ALTO
NEUROSCIENCE

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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

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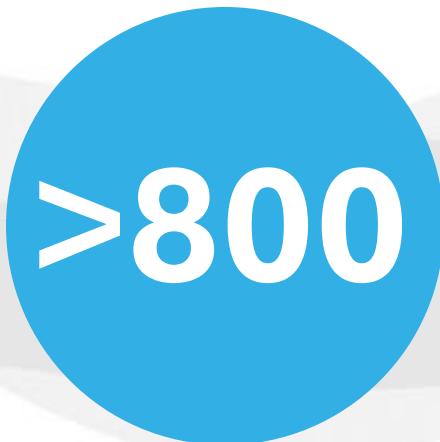
Patients Dosed

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

25+ MILLION

Patient Impact

Opportunity across the portfolio

4

Phase 2 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
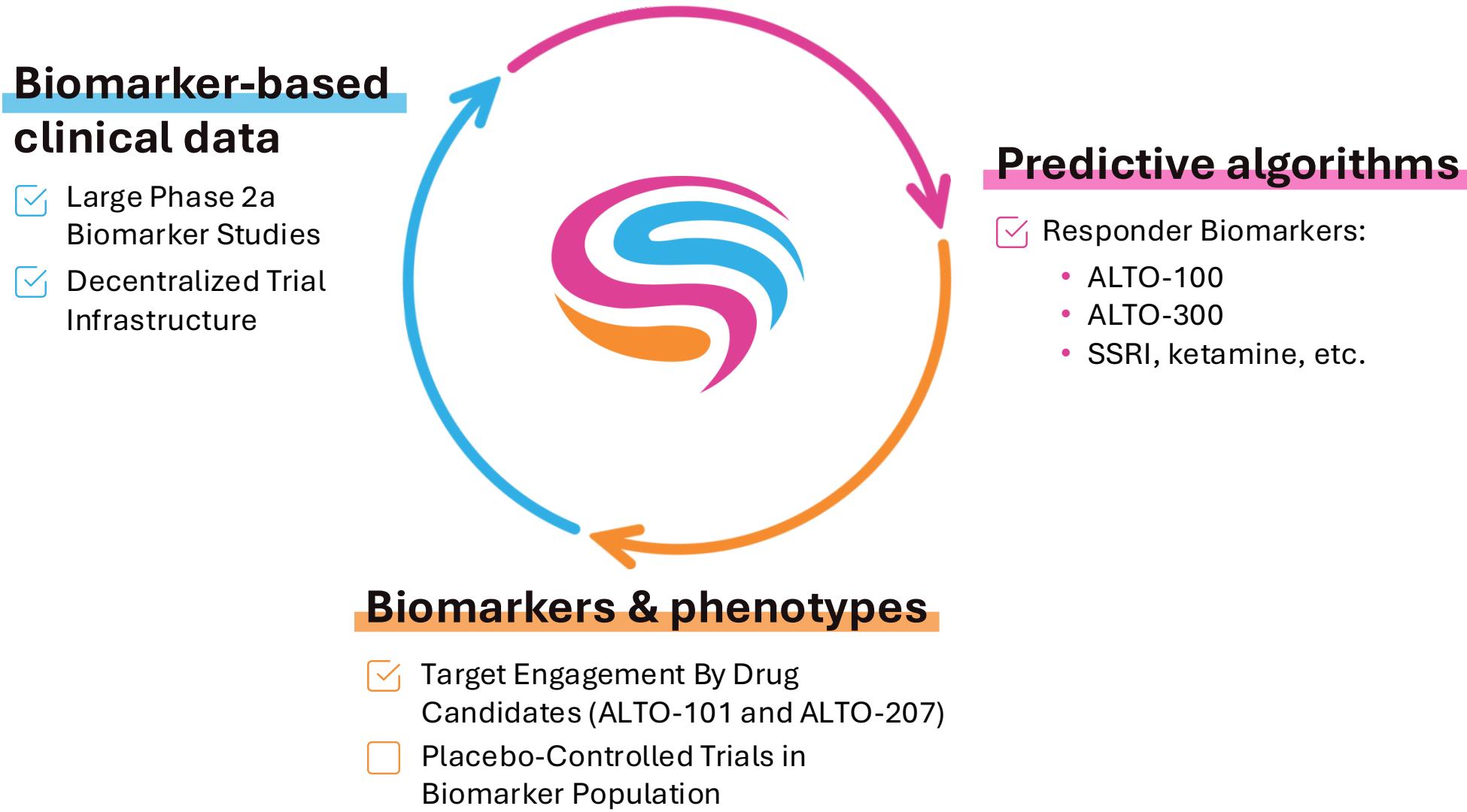
First biomarker-driven pipeline for mental health conditions

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 — Safety & Brain Effects	Phase 2 — Clinical Effect in Biomarker Positive	Phase 3 — Registration Trial(s)	Next Anticipated Milestone
ALTO-100 (BDNF)	**Bipolar Depression**		*Phase 2b Ongoing*		Topline Data 2H 2026
ALTO-300 (MT1/2 & 5HT2C)	**MDD**		*Phase 2b Ongoing*		Topline Data mid-2026
ALTO-207 (D3/D2 & 5-HT3)	**TRD**	*Potentially Pivotal Study */ Phase 2b Planned*			Ph. 2b Initiation mid-2026
ALTO-101 (PDE4)	**Schizophrenia**	*Phase 2 POC Ongoing*			Topline Data 2H 2025
ALTO-203 (H3)	**MDD**	*Phase 2 POC Completed*			
ALTO-202 (NMDA NR2B)	**MDD**				
ALTO-208 (D3/D2 & NK-1)	**Parkinson's Disease**				

*Study qualifying as pivotal is subject to FDA feedback and review of data

Platform

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

Heterogeneous Clinical Populations

Alto Biomarker Platform
- Behavior
- EEG
- Wearable

Example Alto Biomarker
- Cognitive Profile
- EEG Signature
- Sleep/Activity pattern

Biomarker Characterized Population

Likely Responder to Alto Product Candidate
- ALTO-100
- ALTO-300
- Other Product Candidates
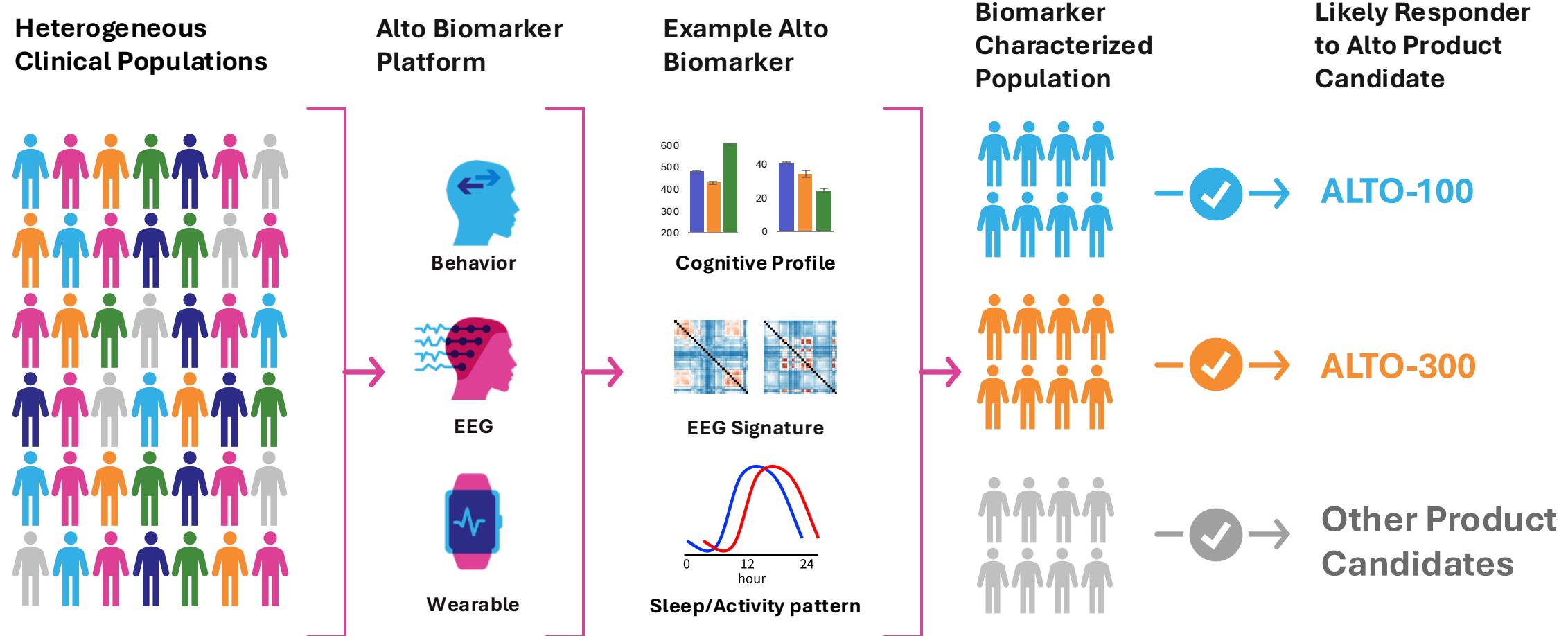
Leveraging proprietary tools, anticipating commercial scale

ALTO-100 biomarker is cognitive test-based

ALTO-300 biomarker is EEG-based
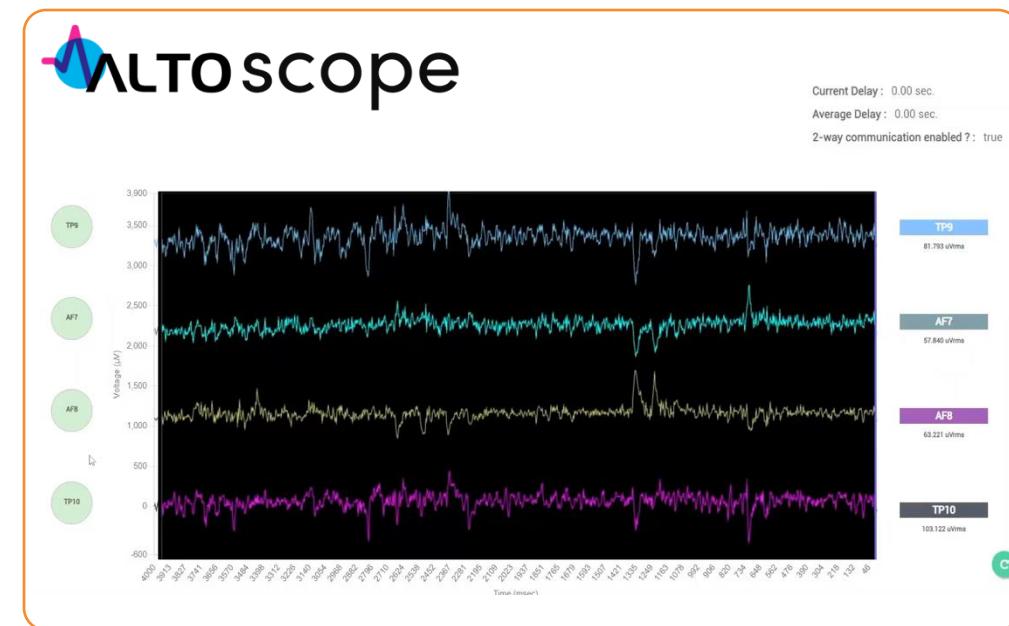
ALTO-300

Phase 2b development for MDD

ALTO-300 proposed mechanism of action: synergy between melatonergic agonism and 5-HT2C antagonism
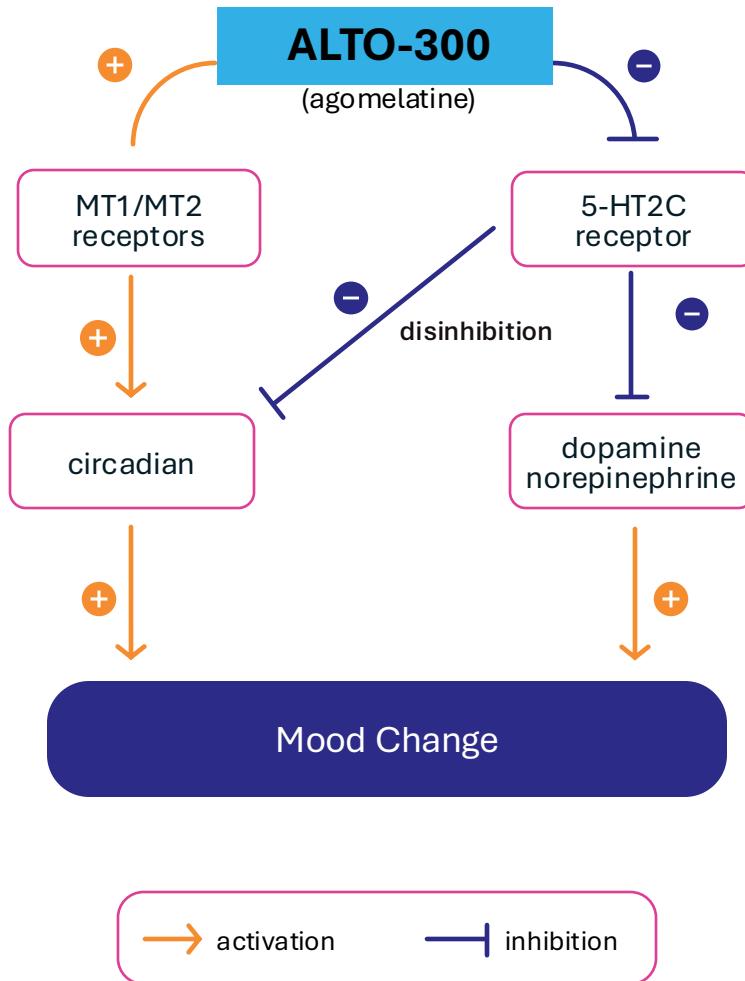
ALTO-300 is a multi-modal antidepressant with a broad range of **synergistic neurobiological effects** that lead to antidepressant activity and favorable tolerability

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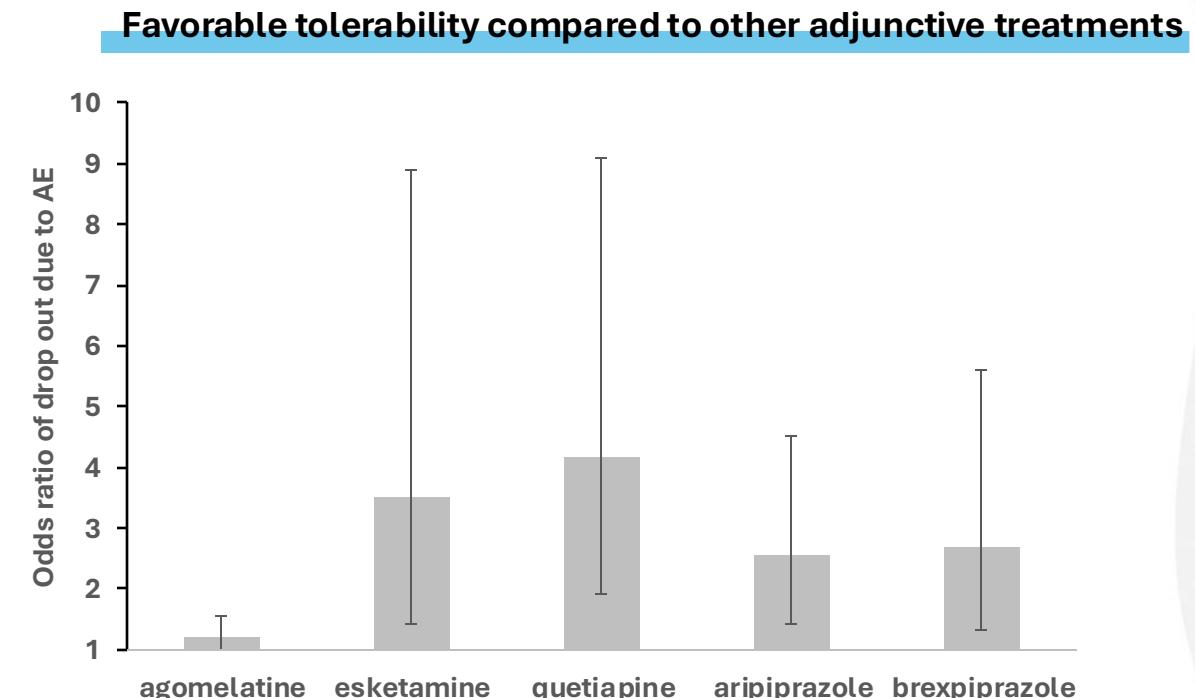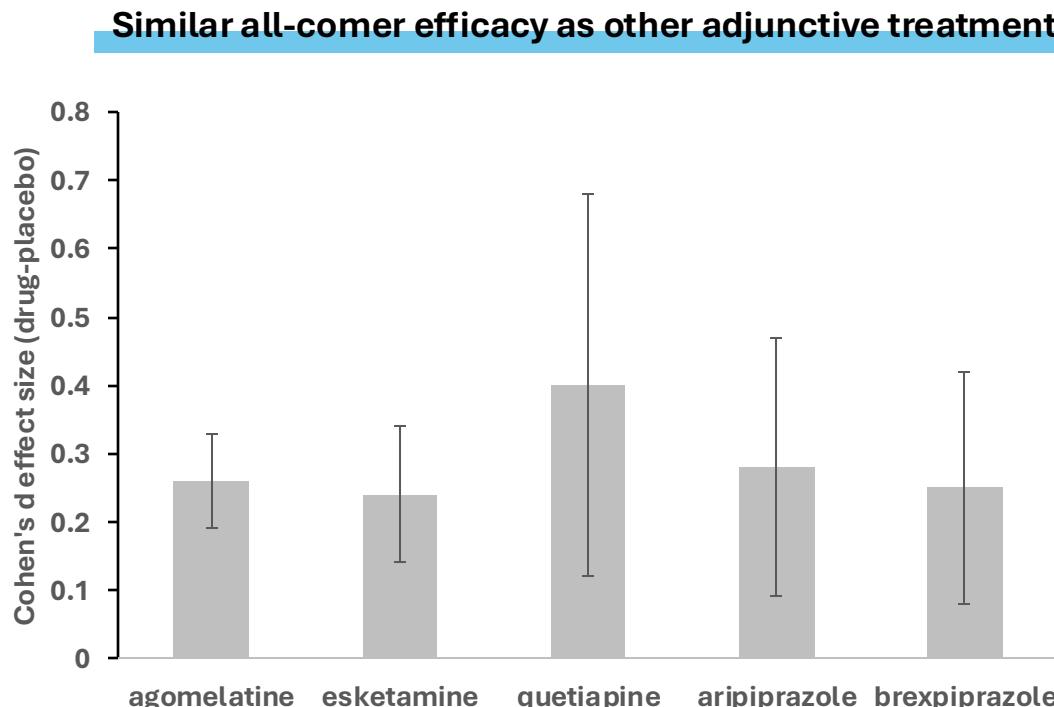
Head-to-head clinical trial data positions ALTO-300 favorably even against SSRI/SNRIs, setting up case for adjunctive use

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)
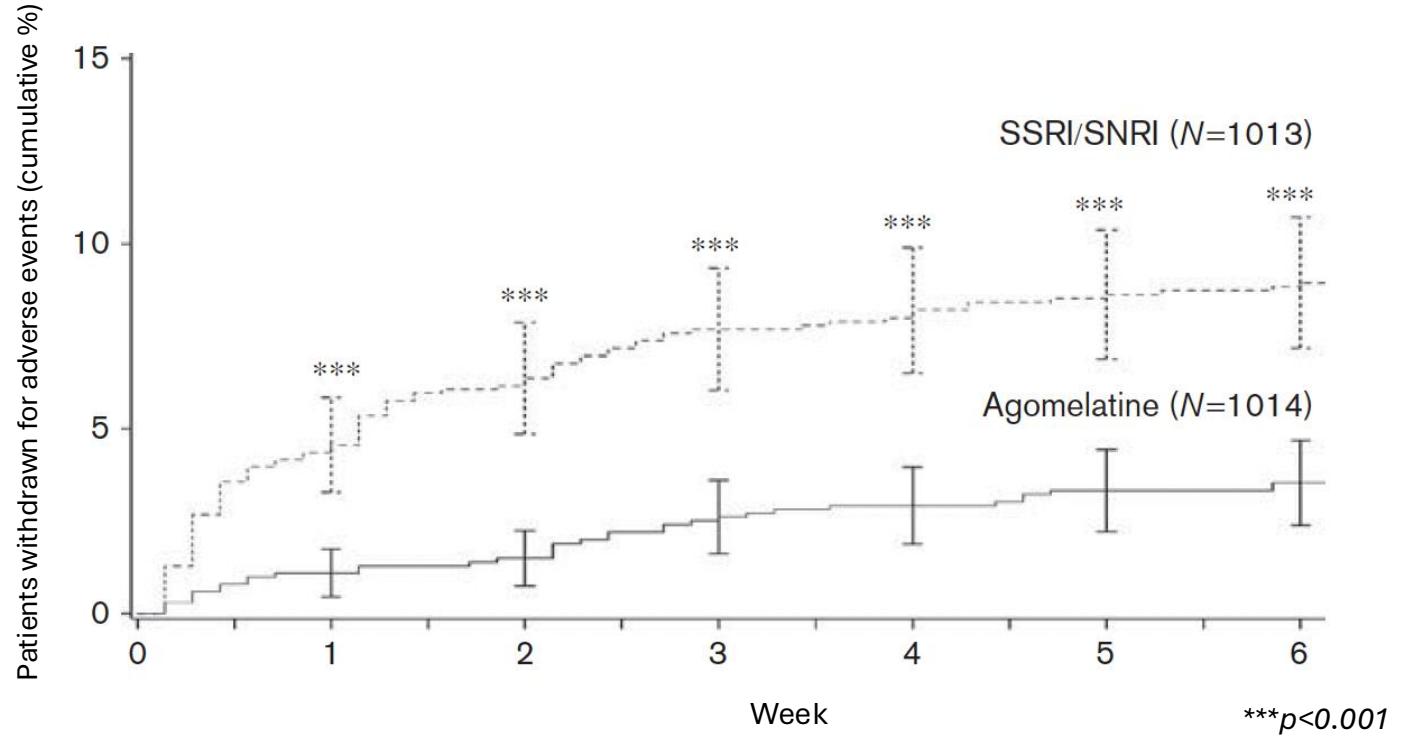
ALTO-300 Phase 2a study design and participant flow

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

EEG

	EEG
Enrolled	239
Baseline Severity (MADRS≥20, PHQ≥10)	194
Biomarker Data	REC 110 / REO 109
QC pass	REC 106 / REO 109
Analysis Sample	Discovery: REC 60 / REO 60 — Test: REC 45 / REO 48

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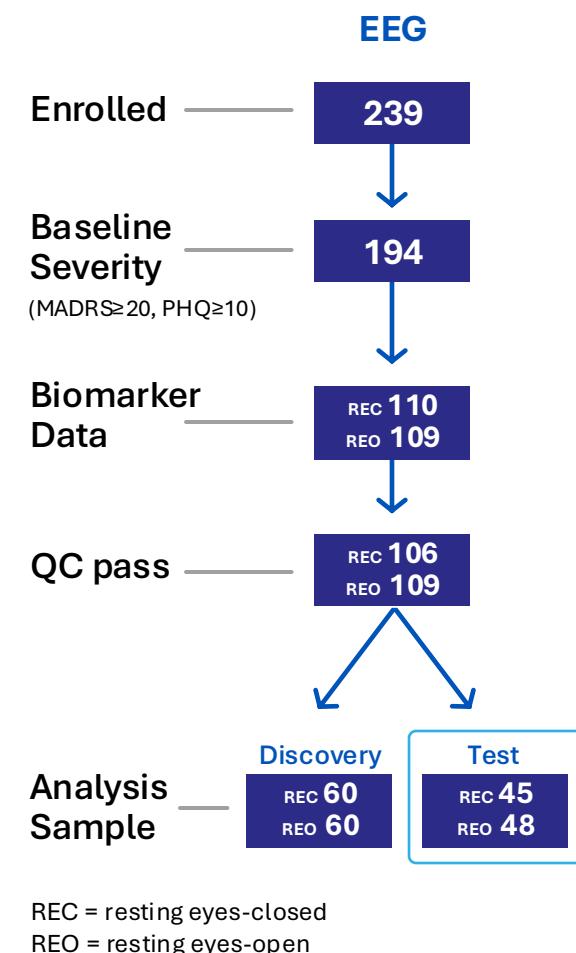
Baseline Demographics

|	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
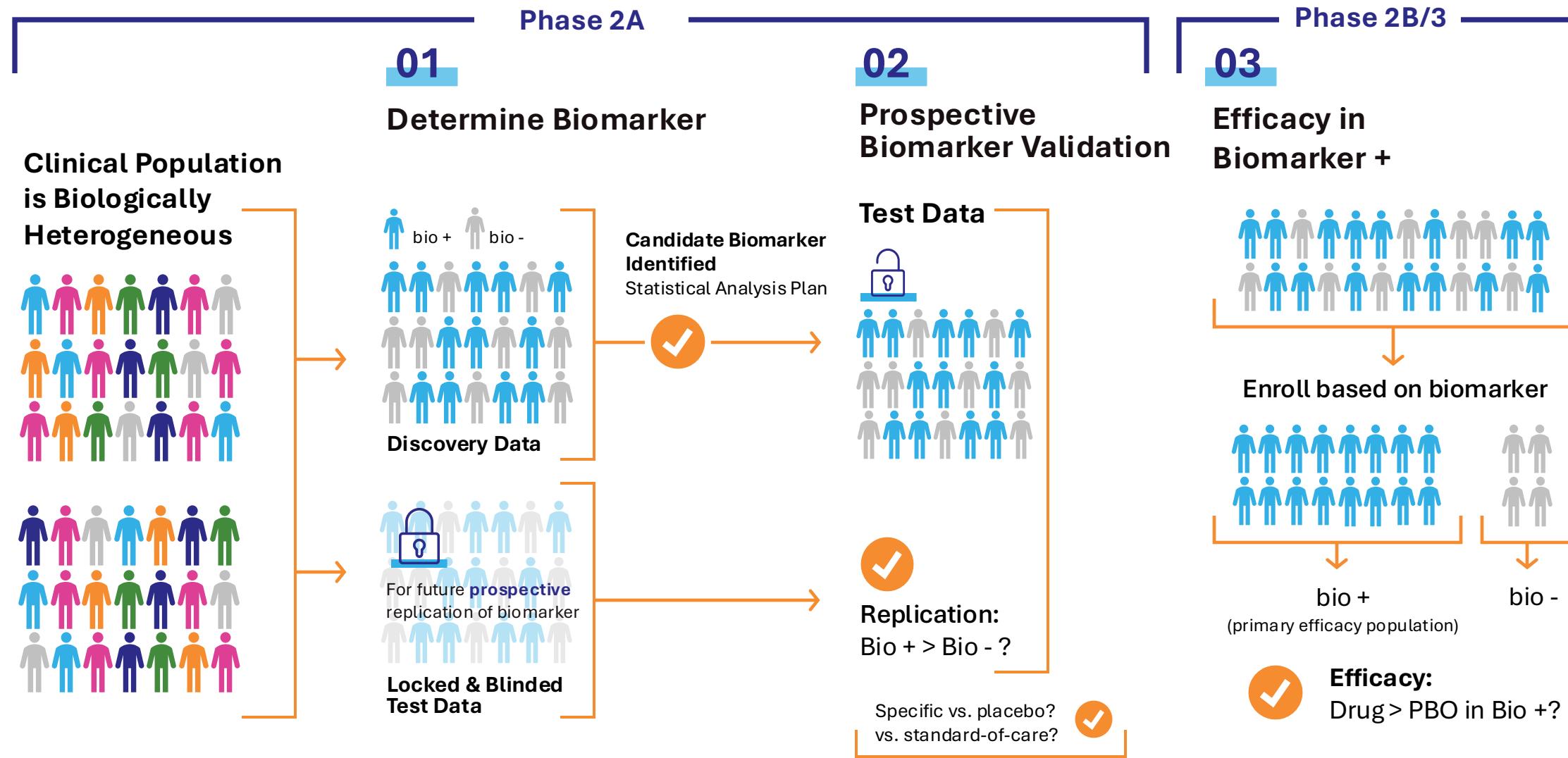
Identified a unique and scalable biomarker for ALTO-300

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


Pretreatment EEG

Subject (S)
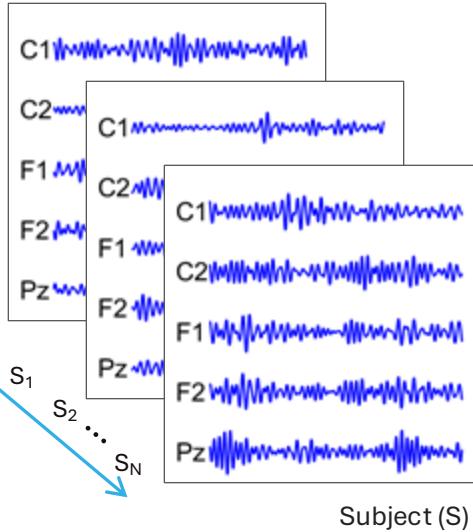
Machine Learning

(weight and reduce to key features (F))
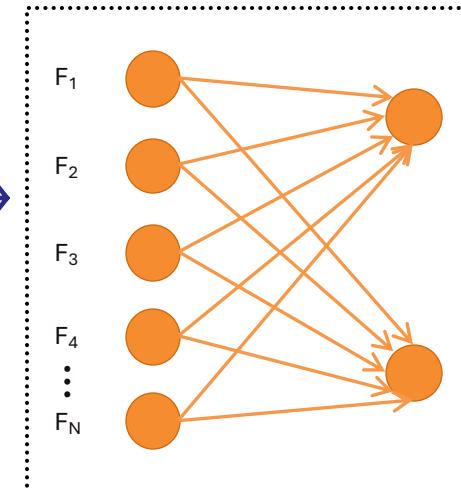
Biomarker

(based on signal dynamics)

positive

negative

Treatment Outcome

Predicted Outcome

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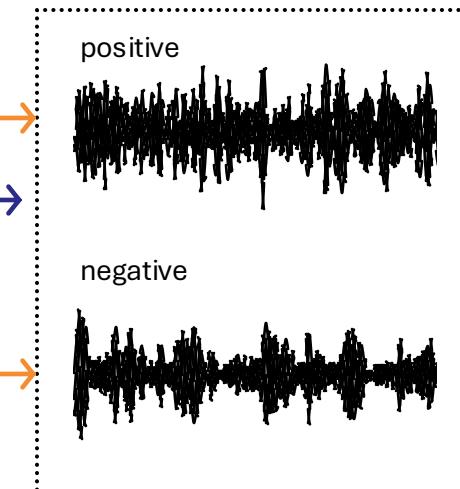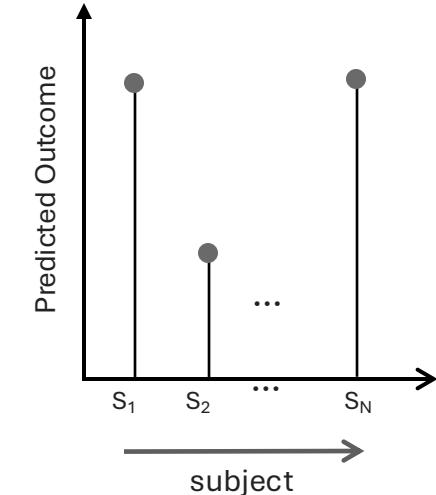
The biomarker is calculated from a single electrode and automatically scored, facilitating scalability

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

01

**Determine Biomarker**

N=60
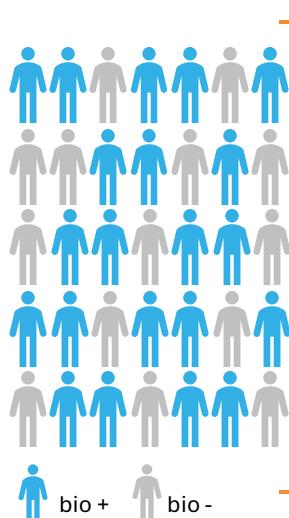
bio +   bio -

02

Prospective Biomarker Validation

N=45
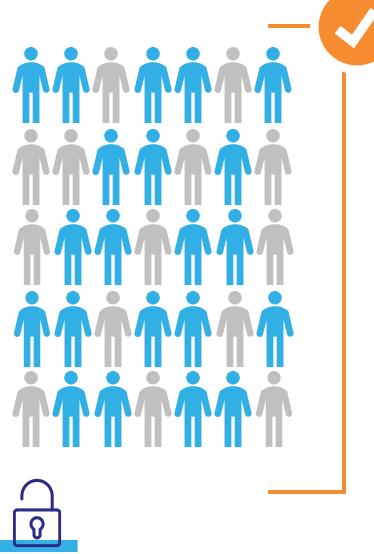
**Prospective Replication in Test Dataset**
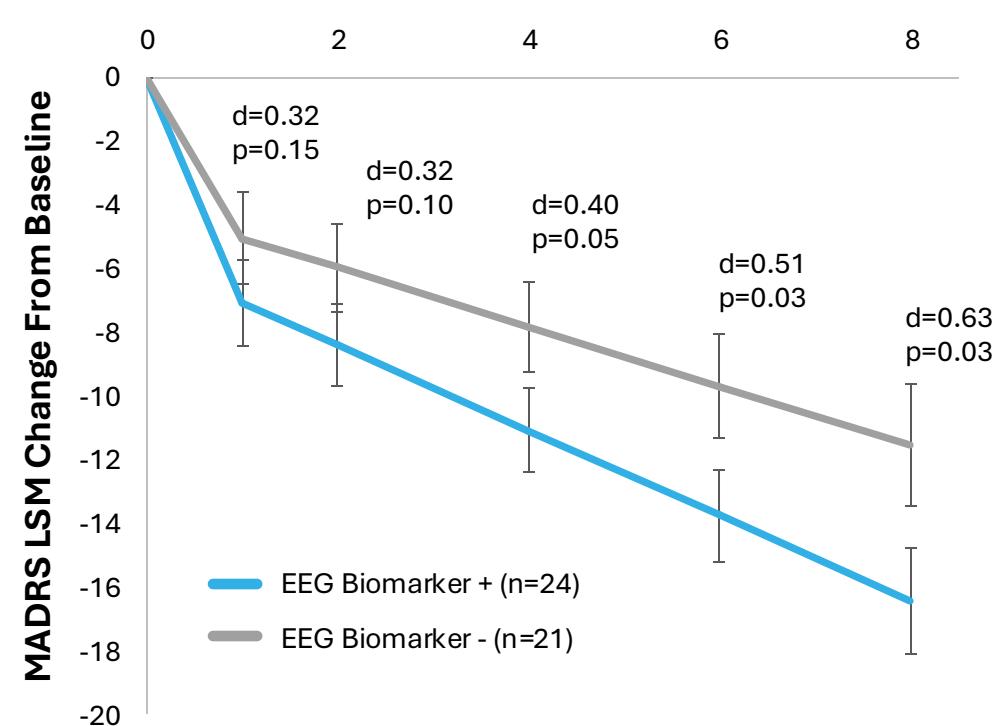
1. Identified EEG signature as predictive
2. Prospectively label patients as bio+/-

# 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 ≥50%) were higher in Bio +

☑ Positive effects observed across CGI and HAM-D

Bar chart: % of Patients Achieving ≥ 50% Improvement vs Week

- EEG Biomarker + (n=55)
- EEG Biomarker − (n=50)

Week 1: p=0.23
Week 2: p=0.07
Week 4: p=0.02
Week 6: p=0.01
Week 8: p=0.07

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

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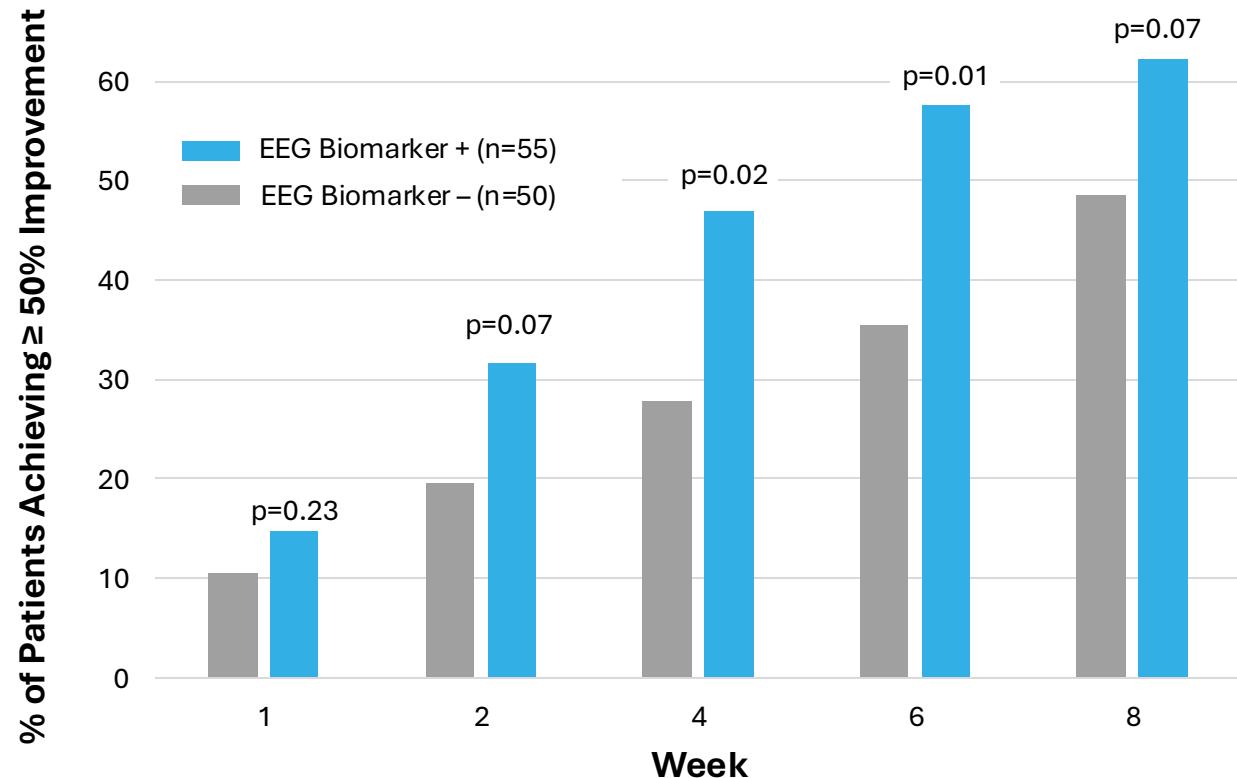
ALTO-300 biomarker: a measure of reduced neural signaling stability

- 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

-0.2   -0.1   0   0.1   0.2

r

Ravindran et al, ACNP 2024
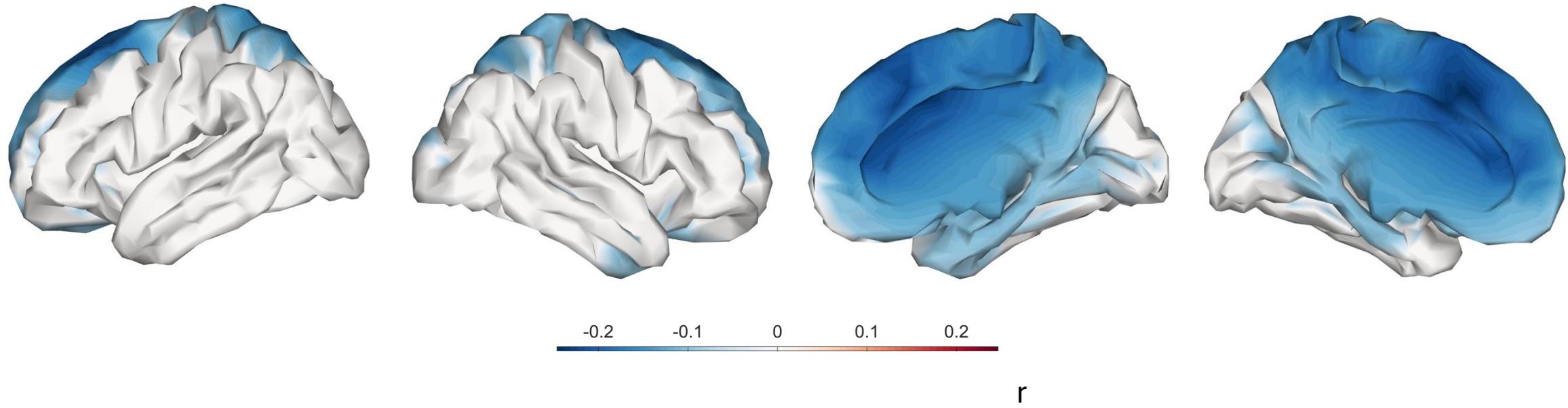
Human and preclinical data demonstrates the link between the mechanism of ALTO-300 and its EEG biomarker

- The biomarker signal reflects increased neural variability, which dopamine acts to reduce
- ALTO-300's MOA includes 5-HT2C antagonism and leads to an increase in dopamine
- Studies test mechanistic link between ALTO-300's EEG biomarker and 5-HT2C/dopamine activity: **increased 5-HT2C activity (which reduces dopamine) or directly depleting dopamine drives the ALTO-300 response biomarker**

Rodent 5-HT2C agonists

R0 60-0175 (n=13)   YM348 (n=10)

- Administered 5-HT2C agonists (R0-0175, YM348) in independent preclinical studies
- Dose-related increase in EEG irregularity (entropy) using the same measure as the human biomarker
- Also led to anhedonic phenotype

Guo et al, SOBP 2025

Human dopamine depletion (n=12)

- Cross-over of dietary dopamine precursor depletion (APTD) or placebo
- Increase (d=0.94) in EEG irregularity using same biomarker as for as ALTO-300 selection

Sundar et al, SOBP 2025 (data from Larson, PLOS One, 2015)

Vs. placebo or vehicle: * $p<0.05$; ** $p<0.01$, *** $p<0.001$

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**

d=-0.21 p=0.86
d=-0.15 p=0.85
d=-0.14 p=0.84
d=-0.13 p=0.81
d=-0.11 p=0.75
d=-0.09 p=0.69

Biomarker + (n=58)
Biomarker - (n=66)
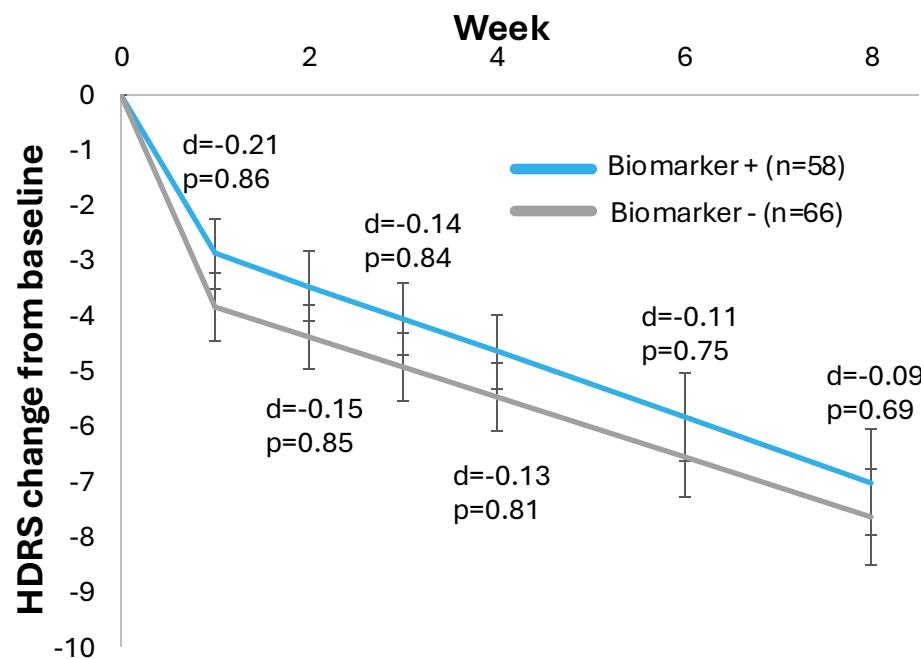
SSRI/SNRI-Treated Patients

d=-0.04 p=0.53

Biomarker + (n=418)
Biomarker - (n=353)
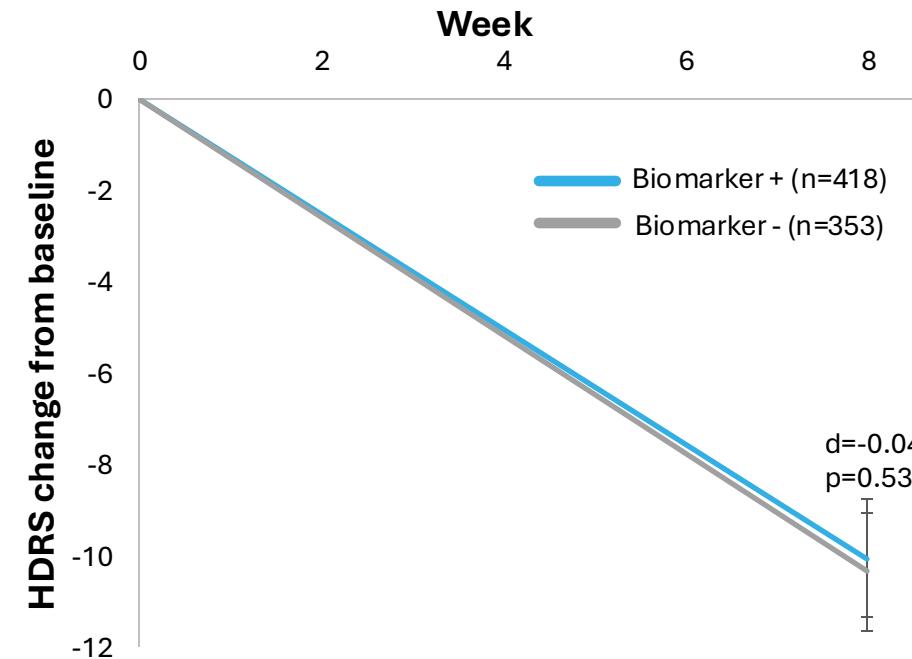
Estimated placebo-adjusted ALTO-300 response: biomarker positive patients
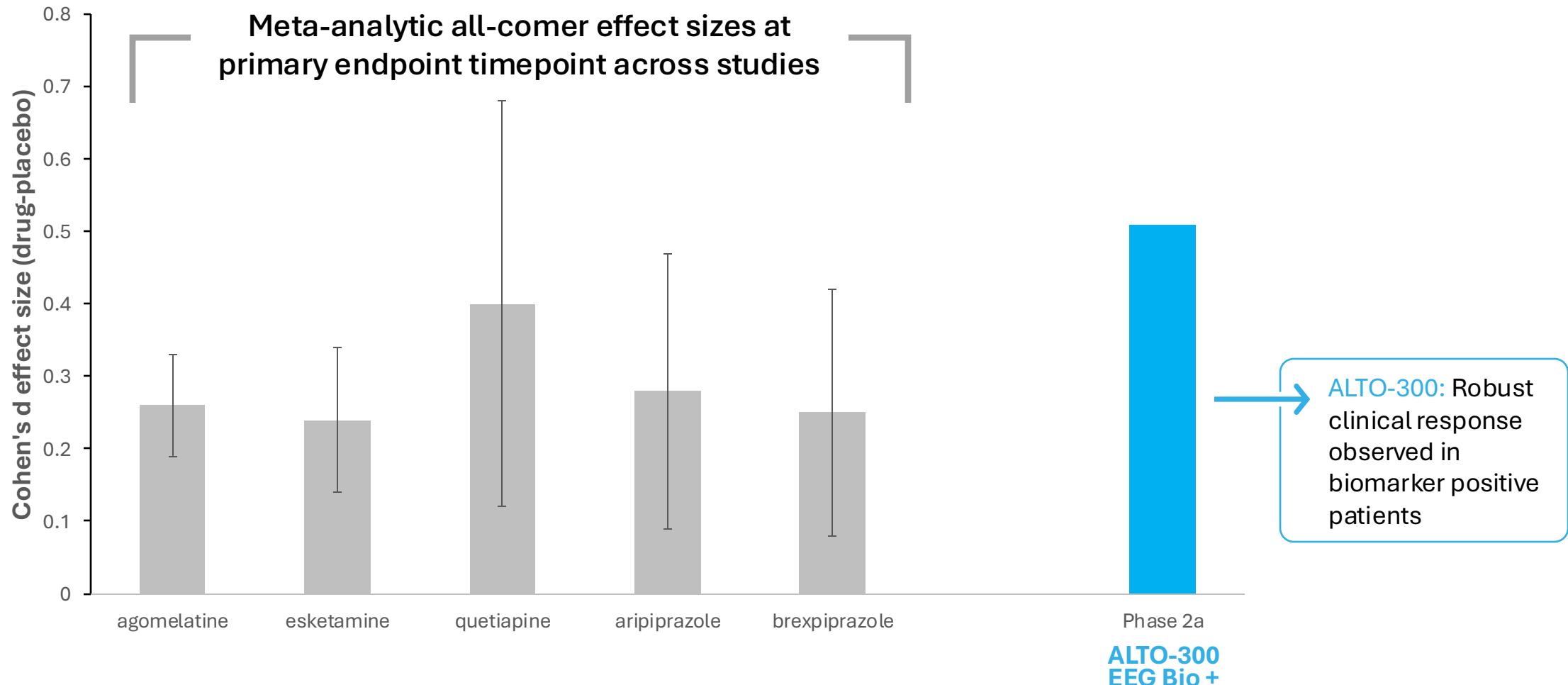
Cohen's d effect size (drug-placebo)

Meta-analytic all-comer effect sizes at primary endpoint timepoint across studies

ALTO-300: Robust clinical response observed in biomarker positive patients

agomelatine   esketamine   quetiapine   aripiprazole   brexpiprazole   Phase 2a
ALTO-300
EEG Bio +

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

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

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)

Study or Subgroup	Agomelatine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 99% CI
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%

Mean Difference IV, Random, 99% CI
-4 -2 0 2 4
Favours agomelatine   Favours placebo

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

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)

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

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 adaptive (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 ≤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
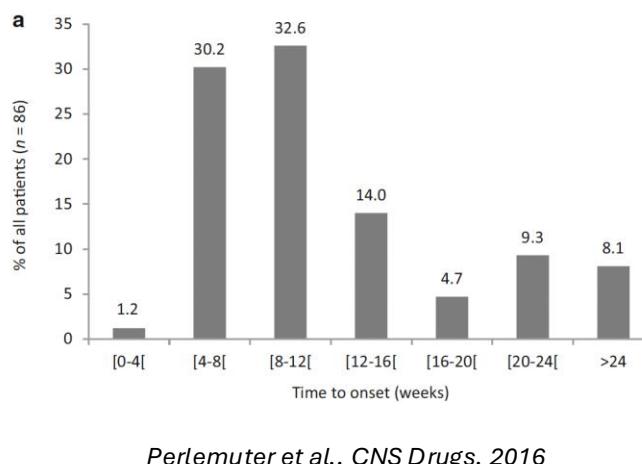
LFT monitoring not expected for ALTO-300 label

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

Screening Period | **6-Week Double-Blind Treatment Period** | **8-Week Open Label Extension**

Wearable   Behavior   EEG

QHS = Once daily at bedtime

25 mg QHS ALTO-300

1:1 Randomization

Placebo

25 mg QHS ALTO-300

PRIMARY OUTCOME: MADRS change in EEG biomarker + population at week 6
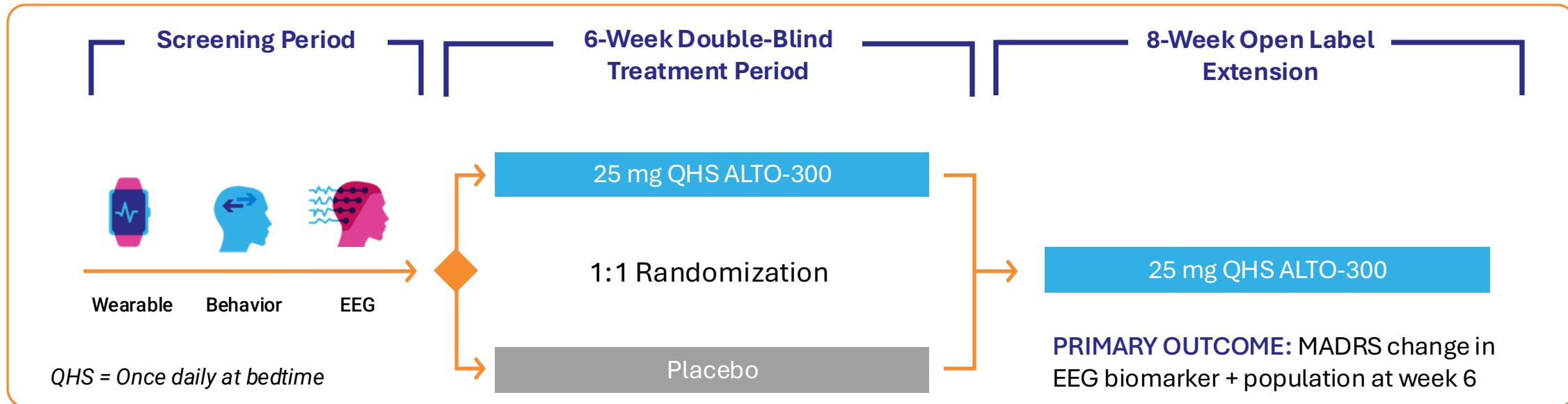
- Design follows **FDA's enrichment guidelines:** powered primary outcome in EEG biomarker positive patients
- **Includes participants with and without the biomarker** and randomization stratified by biomarker status
- Site-based and decentralized – **sites and participants blinded to biomarker status**
- 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

171 — Patients enrolled as of Dec. 17, 2024 interim cutoff

× → **52** — Patients prospectively excluded following detailed site and subject case review -- includes removal of 4 entire sites from analysis sample for study conduct issues identified by Alto

119 — ITT^ population following site and subject review

× → **4** — Per protocol, excluded for mITT* defined MDD symptom threshold

Biomarker Negative
28

Biomarker Positive
87 — mITT* biomarker positive Interim analysis population

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

---

Outcome

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

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

– Futility: Non-binding futility recommendation based on effect size threshold of Cohen's d < 0.20
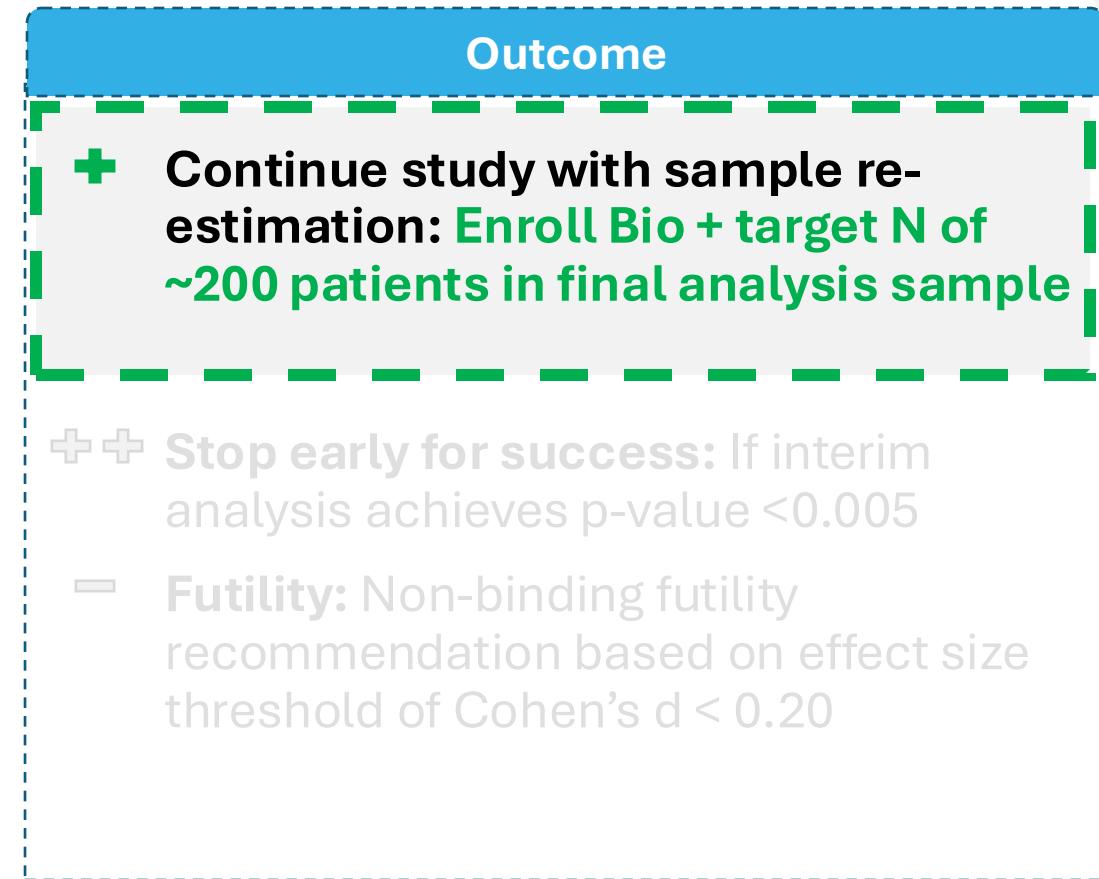
According to standard α spend calculation for a study with 1 interim analysis, conservative success stopping criterial of p≤~0.005 results in final analysis success threshold of p<0.049

ALTO NEUROSCIENCE

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

D2 receptor (similar effects in prefrontal and limbic areas)

Dopamine Neuron

ALTO-207
(D3/D2 agonist & 5HT3 antagonist)

- pramipexole
- ondansetron

Dopamine ↓

D3 receptor

Akt   MAPK

Transcription (CREB)

Striatal Neuron

Nucleus accumbens

↑Plasticity ↑Reward

Novel antagonistic combination:

↑ **D3/D2 agonism for antidepressant effects**

↓ **5-HT3 activity to reduce dose-limiting AEs**

Gut input

D2/D3   **5-HT3 receptor**

CTZ

Midbrain

Vomiting center

↓Nausea/Vomiting

CTZ: chemoreceptor trigger zone

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 significantly higher doses in Phase 1, with 5x faster titration

CTC-501 showed robust clinical effects in a randomized, placebo-controlled, Phase 2a trial; enabling a near-term potentially pivotal* / planned Phase 2b TRD trial with topline data expected in 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

*Study qualifying as pivotal is subject to FDA feedback and review of data

Peer-reviewed publication of PAX-D study demonstrates robust clinical effects of pramipexole in TRD

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

The Lancet Psychiatry

- 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

TRD study: aimed for 3mg/daily dose but only reached 1.35mg/day

Placebo n=30 · Pramipexole n=30

p=0.04
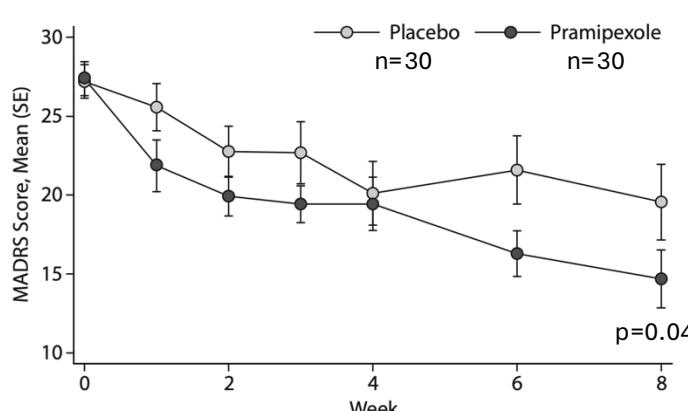
Cusin, Journal of Clinical Psychiatry, 2013

PAX-D TRD study (n=150): striking and sustained clinical efficacy, but high dropout due to AEs

d=0.87*

QIDS-SR$_{16}$ change converts to a MADRS Δ of 7.38 points*

20% stopped pramipexole due to AEs vs 5.3% for placebo (p=0.01)
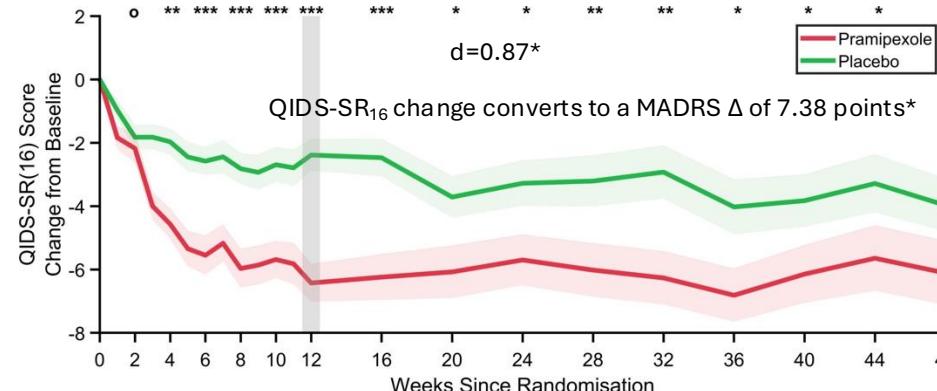
Browning et. al., The Lancet Psychiatry, July 2025

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

placebo (n=34) · pramipexole 0.375mg (n=36) · pramipexole 1mg (n=35)

1mg Δ=6.0, p=0.01

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*

ALTO NEUROSCIENCE

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 ≥1mg/day
  - 1.5% achieved >1.5mg/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**
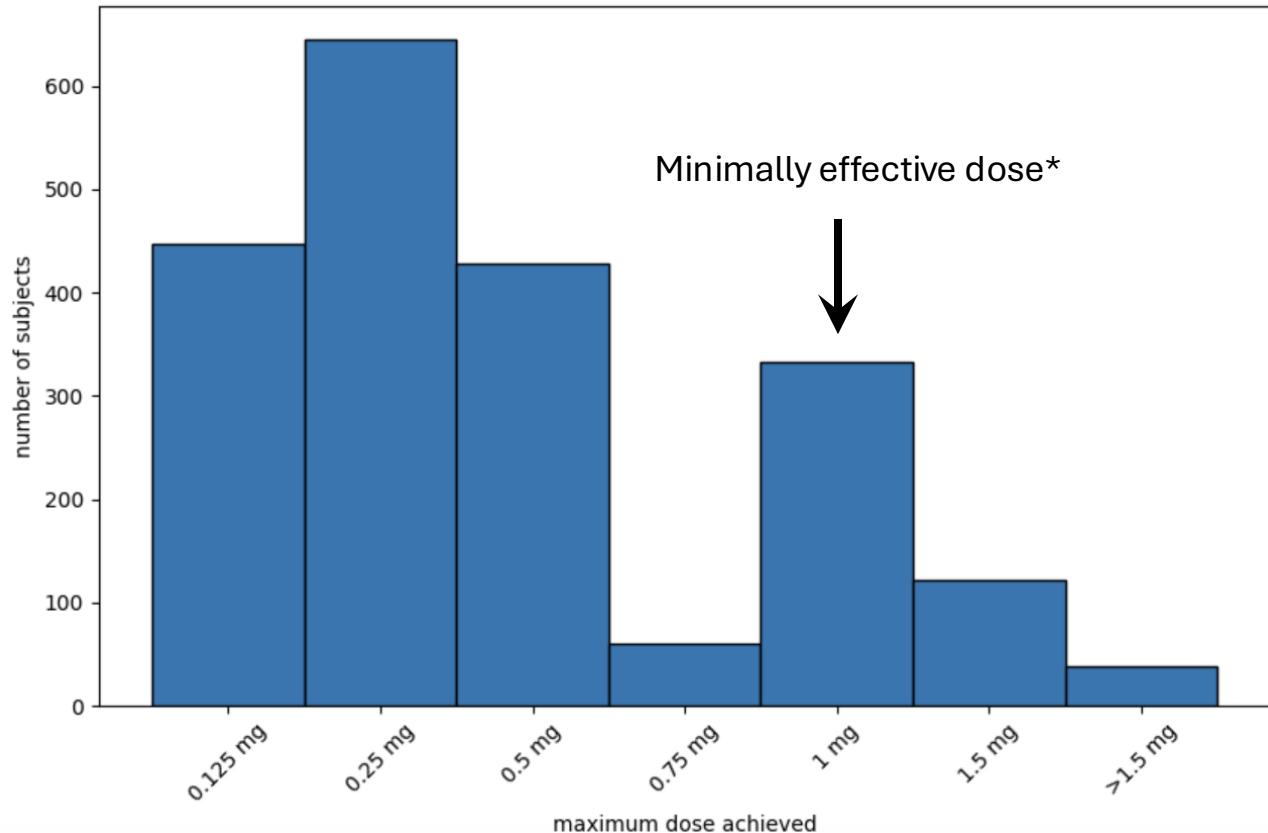
*Cusin et al and Corrigan et al suggest 1-1.5mg is minimally effective dose

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

≥2.5x increase in pramipexole tolerability

Left chart: Proportion tolerating dose (%) vs. Pramipexole daily dose (mg)
Legend: pramipexole, CTC-501

Right chart: Maximum tolerated dose (mg) for pramipexole and CTC-501
2.3mg - Average dose achieved in PAX-D study **with 28-day titration**

*Chase Therapeutics sponsored trial
n.k.a.: now known as
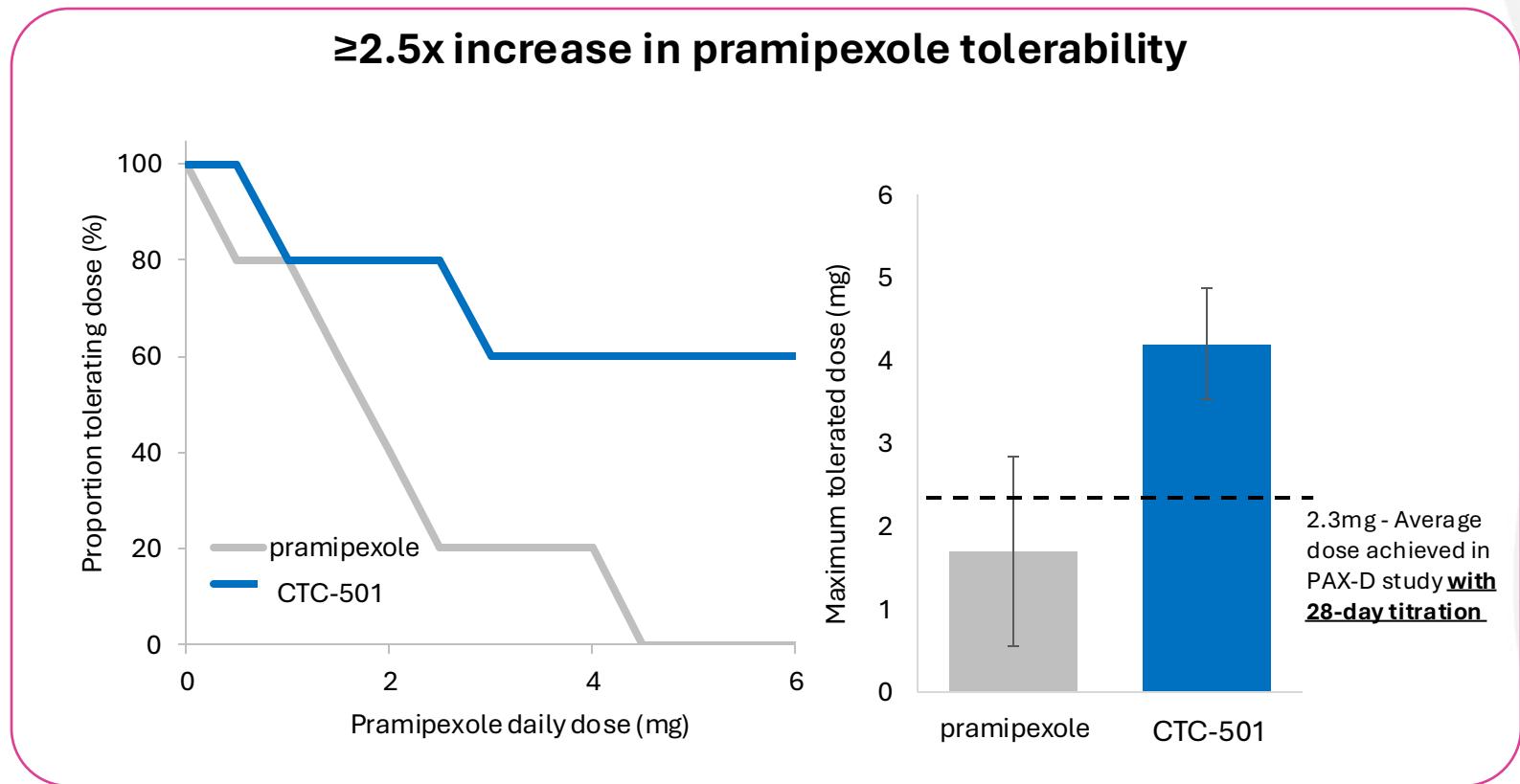
# CTC-501 (n.k.a. ALTO-207) development builds on strong clinical evidence of antidepressant effects

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

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

MADRS – Change from Baseline

CGI-S – Change from Baseline

*Chase Therapeutics sponsored trial
n.k.a.: now known as
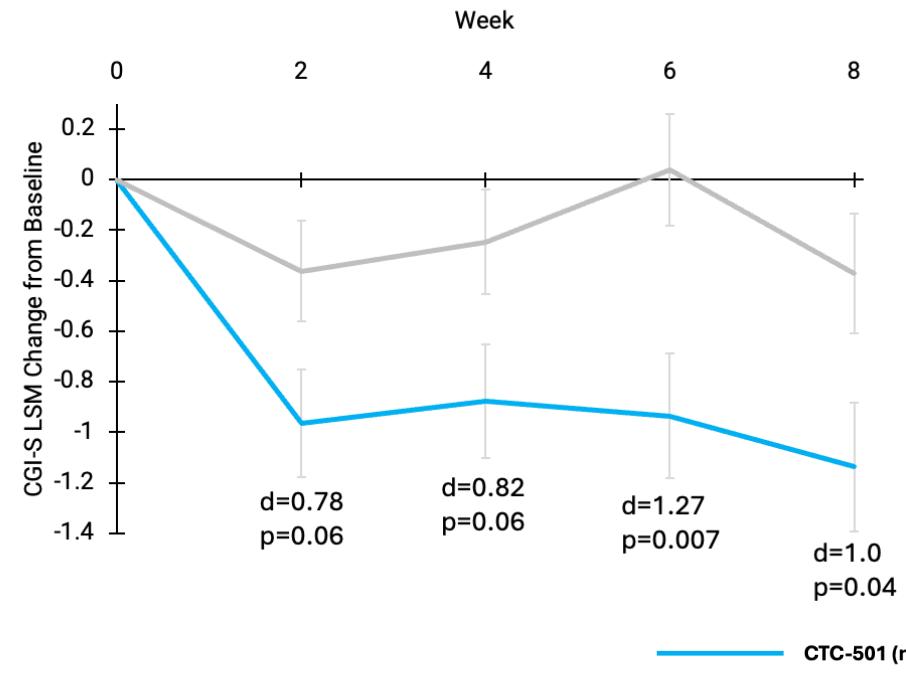
Phase 2a trial of CTC-501 (n.k.a. ALTO-207) in MDD confirmed favorable safety and tolerability profile

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

*Chase Therapeutics sponsored trial

n.k.a.: now known as

ALTO-207 designed to achieve rapid antidepressant effect

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

Pramipexole targeted titration schedules

CTC-501 enabled >5x faster dosing and to a higher target

Legend:
- FDA label
- PAX-D
- Cusin
- Corrigan 1mg
- Chase Ph 1
- Chase Ph 2a

X-axis: Day
Y-axis: Total daily pramipexole dose (mg)
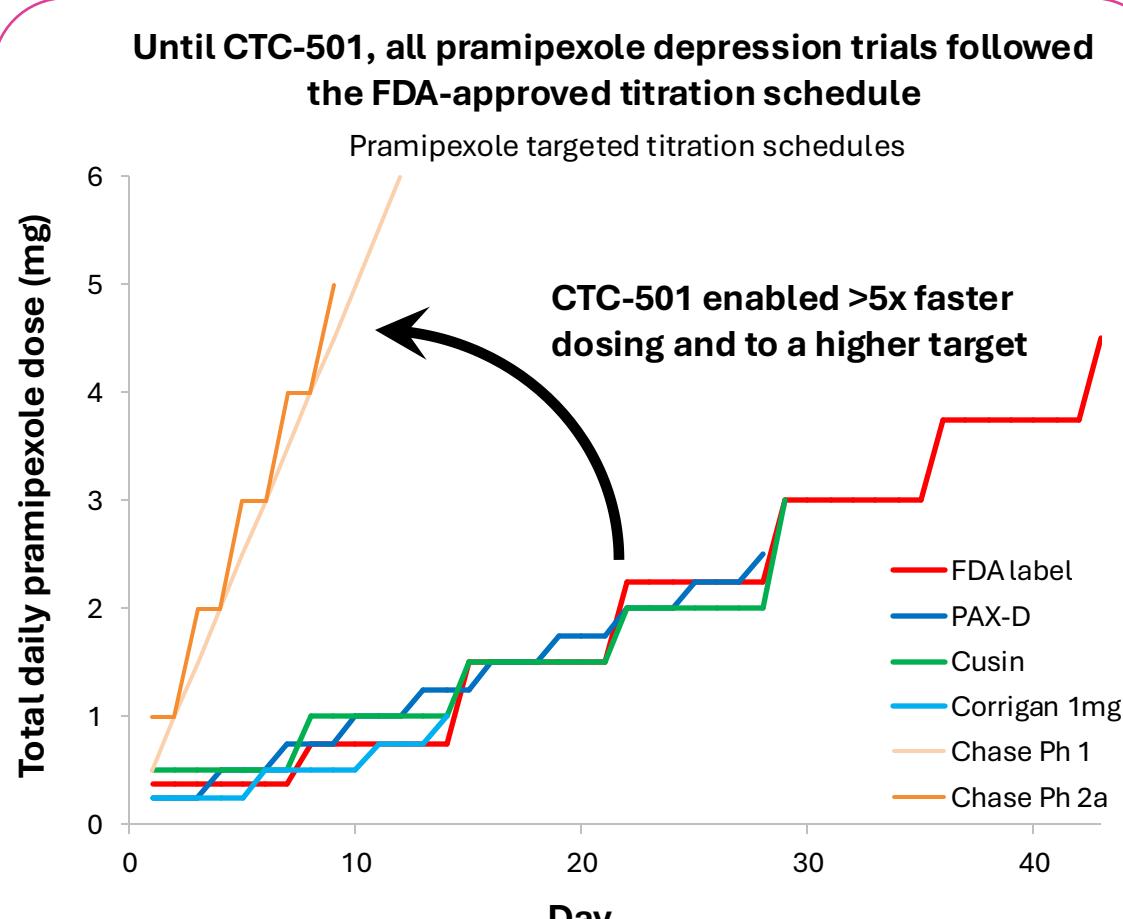
CTC-501 showed the largest clinical effect, with rapid onset due to faster titration with good tolerability

Clear dose response

Pramipexole alone

CTC-501

Current SOC

clinical significance (d=0.25-0.3)

Y-axis: Cohen's d effect size (drug - placebo)

Bars:
- Cusin 1.35 mg/d
- Corrigan 1 mg/d (target)
- PAX-D (8 wk) 2.3mg/d
- CTC-501 4.1 mg/d
- esketamine
- aripiprazole
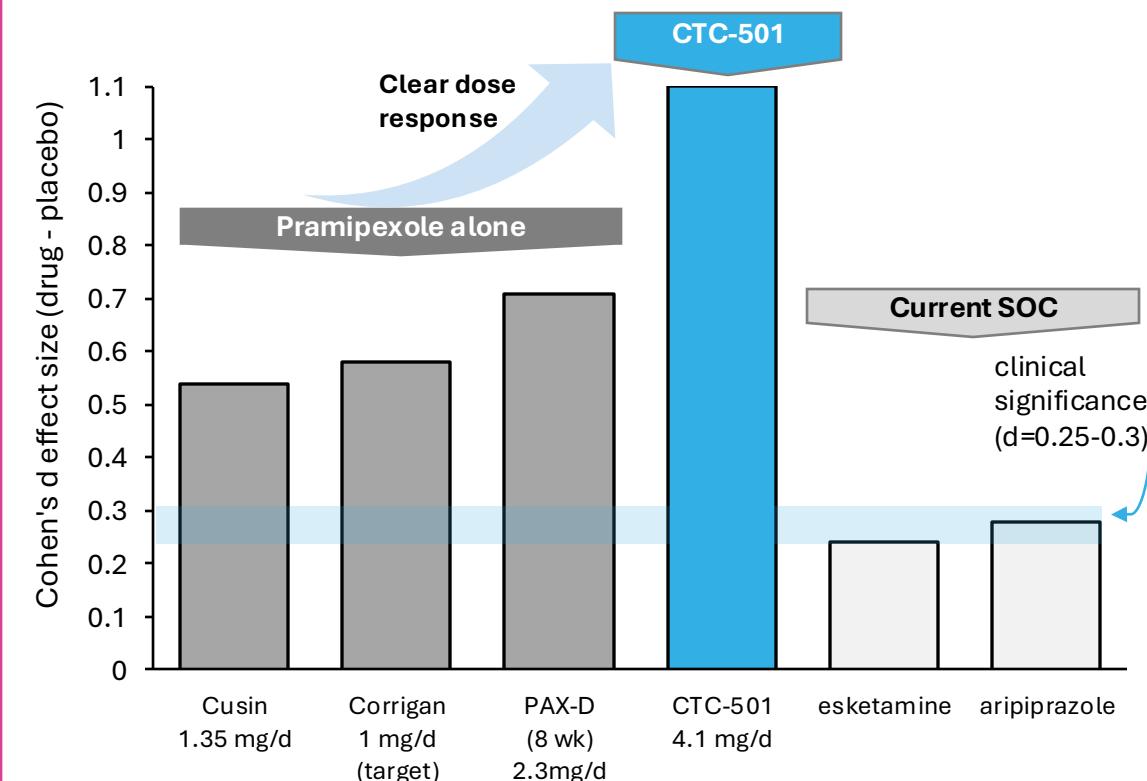
Note: The results shown above are not based on head-to-head trials between the products or product candidates. Study designs and protocols differed, and results may not be comparable.

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

Study qualifying as pivotal is subject to FDA feedback and review of data
TLD: topline data

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

[1]Based on Chase's interactions with the FDA to date; intended regulatory strategy is subject to FDA feedback
Study qualifying as pivotal is subject to FDA feedback and review of data

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 buproprion 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

	COBENFY	Auvelity
Innovation	Antagonistic combination to mitigate AEs in schizophrenia (SZ)	Synergistic combination of two generic medications
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)
Projected/Est. Peak Revenue*	$3bn - $6bn	$1bn - $3bn

Recent combination analogs demonstrate...

- improved tolerability,
- larger effect size,
- more convenient dosing,
- and novel MoA in disease...

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

ALTO-203
(H3 inverse agonist)

H3

↑ **neurotransmitter release**
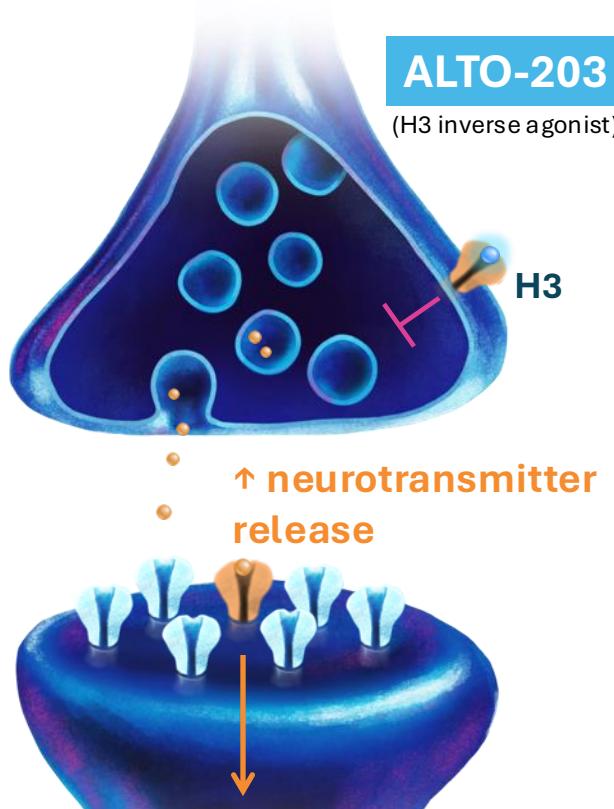
Region- and receptor-specific effects
(mood, cognition, energy, motivation, wakefulness)

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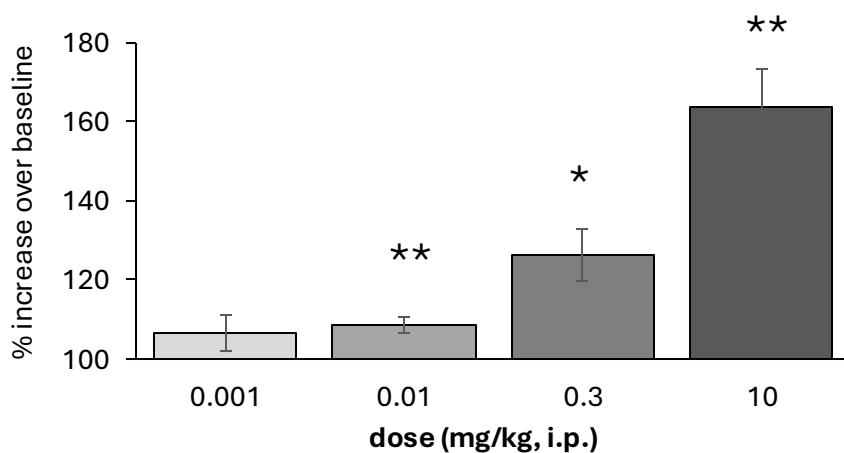
ALTO-203 results plotted as percent increase over baseline from 0-150min post-dose, to compare to timing of pitolisant/modafinil study outcome (* p<0.05; ** p<0.01)

Pitolisant does not increase reward system dopamine (modafinil used as a comparator)
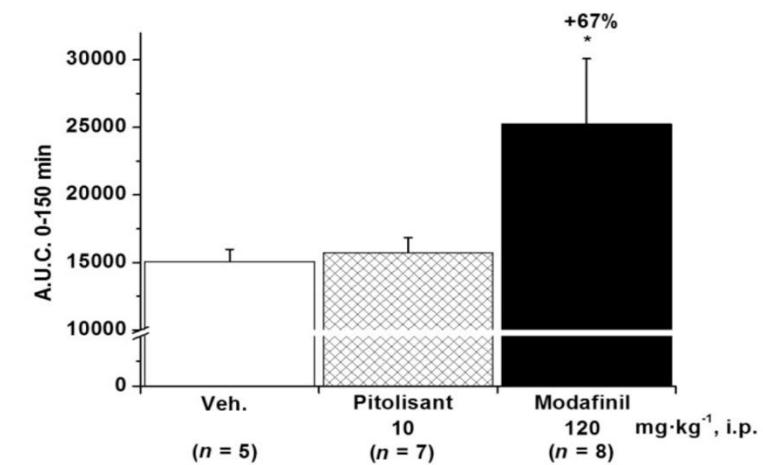
Uguen et al., BJP, 2013

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	☑	☑

ALTO NEUROSCIENCE

Novel investigational PDE4 inhibitor with broad pro-cognitive activity

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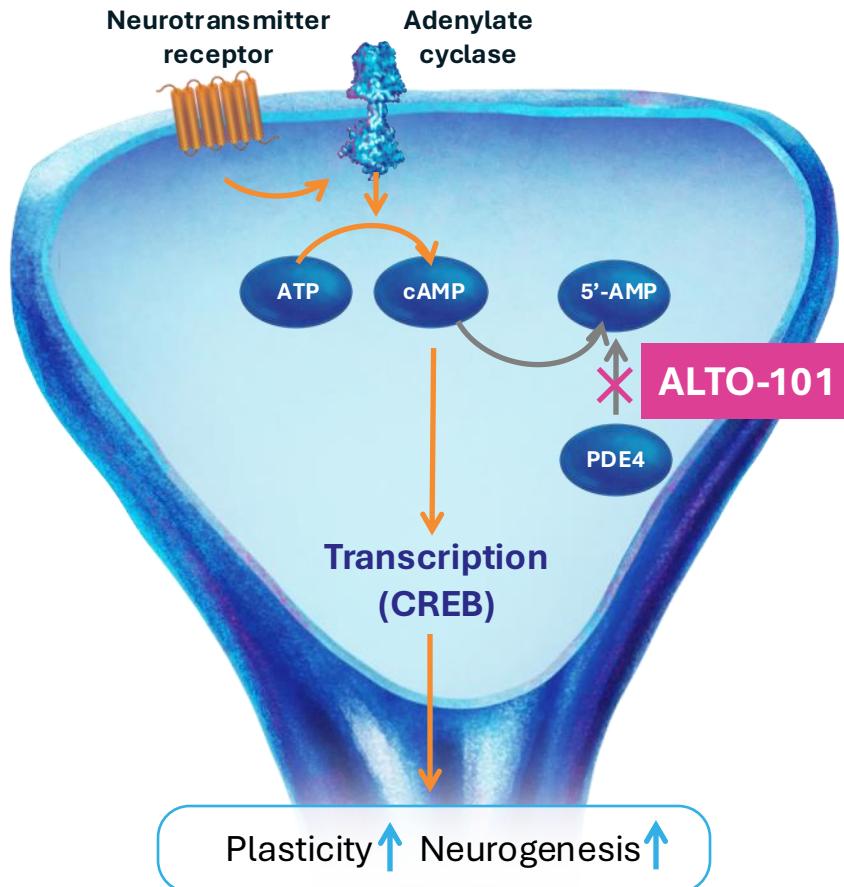
PDE4 inhibition has been of **long-term interest** as a potential pro-cognitive and antidepressant MOA

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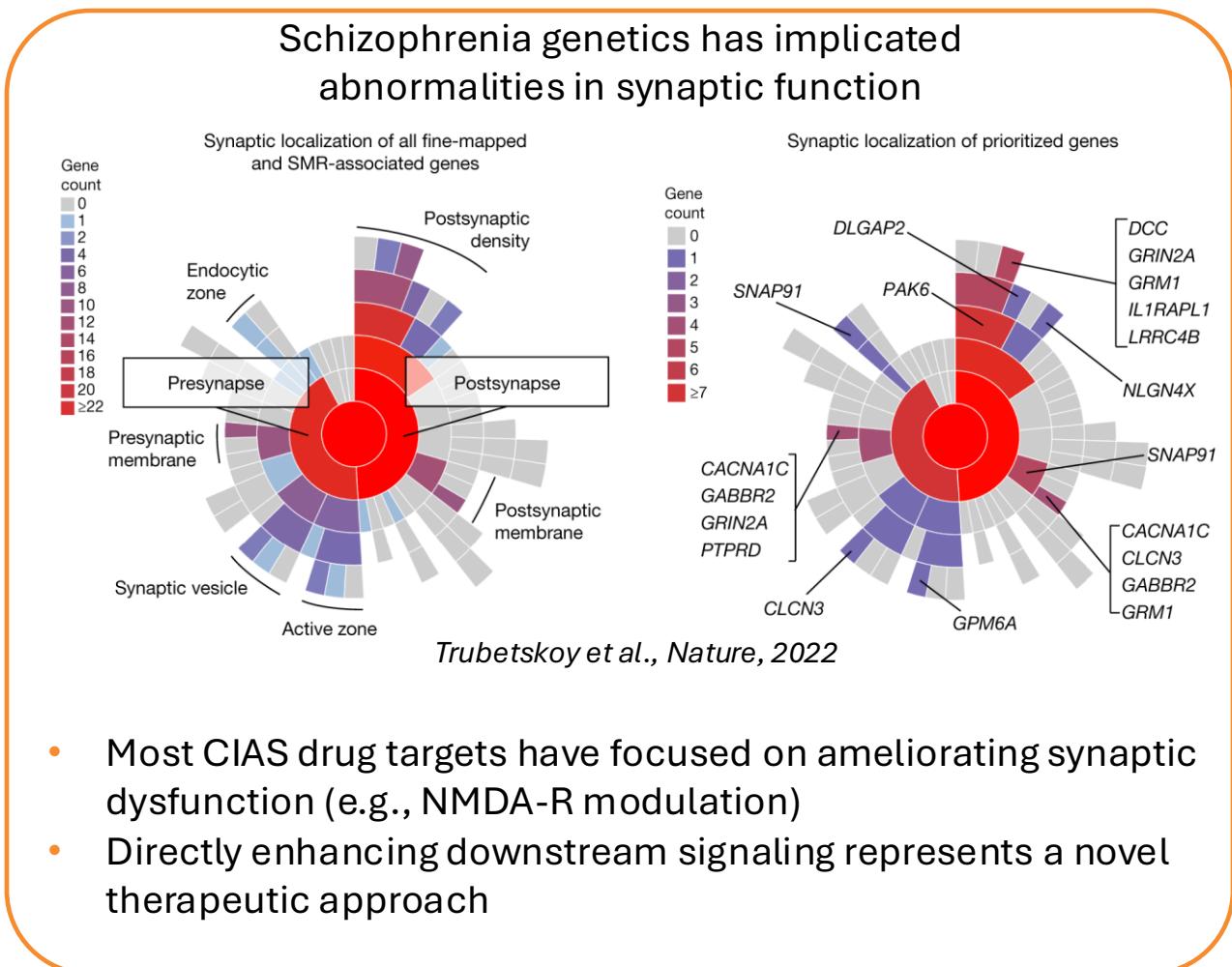
Theta EEG response to auditory stimuli links CIAS pathophysiology and drug PD activity

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

Healthy

Schizophrenia

r=0.29
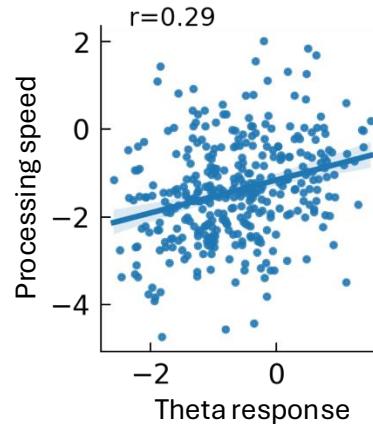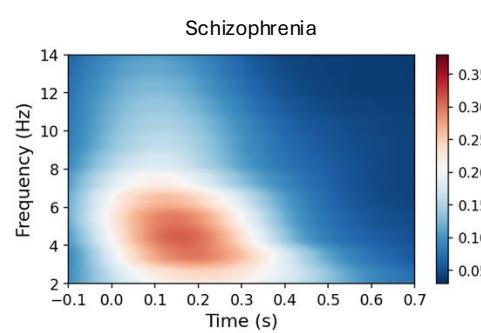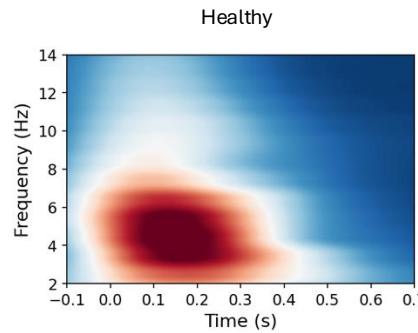
Reduced theta response correlates with poor cognition and worse processing speed

*Wang et al, SOBP 2024

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

Placebo

d=-0.33
p=0.09
0.5 mg

d=-1.05
p=0.00002
1.5 mg

Processing speed

d=0.63
p=0.006

d=0.32
p=0.16

improvement

r=0.49
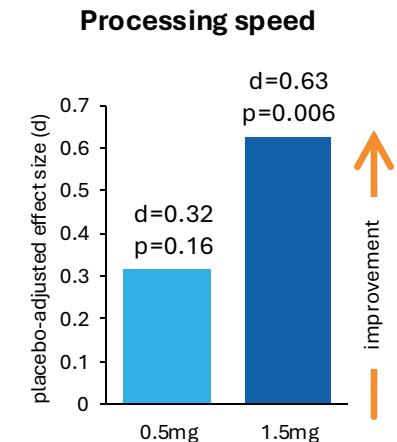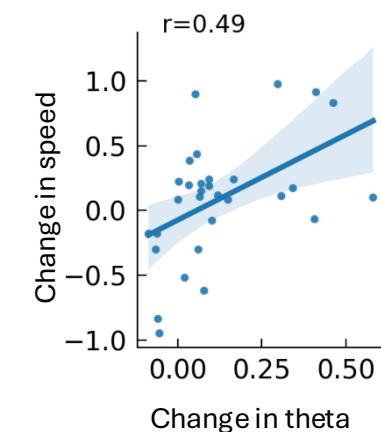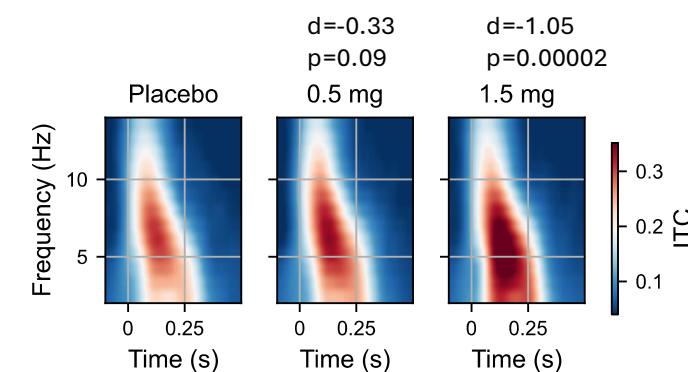
Greater increase in theta response by ALTO-101 correlates with greater improvements in processing speed

ALTO-101 rescues blunted EEG theta response in a preclinical model of schizophrenia

- Schizophrenia is thought to involve NMDA receptor hypofunction
- Administration of MK-801, an NMDA antagonist, models neural and behavioral abnormalities in schizophrenia
- MK-801 reduces EEG theta response in the same auditory task as used in humans
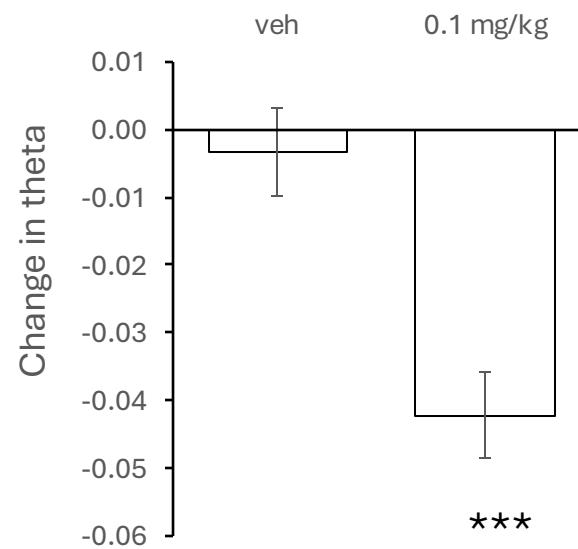
ALTO-101 leads to a dose-dependent rescue of the theta response abnormality induced by MK-801, supporting Alto's Phase 1 human findings and Phase 2 POC study primary outcome

MK-801 0.1mg/kg in all arms

Sundar et al., SOBP, 2025
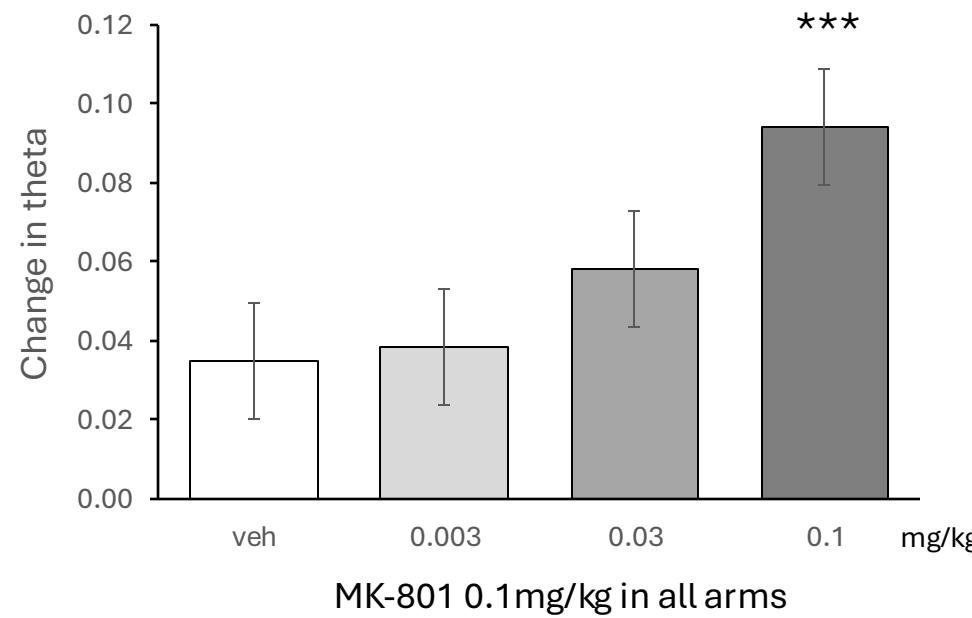
EEG effects of ALTO-101 replicate previously reported PDE4i effects in schizophrenia using a similar study design

ALTO-101 increases mismatch negativity amplitude, a frequently studied schizophrenia biomarker
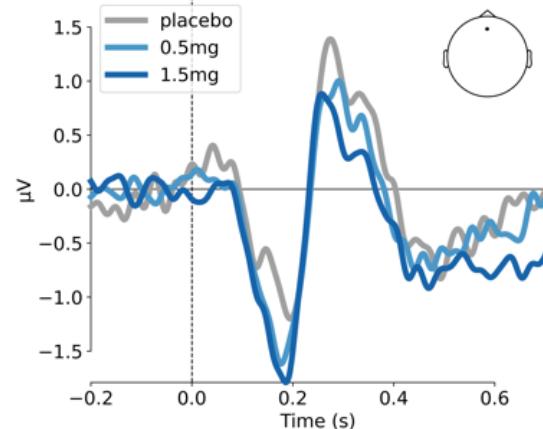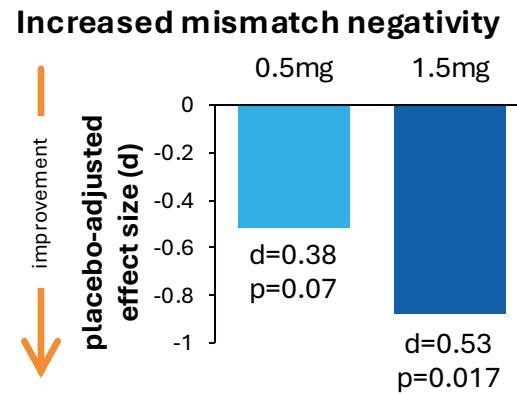
Similar effect demonstrated in an 8-day cross-over treatment study in schizophrenia with the PDE4i roflumilast
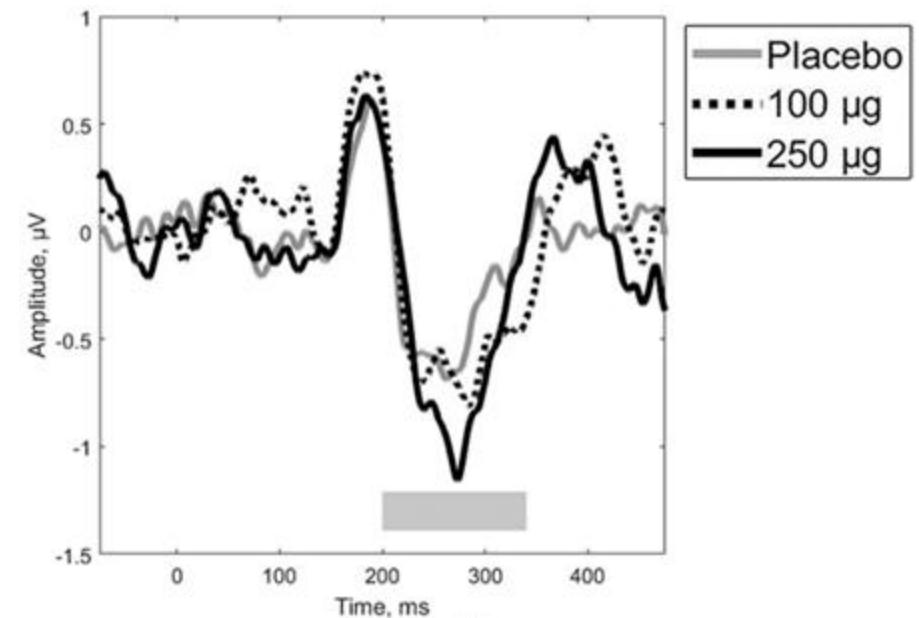
Gilleen et al., J Psychopharm, 2020

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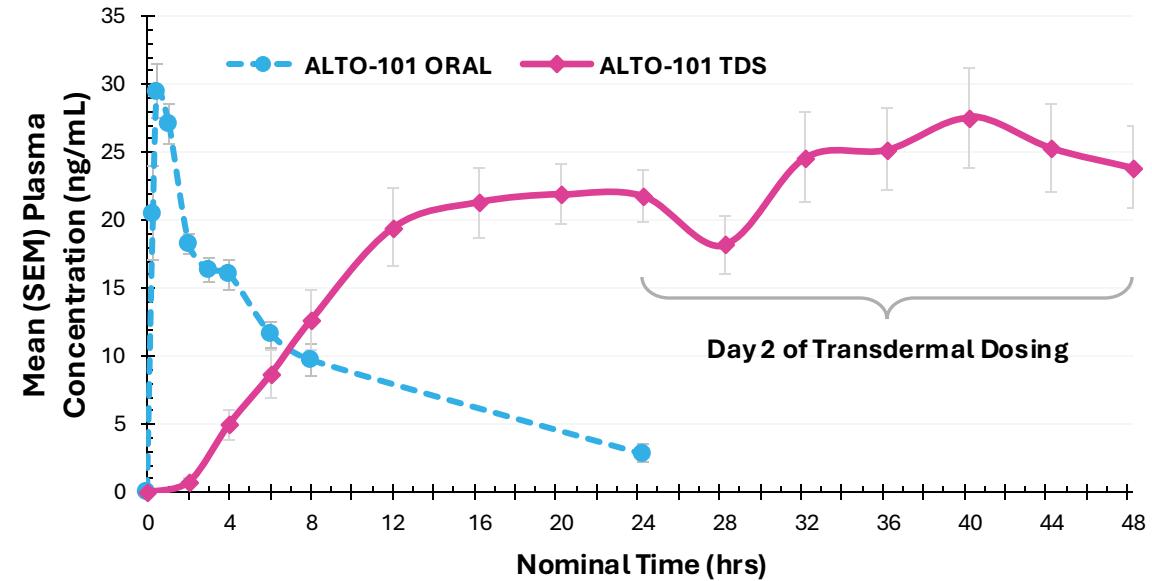
Related Adverse Events >5%	ALTO-101 Oral Formulation (N = 15)	ALTO-101 TDS Formulation (N = 14)
PDE-4i Class-Related AEs		
Dizziness, n (%)	6 (40.0)	1 (7.1)
Nausea, n (%)	3 (20.0)	0
Diarrhea, n (%)	1 (6.7)	0
Dyspepsia, n (%)	1 (6.7)	0
Vertigo, n (%)	1 (6.7)	0
Other AEs		
Headache, n (%)	2 (13.3)	5 (35.7)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

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)

Treatment Period 1:

- **2-way Cross-over, Double-blind, Placebo-controlled design**

Screening Visits 1 and 2

Daily ALTO-101 TDS for 10 days

Daily PBO TDS for 10 days

Treatment Period 2:

Daily ALTO-101 TDS for 10 days

Daily PBO TDS for 10 days

Washout 6-14 days

Safety Follow-up Visit

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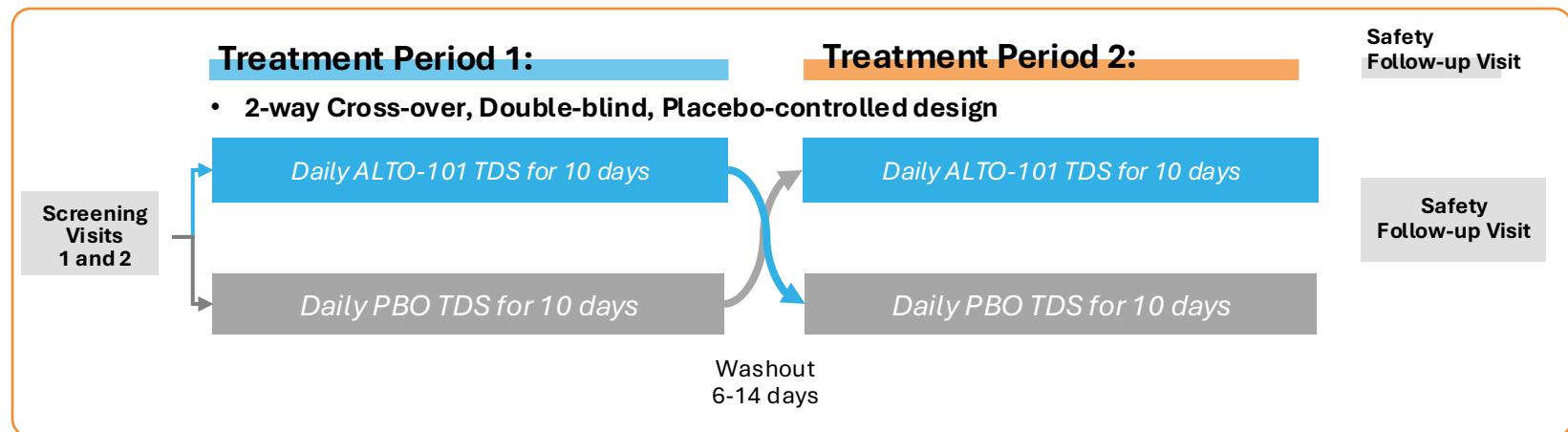
Primary outcome: Effects of ALTO-101 on theta band activity, an EEG-based measure of PD activity correlating to cognitive function, after 5 and 10 days of dosing of ALTO-101 compared to placebo in two treatment periods

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

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

ALTO NEUROSCIENCE

ALTO-100

MDD and Bipolar Depression

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

Healthy

MDD with poor memory/cognition

Post-treatment

ALTO-100

Hippocampus

Reduction in hippocampal plasticity and neurogenesis (contributing to mood + memory)

Increase in Plasticity & Neurogenesis

BDNF

TrkB

GPCRs

Akt

MEK

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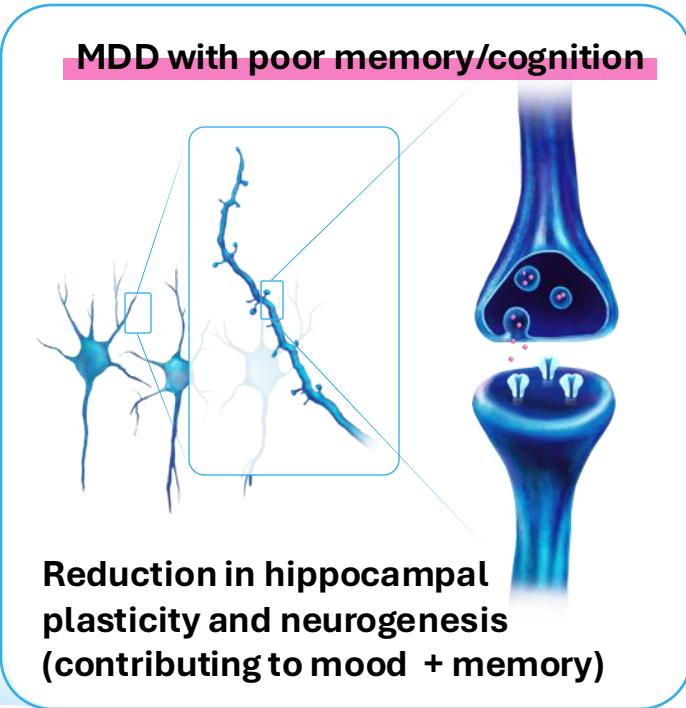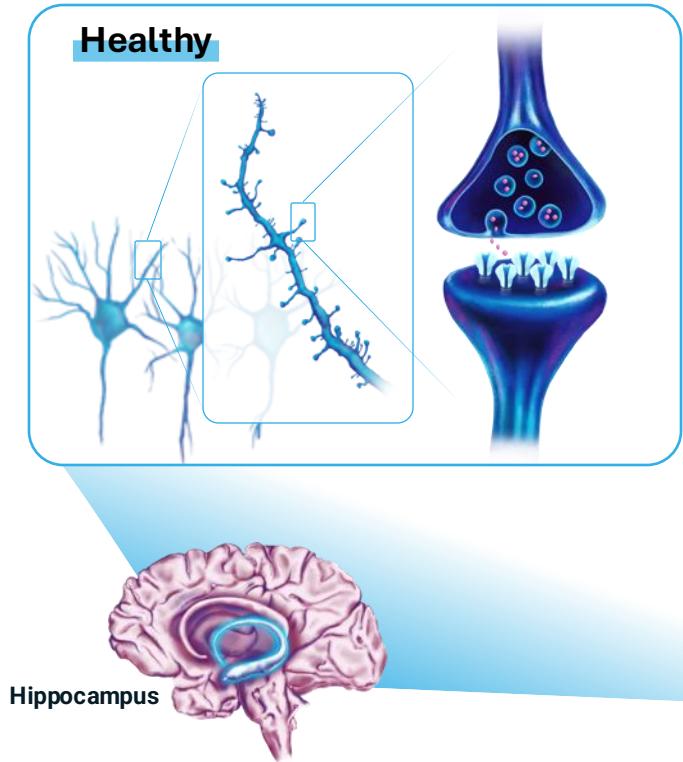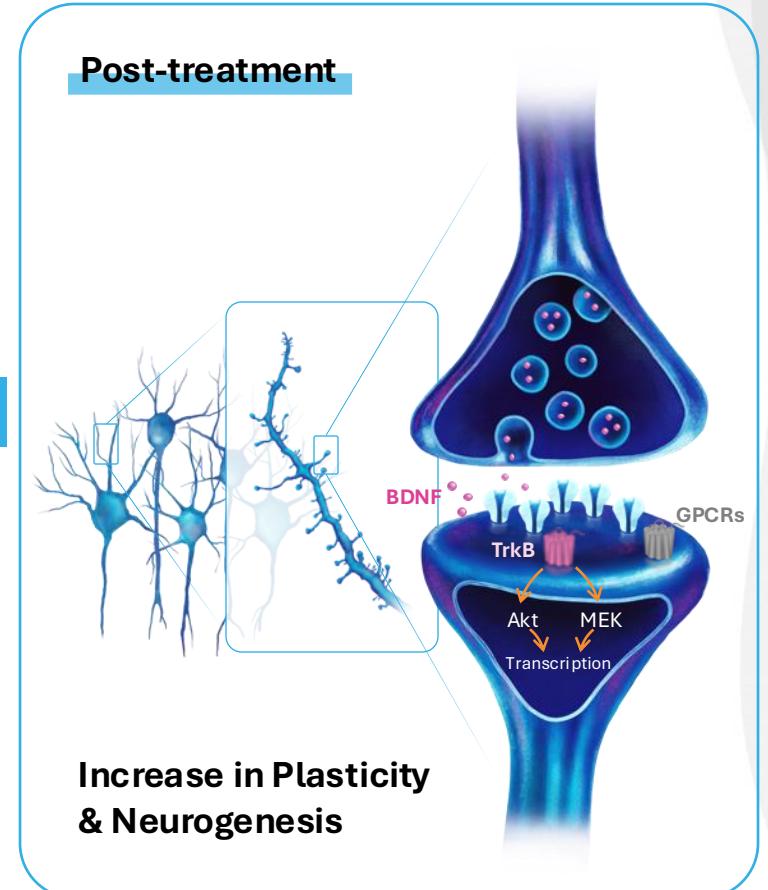
ALTO-100: developed to enhance hippocampal neuroplasticity, and improve cognition and mood

Plasticity ↑ Neurogenesis ↑
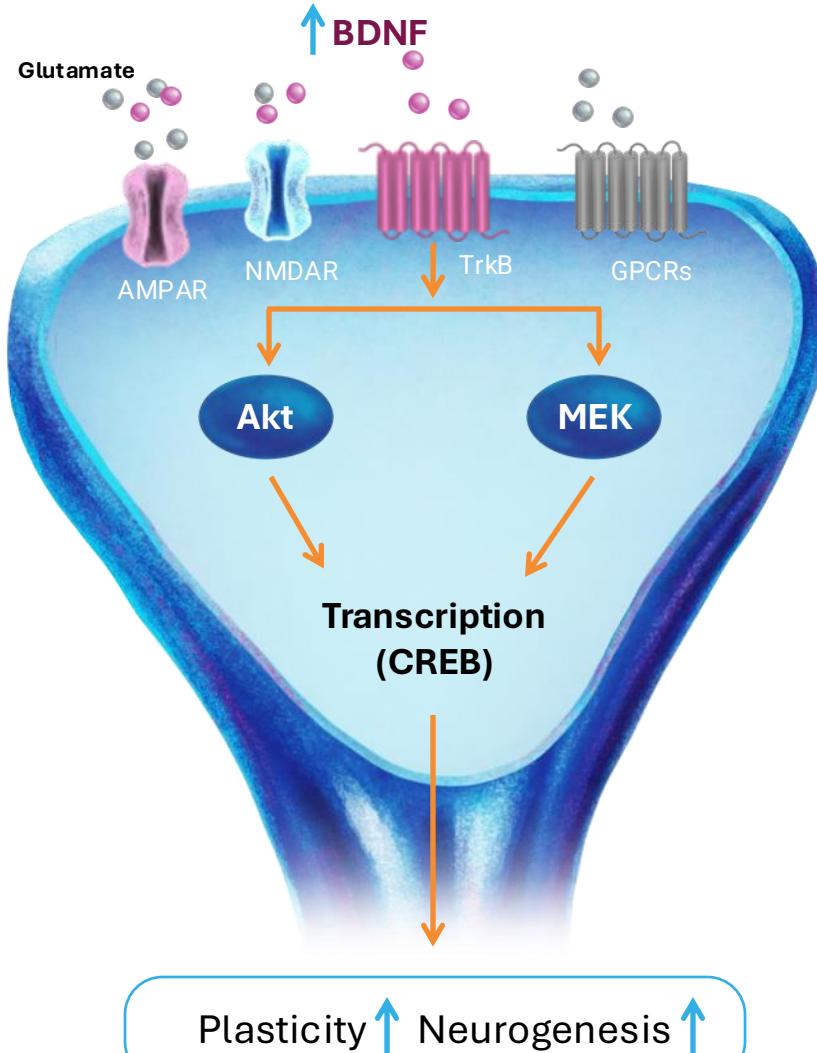
Identified based on a neurogenesis functional screen

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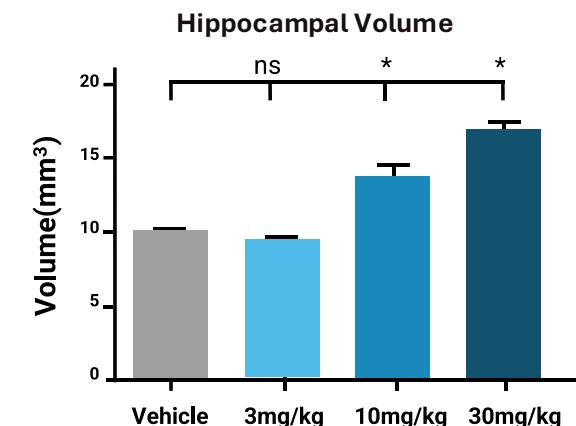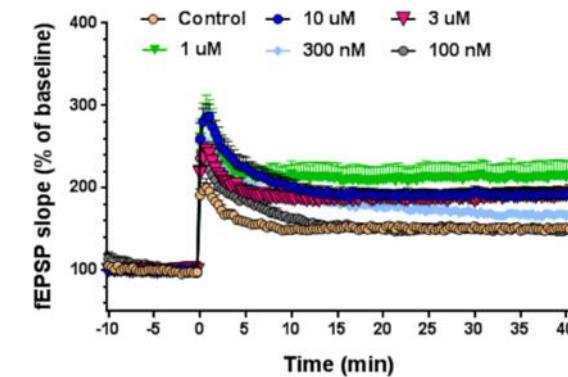
Completed ALTO-100 Phase 2b biomarker-guided trial in MDD
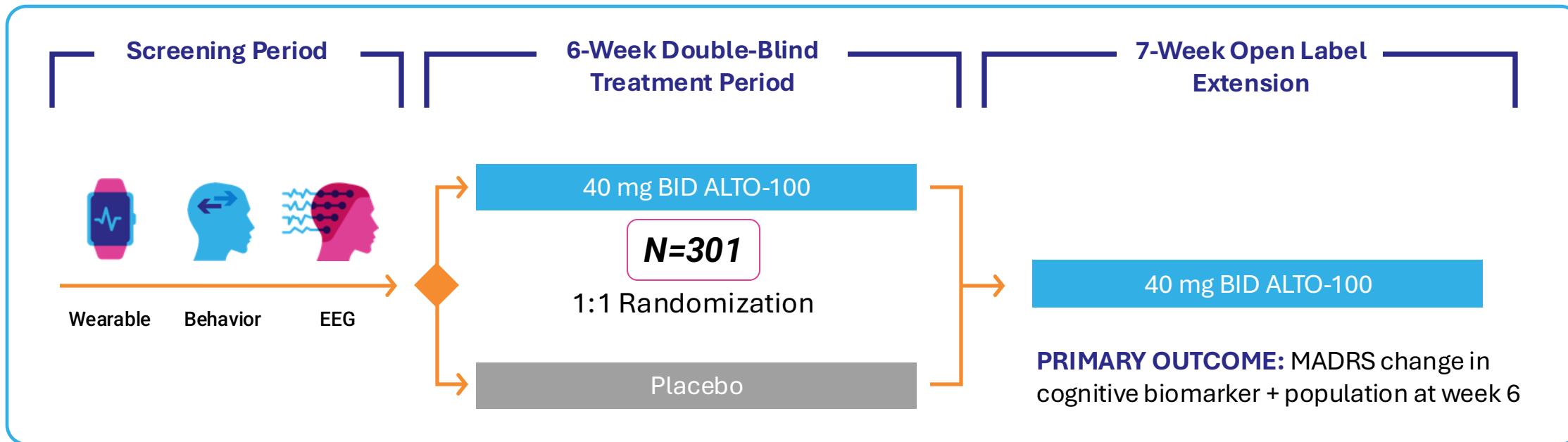
Screening Period

Wearable Behavior EEG

6-Week Double-Blind Treatment Period

40 mg BID ALTO-100

N=301

1:1 Randomization

Placebo

7-Week Open Label Extension

40 mg BID ALTO-100

PRIMARY OUTCOME: MADRS change in cognitive biomarker + population at week 6

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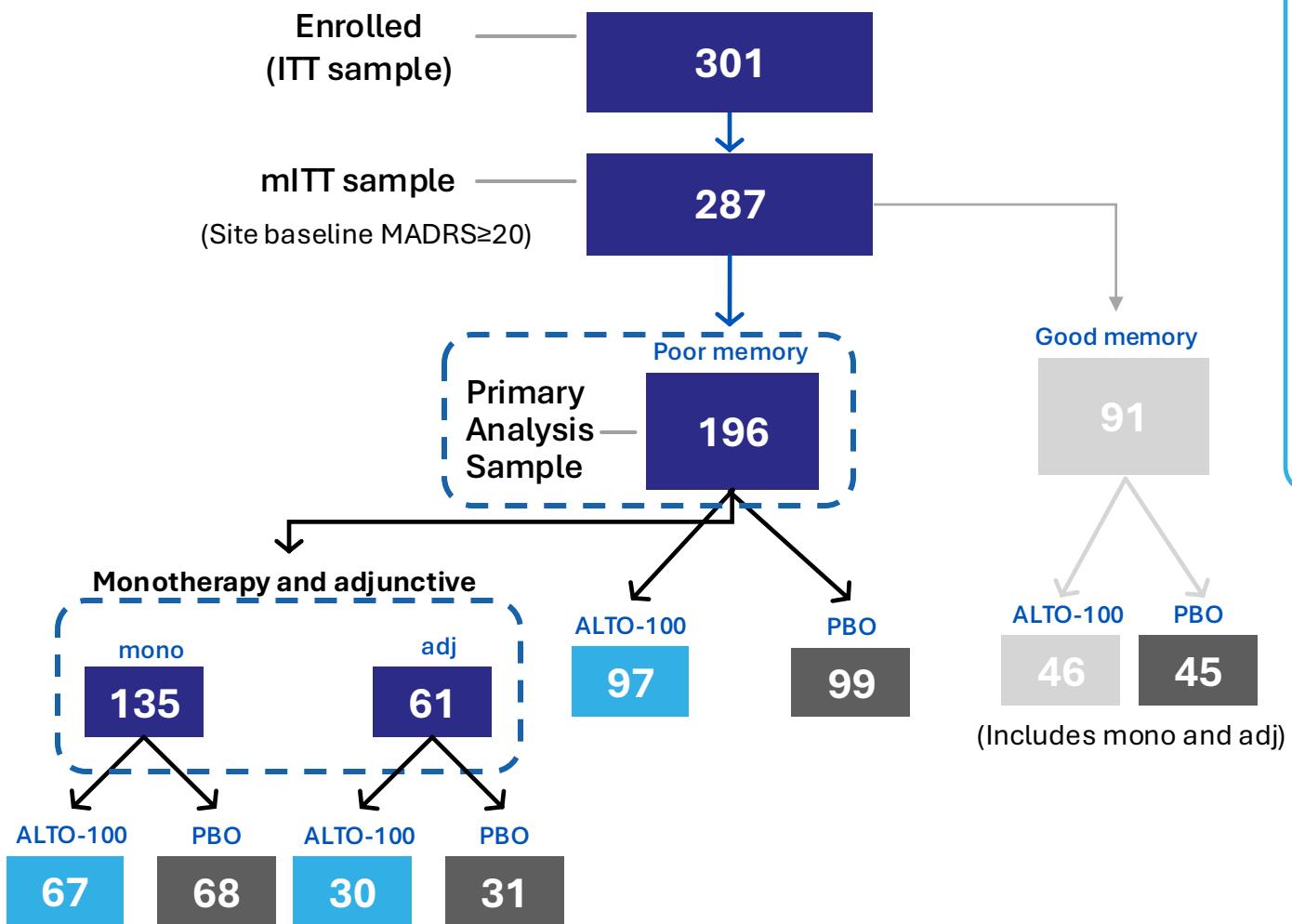
Screening visit structure (key elements):
1. Visit 1:
   - Severity and diagnosis (at site), PHQ
   - SAFER including MADRS (MGH)**
2. Visit 2:
   - Biomarker baseline (at site), PHQ
3. Visit 3:
   - Clinical baseline MADRS (at site), PHQ

* 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

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
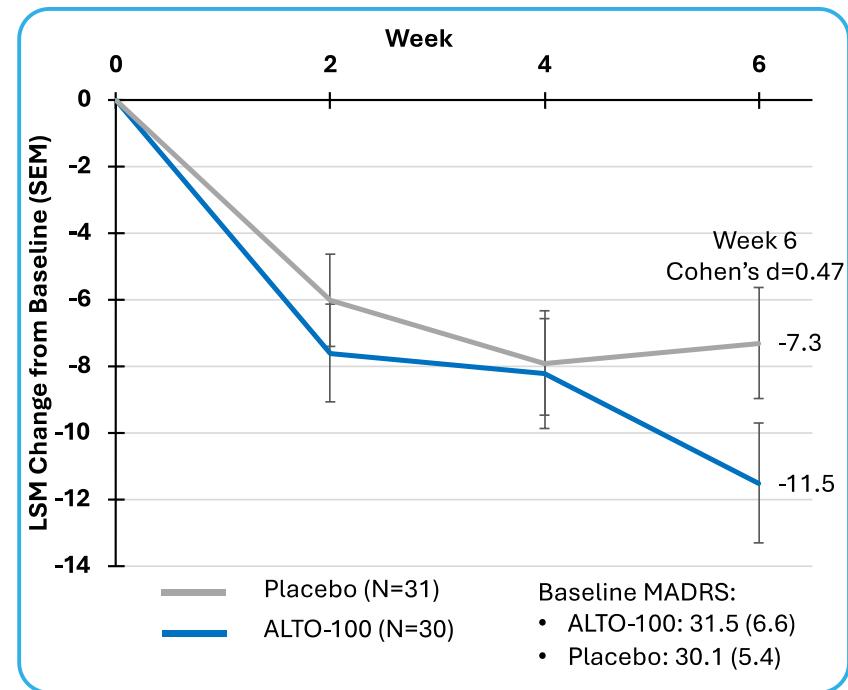
Compliance rate among monotherapy and adjunctive patients in PK sample*
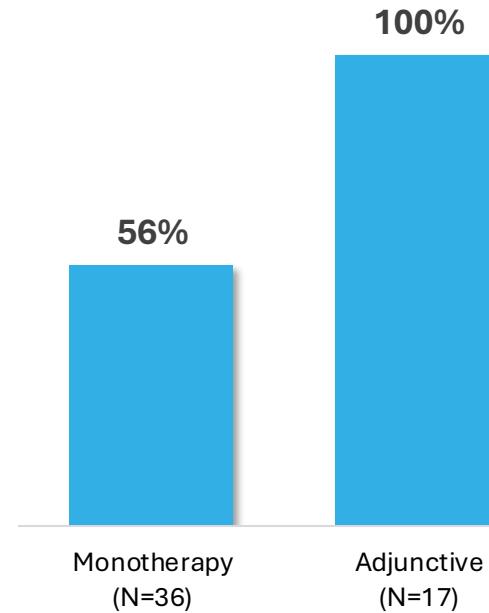
Only a subset of sites within the study were setup to evaluate PK levels

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

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

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

Bio + confirmed compliant patients vs. all placebo
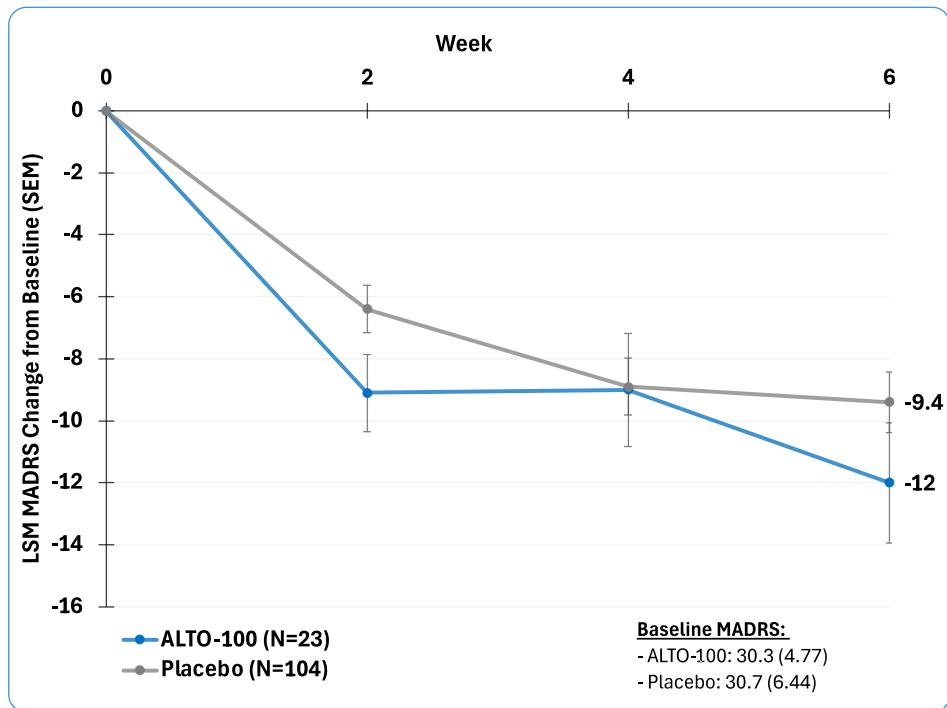
Bio + vs. bio – in confirmed compliant patients

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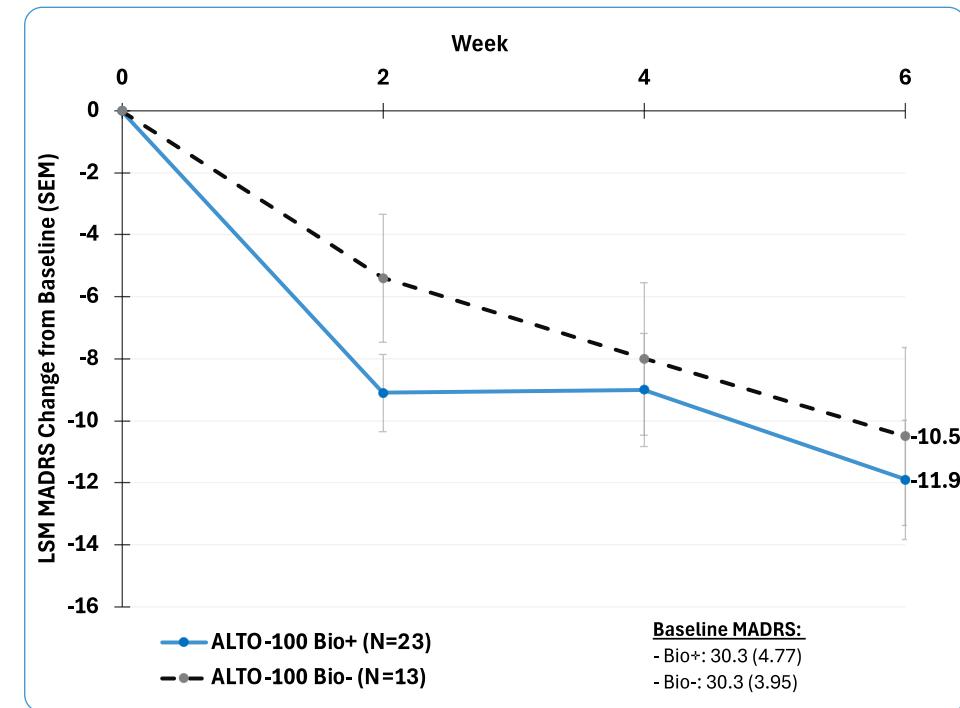
ALTO-100 was well tolerated

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

ALTO NEUROSCIENCE

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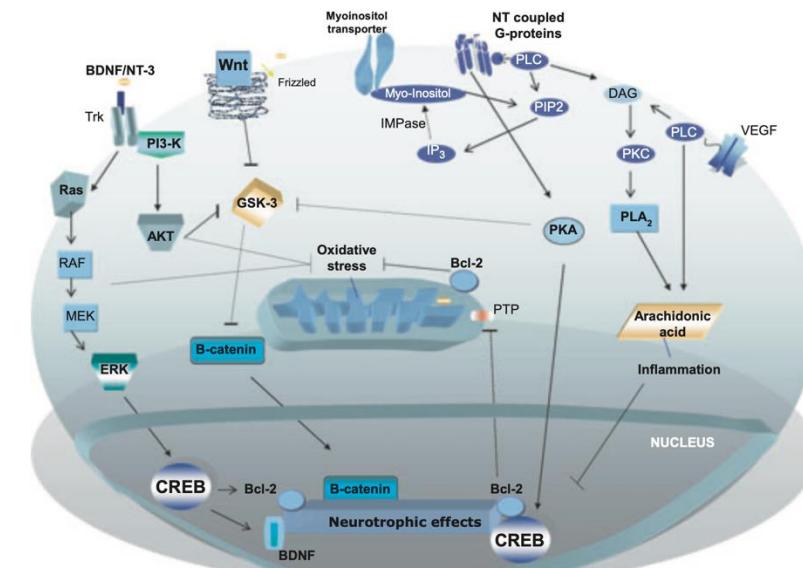
Soeiro-de-Souza et al, *Acta Psych Scan*, 2012

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

Evaluating ALTO-100 as an ***adjunctive treatment*** to an existing mood stabilizer (no antipsychotics)
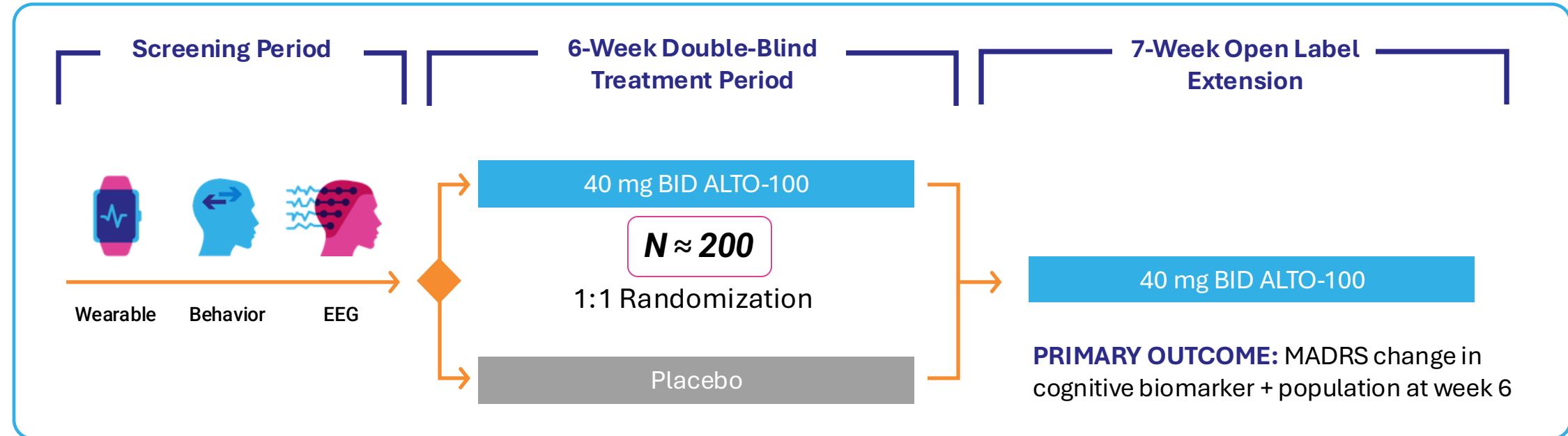
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$N \approx 200$

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- **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

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

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ultragenyx · Bristol Myers Squibb · ALKAHEST A Grifols Company · teva · Takeda · Pfizer · Lundbeck

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Andrew Dreyfus
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Gwill York
Founding Managing Director, Lighthouse Capital Partners

Amit Etkin, MD, PhD
CEO, Alto Neuroscience

Multiple near-term clinical milestones expected

Capitalized through multiple clinical milestones:
$161mm^ as of March 31, 2025 → Expected cash runway into 2028

2025

☑ **ALTO-203 MDD POC data (2Q 2025)** ☐ **ALTO-101 CIAS POC data (2H 2025)**

2026

☐ **ALTO-300 Phase 2b MDD data (mid-2026)** ☐ **ALTO-100 Phase 2b BPD data (2H 2026)**

2027

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