteers (Van Duinen et al, *Neuropharmacology*, 2018)

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** adherence properties. No application site reactions that led to patch removal or intolerance.
- **Allows** QD dosing in trials (vs. BID or TID for oral)



	ALTO-101 Oral Formulation (N = 15)	ALTO-101 TDS Formulation (N = 14)
Related Adverse Events >5%		
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

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:

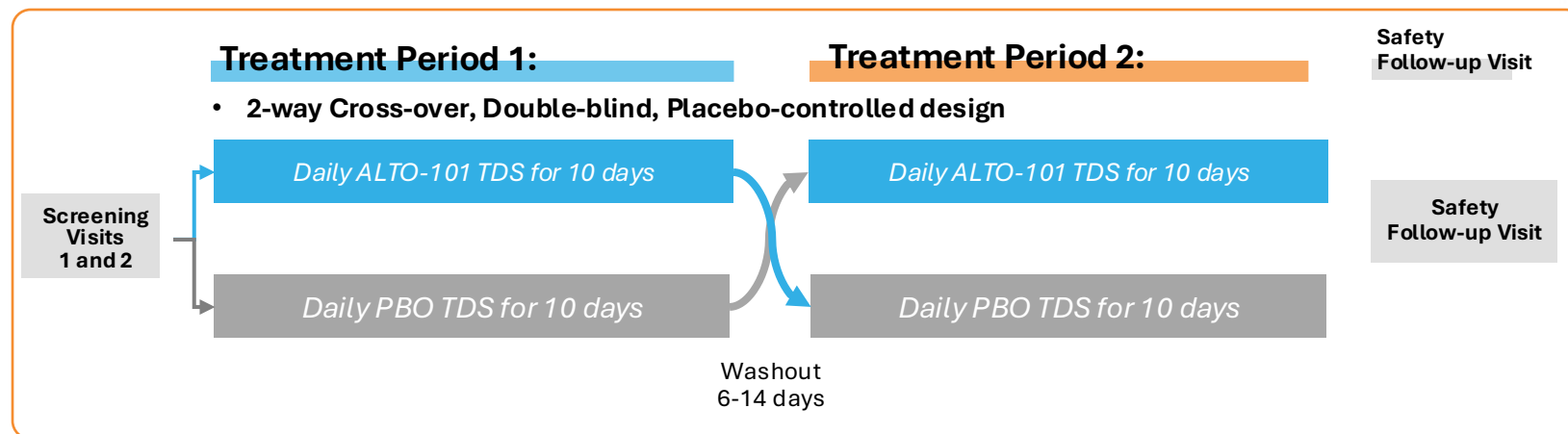
A two-way crossover, double-blind, placebo-controlled study with ALTO-101 and placebo:

Treatment Periods 1 + 2:

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

Number of participants:

60-70 completers
(two dosing periods each)



Primary outcome: Theta response

Other outcome measures: Cognition (processing speed, memory), PK, safety, tolerability

Proof-of-concept study is designed to provide clear understanding of effects on well characterized EEG markers and cognitive performance

Topline data readout expected 1Q 2026

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



\$0.3bn

2021 SALES



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



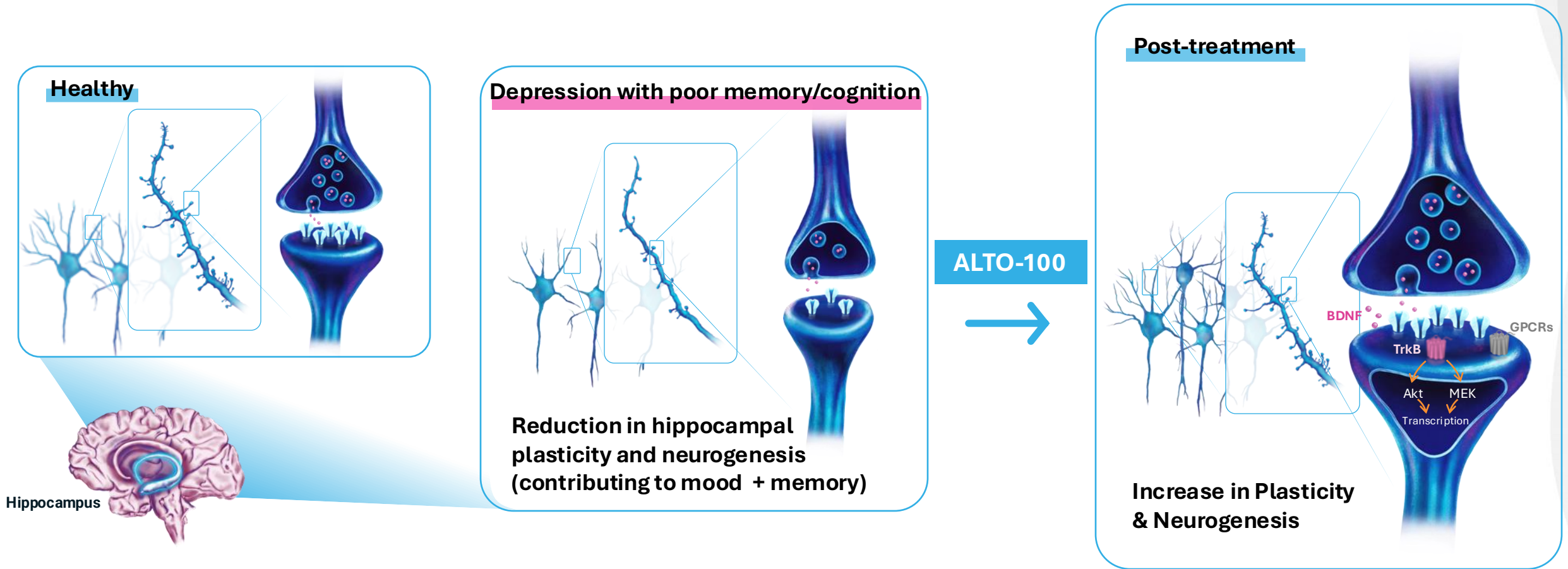
CNS

- 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

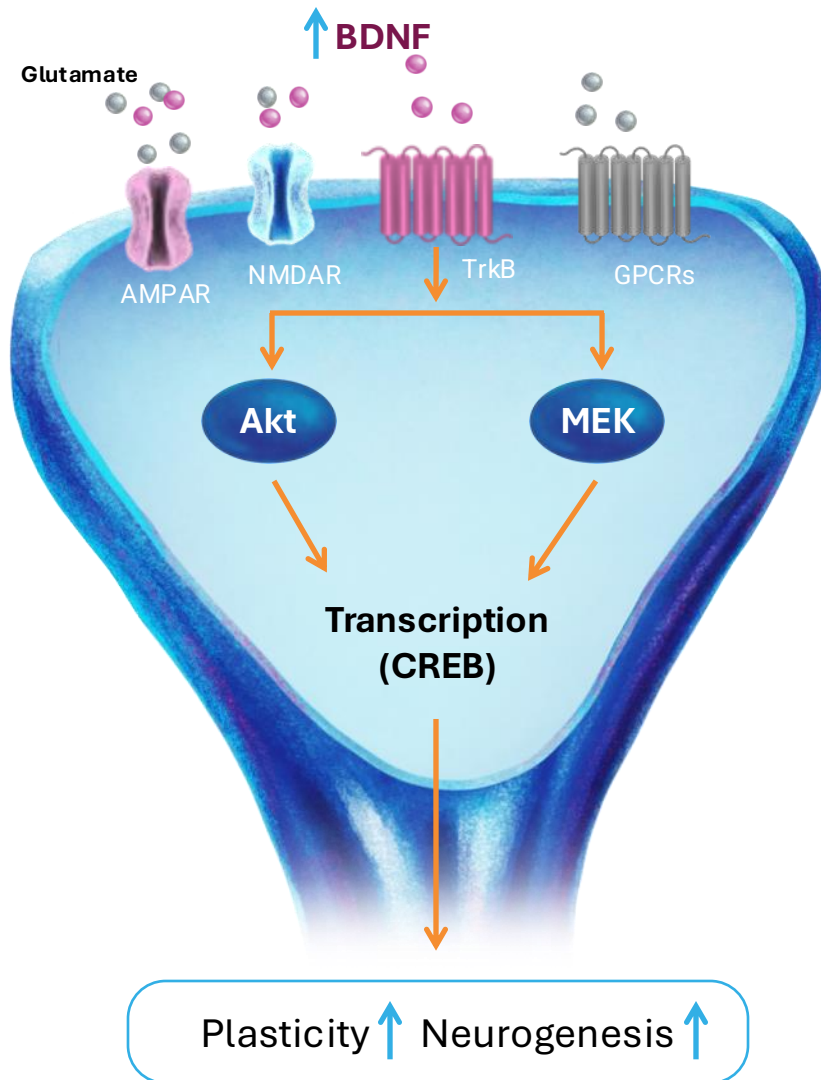
ALTO-100

MDD and Bipolar Depression

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



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



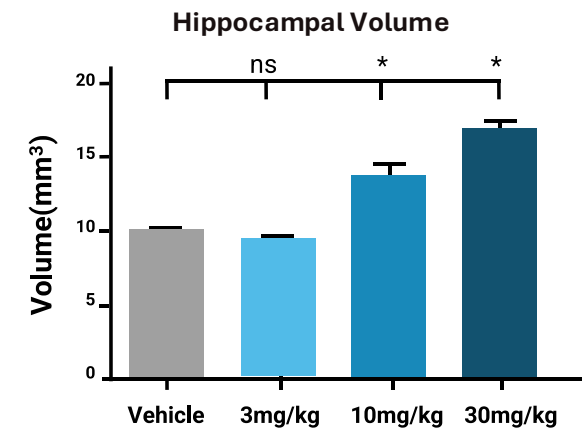
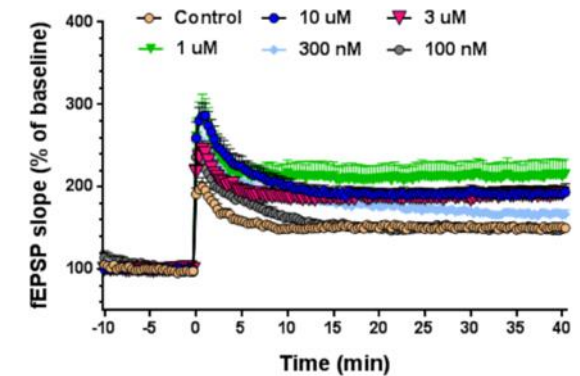
Identified based on a neurogenesis functional screen

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

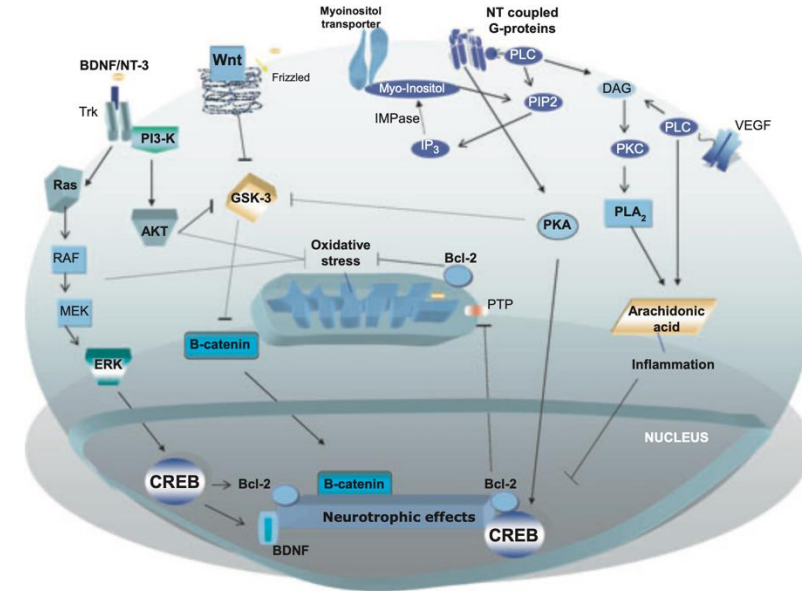


Rationale for ALTO-100 in poor memory/cognition patients with bipolar depression

- 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
- 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)

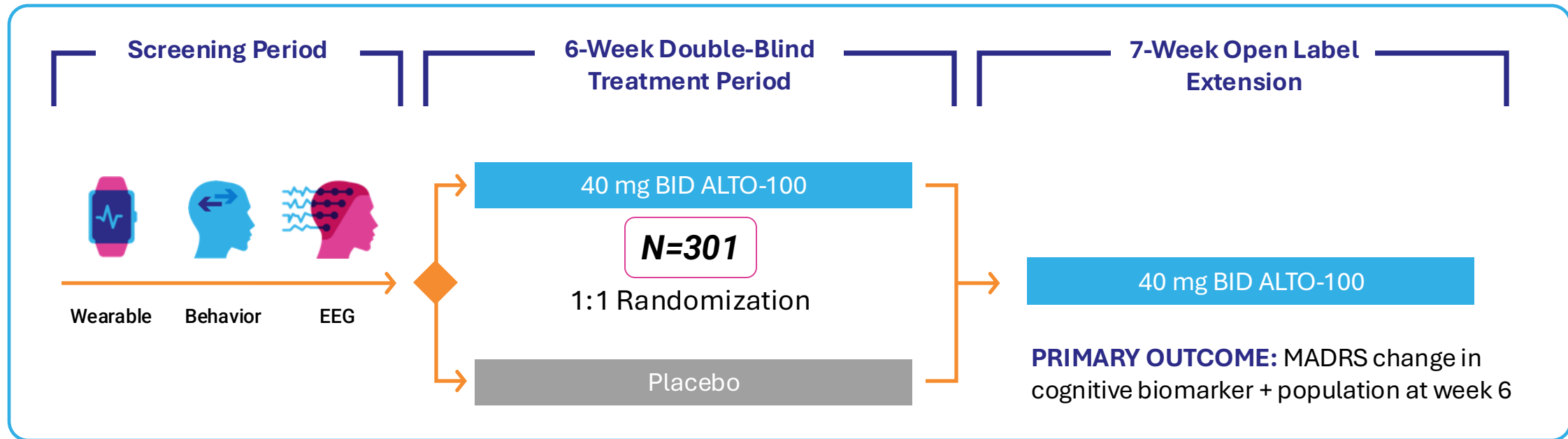
Clinical overview

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



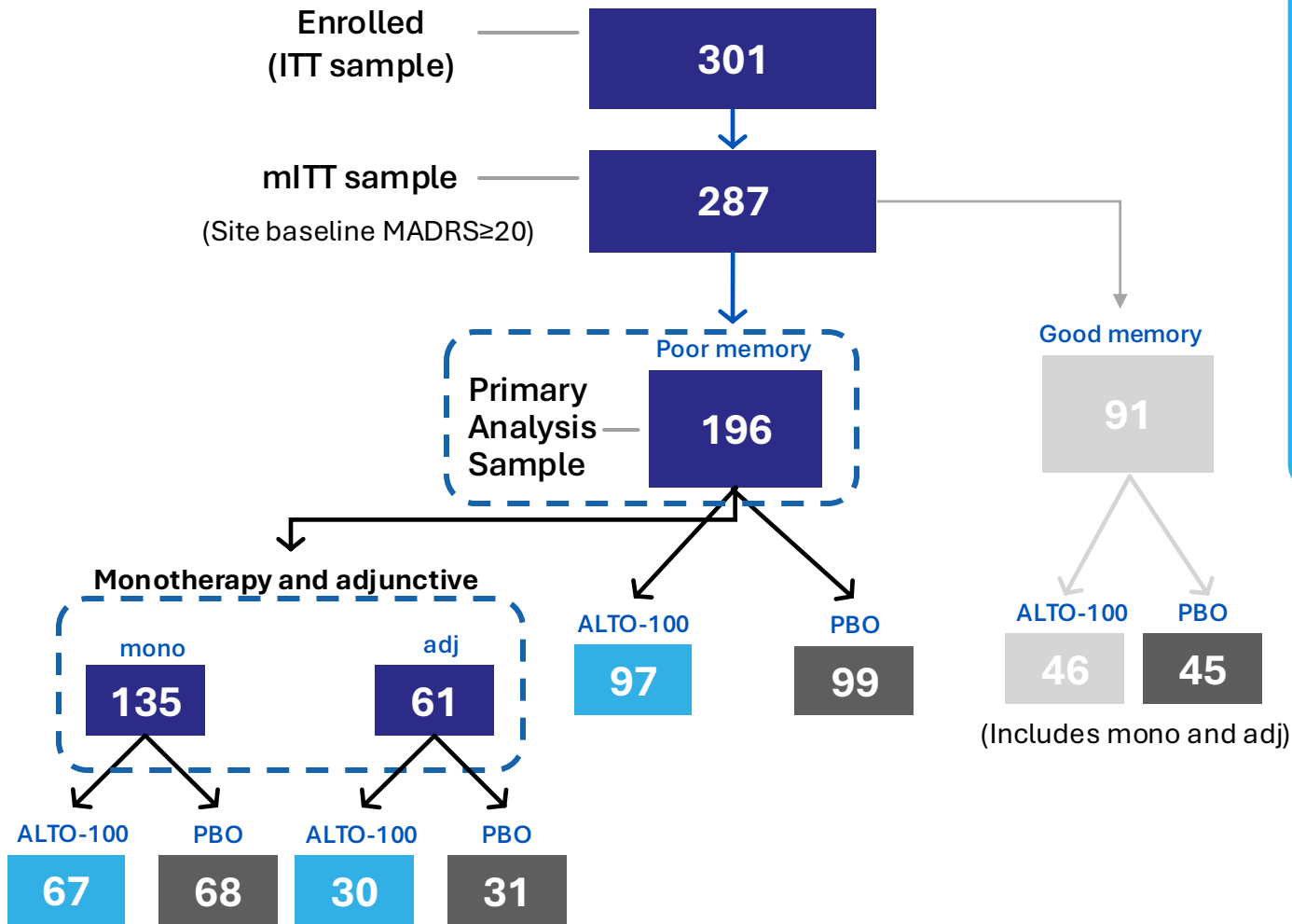
Soeiro-de-Souza et al, *Acta Psych Scan*, 2012

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%

Summary of ALTO-100 Phase 2b MDD results

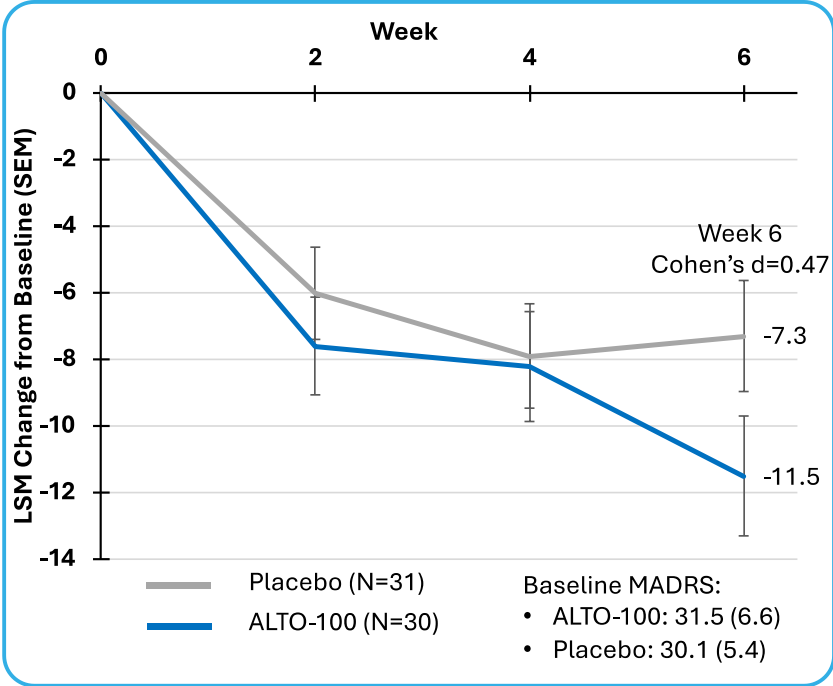
Analysis Population	Sample Size (n)		Mean Baseline MADRS (SD)		Week 6 LSM MADRS Change (SE)		Cohen's d	p
	ALTO-100	Placebo	ALTO-100	Placebo	ALTO-100	Placebo		
All Bio + mITT (Primary)	97	99	31.2 (5.4)	31.5 (5.4)	-10.3 (1.0)	-9.8 (1.0)	0.05	> 0.1
Monotherapy Bio + mITT (Key Secondary)	67	68	31.0 (4.8)	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

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

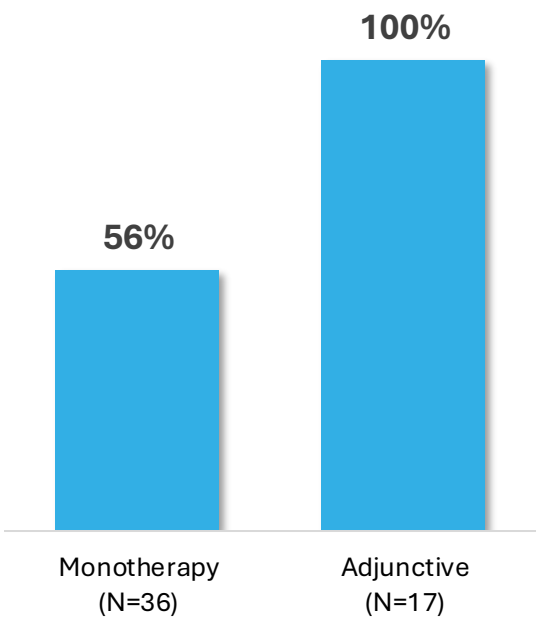
Adjunctive population demonstrated clinically meaningful response to ALTO-100 and had significantly higher compliance

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*

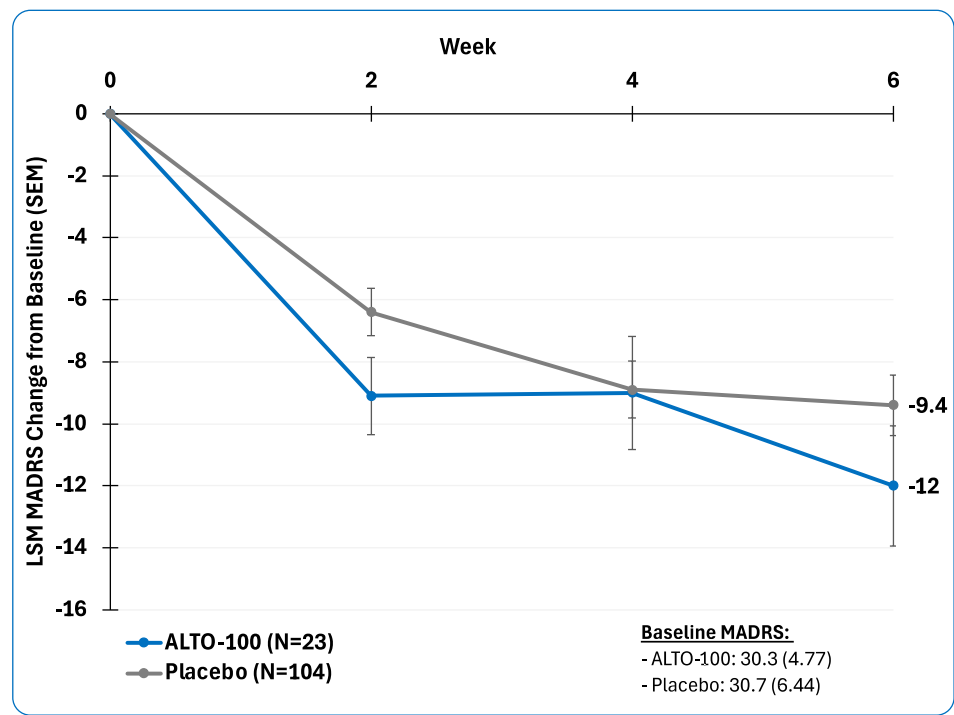


*Only a subset of sites within the study were setup to evaluate PK levels

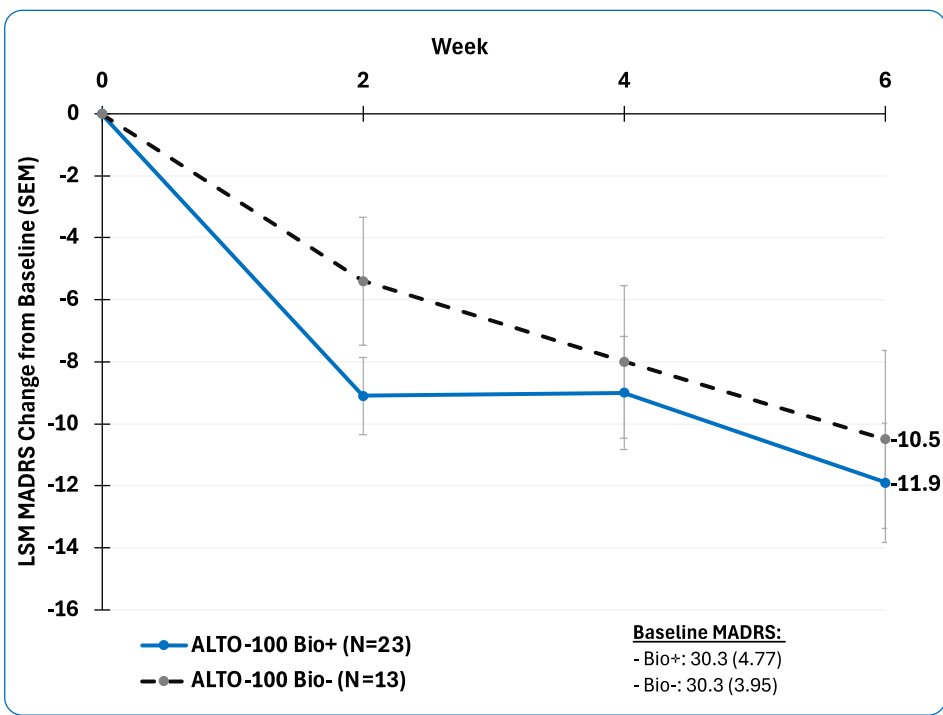
We believe the adjunctive signal is the most indicative of the ALTO-100 effect based on the clinically meaningful signal & high compliance rate

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



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 $\geq 5\%$ of the Population

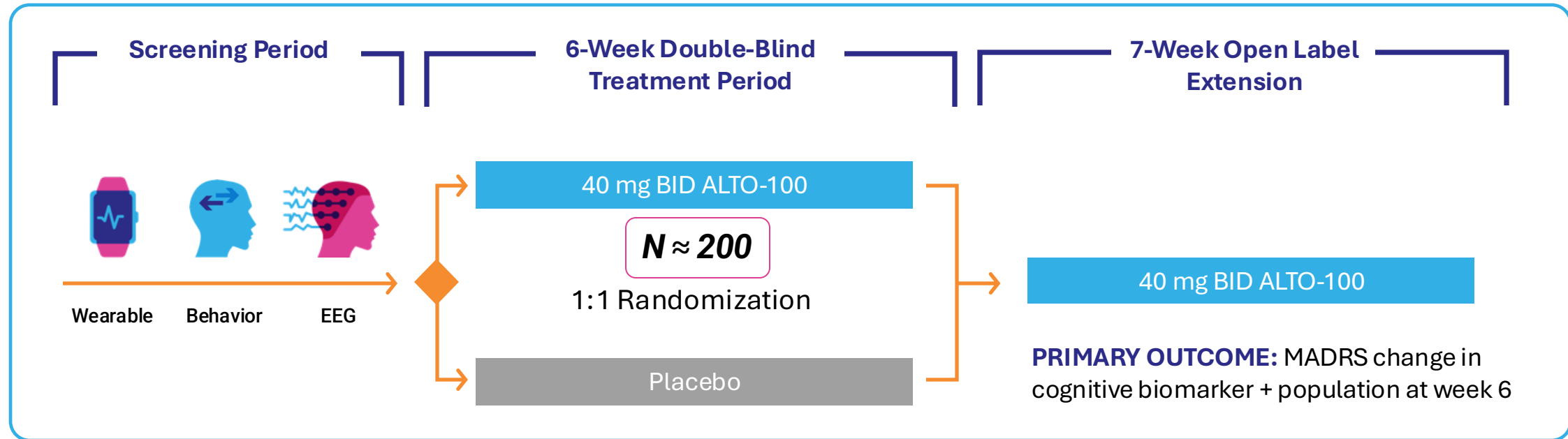
Safety Analysis Set

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

- TEAEs consistent with prior ALTO-100 studies

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

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



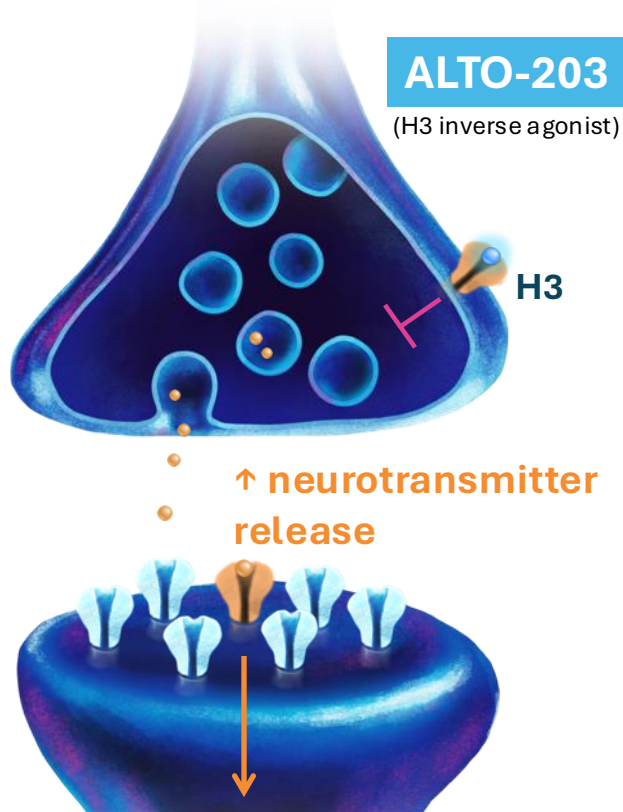
- Design follows **FDA's enrichment guidelines**: powered primary outcome in memory biomarker positive patients
- **Includes participants with and without the biomarker** and randomization stratified by biomarker status
- **Sites, participants and Alto staff blinded to biomarker status**
- **Central review** (MGH-CTNI SAFER interview) of all participants before randomization
- **96% PK positivity** in blinded analysis of 1st cohort – supporting efforts to reduce non-compliance risk

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

ALTO-203

Novel H3 inverse agonist

ALTO-203: An investigational H3 inverse agonist with effects across multiple major neurotransmitter systems



Region- and receptor-specific effects
(mood, cognition, energy, motivation, wakefulness)

Main effect of enhancing release

Dopamine

- Mood
- Reward Processing
- Sustained Attention

Norepinephrine

- Alertness
- Sustained Attention

Acetylcholine

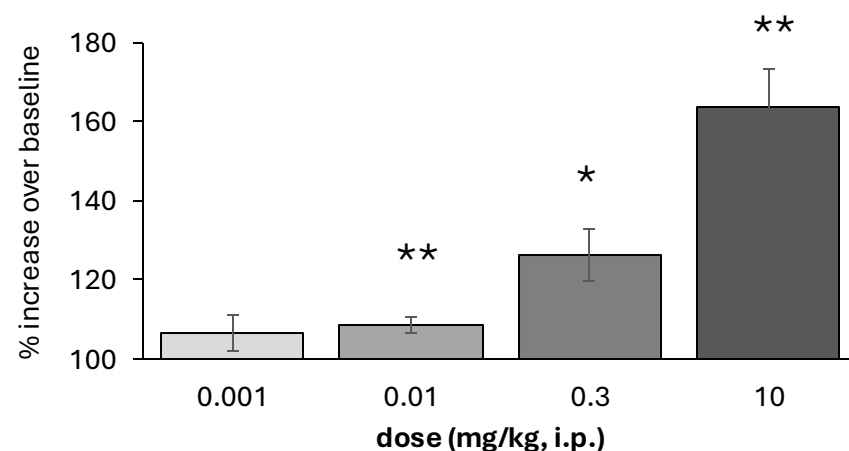
- Sustained Attention
- Learning and Memory

Histamine

- Wakefulness

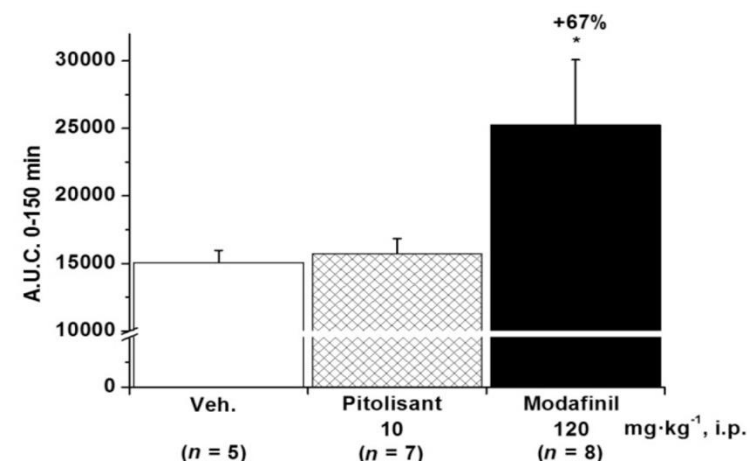
ALTO-203 showed ability to increase reward system dopamine, unlike the only approved H3 (pitolisant)*

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

Positive pharmacodynamic effects from exploratory proof-of-concept study of ALTO-203

Effects replicated key findings from completed Phase 1 study

Study Population:

Patients with MDD with anhedonia and who were 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:

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

Topline pre-specified results

Identified an EEG biomarker predictive of patient response

- *Theta/beta ratio: commonly used EEG index of cortical arousal and attentional control*

	Phase 1	Phase 2a
Improvements in alertness, mood	☒	☐ High placebo response
Improvements in sustained attention	☒	☒
Reduction in EEG theta/beta ratio	☒	☒
Increase in wakefulness	☒	☒
Greater attention improvements in high theta/beta individuals	☒	☒

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 and
Chief Business Officer



Erin McQuade
General Counsel and Chief
Administrative Officer



Jonathon Parker, PhD
SVP, Head of Regulatory Affairs



Melissa Berman
VP, Finance & Accounting and
Controller



Michelle Moran
VP, Quality Assurance



**Patricio O'Donnell,
MD PhD**
VP, Translational Medicine



Christopher Martin
VP, CMC Operations



Board of directors

Husseini Manji, MD
Former Global Head of
Neuroscience JNJ

Christopher Nixon Cox
CEO, Lightswitch Capital

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

Gwill York
Founding Managing Director,
Lighthouse Capital Partners

Raymond Sanchez, MD
Senior Advisor Bain Capital
Life Sciences

Amit Etkin, MD, PhD
CEO, Alto Neuroscience

Multiple near-term clinical milestones expected

Capitalized through multiple clinical milestones:

\$184.2mm^ as of October 31, 2025 → Expected cash runway into 2028, now including expanded execution on ALTO-207 for TRD

2026

- ☐ ALTO-101 CIAS POC data (1Q 2026)
- ☐ ALTO-207 Phase 2b Initiation (1H 2026)
- ☐ ALTO-300 Phase 2b MDD data (mid-2026)
- ☐ ALTO-100 Phase 2b BPD data (2H 2026)

2027

- ☐ ALTO-207 Phase 3 initiation
- ☐ ALTO-207 Phase 2b (potentially pivotal*) TRD data