# ALTO NEUROSCIENCE

**NYSE:** ANRO — Investor Day, Sept. 9, 2024

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***ALTO-100 Phase 2b MDD data remains blinded to the Alto team – database locking activities ongoing***

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# Precision Medicine for the Brain is Here.

## OUR VISION

To redefine the approach to psychiatric drug development which matches the right patient with the right Alto drug

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# Today's participants

## Alto executive management team

**Amit Etkin, MD PhD**
Chief Executive Officer

**Adam Savitz, MD PhD**
Chief Medical Officer

**Michael Hanley**
Chief Operating Officer

**Jessica Powell**
Chief Development Officer

**Nick Smith**
Chief Financial Officer

## External expert perspective

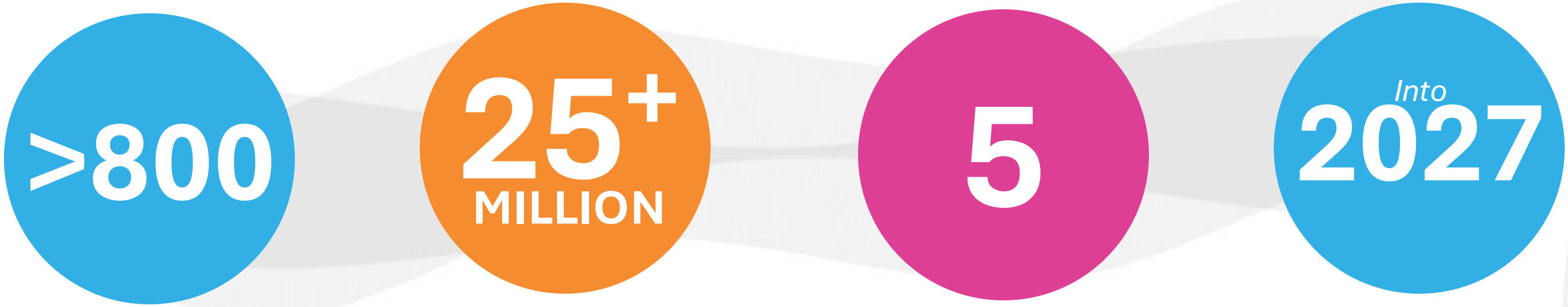
**Gerard Sanacora, PhD MD**
*George D. and Esther S. Gross Professor of Psychiatry, Director of Yale Depression Research Program, Yale University*

# Today's Agenda

- **Alto Neuroscience Overview and Background** – Amit Etkin, MD, PhD – Founder & CEO
- **Understanding Major Depressive Disorder (MDD) with Poor Memory** - Amit Etkin, MD, PhD – Founder & CEO
  - *Clinician Perspective - Dr. Gerard Sanacora*
- **Mechanism of ALTO-100 & Link to Patient Population** – Amit Etkin, MD, PhD – Founder & CEO
- **ALTO-100 Clinical Development**
  - Development history – Amit Ekin, MD, PhD – Founder & CEO
  - Phase 2b clinical study overview and baseline characteristics
    - Adam Savitz, MD, PhD - Chief Medical Officer
    - Jessica Powell – Chief Development Officer
- **Commercialization Considerations** – Michael Hanley – Chief Operating Officer
  - Overview of cognition biomarker data – audience performance
- **Expert Perspective** - *Gerard Sanacora, PhD MD -- George D. and Esther S. Gross Professor of Psychiatry, Director of Yale Depression Research Program, Yale University*
- **Question & Answer**

# Alto by the numbers

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




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

**Patient Impact**
Opportunity across the portfolio

**Phase 2 Data Read Outs**
Expected in the next 2.5 years

**Cash**
Runway

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# A core problem in psychiatry: unguided treatments work poorly

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

Average

### Current Approach

Trial-and-error, mostly failures

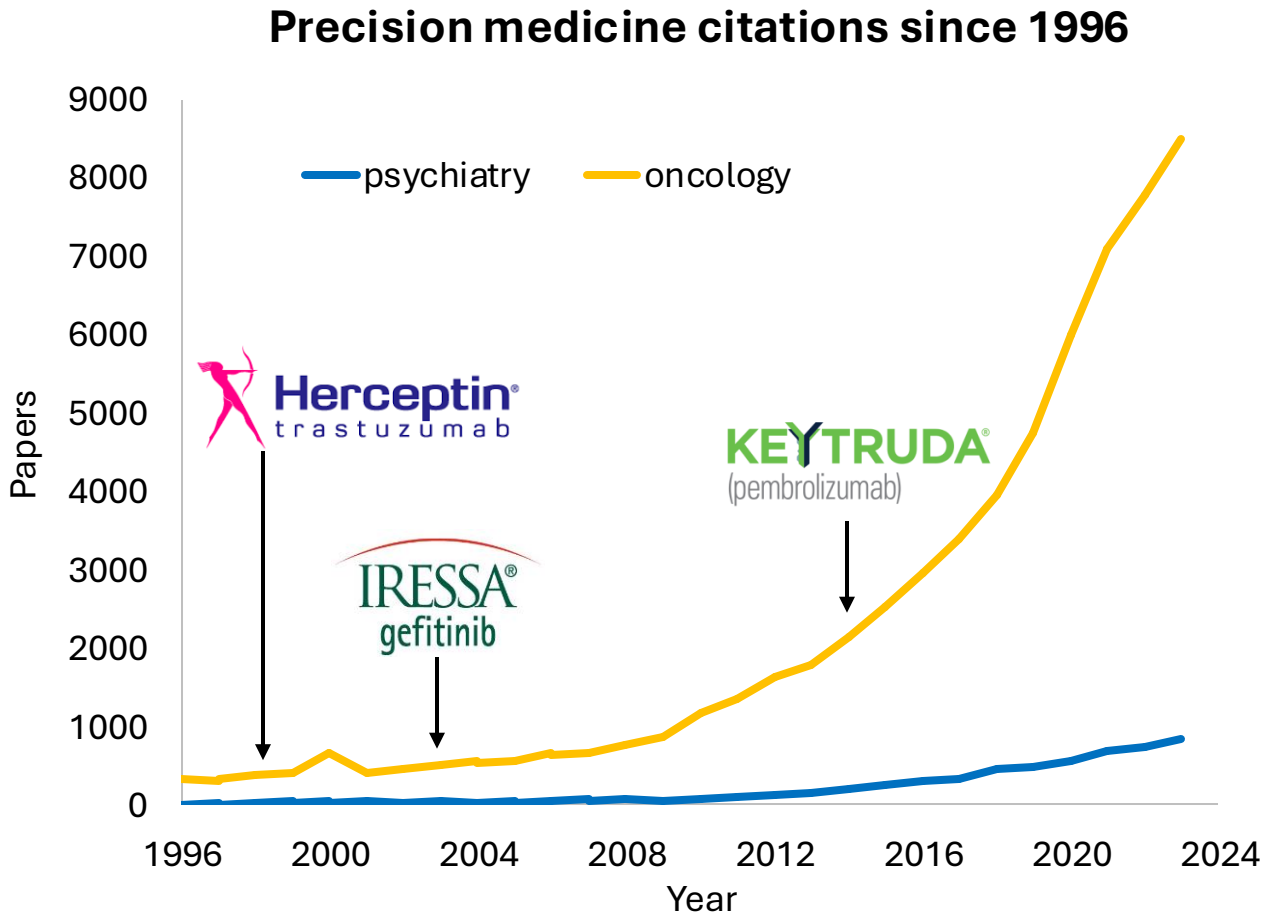
Average

### Alto's Precision Psychiatry Approach

Differentiated drug profile
Broad utilization of pharmacodynamic biomarkers
Prospectively replicate predictive biomarkers for improved patient selection

# Precision medicine has brought substantial innovation to other areas, yet psychiatry is largely untapped

- Precision oncology impact has increased exponentially since the early 2010s with the rise of immuno-oncology and scalable approaches
- While growing, the rate of increase in precision psychiatry has lagged substantially despite similar technological advancements for facilitating innovation
- Precision medicine in psychiatry presents an opportunity to target large high-need markets with little previous innovation




Pubmed results: precision + treatment + [psychiatry/oncology]

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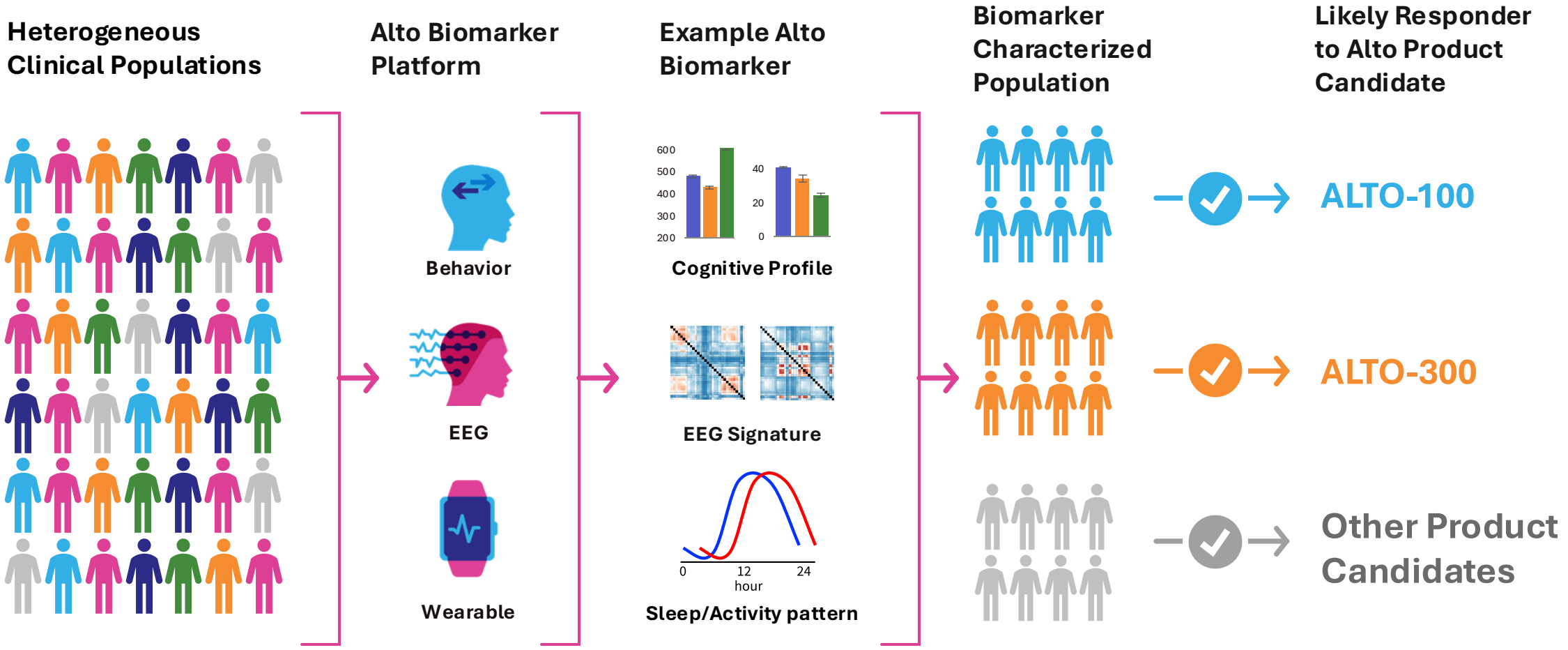
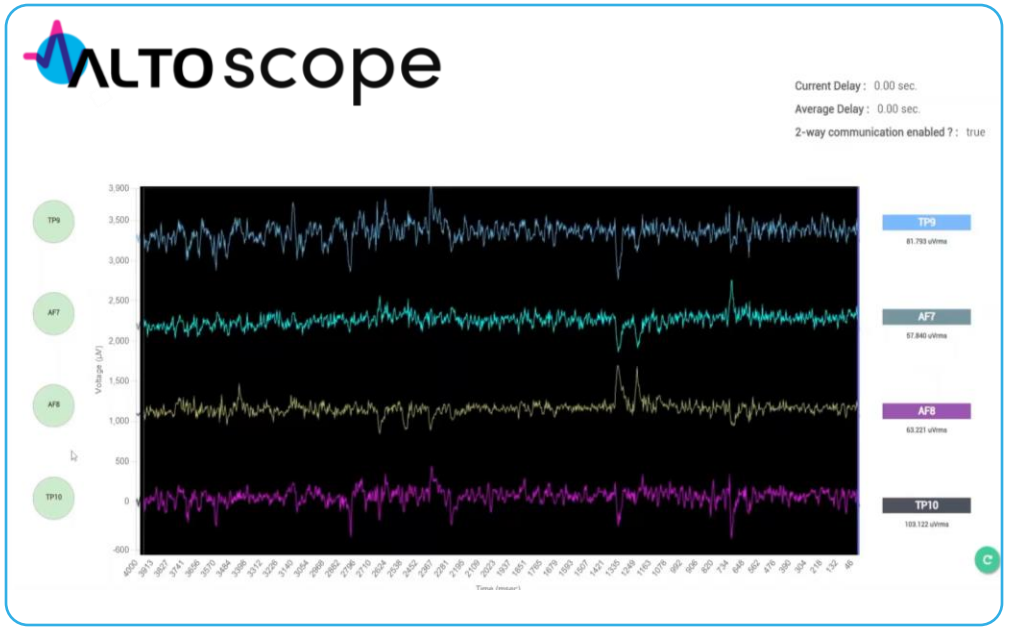
# We leverage a suite of biomarkers designed to segment patients and drive improved clinical outcomes



# Leveraging proprietary tools, anticipating commercial scale

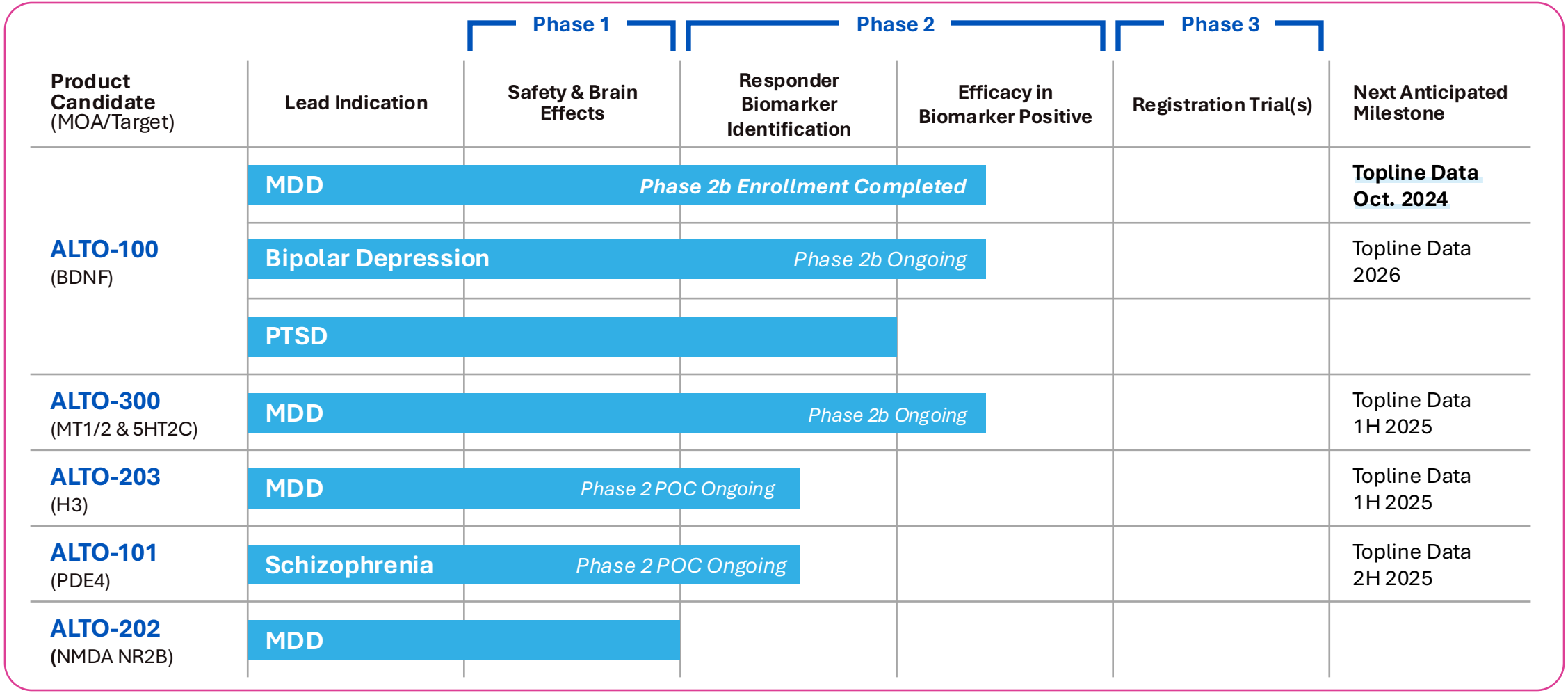
## ALTO-100 biomarker is cognitive test-based


## ALTO-300 biomarker is EEG-based



# First biomarker-driven pipeline for neuropsychiatric conditions

Advancing towards multiple near-term milestones across pipeline of independent programs leveraging our biomarker strategy to systemically reduce development risks



# Addressing common investor questions

- How do I think about this novel MoA (i.e., not targeted by others)?
- What weight and interpretation do I give the original third-party all-comer Phase 2 study?
- How much does the single-arm Phase 2a trial with a prospectively replicated enrichment reduce development risk of the Phase 2b study?
- To what degree has placebo response been accounted for, either in the biomarker selection or trial execution?
- What does a potential Phase 3 program look like, and can Alto execute it through your in-house clinical operations team and approach?
- Given that this precision psychiatry approach is new for clinicians, how readily will clinicians adopt the biomarker tests?

# ALTO-100 could be a highly differentiated new treatment option in an underserved patient population

| | |
|---|---|
| **Target Population(s)** | 1. MDD with poor memory biomarker<br>2. Bipolar depression with poor memory biomarker |
| **MoA and Route of Administration** | Potentially first-in-class oral small-molecule, enhancing hippocampal neuroplasticity |
| **Efficacy Target** | Effect size ≥ 0.3 in poor cognition patients with MDD |
| **Safety** | Favorable tolerability<br>• No weight gain or movement disorders<br>• No sexual dysfunction |
| **Regulatory, IP & Commercial** | Data exclusivity: 5 years NCE protection<br>IP estate protecting to early 2040s<br>Patient identification through web-based cognitive test |

# **MDD with poor memory/cognition:** Mechanistic insights into a depression subgroup with high unmet need

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# The neuroplasticity deficit framework for MDD has been a focus for over two decades

**Overview of this framework:**

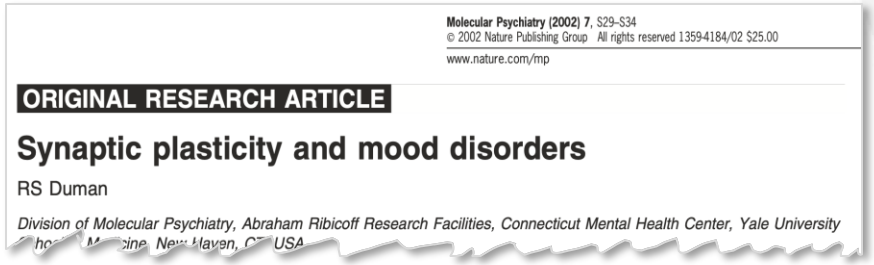
- Neuroplasticity: the brain's ability to adapt to changing external or internal stimuli; underlies functions like memory and cognition
- Neuroplasticity deficit framework of depression: impaired neuroplasticity results in being "stuck" in maladaptive negative emotional biases, together with poor cognition (sometimes called the neurotrophin hypothesis)
- Supported by extensive literature

**No prior effort has taken Alto's differentiated approach:**

- Selectively target patients based on demonstrated evidence of impaired hippocampal neuroplasticity
- Product candidate specifically designed to enhance neuroplasticity

**Example early reviews:**

**2002**


Molecular Psychiatry (2002) 7, S29–S34
© 2002 Nature Publishing Group All rights reserved 1359-4184/02 $25.00
www.nature.com/mp

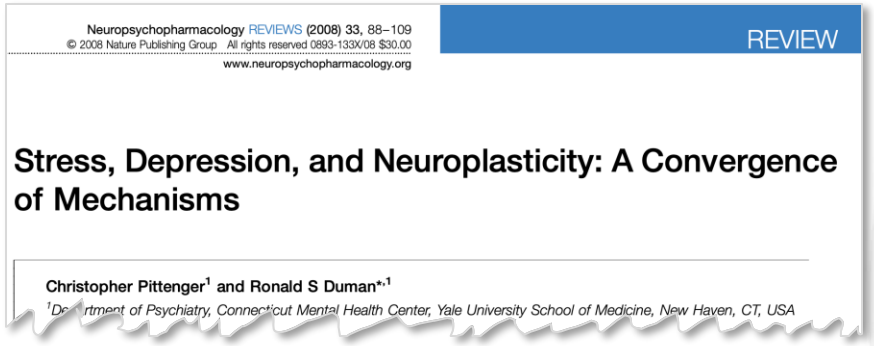
ORIGINAL RESEARCH ARTICLE

Synaptic plasticity and mood disorders

RS Duman

Division of Molecular Psychiatry, Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, Yale University

**2008**


Neuropsychopharmacology REVIEWS (2008) 33, 88–109
© 2008 Nature Publishing Group All rights reserved 0893-133X/08 $30.00
www.neuropsychopharmacology.org

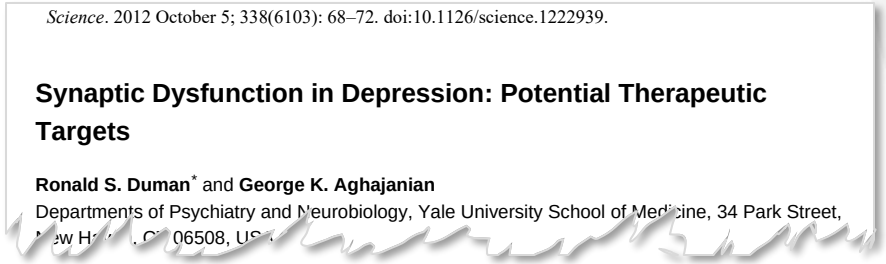
REVIEW

Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms

Christopher Pittenger[1] and Ronald S Duman*,[1]

[1]Department of Psychiatry, Connecticut Mental Health Center, Yale University School of Medicine, New Haven, CT, USA

**2012**


*Science*. 2012 October 5; 338(6103): 68–72. doi:10.1126/science.1222939.

Synaptic Dysfunction in Depression: Potential Therapeutic Targets

**Ronald S. Duman*** and **George K. Aghajanian**

Departments of Psychiatry and Neurobiology, Yale University School of Medicine, 34 Park Street,

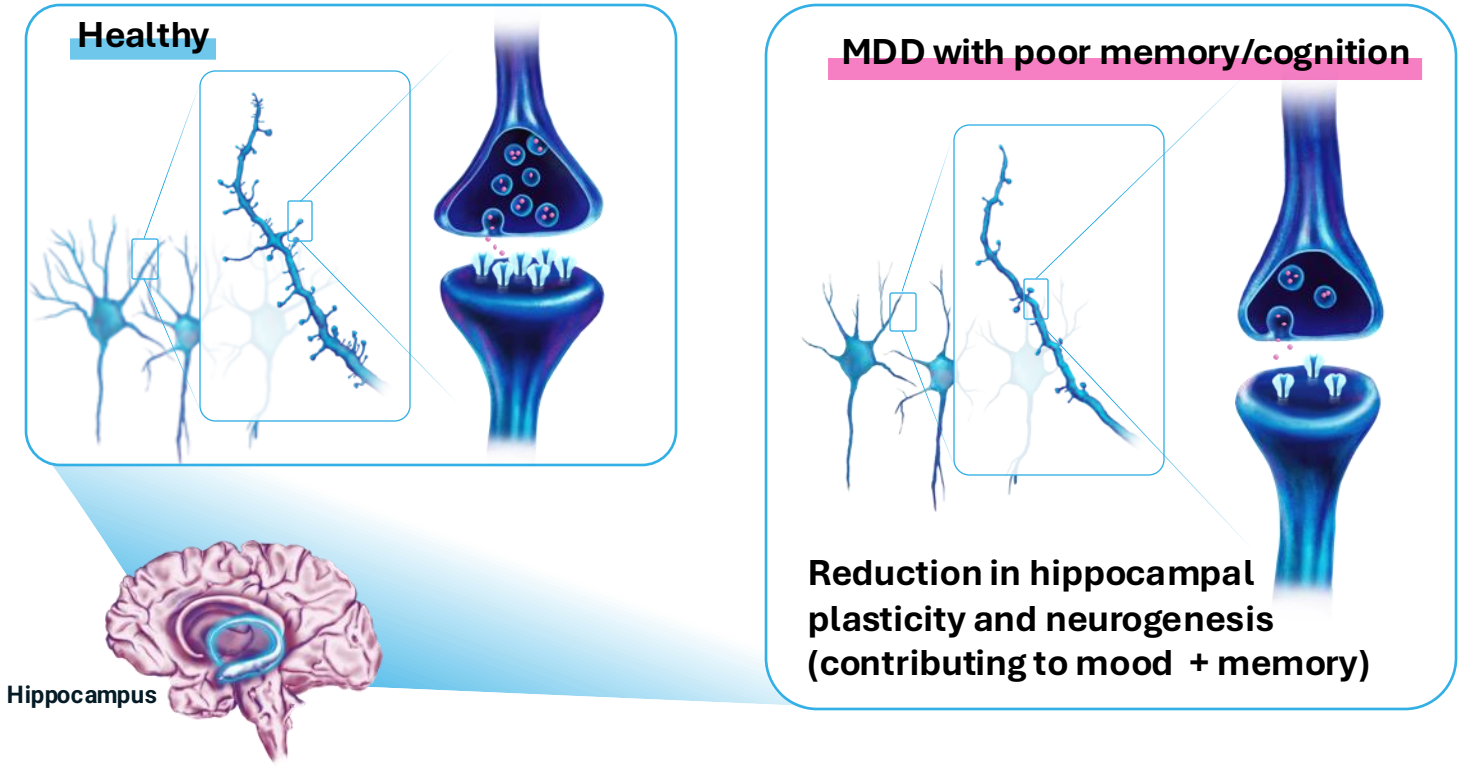
# Extensive evidence behind the neuroplasticity framework, the role of BDNF signaling, and neurogenesis

**Humans, *in vivo:***

- ↓ hippocampal volumes
- ↓ memory (along with other aspects of cognition)
- ↓ synaptic density (SV2A PET)
- Relationship between memory/cognition and volume/synaptic density

**Humans, post-mortem:**

- ↓ cell number and synapses in hippocampus
- ↓ expression of glutamate receptors, plasticity-related genes, BDNF/TrkB

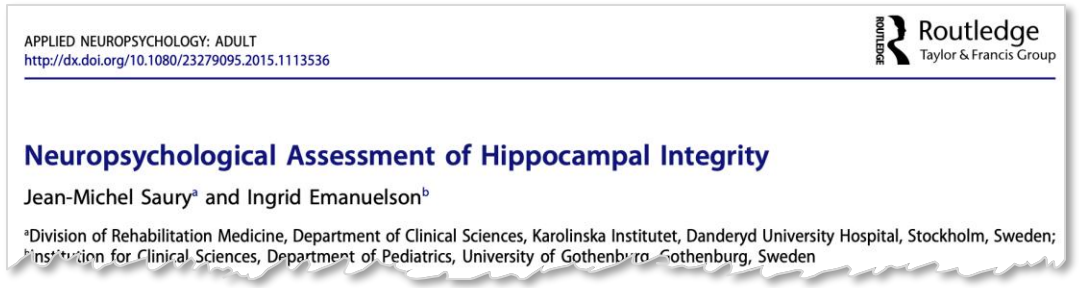



**Preclinical models:**

- Memory/cognition, plasticity and mood analogs impaired by stress
- BDNF signaling reduced, and when provided into the hippocampus, rescues phenotype
- Longer-term antidepressant effects require neurogenesis

# Hippocampus-dependent verbal memory biomarker

The Rey Auditory Verbal Learning Test (RAVLT) is a long-established and very well-validated measure of hippocampal function and neuroplasticity



APPLIED NEUROPSYCHOLOGY: ADULT
http://dx.doi.org/10.1080/23279095.2015.1113536

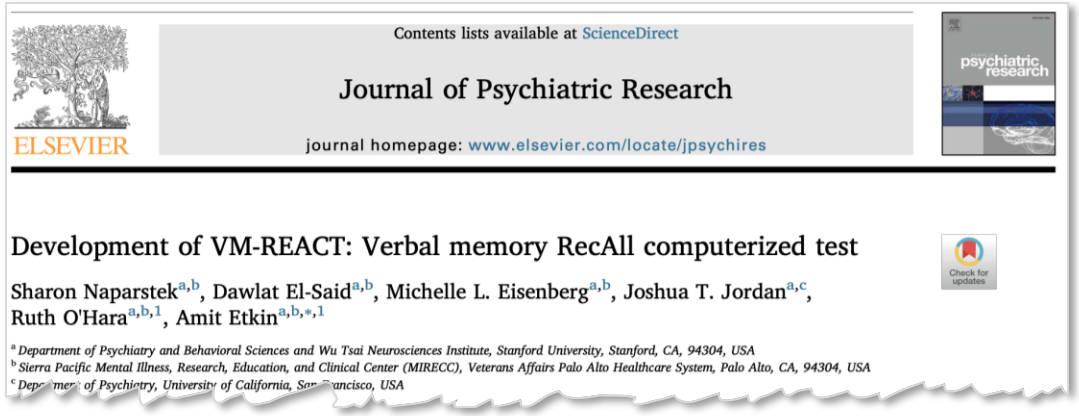
Routledge
Taylor & Francis Group

**Neuropsychological Assessment of Hippocampal Integrity**

Jean-Michel Saury[a] and Ingrid Emanuelson[b]

[a]Division of Rehabilitation Medicine, Department of Clinical Sciences, Karolinska Institutet, Danderyd University Hospital, Stockholm, Sweden; [b]Institution for Clinical Sciences, Department of Pediatrics, University of Gothenburg, Gothenburg, Sweden

Which we adapted and validated for **self-administered** computerized testing (VM-REACT) at Stanford



Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

ELSEVIER

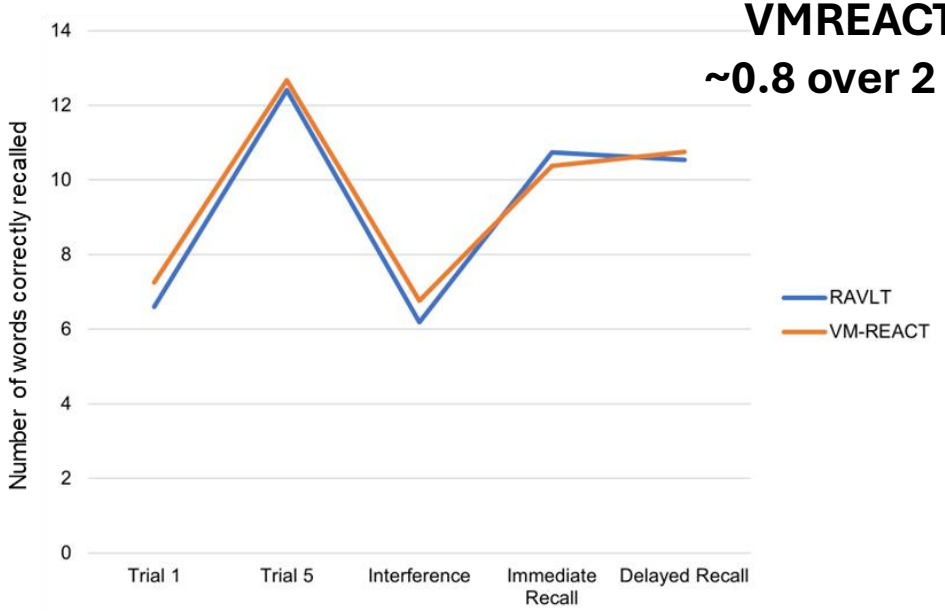
**Development of VM-REACT: Verbal memory RecAll computerized test**

Sharon Naparstek[a,b], Dawlat El-Said[a,b], Michelle L. Eisenberg[a,b], Joshua T. Jordan[a,c], Ruth O'Hara[a,b,1], Amit Etkin[a,b,*,1]

[a] Department of Psychiatry and Behavioral Sciences and Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA, 94304, USA
[b] Sierra Pacific Mental Illness, Research, Education, and Clinical Center (MIRECC), Veterans Affairs Palo Alto Healthcare System, Palo Alto, CA, 94304, USA
[c] Department of Psychiatry, University of California, San Francisco, USA

Our adaptation (VM-REACT) in our proprietary cognitive battery (Spectra) closely matches performance on the RAVLT

**VMREACT ICC: ~0.8 over 2 months**




**The ALTO-100 memory marker is a well-validated and highly reliable measure, thus well-suited to treatment selection in clinical practice**

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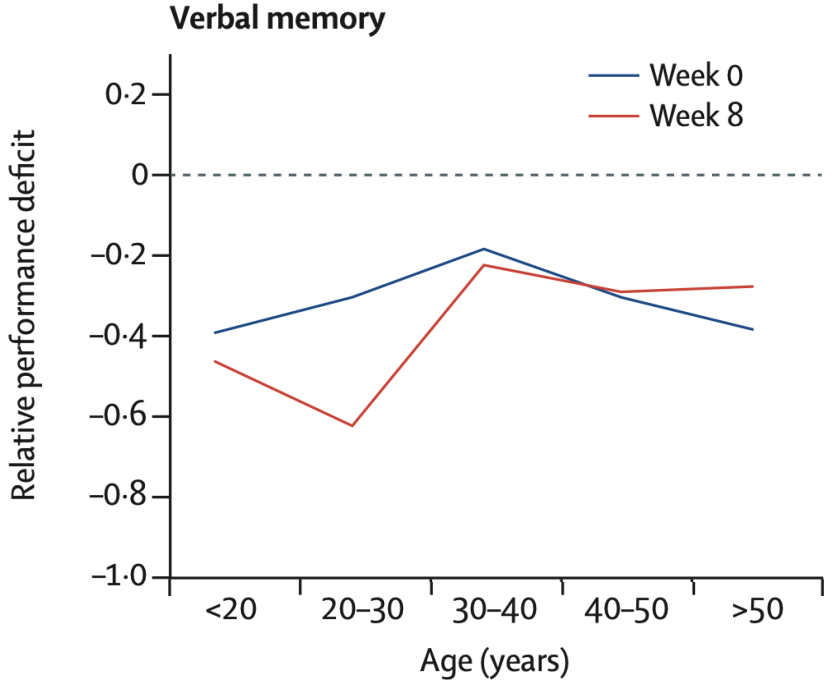
# MDD with poor memory/cognition is a common and persistent form of depression

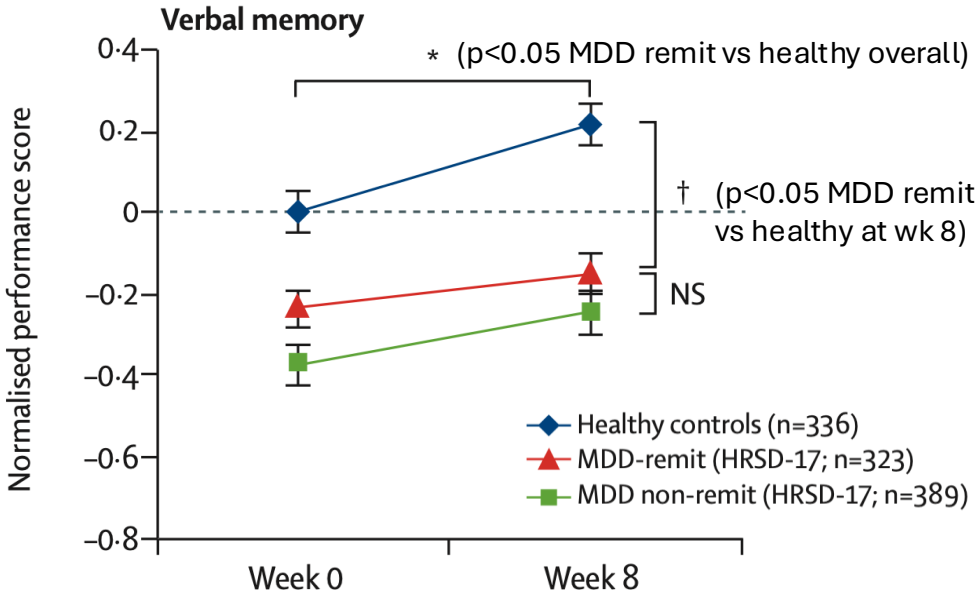
## *30-50% of MDD patients have poor memory/cognition*

In a study of N=1,008 MDD patients in an 8-week SSRI/SNRI treatment study and N=336 healthy individuals:

**Impaired cognition, regardless of treatment, is evident across ages**




**Symptomatic remission, including on cognitive symptoms, is not associated with change in cognition**




Shilyansky et al., *Lancet Psych*, 2016

# High unmet treatment need for MDD patients with poor memory/cognition

Poor memory has been shown to predict treatment resistance, leading to nearly twice the rate of psychiatric hospitalization

Cognitively impaired patients have a lower probability of treatment response to SSRI/SNRI

Pro-cognitive antidepressants including vortioxetine do not improve clinical response for cognitively impaired patients

Poor memory predicts treatment resistance (N=229)

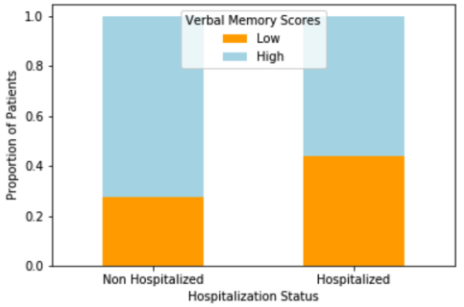
**Table 5.** Final statistical model including the variables associated with a higher risk of treatment-resistant depression.

| | *B* | SE | Significance (p-value) | Exp (*B*) |
|---|---|---|---|---|
| Verbal memory | −0.703 | 0.193 | <0.001 | 2.020[a] |
| Severity | 0.255 | 0.125 | 0.042 | 1.290 |
| Antipsychotics | 1.367 | 0.367 | <0.001 | 3.924 |
| Anticonvulsants | 0.813 | 0.397 | 0.040 | 2.254 |
| Constant | −1.900 | 0.367 | <0.001 | 0.150 |

Abbreviations: CI, confidence interval; SE, standard error.
[a]Those values represent 1/0.495 and CI: 1/0.723–1/0.339.

Lopez-Sola et al, *Euro Psych*, 2020

Psychiatric hospitalization rates greater for poor memory patients (HR 1.84, p=0.03; N=398)




Sankar et al, *eClinMed*, 2023

Lower probability of treatment response in cognitively impaired patients with SSRI/SNRI (OR 0.69, p=0.03; N=1008)

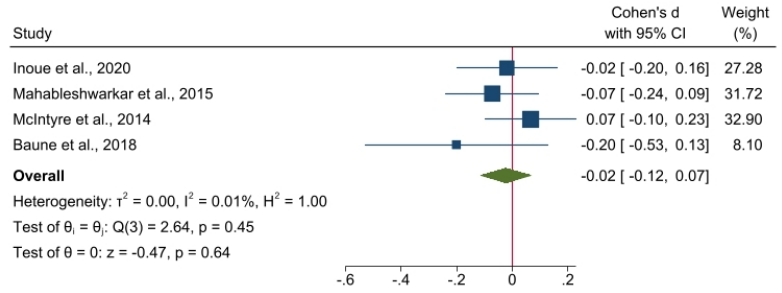
Neuropsychopharmacology (2015) 40, 1332–1342

www.neuropsychopharmacology.org

A Cognitive–Emotional Biomarker for Predicting Remission with Antidepressant Medications: A Report from the iSPOT-D Trial

Amit Etkin*[,1,2], Brian Patenaude[1,2], Yun Ju C Song[3], Timothy Usherwood[4], William Rekshan[5,6], Alan F Schatzberg[1], A John Rush[7] and Leanne M Williams*[,1,2,3]

Even a pro-cognitive antidepressant like vortioxetine does not work better clinically for cognitively impaired patients (N=1,553)




Jordan et al., *J Clin Psych*, 2024

# MDD with poor memory/cognition is a disabling form of depression, independent of depressive symptoms

*Extensive literature has shown poor memory/cognition relates to disability and dysfunction in MDD*

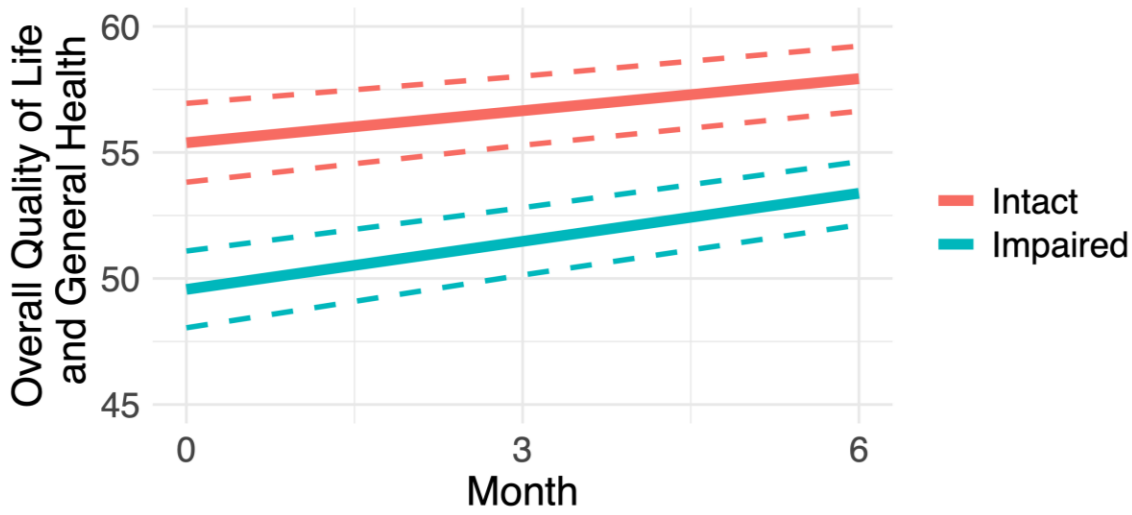
*Building on this we found:*

Poor cognition predicts both worse functional capacity (performance-based test) and functional impairment (clinician-rated); N=101

| Variable | Functional Capacity β (P-Value) | Functional Impairment β (P-Value) |
|---|---|---|
| Global Cognition | **0.45 (< 0.001)*** | **-0.30 (0.001)*** |
| MADRS | -0.04 (0.733) | 0.20 (0.046) |
| PDQ-D | 0.00 (0.961) | **0.25 (0.011)*** |

Jordan et al, *Biol Psych*, 2024

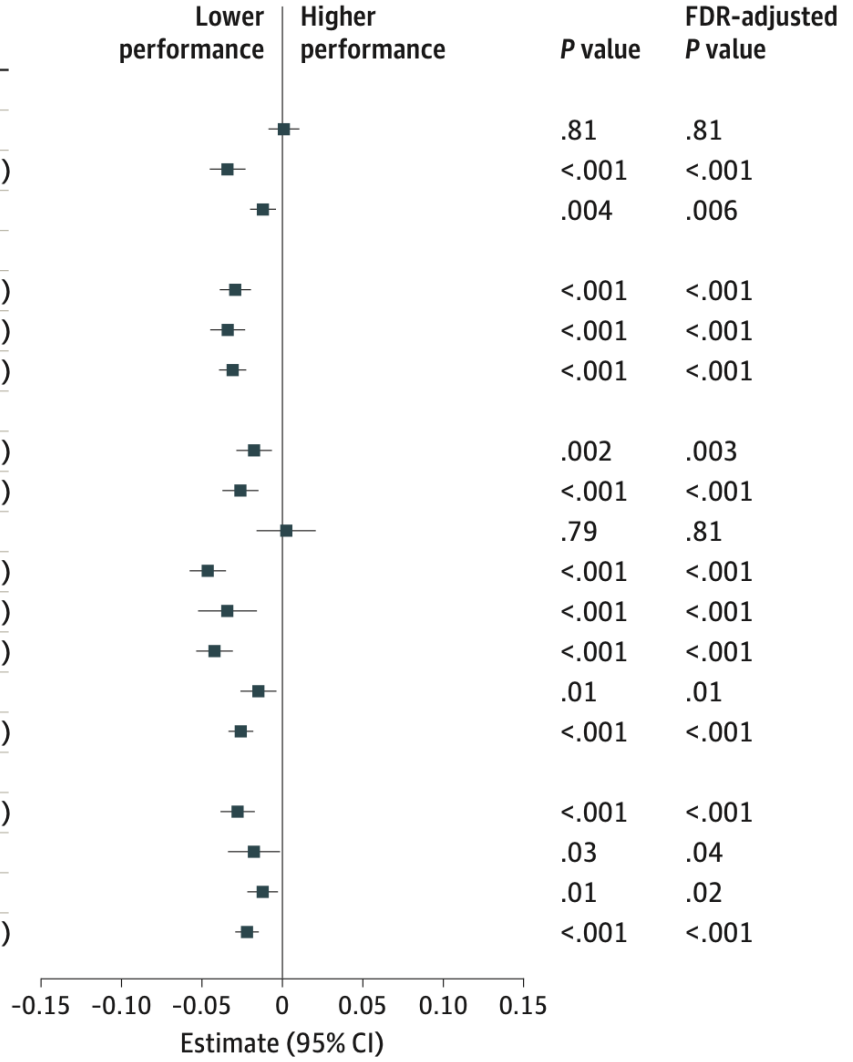
Poor cognition is stably associated with poor functioning over a 6 month follow-up period, independent of MDD symptoms (N=391)



# Genetic risk for MDD is associated with poor memory/cognition

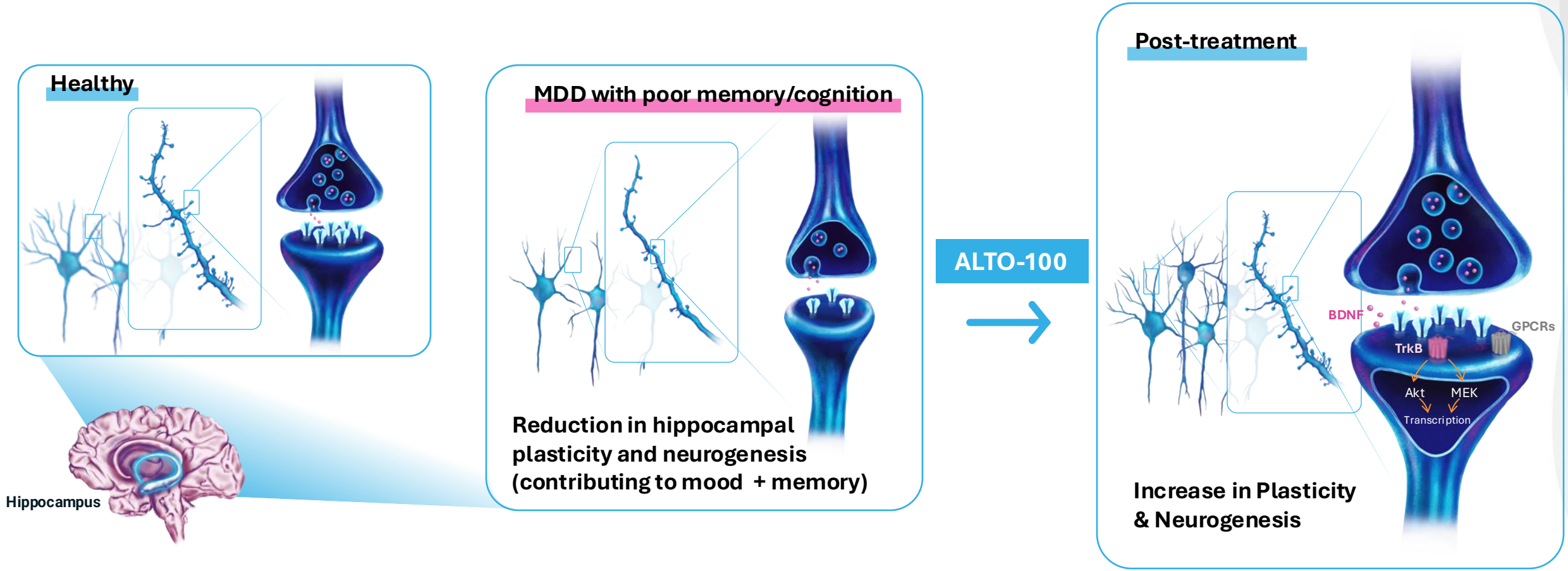
*Demonstrates relationship between cognition and core disease processes (e.g. polygenic MDD risk score)*

| Cognitive function | Participants, No. | Estimate (95% CI) | *P* value | FDR-adjusted *P* value |
|---|---|---|---|---|
| Processing speed | | | | |
| Reaction time | 38 656 | 0 (-0.01 to 0.01) | .81 | .81 |
| Symbol-digit | 27 928 | -0.03 (-0.04 to -0.02) | <.001 | <.001 |
| Processing speed composite | 38 743 | -0.01 (-0.02 to 0) | .004 | .006 |
| Reasoning | | | | |
| Verbal-numerical | 38 198 | -0.03 (-0.04 to -0.02) | <.001 | <.001 |
| Matrix patterns | 27 917 | -0.03 (-0.04 to -0.02) | <.001 | <.001 |
| Reasoning composite | 38 401 | -0.03 (-0.04 to -0.02) | <.001 | <.001 |
| Attention and executive | | | | |
| Digit span | 28 572 | -0.02 (-0.03 to -0.01) | .002 | .003 |
| Trails A time | 27 873 | -0.03 (-0.04 to -0.01) | <.001 | <.001 |
| Trails A errors | 27 932 | 0 (-0.02 to 0.02) | .79 | .81 |
| Trails B time | 27 149 | -0.05 (-0.06 to -0.03) | <.001 | <.001 |
| Trails B errors | 27 758 | -0.03 (-0.05 to -0.02) | <.001 | <.001 |
| Trails B-A time | 27 149 | -0.04 (-0.05 to -0.03) | <.001 | <.001 |
| Tower test | 27 682 | -0.01 (-0.03 to 0) | .01 | .01 |
| Attention and executive composite | 28 865 | -0.03 (-0.03 to -0.02) | <.001 | <.001 |
| Memory | | | | |
| Visual memory-6 pairs | 38 259 | -0.03 (-0.04 to -0.02) | <.001 | <.001 |
| Visual memory-8 pairs | 15 243 | -0.02 (-0.03 to 0) | .03 | .04 |
| Verbal paired association | 28 216 | -0.01 (-0.02 to 0) | .01 | .02 |
| Memory composite | 38 554 | -0.02 (-0.03 to -0.01) | <.001 | <.001 |




Cullen et al., *JAMA Psych*, 2023

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

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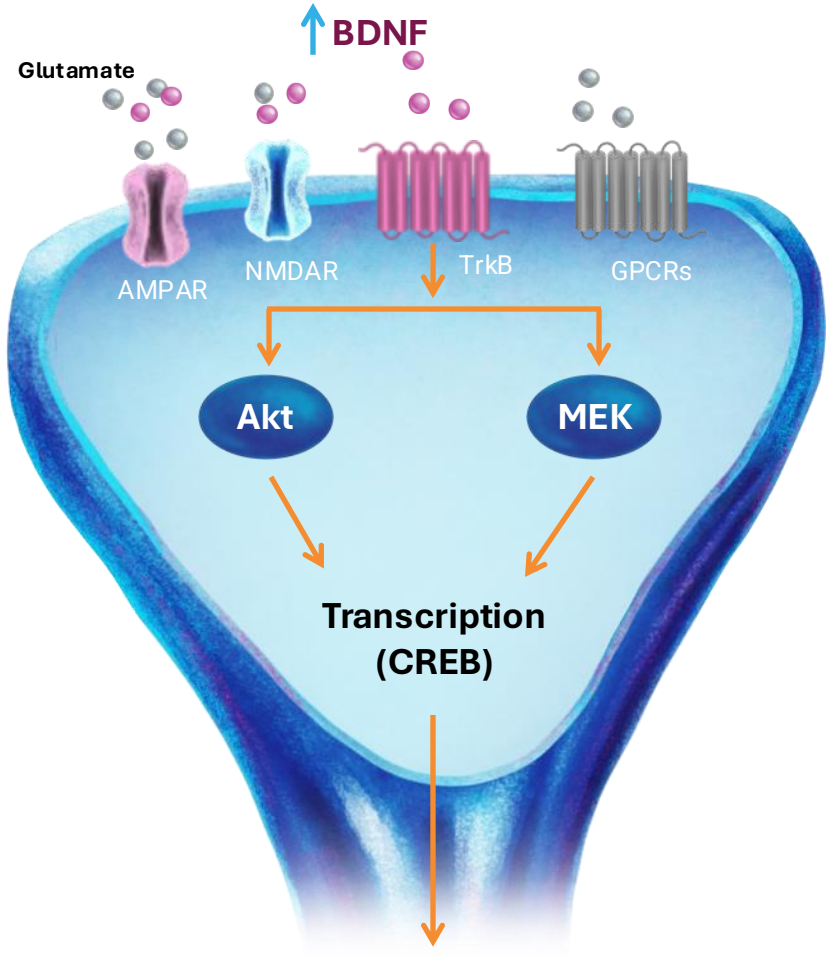
**ALTO-100 mechanism of action:** Enhances hippocampal neuroplasticity across multiple time scales, leveraging BDNF signaling

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




Plasticity ↑ Neurogenesis ↑

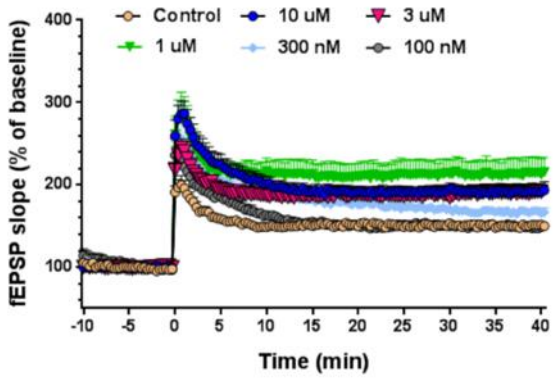
**Identified** based on a neurogenesis functional screen

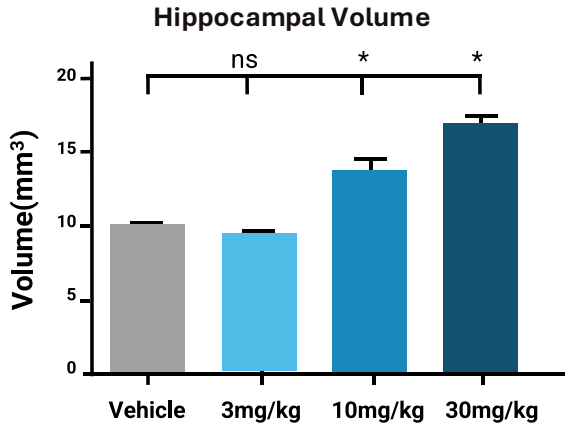
Preclinically, **increases** synaptic and cellular plasticity across multiple time scales, hippocampal volume

**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



# Motivation for ALTO-100's Discovery and Preclinical Validation

**Ablating hippocampal neurogenesis has been shown to eliminate the effects of antidepressants in mice**

Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants

Luca Santarelli,[1]* Michael Saxe,[1]* Cornelius Gross,[1] Alexandre Surget,[2] Fortunato Battaglia,[3] Stephanie Dulawa,[1] Noelia Weisstaub,[1] James Lee,[1] Ronald Duman,[4] Ottavio Arancio,[3] Catherine Belzung,[2] René Hen[1]†

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**Motivated Neuralstem to screen >10,000 compounds for pro-neurogenic capacity**

Objective: enhance hippocampal plasticity with an aim to improve cognition and mood

- Advanced multiple compounds for testing in secondary *in vivo* and *in vitro* screens
- One compound advanced to IND enablement

**<u>All animal models tested</u> showed pro-cognitive or neuro-restorative effect of ALTO-100, supporting plasticity impact**

- ✓ Healthy mice & rats
- ✓ Angelman's
- ✓ Alzheimer's
- ✓ Radiation damage
- ✓ Stroke
- ✓ Down's
- ✓ Diabetic neuropathy
- ✓ Depression
- ✓ Neurogenesis

***In vitro* pro-plasticity effects also shown, including long before neurogenesis is relevant or independent of it**

- ✓ Long-term potentiation (2-3 hours)
- ✓ Neurite outgrowth (36 hours)
- ✓ Neuronal network maturation

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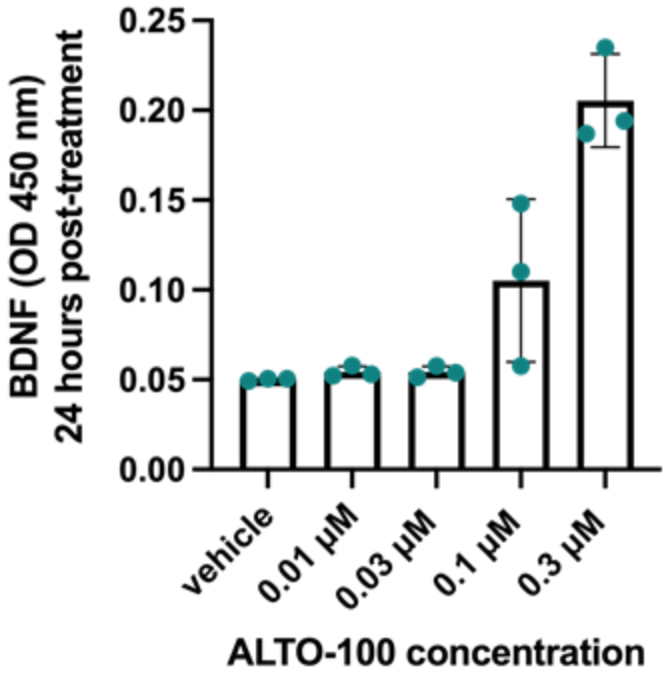
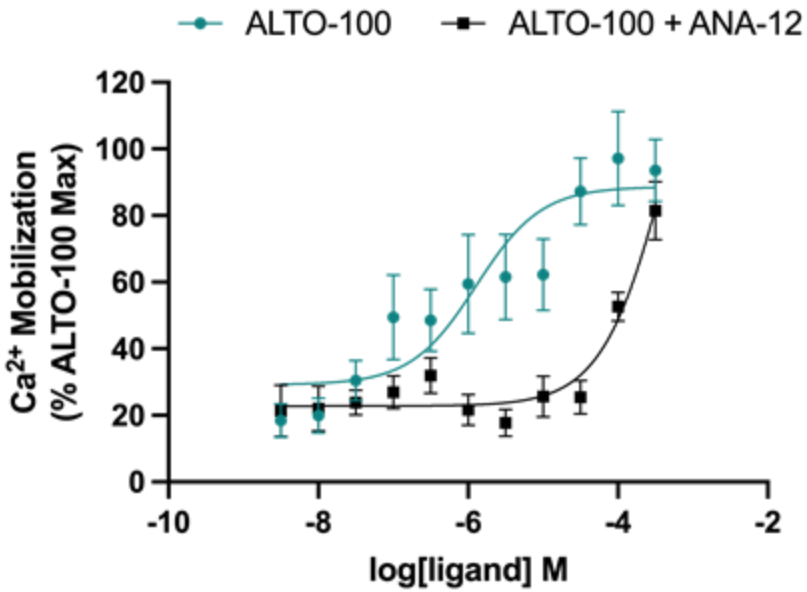
# ALTO-100 results in an immediate increase in BDNF release, with downstream effects dependent on BDNF signaling

*BDNF has been shown to increase hippocampal neuroplasticity, neurogenesis, and improve cognition and mood analogs –* ***ALTO-100 leverages this pathway for its downstream effects***

*ALTO-100 increased immediate BDNF release in neurons*



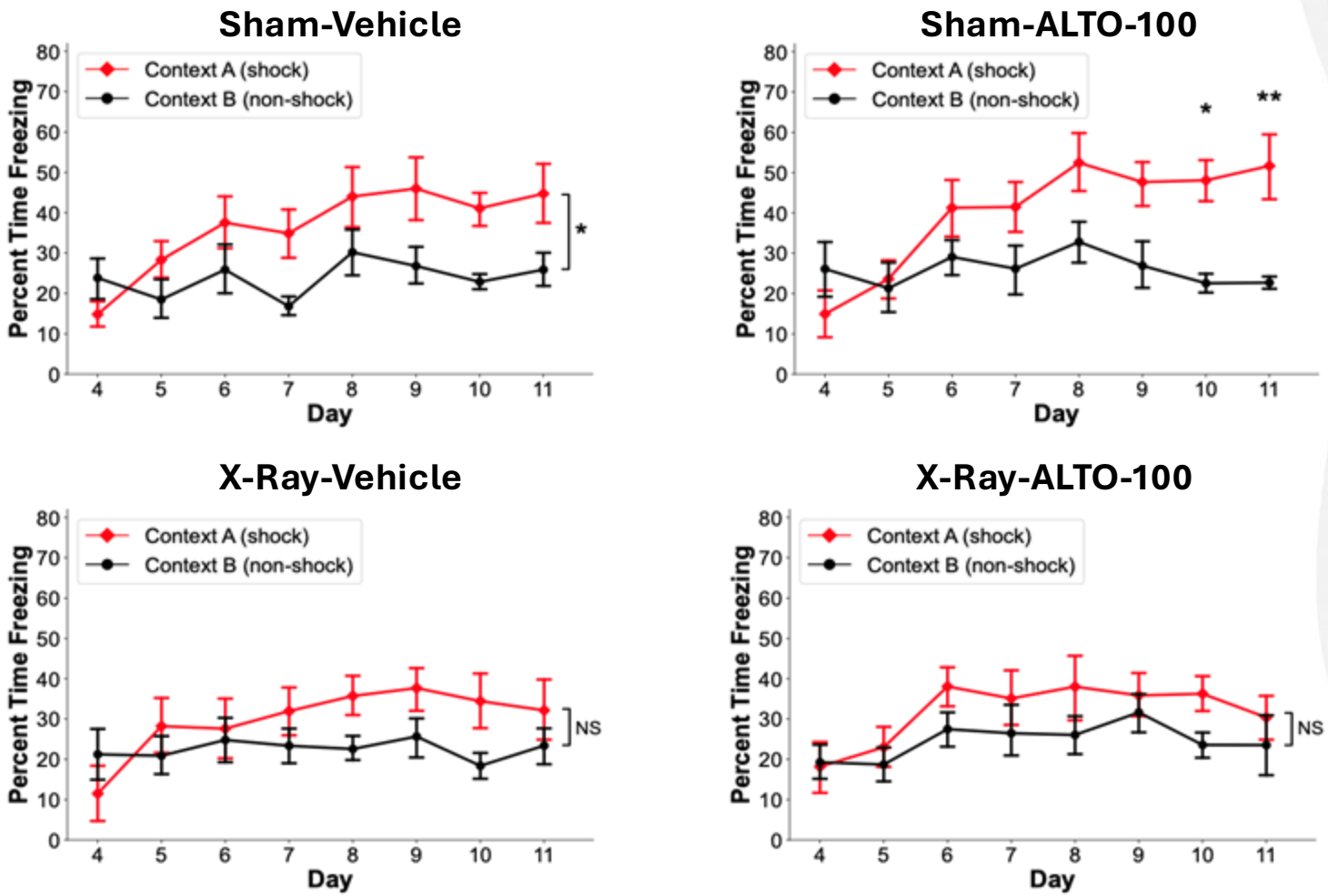

*Blocking the BDNF receptor TrkB (with ANA-12) blunted upstream (calcium) and downstream (CREB) effects of ALTO-100 in neurons*



# ALTO-100 resulted in neurogenesis-dependent memory enhancement

- Hippocampal neurogenesis drives pattern separation, which is impaired by stress in depressed patients
- Pattern separation task: animal learns to distinguish between subtly different safe and dangerous contexts
- X-ray irradiation ablates dividing cells only (i.e. neurogenesis)
- Work done by Rene Hen's lab at Columbia (same as Santarelli et al.)

**ALTO-100 enhances pattern separation memory, which is blocked by x-ray irradiation (i.e. is neurogenesis-dependent)**




*Chung et al., SFN, 2023*

# Work done to define the direct target for ALTO-100: potentially first-in-class molecular mechanism

**Block downstream effects in neurons with:**

- Pharmacological inhibition using multiple different antagonists
- Genetic knockout via CRISPR

**Endow sensitivity in non-neuronal cells via exogenous expression of target, eliminated by use of antagonist**

**Demonstrate interaction with target:**

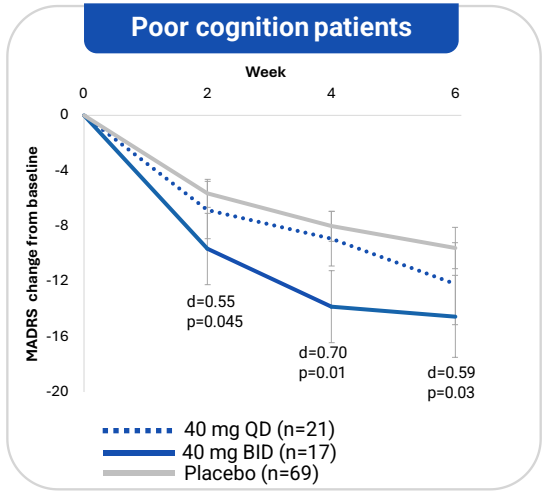
- Physical binding experiments
- Computational docking into known allosteric pocket
- Can drive new molecule creation

**Poor memory ALTO-100 biomarker:** Identification, prospective replications, and demonstration of specificity vs. placebo

# Poor memory patients respond better to ALTO-100 and not placebo: two prospective, two retrospective, and two placebo datasets

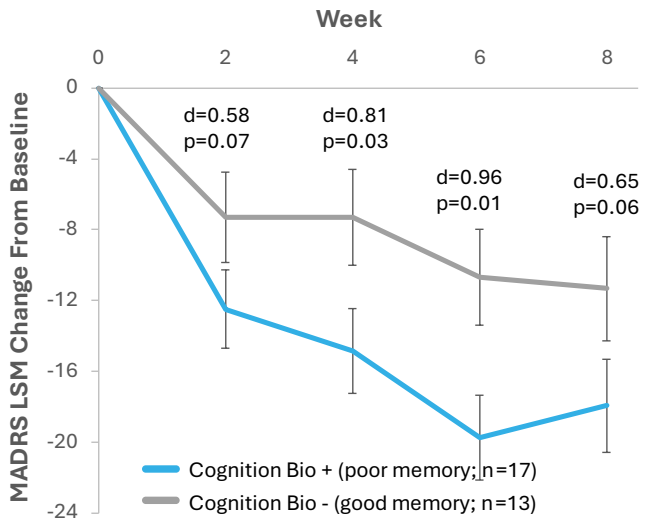
*Prior to acquisition by Alto*

**Retrospective analysis of Neuralstem study**

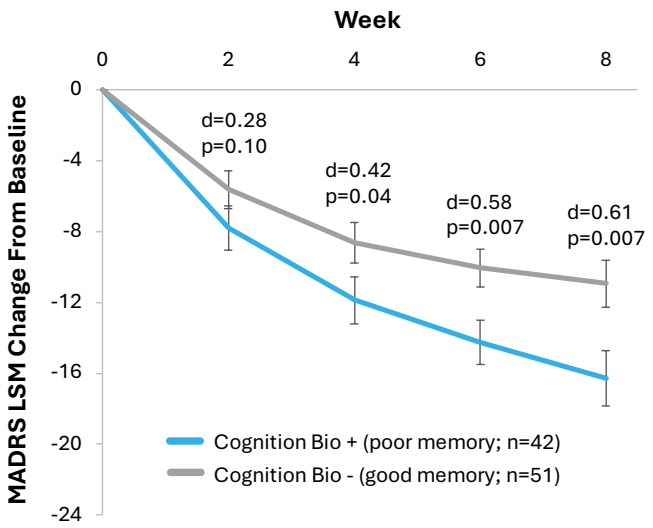



## *Phase 2a completed by Alto: prospective memory marker replication*

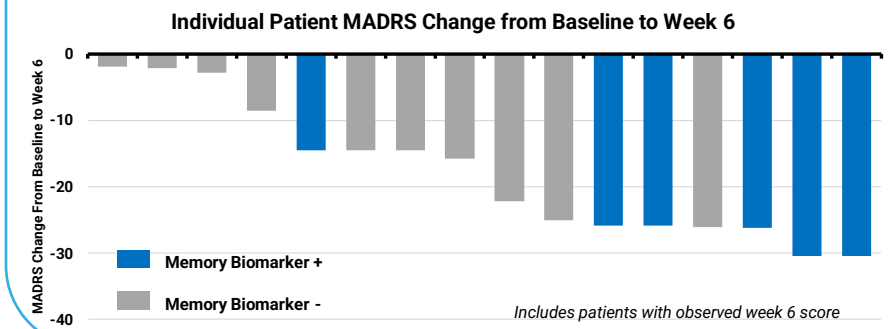
### Discovery Data Set



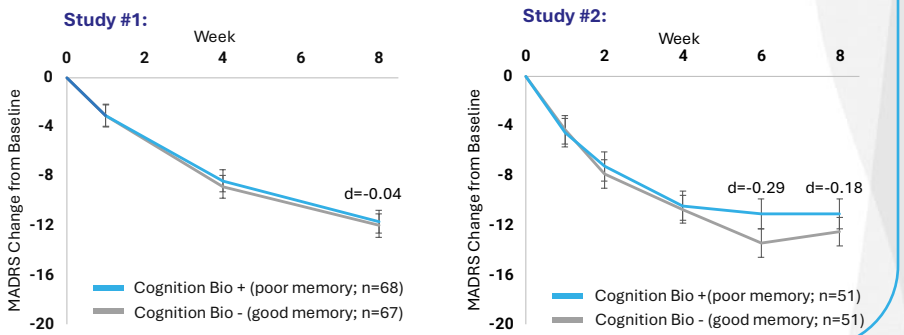

### Prospective Test Data Set




## *Alto Phase 2 decentralized replication*




## *No difference in two placebo datasets*

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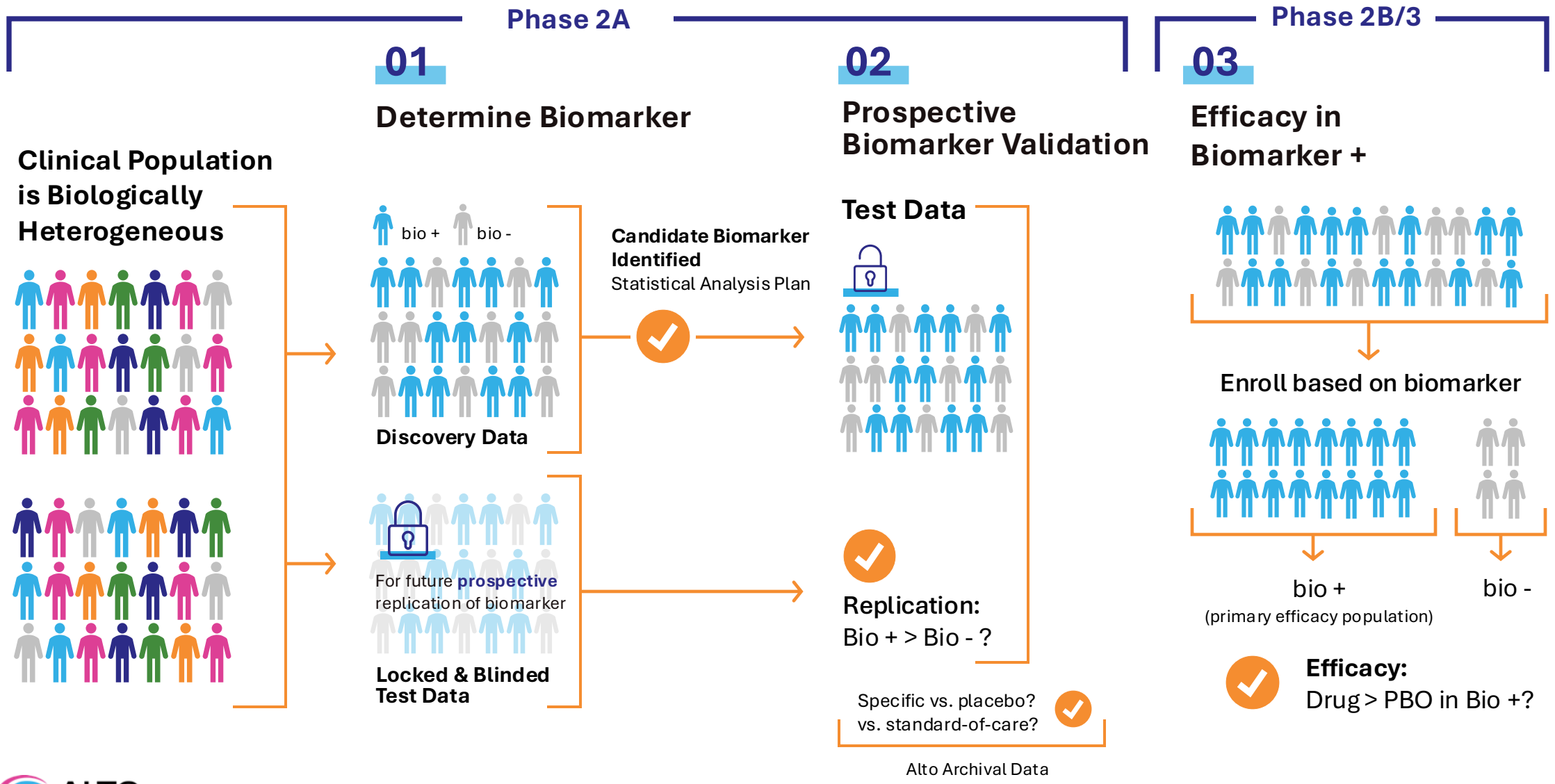
# Alto's precision drug development approach



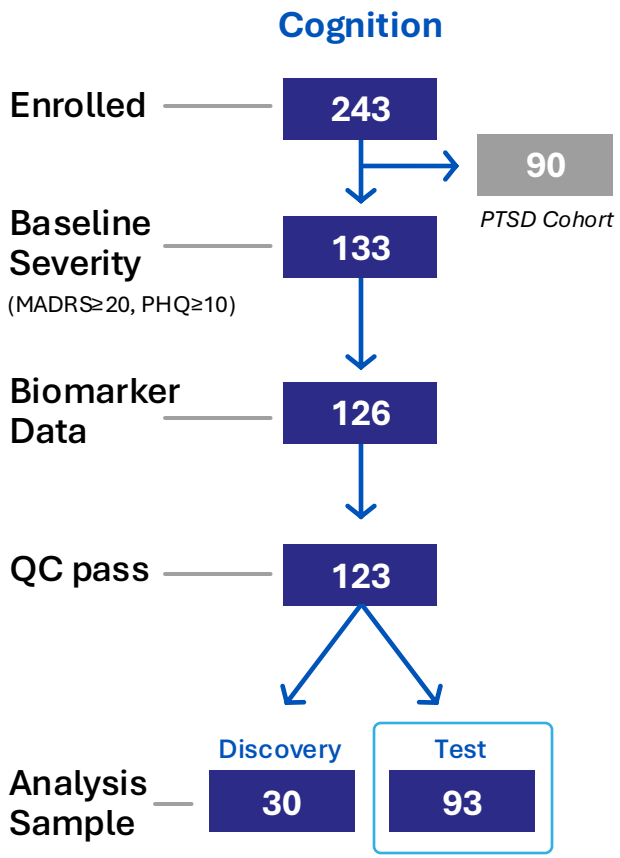
# ALTO-100 Phase 2A study design and participant flow

## Patient Population

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

## Treatment and Biomarkers

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




## MDD Cohort Baseline Demographics

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

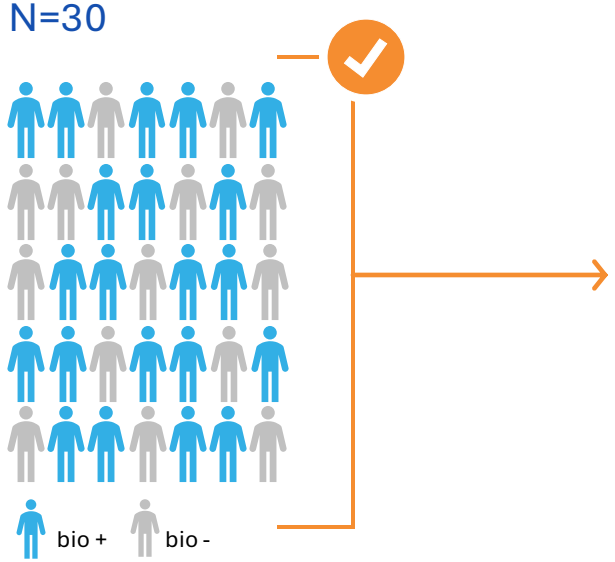
**No baseline/clinical characteristics were shown to impact results of biomarker outcomes**

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

**01**

**Determine Biomarker**

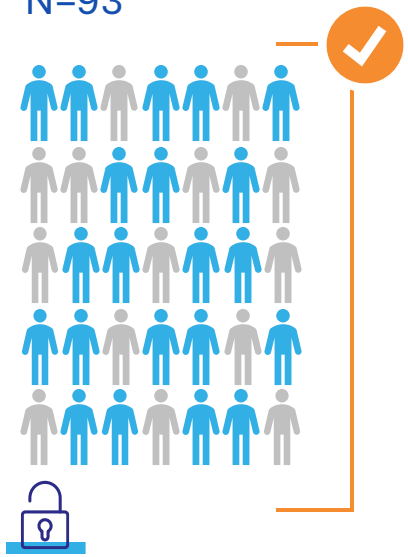
N=30



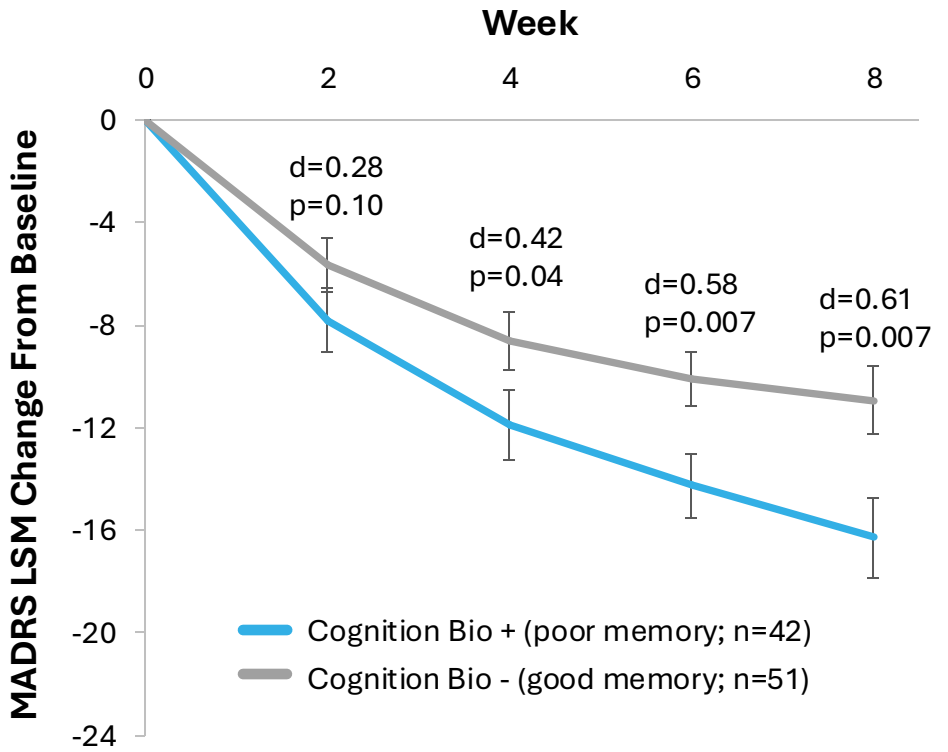

**02**

**Prospective Biomarker Validation**

N=93



## Prospective Replication in Test Dataset




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

**Enrichment at 6 weeks:**

- Monotherapy: d=0.66
- Adjunctive: d=0.56

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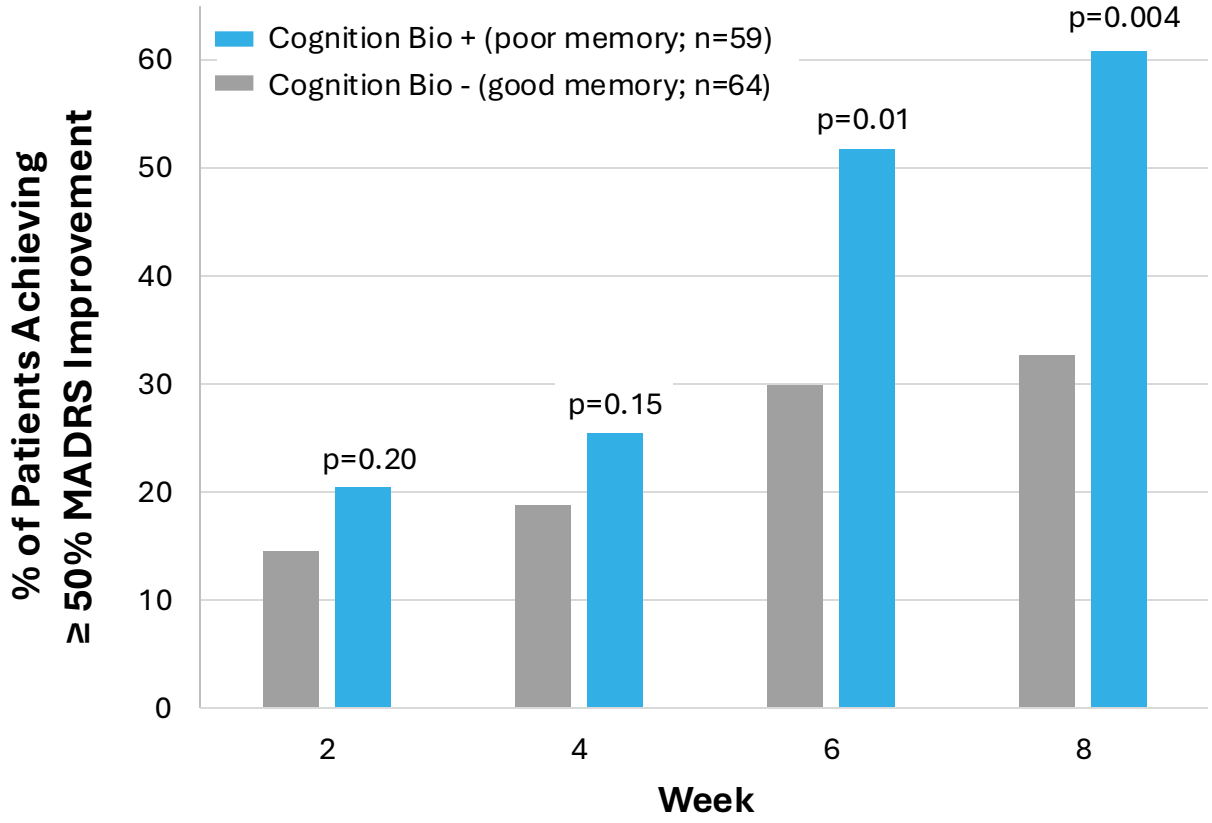
# Poor memory/cognition patients derived greater benefit from ALTO-100

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

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



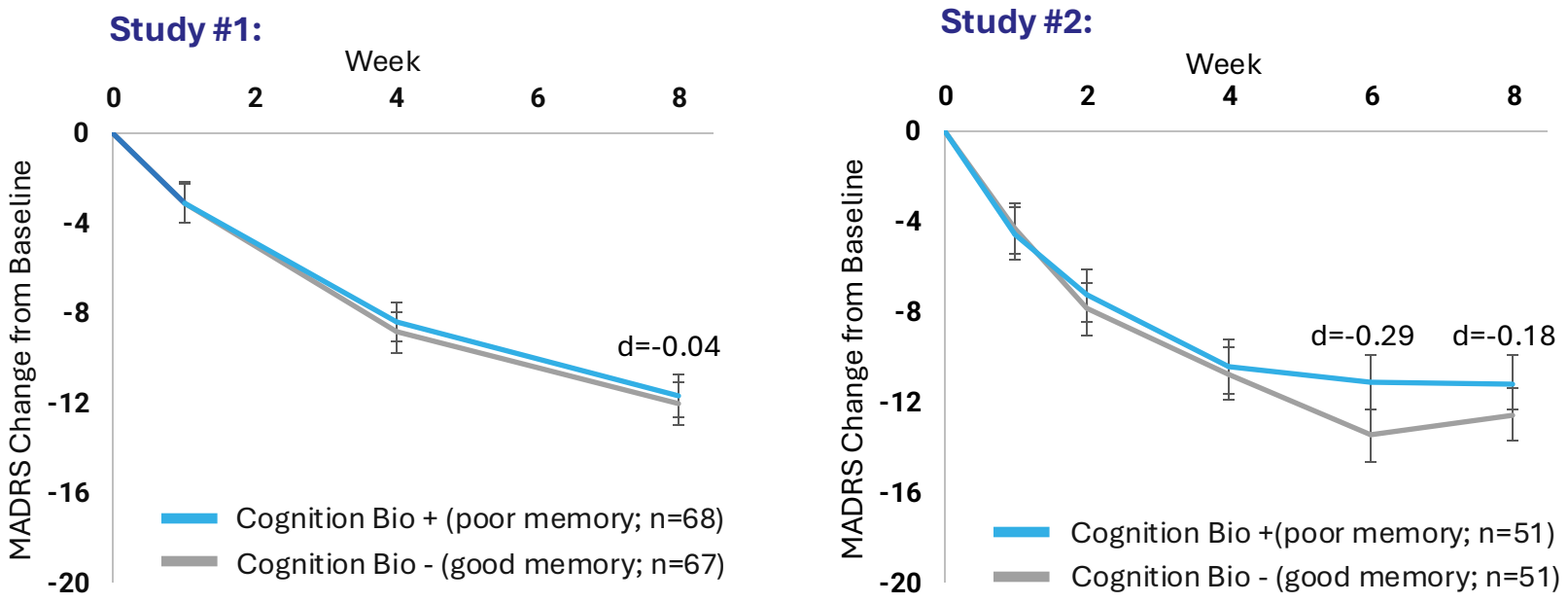

CGI – Clinician Global Impression of Severity

# Poor memory did not predict higher placebo response

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

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

## Placebo-treated Patients

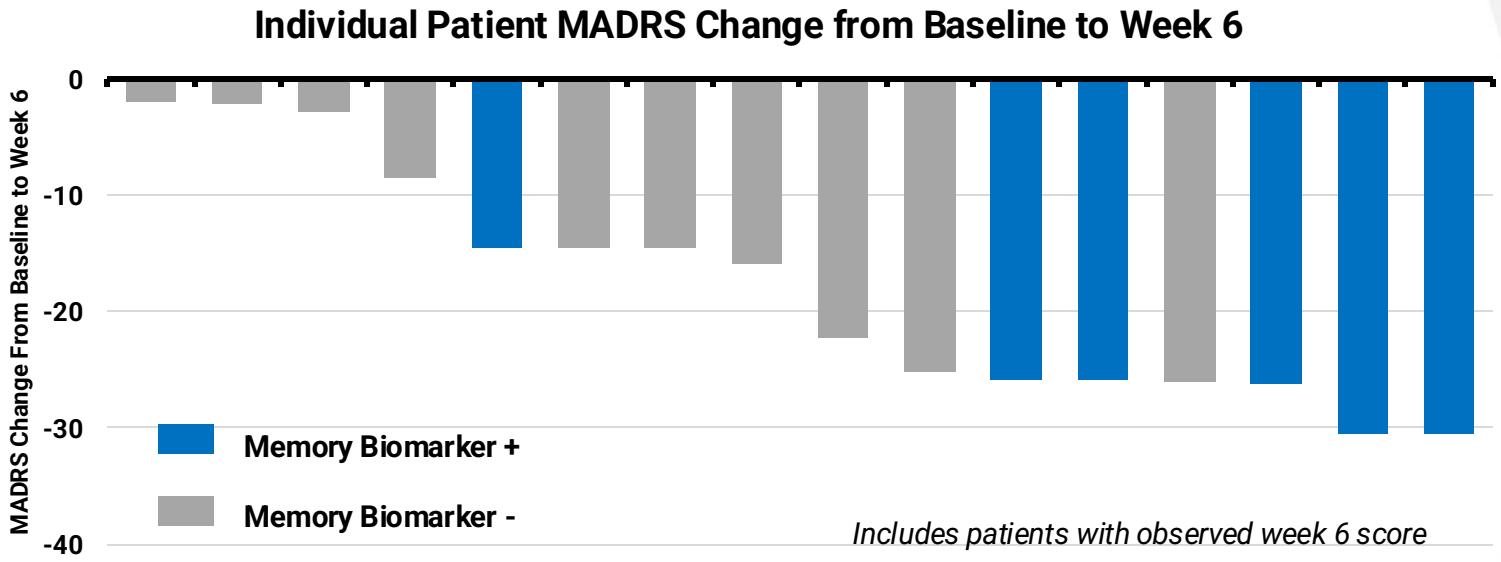


# Pilot decentralized study of ALTO-100 in MDD demonstrates feasibility of at-home biomarker collection and consistency of biomarker results

## Study Summary

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

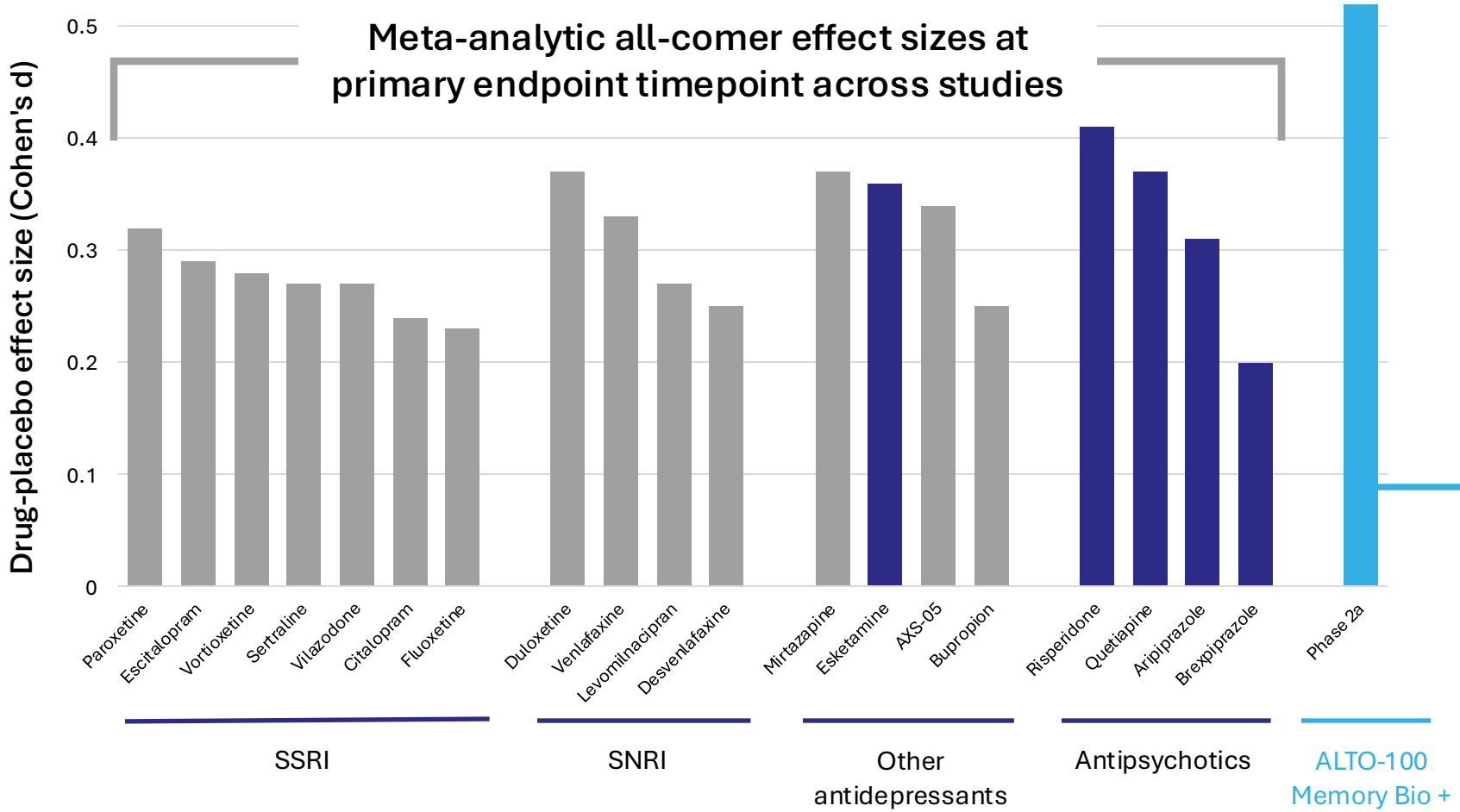
  (same memory biomarker as ongoing Ph. 2b)
- Analysis completed May 2024




## Key Takeaways

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

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




**Comparison all-comer effects:**

monotherapy

adjunctive

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

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

The results shown above are not based on head-to-head trials between the products or product candidates. Study designs and protocols differed, and results may not be comparable.

# ALTO-100 was well tolerated: Alto Phase 2A study

## Overall Treatment Emergent Adverse Events (TEAEs)

Safety Analysis Set

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

| | % of TEAEs |
|---|---|
| Related TEAEs (by TEAE) | 40.2 |

**Note:** participants may have had more than one AE

## TEAEs for ≥5% of the Population

Safety Analysis Set

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

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

# We systematically ruled out potential confounders

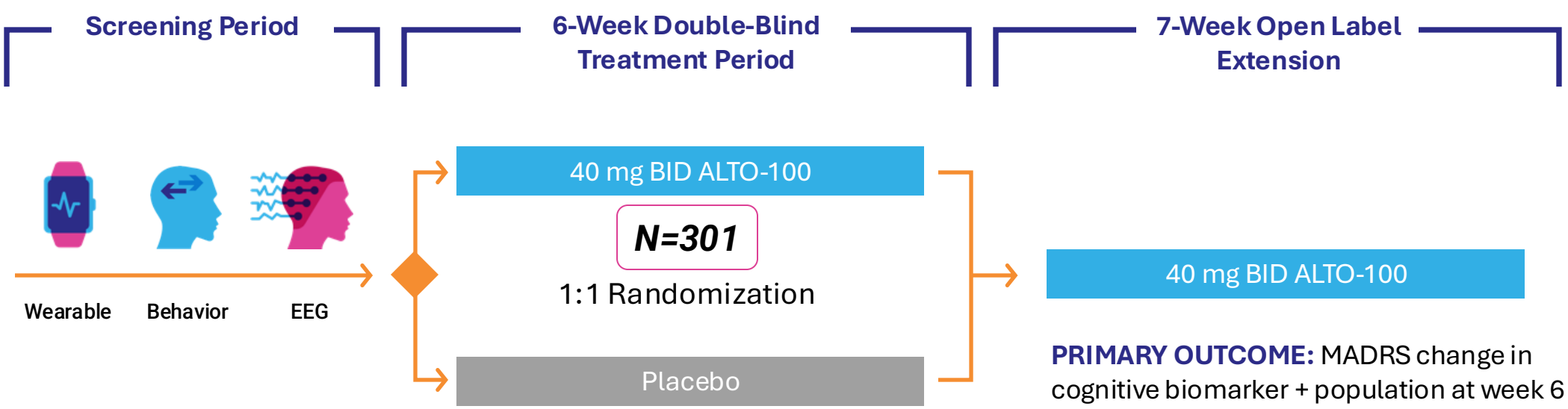
| | |
|---|---|
| ⊗ **Background medications** | • Similar enrichment for monotherapy vs. adjunctive<br>• In adjunctive, SSRI vs. SNRI similar |
| ⊗ **Clinical factors** | • Comorbidity (e.g., GAD) did not impact<br>• Similar enrichment for treatment resistant patients<br>• Self-reported cognition (including memory) not predictive |
| ⊗ **Cognitive factors** | • Verified after prospective replication that memory performed better than any other cognitive factor |
| ⊗ **Severity** | • No systematic relationship to severity, and severity does not confound – poor memory patients not simply more symptomatic<br>• Extensive prior literature also shows that greater severity does not lead to greater drug separation (e.g., Hieronymus et al., Lancet Psych, 2019) |

# **Phase 2b study:**
# Design, rationale, and baseline data*

*Data presented are provisional as database lock has not yet been completed data remain blinded

# ALTO-100 Phase 2B biomarker-guided trial in MDD

**Enrollment completed – topline data expected Oct. 2024**




- Design follows **FDA's enrichment guidelines:** powered primary outcome in memory biomarker positive
- Site-based and decentralized – **34 sites across the US**
- Randomization stratified on biomarker and monotherapy/adjunctive
- Primary MDD but allows co-morbid anxiety disorders and PTSD
- **Biomarkers repeated** after double blind and open label

**Trial design and execution similar to anticipated Phase 3 trial**

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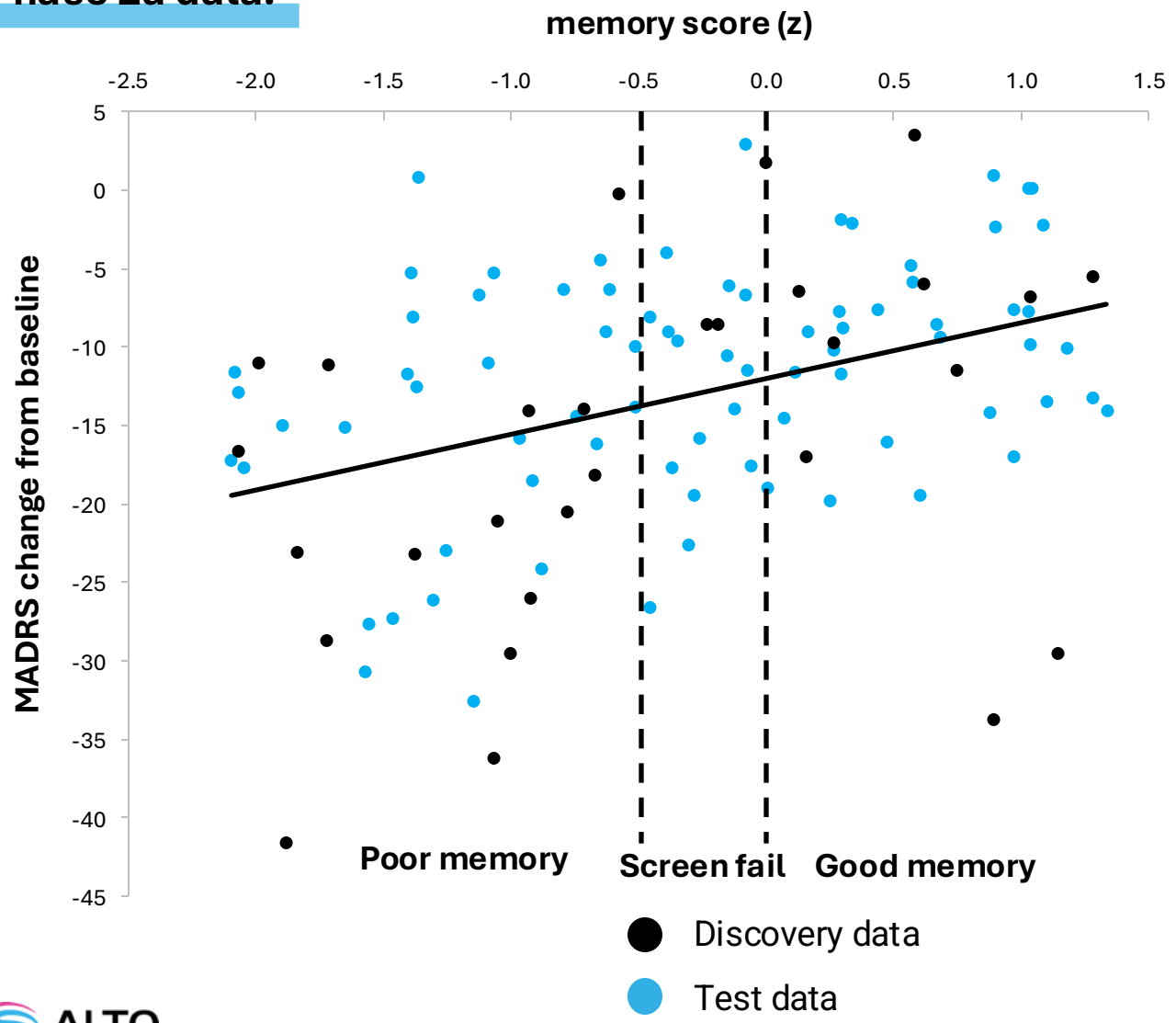
# We have carefully thought through the overall study design to ensure high-quality data interpretation

| Design Decisions | Rationale |
| --- | --- |
| Enroll poor memory (powered analysis) & good memory patients | Describe enrichment & mitigate expectation bias for patients and sites |
| Placebo mitigation efforts:<br>• 1:1 randomization<br>• Third-party eligibility assessment (SAFER)<br>• Blind patients, sites, and Alto Clin Ops to biomarker status and ratio | Best practices for managing placebo response & reducing biomarker expectation bias potential |
| Monotherapy and adjunctive patients | Similar enrichment & more reflective of real-world care |
| Include open-label extension | Decrease patient concern about receiving placebo |

# Verbal memory biomarker thresholds for study inclusion

**Phase 2a data:**




- Continuous relationship between memory impairment and better response
- **Poor memory** defined as z≤-0.5
  - Targeted N=200 for powering at d=0.4
  - Threshold intuitive for clinicians (mild or greater impairment)
- **Good memory** defined as z≥0
  - Under-sampled as enrichment assessed qualitatively
- **Screen fail** intermediate, reflecting margin of error for the memory test

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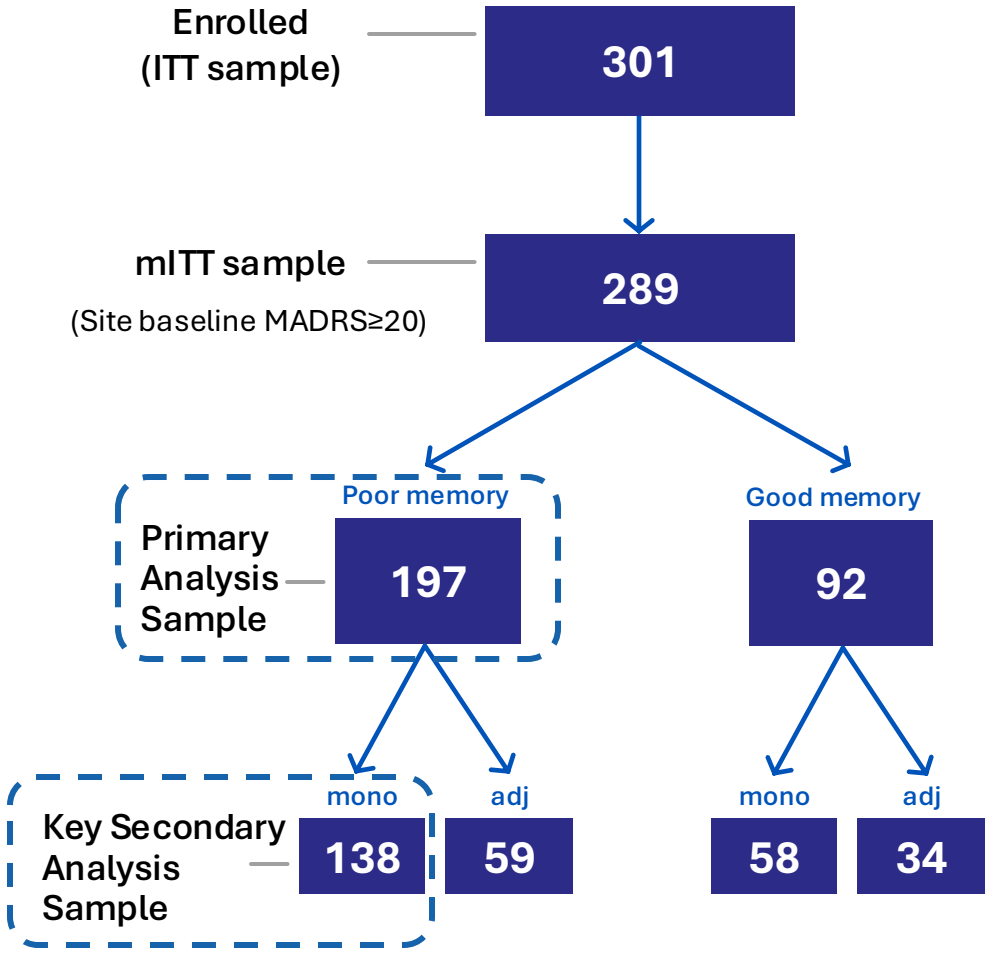
# FDA interactions support Phase 2b study interpretation

- Early feedback on protocol led to an increase from N=200 to 266 to enable better powering of monotherapy (largest subgroup)
- June 2024 Type C meeting, focusing on enrichment approach via memory test:
  - Outcome in line with expectations
  - Provided FDA clarity on rationale for enrichment approach
  - Phase 2b data expected to guide Phase 3 program
- Anticipate End of Phase 2 meeting based on Phase 2b data to align on Phase 3 design
- At least one Phase 3 will likely include the entire MDD population (powered for a primary outcome in poor memory patients) to fully describe risk-benefit relationship for the patients negative on the memory marker

# Phase 2B study flow, enabled by robust biomarker collection




**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*

# Phase 2b: poor and good memory patients are well-matched

- No difference in depression severity or any other demographic factor (e.g. age)
- Overall severity in line with expectations, consistent visit-wise across MADRS and PHQ
- Shows cognition is an independent facet of MDD not confounded by clinical variables
- **Notably, no evidence for score inflation on the site MADRS**

| Characteristic | Poor memory (N=197) | Good memory (N=92) | P-value |
|---|---|---|---|
| Age | 44.80 (12.59) | 43.50 (13.52) | 0.426 |
| Sex – Female | 122 (61.93%) | 53 (57.61%) | 0.286 |
| Non-Hispanic White | 111 (56.35%) | 51 (55.43%) | 0.885 |
| Black/African-American | 44 (22.34%) | 14 (15.22%) | 0.159 |
| Education (≥ 16 years) | 69 (35.03%) | 37 (40.22%) | 0.394 |
| MADRS – SAFER (determines inclusion) | 32.89 (5.33) | 32.83 (5.50) | 0.921 |
| MADRS – Visit 3 (treatment baseline) | 31.39 (5.51) | 30.74 (5.19) | 0.384 |
| PHQ-9 – Visit 1 | 17.38 (4.16) | 17.24 (3.66) | 0.780 |
| PHQ-9 – Visit 2 | 16.77 (4.14) | 16.25 (3.55) | 0.298 |
| PHQ-9 – Visit 3 | 15.96 (4.34) | 15.79 (4.06) | 0.757 |

mITT population: randomized population with MADRS at visit 3 ≥ 20 (N=289).

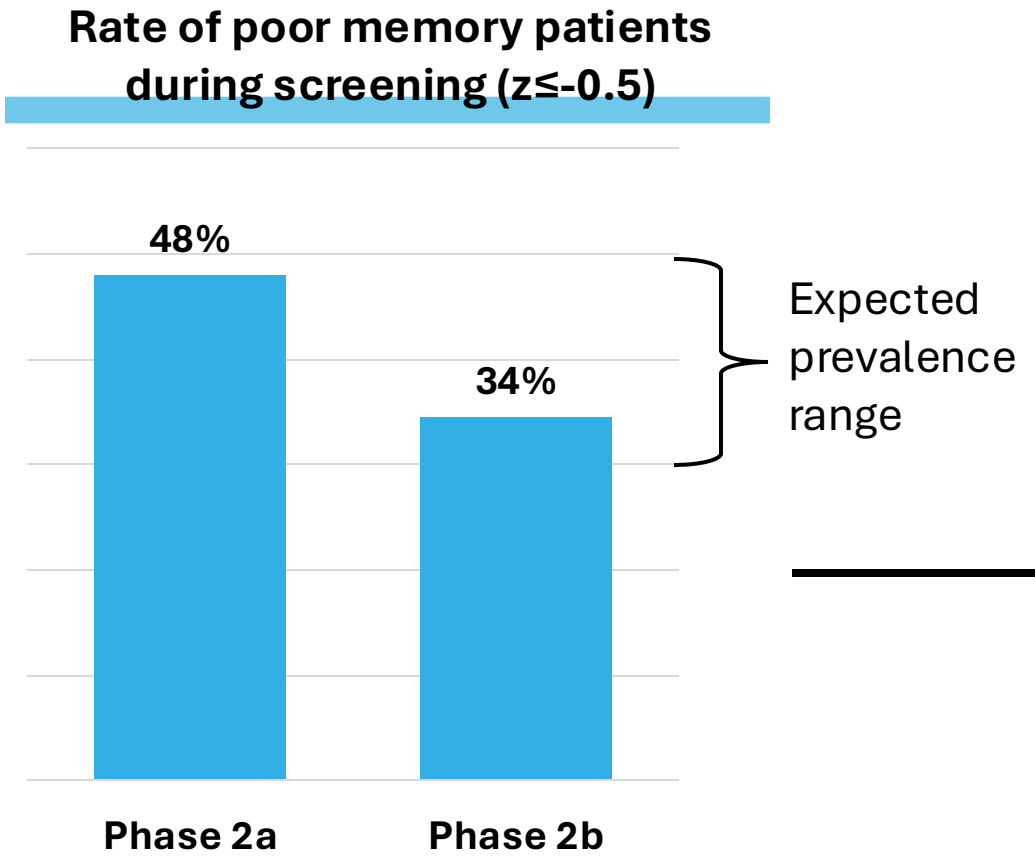
# Phase 2b: similar severity for mono vs. adjunctive (poor memory)

- Within poor memory group, similar clinical profile for monotherapy and adjunctive patients
- No difference in years since first episode (mean: 19.3) or number of episodes
- Racial difference may reflect difference in access to healthcare

| Characteristic | Mono (N=138) | Adjunctive (N=59) | P-value |
|---|---|---|---|
| Age | 44.66 (12.44) | 45.19 (13.10) | 0.789 |
| Sex – Female | 85 (61.59%) | 37 (62.71%) | 0.882 |
| Non-Hispanic White | 71 (51.45%) | 40 (67.80%) | 0.034* |
| Black/African-American | 37 (26.81%) | 7 (11.86%) | 0.021* |
| Education (≥ 16 years) | 43 (31.16%) | 26 (44.07%) | 0.082 |
| MADRS – SAFER (determines inclusion) | 33.01 (5.27) | 32.63 (5.50) | 0.648 |
| MADRS – Visit 3 (treatment baseline) | 31.59 (5.06) | 30.88 (6.09) | 0.396 |
| PHQ-9 – Visit 1 | 17.54 (4.14) | 17.00 (4.22) | 0.402 |
| PHQ-9 – Visit 2 | 17.06 (4.05) | 16.10 (4.30) | 0.138 |
| PHQ-9 – Visit 3 | 16.12 (4.04) | 15.58 (4.98) | 0.419 |

mITT primary outcome population (N=197)

# Importance of patient selection: underpins ability to consistently identify the same patient population across studies




Screening population less impaired on memory in Phase 2a vs Phase 2b (p=0.004)

**When selecting patients based on memory, Phase 2a and 2b populations are now highly similar**

- Well-matched on depression severity and cognition, supporting generalization from Phase 2a to Phase 2b
- **Degree of cognitive impairment is substantial:** ~1.4 SD below the healthy mean is approximately the average in patients with schizophrenia

| Characteristic | Phase 2a poor mem (N=59) | Phase 2b poor mem (N=197) | P-value |
|---|---|---|---|
| MADRS – study baseline | 31.64 (4.83) | 31.38 (5.38) | 0.736 |
| PHQ-9 – study baseline | 15.86 (3.98) | 15.96 (4.34) | 0.881 |
| Global Cognitive Composite | -1.43 (0.80) | -1.39 (0.88) | 0.751 |
| Memory score | -1.20 (0.51) | -1.11 (0.43) | 0.184 |

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# Alto's in-house clinical operations approach

**Individual**

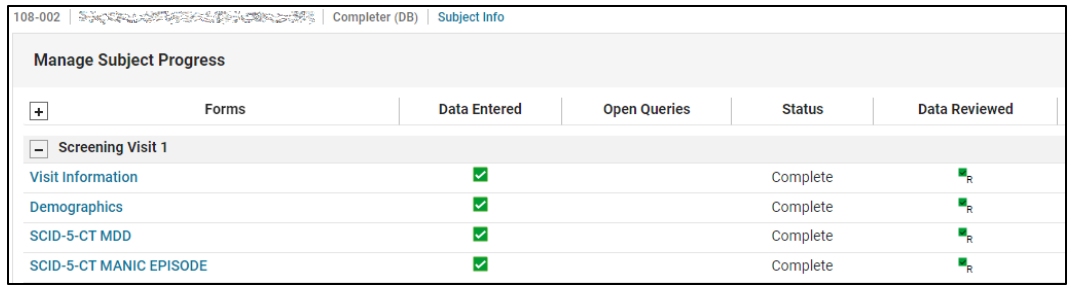
- ✓ Direct Data Entry
- ✓ Real Time Data Review
- ✓ Eligibility review
- ✓ Onsite/Remote RBM
- ✓ Independent, external raters confirm MDD

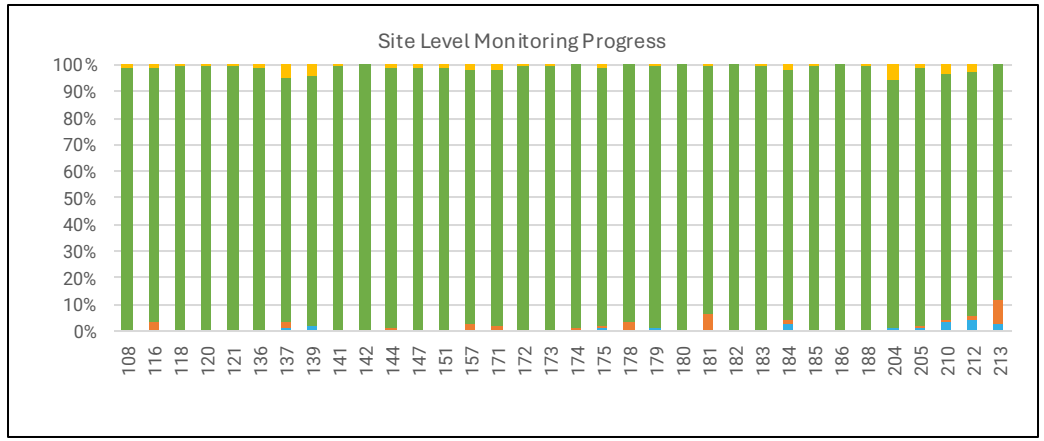
**Cumulative**

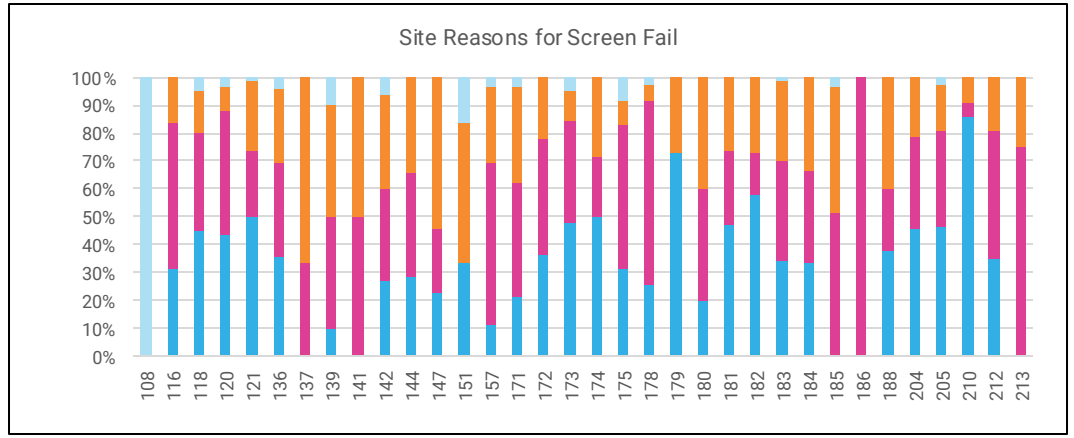
- ✓ Biweekly Cumulative Data Reviews
- ✓ Timely identification of site issues
- ✓ Monthly safety reviews
- ✓ Monthly Protocol Deviation Review
- ✓ Early identification of missing data

**Trend Analysis**

- ✓ Optimized Site Selection (100+ sites)
- ✓ **34 Sites: 25 Professional CNS, 5 Academic/VA, 4 DCT**
- ✓ Trend Analysis of key performance metrics
- ✓ Ensures Balanced Study Population



# Statistical analysis plan for key outcomes

## Primary outcome

- mITT poor memory population
- Powered at 80% for d=0.4

Step-down test, no alpha spend if primary is positive

## Key secondary outcome

- mITT poor memory monotherapy
- Powered at 80% for d=0.5

Clinical analyses focus on change in MADRS from baseline, with response rates, CGI-S and PROs as secondary outcomes

*Study enrollment was guided by the poor memory primary outcome sample size with an expectation of ~2/3 being monotherapy*

- Analyses guided by trial design, unmet clinical need of poor memory MDD
- Will also look at a more cognitively impaired mITT subpopulation that may further enhance enrichment (only threshold will be z≤-1.0, encompassing 53% of mITT poor memory group; powered at 80% for d=0.55)
- Full mITT population will reflect likely all-comer effect only if there is no enrichment seen (powered at 80% for d=0.33)
- Good memory mITT outcomes will be described qualitatively as is not powered and not expected to be statistical for enrichment
- Analyses of change in memory and global cognition in mITT poor memory population as well, though not expected to be part of the clinical efficacy package

# Summary of key factors for potential Phase 2b success

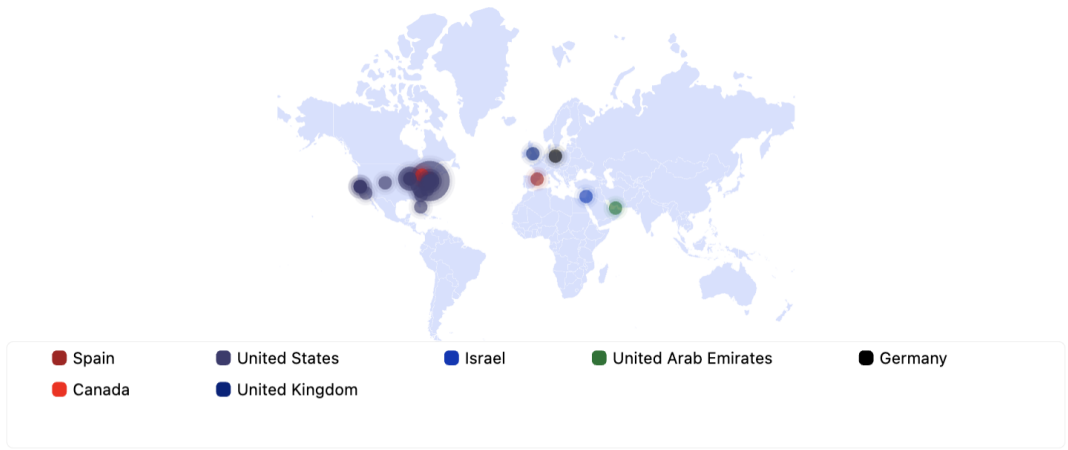
- Target population, drug MOA and memory-based enrichment all strongly theoretically motivated
- High unmet clinical need as poor memory/cognition patients more chronic and disabled, with worse response to standard of care
- Two prospective replications (along with two retrospective analyses) all indicate better response in poor memory patients
- Multiple external datasets show placebo response is similar or slightly worse in poor memory patients
- Drug consistently well-tolerated (>400 patients dosed prior to the Phase 2b)
- Multiple design elements targeted at mitigation of placebo response with tight trial execution and baseline data supportive of well-chosen and well-matched groups

# Results from Spectra

# Dashboard

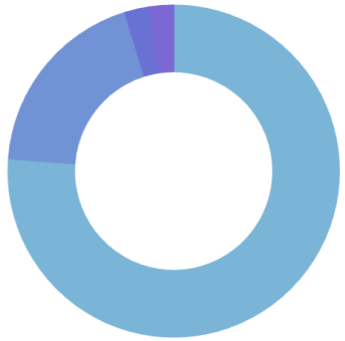
## Location

All Countries




## System Specifications

Browser | OS Name



Chrome 76.19%
Edge 19.05%
Safari 2.38%
Firefox 2.38%

Laptop 100.0%
Tablet 0.0%
Mobile 0.0%

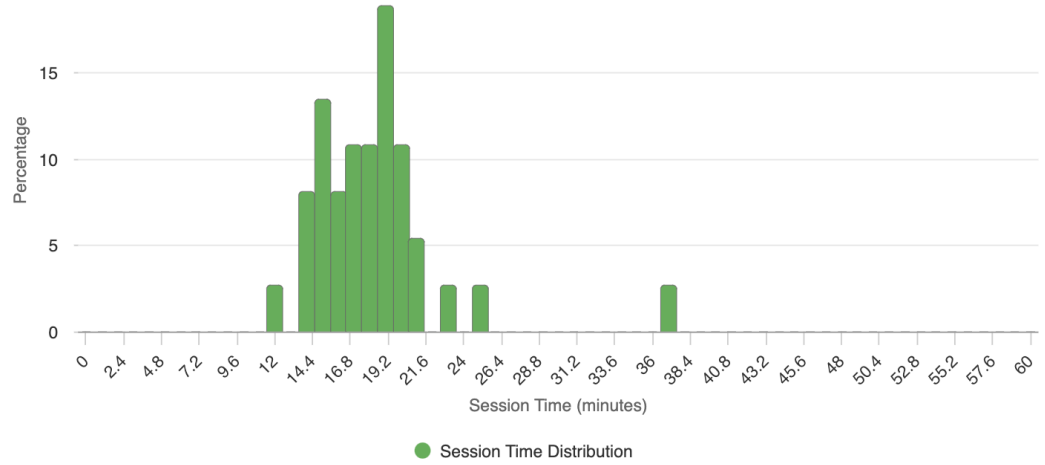
## User Demographics

### Gender


### Dominant Hand

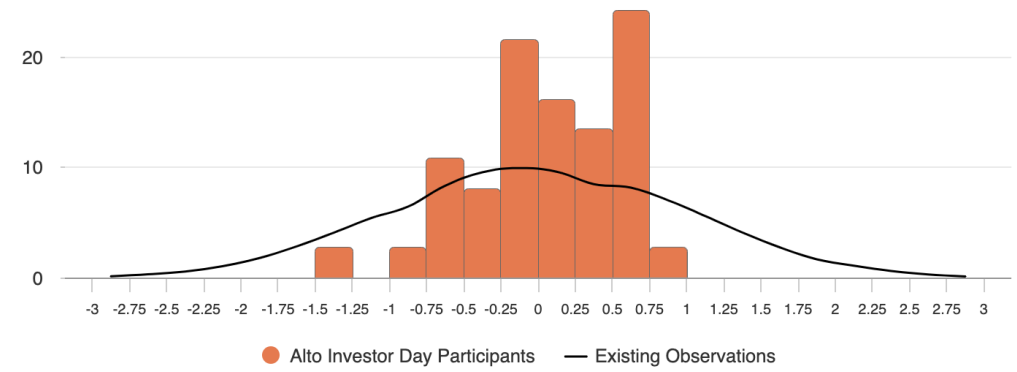

### Languages


## Session Time

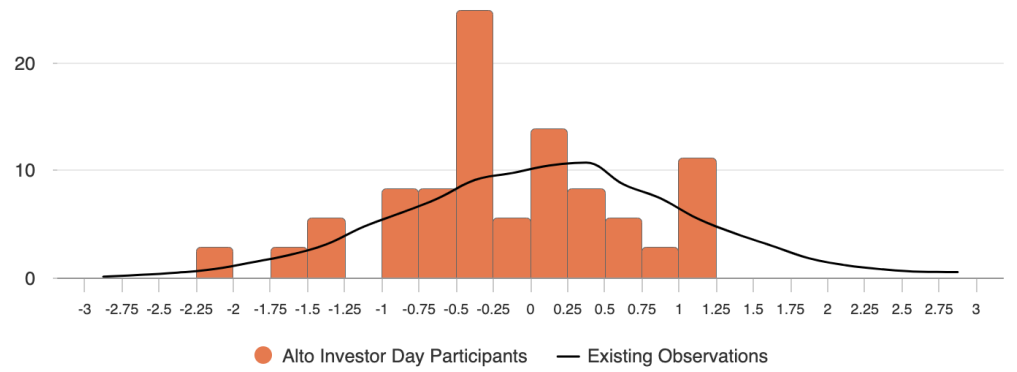


# Dashboard

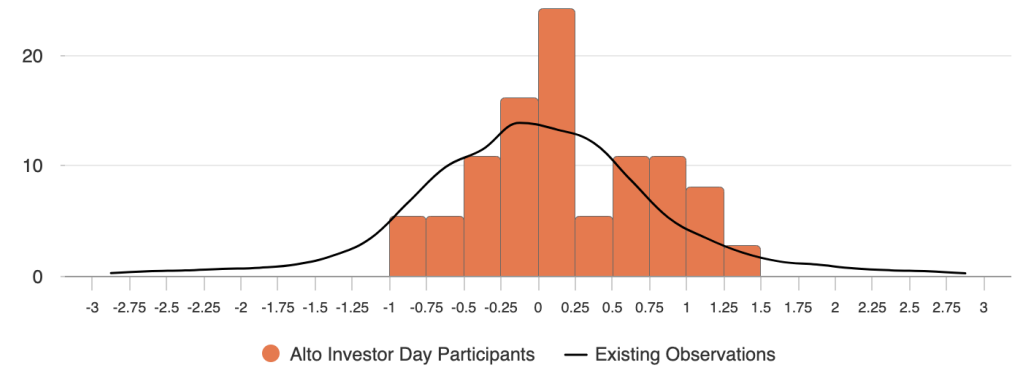
## Memory



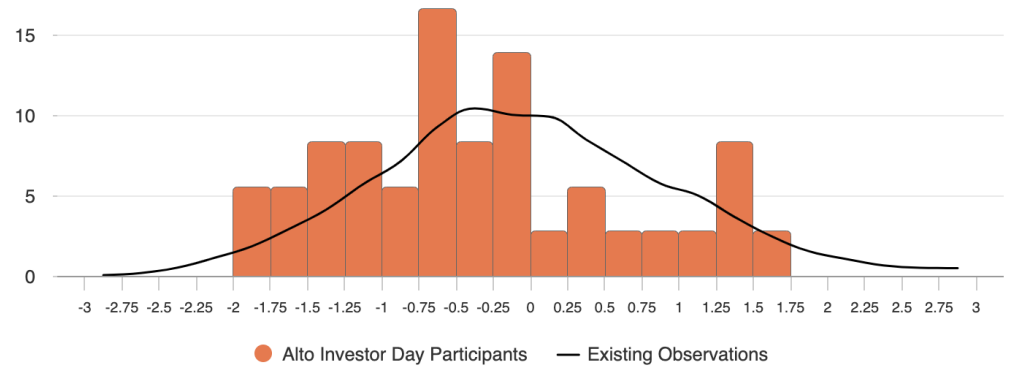

## Speed




## Strategy



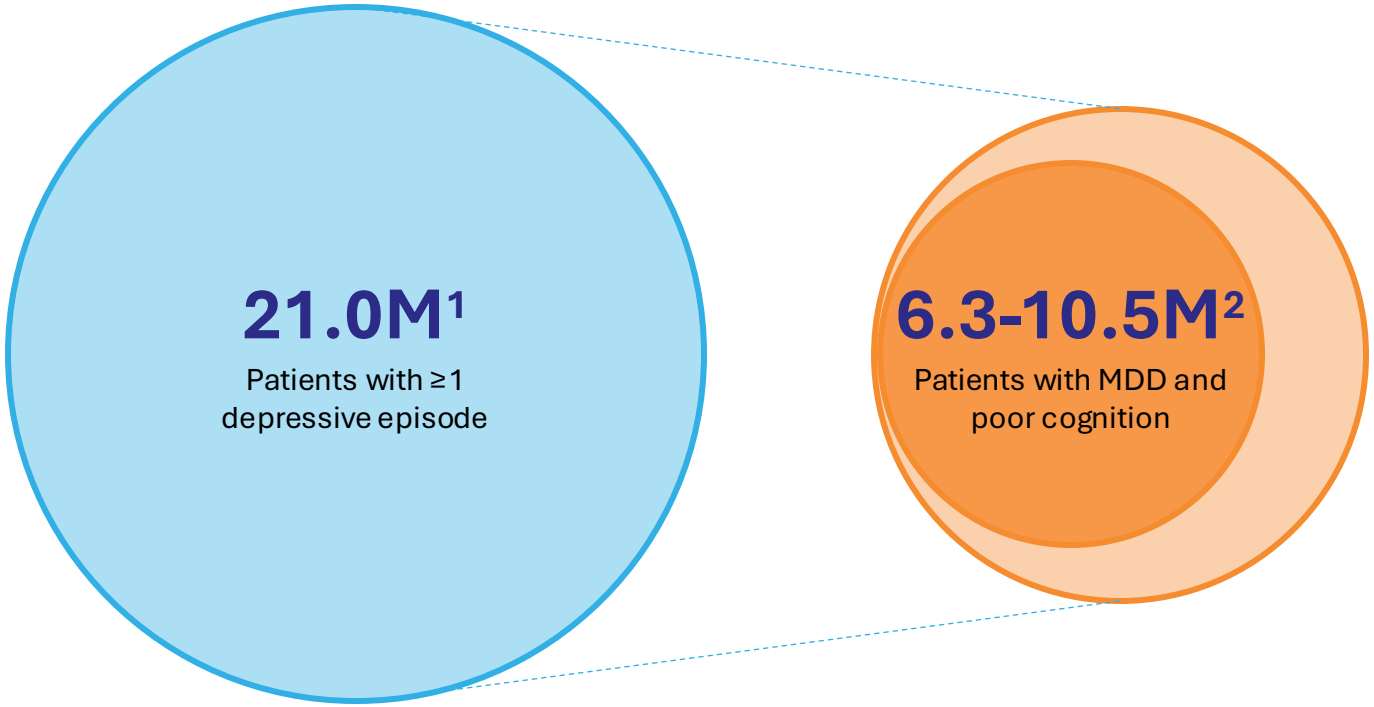

## Reward



**Commercial considerations:**
Unique opportunity afforded by the precision psychiatry approach

# Patients with MDD and poor cognition represent a large, underserved, and readily addressable population

## Patients with MDD and poor cognition represent an estimated 30-50% of the overall MDD population




## Patients with schizophrenia

*For reference, the number of patients with MDD and poor cognition is estimated to be **2-4x larger** than the schizophrenia population*


1 SAMHSA's 2021 National Survey on Drug Use and Health (accessed 09/02/2024)
2 Data on file
3 Schizophrenia Fact Sheet, Treatment Advocacy Center (accessed 09/02/2024)

# Prescribers recognize the need for targeted therapies with novel mechanisms and improved clinical profiles

***In recent market research, prescribers provided perspective on the management of MDD***

## Among adult patients with MDD…

**64%**
estimated to have some degree of impaired cognition

**45%**
unable to meet treatment goals with current options

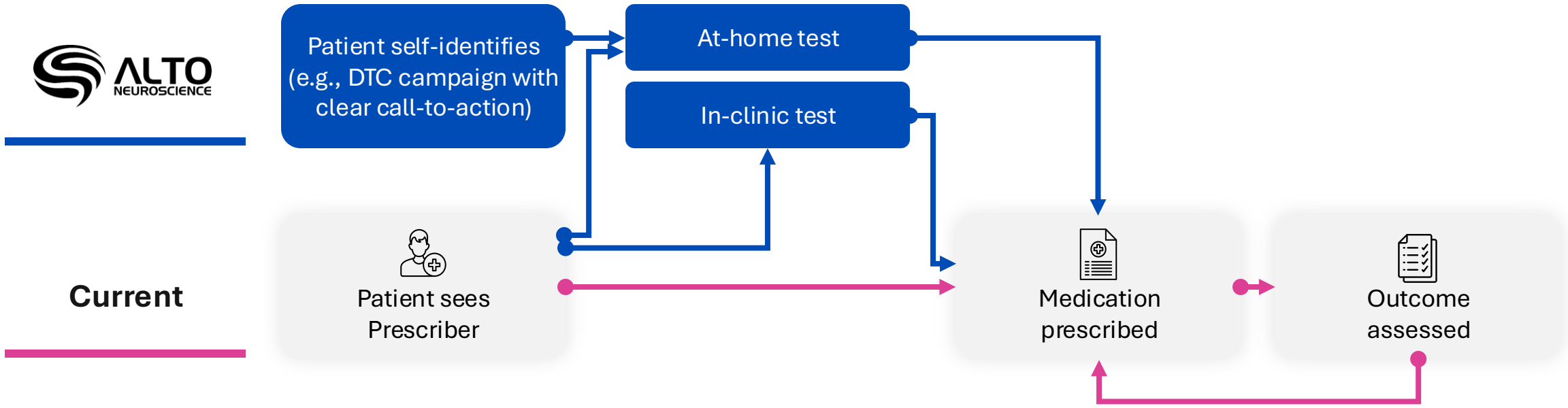
## Top unmet needs

| | |
|---|---|
| **Mechanism of action** | New and targeted mechanisms |
| **Precision** | Predictive biomarkers leading to personalized therapies |
| **Efficacy** | Improved efficacy and faster onset of action |
| **Tolerability** | Improved AE profile (sexual, weight gain, insomnia, anxiety) |

***"We need more effective treatments. That may hinge on the idea that we're often not personalizing treatment, and instead kind of prescribing hit-or-miss treatments."***

*Source: MDD prescriber market research, August 2024 (n=12)*

# Readily scalable cognitive testing enables multiple routes to ALTO-100 utilization and drives market penetration



# The MDD market is ripe for a precision medicine approach

***HCPs view Alto's cognitive test as predictive, reliable, and easy to integrate into practice***

## Physicians expressed a strong desire for a biomarker-based treatment approach …

- Personalized treatment limited by lack of predictive tools and novel mechanisms
- Existing trial-and-error approach results in suboptimal outcomes

## … and a strong willingness to incorporate Alto's cognitive biomarker test into clinical practice

**6.3**
*(on a 1-7 scale)*
comfort level recommending Alto's cognitive assessment to patients with MDD

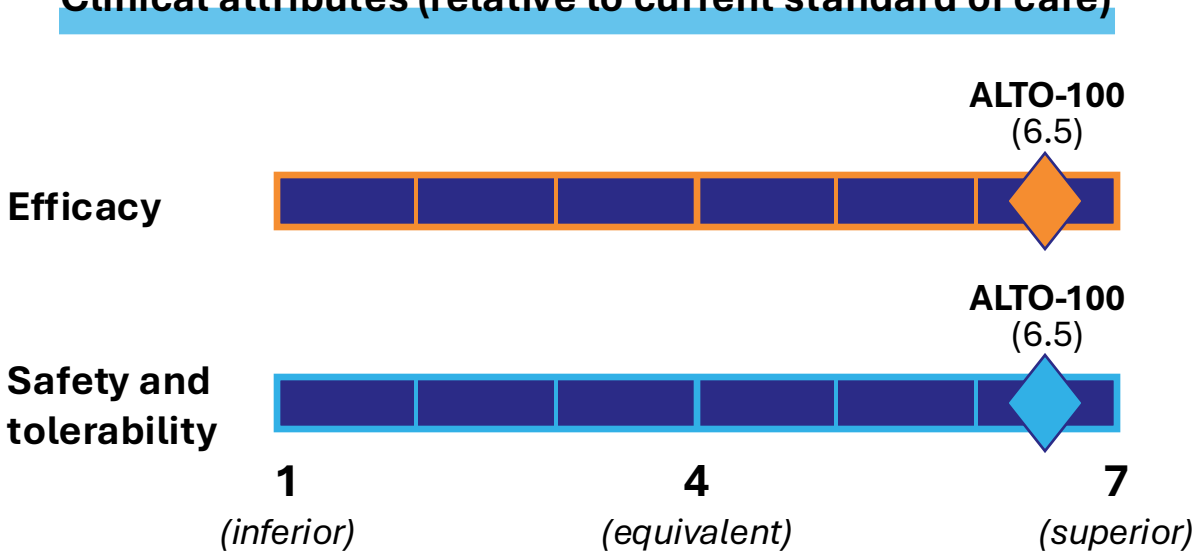
**80%**
of patients with MDD to be referred for testing

*Source: MDD prescriber market research, August 2024 (n=12)*

# Prescribers view ALTO-100's clinical profile very favorably

***Perceived access restrictions represent the biggest barrier to early use***

**HCPs view the ALTO-100 clinical profile as highly differentiated from current treatment options**




*"**I would test most patients** that are referred to me. **I just can't think of a reason not to** refer patients for this test."*

*"I would probably **do it on most or all of my patients** as part of my initial workup, the same way I would check a thyroid and maybe do some other tests."*

*"If somebody is already taking medication and not improving or has residual symptoms, **this is the next step** after treatment as usual."*

*"If a patient tests positive, **why wouldn't I use [ALTO-100]**? The only reason I can think of is access."*

***HCPs indicated that they would prescribe ALTO-100 to virtually every biomarker-positive patient***

*Source: MDD prescriber market research, August 2024 (n=12)*

# Payers recognize the potentially unique economic and clinical rationale resulting from a targeted biomarker approach and compelling clinical profile

***In recent market research, payers provided perspective on their management of MDD***

- While payers currently control the MDD treatment algorithm, they acknowledged ALTO-100's strong value proposition
- A compelling health economics and outcomes research (HEOR) story has the potential to positively impact how payers manage ALTO-100 and address barriers to access

*"(There is) **a good clinical story** to tell here. A predictive tool like **this could have a really significant positive impact.**"*

*"**I'm in favor** of any kind of test that can narrow choices and have a **better success at treatment**."*

*"By determining a patient's likelihood to respond, you can **avoid unneeded therapy and can save money** while still giving them the **best shot at a response**."*

*Source: MDD payer market research, August 2024 (n=6)*

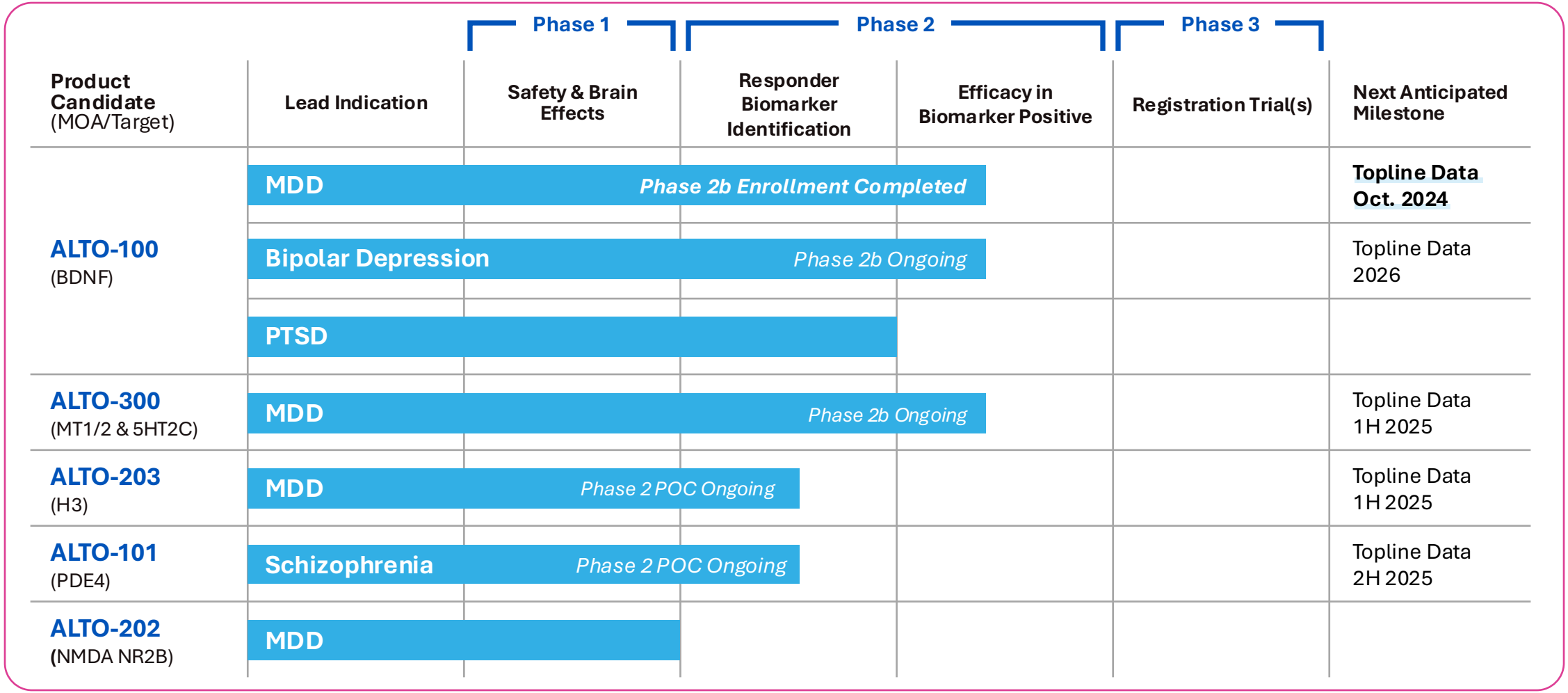
# ALTO-100: A clear path to commercialization and significant commercial potential

- Large and readily identifiable patient population
- Substantial unmet need due to the heterogeneity of disease, lack of diverse MOAs, and limited treatment effect among available therapies
- Strong receptivity to a cognitive biomarker test that is highly predictive, reliable, easy to use, and largely aligned with clinical practice
- Clear interest in ALTO-100 due to tight alignment with unmet needs in MDD
- Compelling economic and clinical value proposition with the potential to help payers rethink established access strategies

**Broader Alto pipeline:**
Multiple Phase 2 studies across drugs and populations

# First biomarker-driven pipeline for neuropsychiatric conditions

Advancing towards multiple near-term milestones across pipeline of independent programs leveraging our biomarker strategy to systemically reduce development risks



# Expert perspective:

## Gerard Sanacora, MD PhD

*George D. and Esther S. Gross Professor of Psychiatry*
*Director, Yale Depression Research Program*
*Yale University*

# External expert perspective

## Gerard Sanacora, PhD MD

*George D. and Esther S. Gross Professor of Psychiatry, Director of Yale Depression Research Program, Yale University*

Dr. Sanacora's work has focused largely on elucidating the pathophysiological mechanisms associated with mood and other neuropsychiatric disorders and using this information to inform the development of novel treatment strategies. His preclinical research laboratory explores the effects of stress and pharmaceutical agents on cellular biology, neurophysiology and behavior. His clinical laboratory employs novel imaging methodologies to investigate the pathophysiology of mood and other neuropsychiatric disorders. In addition, he has served as principal investigator on several large clinical trials investigating the efficacy and safety of newly developed therapeutic agents for the treatment of mood disorders. Dr. Sanacora is a Fellow of the American College of Neuropsychopharmacology.

# A Discussion of the Relevant Conceptualization and Clinical Treatment of Major Depressive Disorder

Gerard Sanacora M.D., Ph.D.

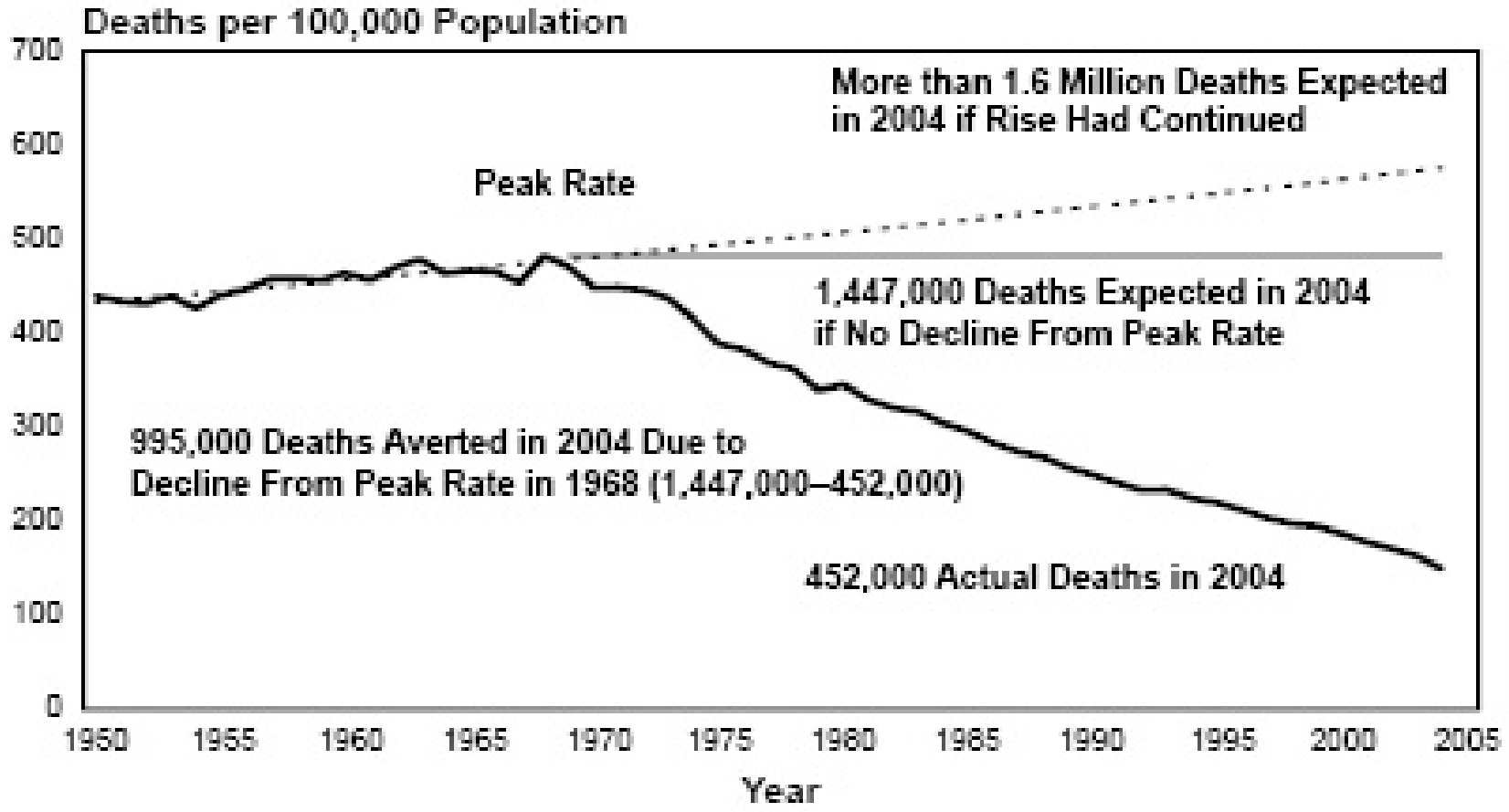
George D. Gross and Esther S. Gross Professor of Psychiatry, Yale University School of Medicine

Director Yale Depression Research Program

Co-Director Yale New Haven Hospital Interventional Psychiatry Service

The Yale School of Medicine

# Death Rates* for Coronary Heart Disease, United States, 1950–2004 Actual Rate and Expected Rates if Rise had Continued or Reached a Plateau




*Age-adjusted.
National Institutes of Health. National Heart, Lung, and Blood Institute. www.nhlbi.nih.gov/about/factbook-06/chapter4.htm. Accessed September 1, 2015.

# Depression is the leading cause of disability worldwide and is a major contributor to the overall global burden of disease

World Health Organization

## US Suicide rates overall appear to be increasing

## A large percentage of patients do not receive an adequate response to current antidepressant medications

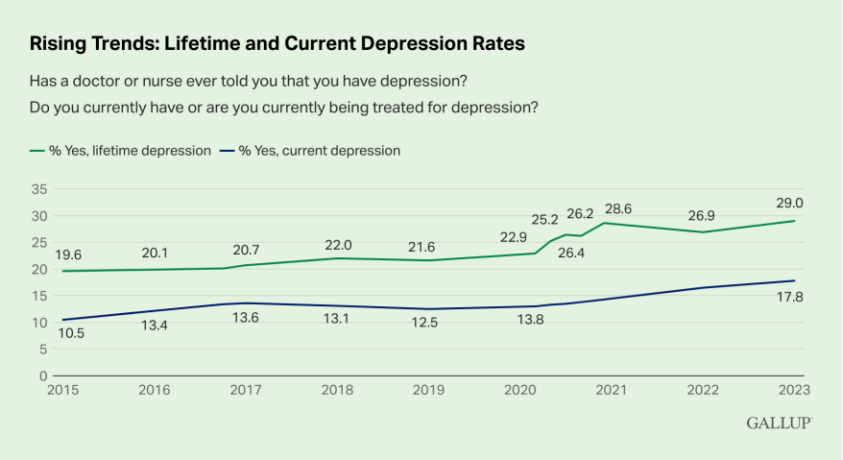
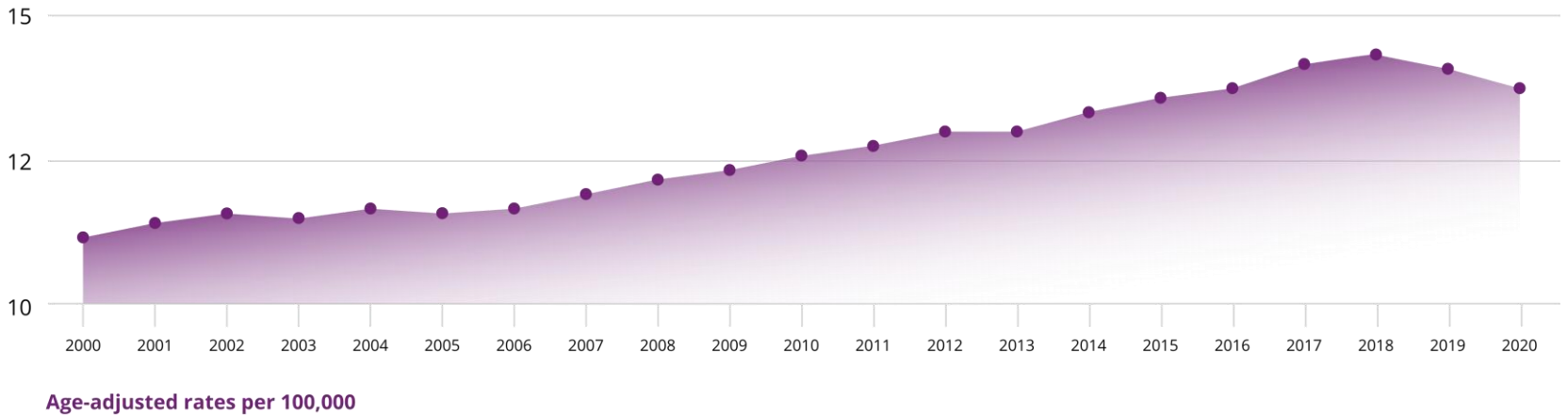



Table 1. Results at Each Level of Treatment in STAR*D[a]

| Level | Remission Rate (%) | Intolerance Rate (%)[b] | Relapse During 1-Year Follow-Up (%) |
|---|---|---|---|
| 1 | | | |
| Citalopram monotherapy | 36.8 | 16 | 40 |
| 2 | | | |
| Any level 2 treatment | 30.6 | 19 | 55 |
| Any switch | 27 | 23 | |
| Bupropion SR | 26 | 27 | |
| Sertraline | 27 | 21 | |
| Venlafaxine XR | 25 | 21 | |
| CT | 31 | 17 | |
| Any combination/augmentation | 35 | 16 | |
| Bupropion SR + citalopram | 39 | 13 | |
| Buspirone + citalopram | 33 | 21 | |
| CT + citalopram | 31 | 9.2 | |
| 3 | | | |
| Any level 3 treatment | 13.7 | 26 | 65 |
| Any switch | 11 | 32 | |
| Mirtazapine | 8 | 32 | |
| Nortriptyline | 13 | 33 | |
| Any combination/augmentation | 21 | 15 | |
| Lithium + prior ADT | 15 | 21 | |
| Triiodothyronine + prior ADT | 26 | 10 | |
| 4 | | | |
| Any level 4 treatment (switch) | 13.0 | 34 | 71 |
| Tranylcypromine | 15 | 40 | |
| Mirtazapine + venlafaxine XR | 16 | 20 | |

Zisook S, et al. *J Clin Psychiatry*. 2008;69(7):1184-1185.

ADT = antidepressant treatment; CT = cognitive therapy; STAR*D = Sequenced Treatment Alternatives to Relieve Depression; SR = sustained release; XR = extended release.

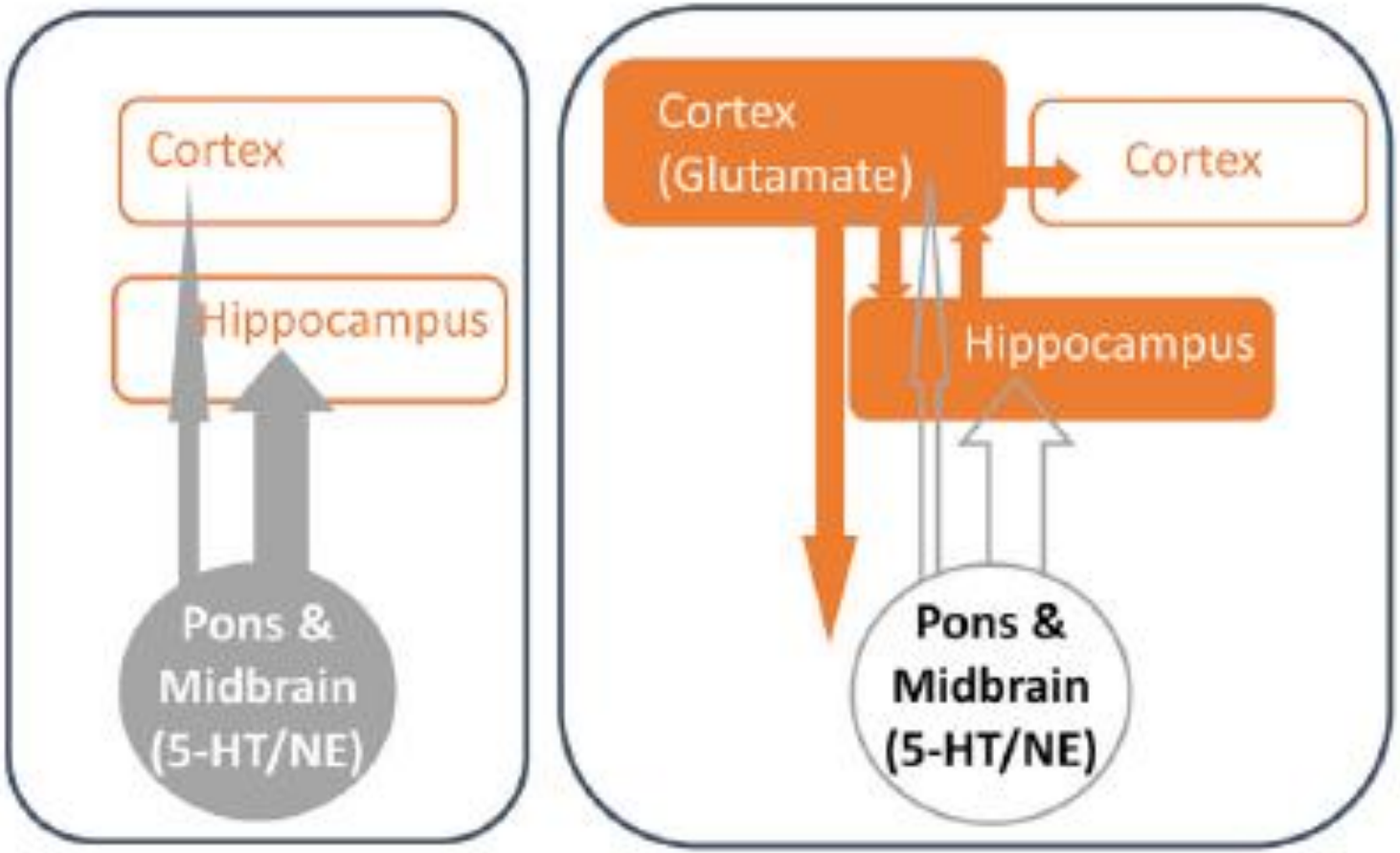



https://www.cdc.gov/suicide/suicide-data-statistics.html

# Changing Theories of Mood Disorder Pathophysiology

**Historically dominant monoaminergic theory**

**Shift to cortical and limbic pathology**




*"If one viewed depression as a disorder of cortico-limbic function, then glutamatergic and GABAergic signaling would be implicated. This perspective shift led us to test the effects of the NMDA glutamate receptor antagonist as a probe of alterations in glutamate signaling associated with depression."*

Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS. Neuron. 2019 Mar 6;101(5):774-778

# Typical Patient Journey

**1. Symptom Recognition**

- **Self-awareness:** The patient or those close to them may notice symptoms and recognize that something is wrong.
- **Screening and Assessment:** PCPs commonly use standardized screening tools like the PHQ-9 (Patient Health Questionnaire) to assess the severity of depression during regular office visits.

**2. Help Seeking**

- **Primary Care Provider (PCP) Visit:** The patient often begins by visiting a PCP.
- **Mental health specialist:** Commonly a LCSW, a psychologist or some other form of licensed therapist may be sought.

**3. Diagnostic Process**

- **Evaluation:** PCP or mental health professional conducts a thorough evaluation, including a detailed psychiatric history, family history, and an assessment of symptoms and possibly a more focused medical work up.
- **Diagnosis:** MDD is a ***diagnosis of exclusion***, after the clinician rules out other possible mental health disorders or medical conditions that could cause depressive symptoms, if criteria from the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) are met, the clinician will diagnose the patient with MDD.

**4. Treatment Planning**

•**Collaborative Discussion:** The patient and clinician discuss treatment options, which may include psychotherapy, medication, lifestyle changes, or a combination of these (*largely based on clinician's own expertise)*.

- •**Lifestyle Modifications:** Recommendations might include regular exercise, improved sleep hygiene, nutrition, and stress management techniques.
- •**Psychotherapy:** Cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), or other supportive therapies are common choices.
- •**Pharmacotherapy:** Antidepressants (e.g., SSRIs, SNRIs, or atypical antidepressants) may be prescribed, depending on the severity of symptoms and patient preferences.

**5. Initial Treatment Phase**

- •**Medication Initiation:** If prescribed, the patient begins taking antidepressants, with some level of follow-up visits to monitor for side effects and effectiveness.
- •**Therapy Sessions:** The patient attends regular therapy sessions for either limited course (i.e. CBT) or open-ended time (supportive).

**6. Ongoing Management**

- **Monitoring:** The patient's progress is *"closely"* monitored either by either patient's and clinician's general overall impression or through some symptom focused metrics.

**Satisfactory response:** May continue in care for an undetermined period, common recommendations from 6mos-1yr**.**

- **Unsatisfactory response:** Several options based on level of severity, prior response, and patient preference (Typically where Psychiatrist becomes involved).
  - **Modify existing treatment:** (i.e. increase/decrease dose, change timing of dosing)
  - **Switch treatment:** Consider other treatment choice (i.e. new medication, shift if psychotherapy approach)
  - **Augment Treatment:** Add new treatment on top of existing treatment
  - **Consider referral to higher level of care:** Possible referral to Specialists (*psychopharmacologist*), Interventional Programs (TMS, IN Esketamine, ECT), IOP, or inpatient hosptials

**7. Long-term Management**

**Maintenance Therapy:** For many patients, long-term or maintenance therapy (medication and/or psychotherapy) is recommended to prevent relapse.

**Relapse Prevention:** Education on recognizing early signs of relapse and strategies to manage them are key components.

**8. Crisis Intervention (If Needed)**

**Emergency Care:** In cases of severe symptoms or suicidal ideation, immediate intervention is required, potentially involving hospitalization or intensive outpatient care.

# Precision Medicine for the Brain is Here.

## OUR VISION

To redefine the approach to psychiatric drug development which matches the right patient with the right Alto drug

ALTO NEUROSCIENCE