Precision Drug Development Using Resting State EEG

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ISCTM

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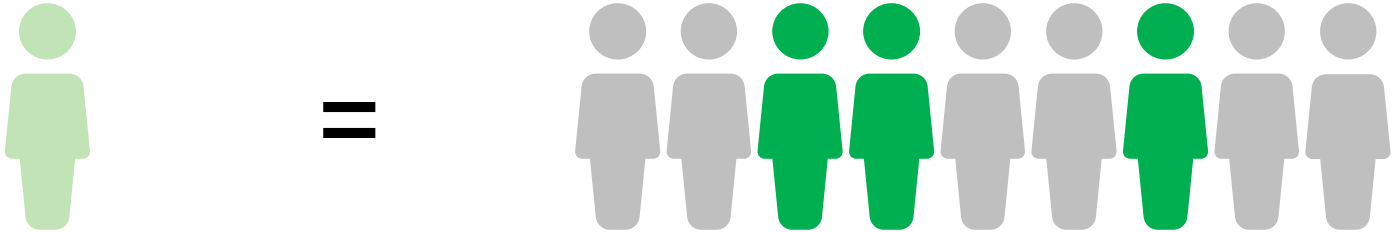
- DISCLOSURES: ADAM SAVITZ

- Full-time employee of Alto Neuroscience and holds equity in the company
- Former employee of Janssen R&D and holds equity in Johnson & Johnson

A CORE PROBLEM IN PSYCHIATRY: UNGUIDED TREATMENTS WORK POORLY

Small effects on average = **...due to large heterogeneity in patients' biology**



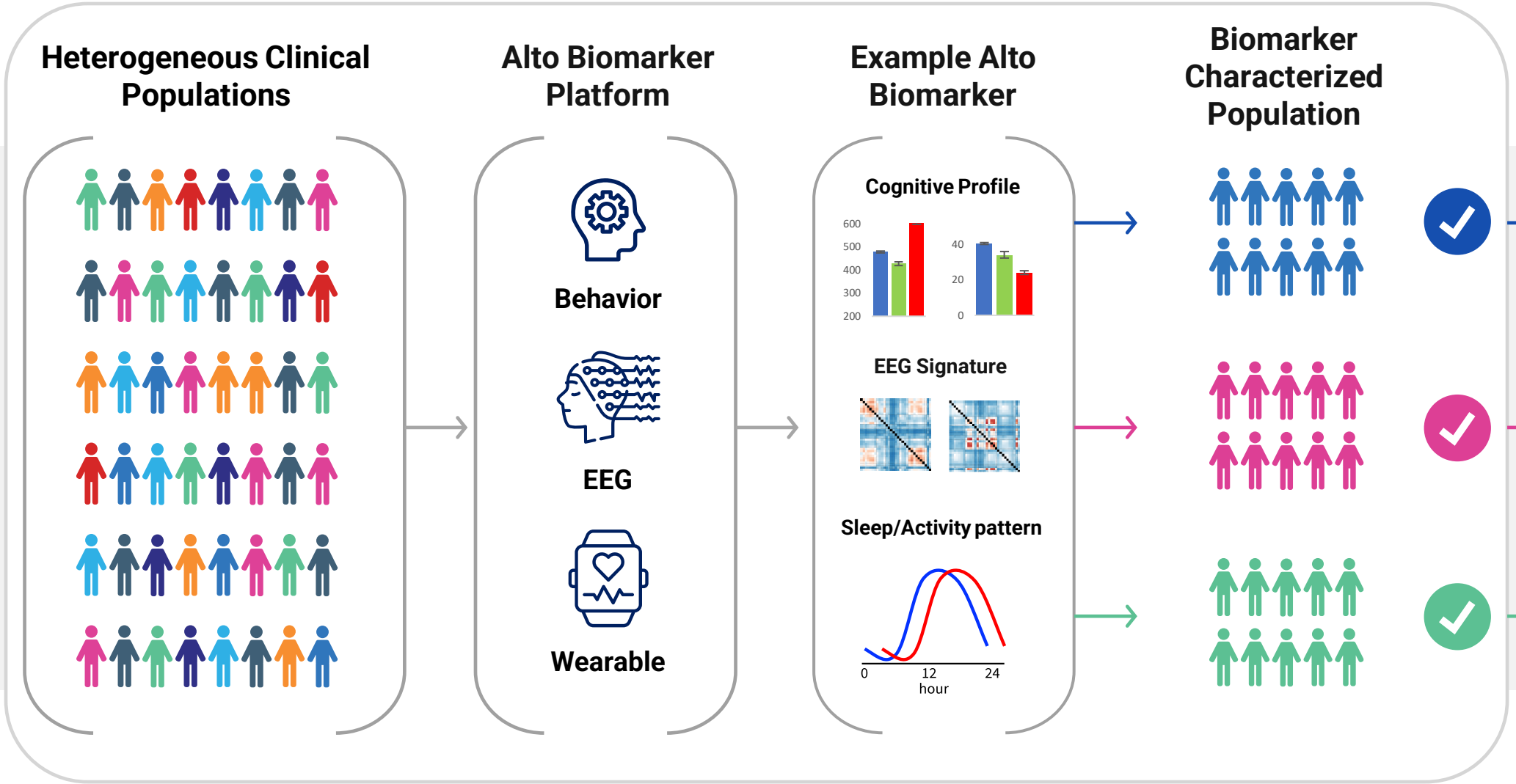
Current Approach

Trial-and-error, mostly failures

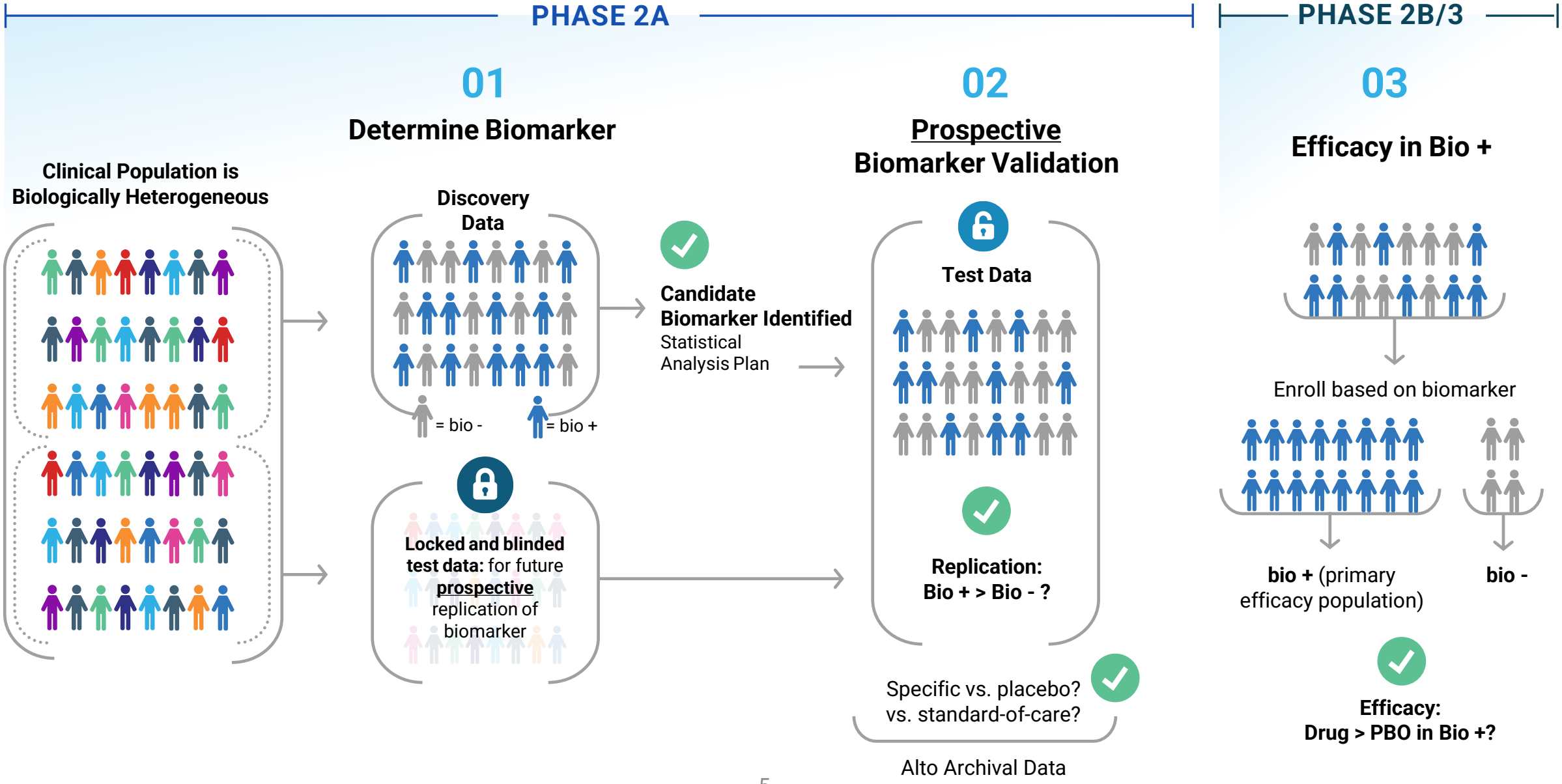
Precision Psychiatry

Differentiated drug profile

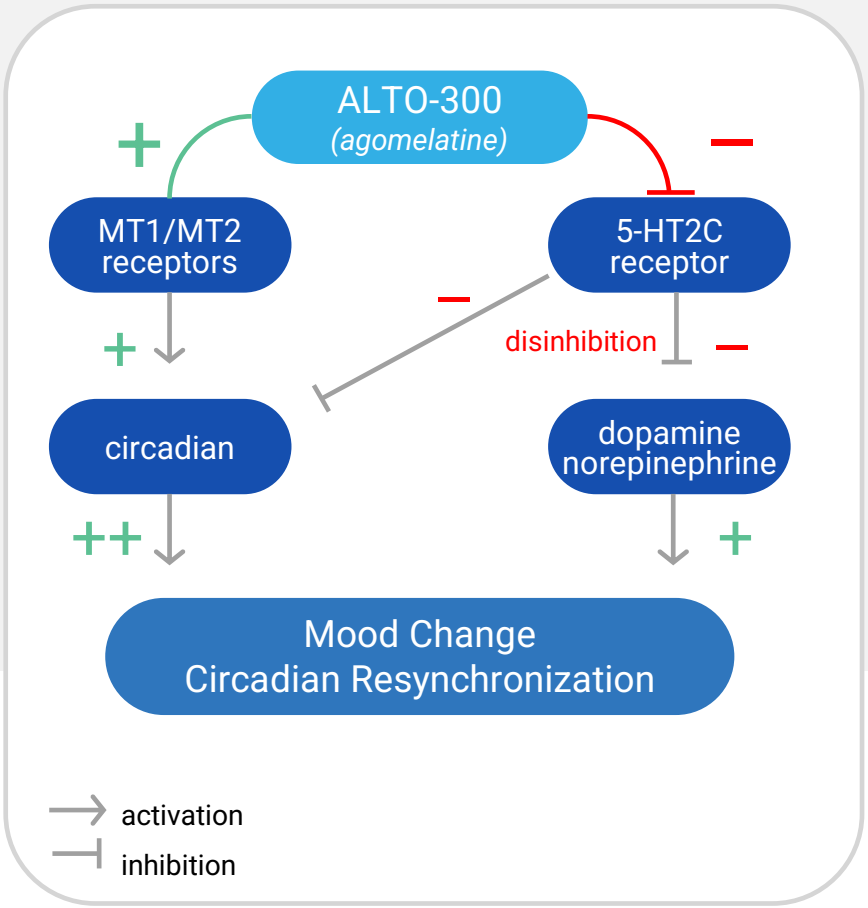
ALTO'S SUITE OF BIOMARKERS DESIGNED TO SEGMENT PATIENTS TO DRIVE IMPROVED OUTCOMES



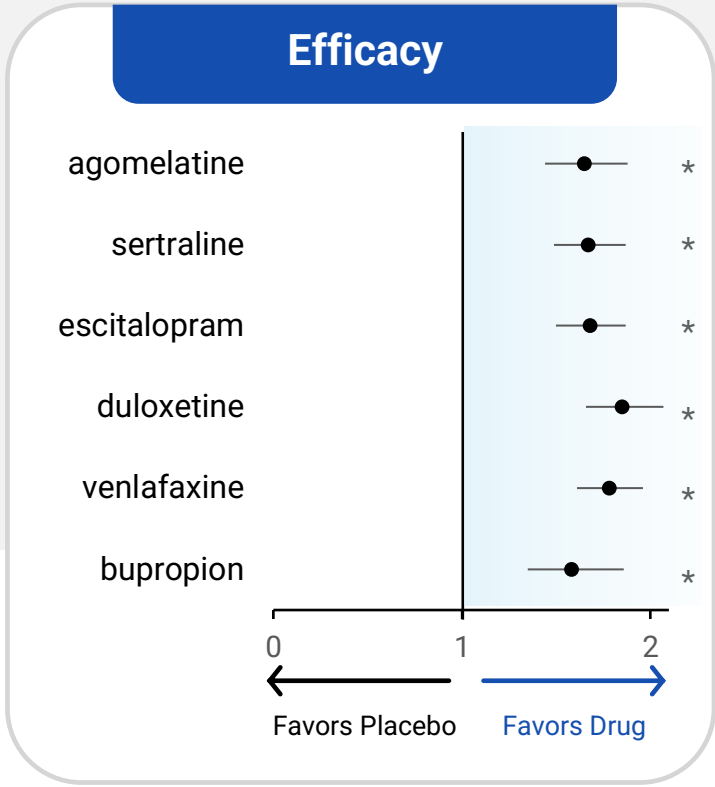
ALTO'S PRECISION DRUG DEVELOPMENT APPROACH

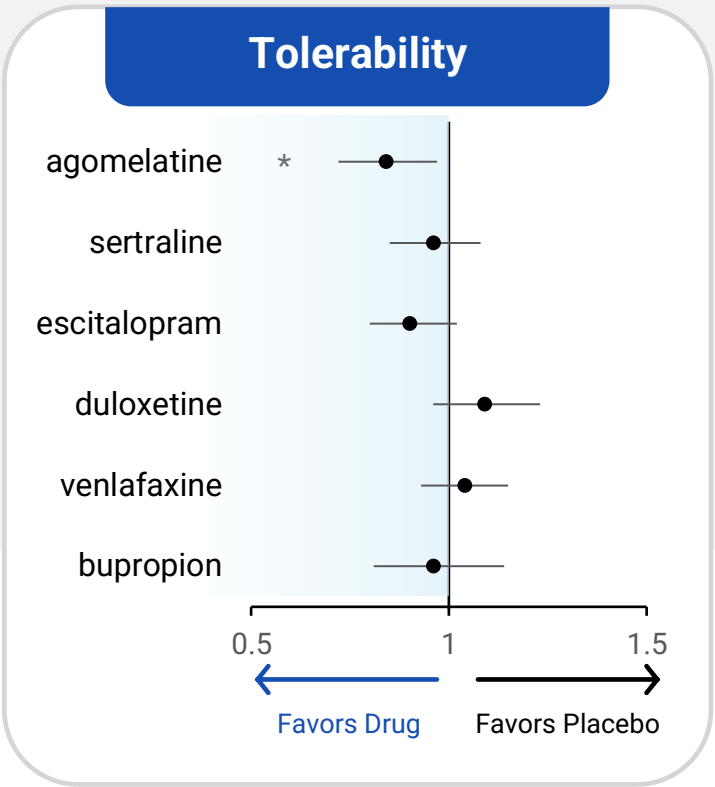


ALTO-300 PROPOSED MECHANISM OF ACTION AND KEY POINTS



Agomelatine: Monotherapy antidepressant in EMA and Australia. Well suited for precision approach





Plots from Cipriani et al., Lancet, 2018
*shows odds ratios, * p<0.05*

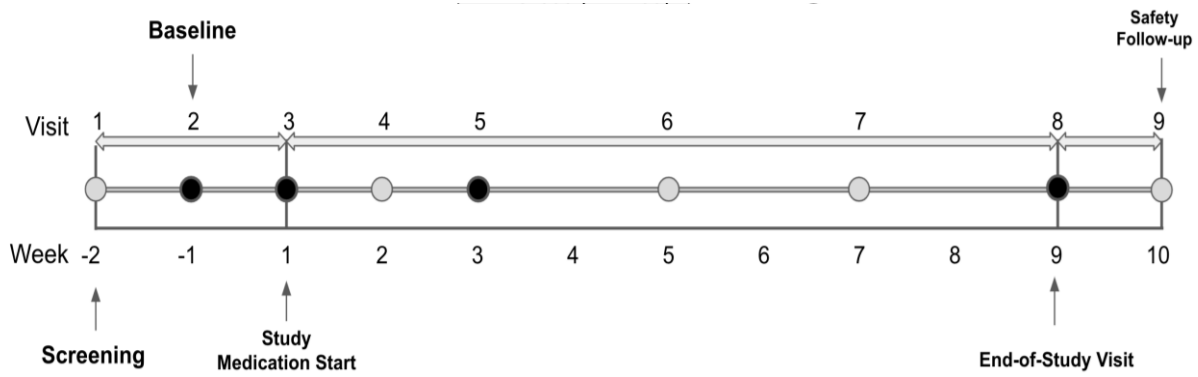
PHASE 2A STUDY DESIGN

Patient Population

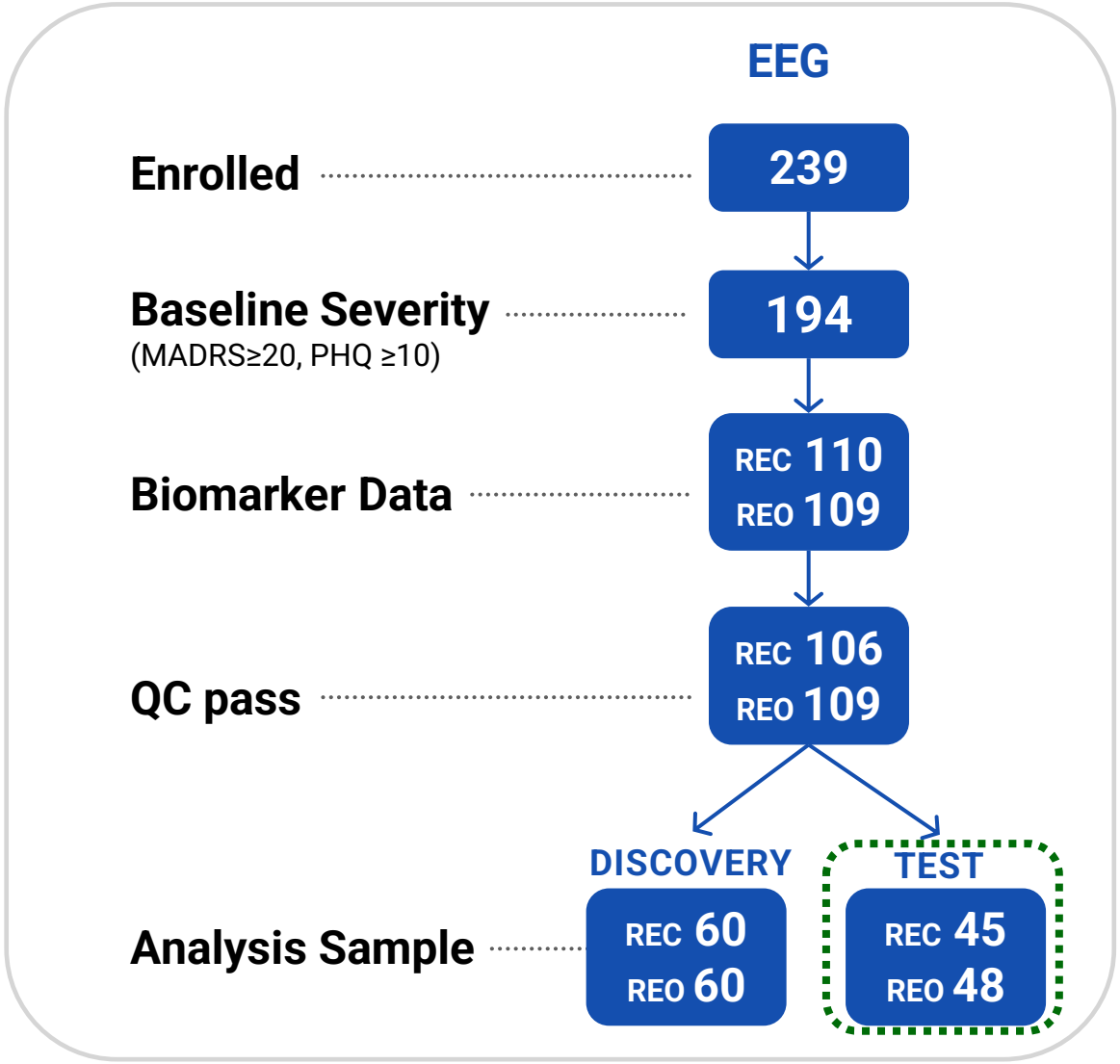
- Adults 18-74 years old
- Moderate to severe MDD
- **Adjunctive** (<50% response to current drug)
- **45% of EEGs done at home**

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



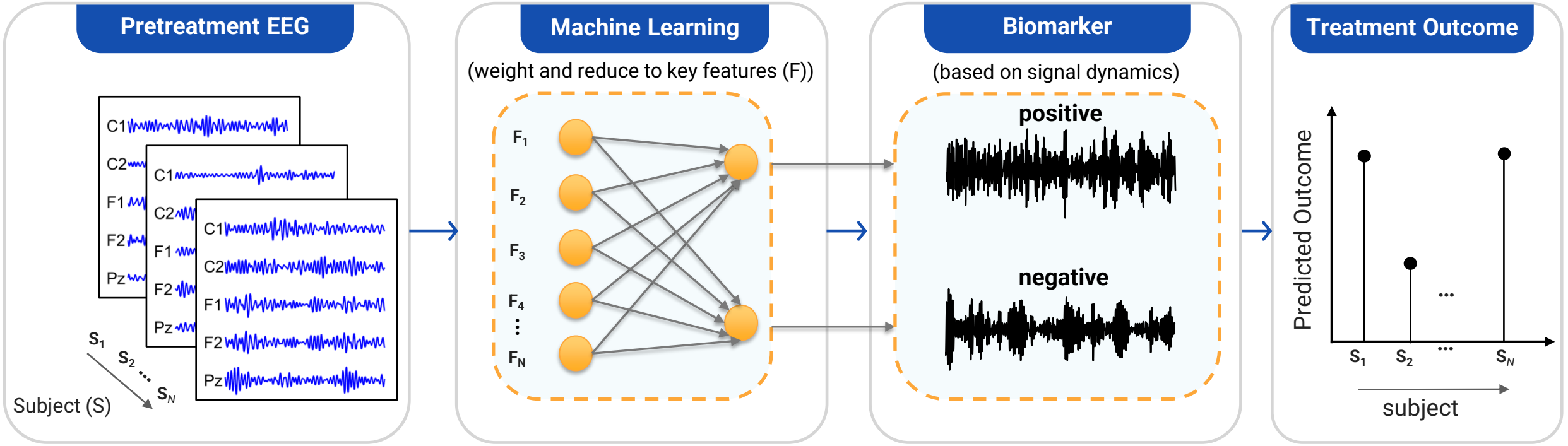
PARTICIPANT FLOW AND DEMOGRAPHICS



REC: resting eyes-closed REO: resting eyes-open

Characteristic	Cognition bio - M, SD (or %)	Cognition bio + M, SD (or %)
Age	41.36 (15.31)	42.71 (14.97)
Female	35 (70.00%)	57 (85.45%)
Education (16+)	23 (46.00%)	28 (50.91%)
BMI	30.88 (8.85)	32.73 (7.76)
White	36 (72.00%)	45 (81.82%)
MADRS	27.40 (4.94)	28.20 (5.08)
HDRS	19.44 (4.90)	19.02 (5.02)
CGI-S	4.52 (0.68)	4.38 (0.65)
PHQ-9	15.48 (3.35)	16.16 (4.33)
Age	41.36 (15.31)	42.71 (14.97)

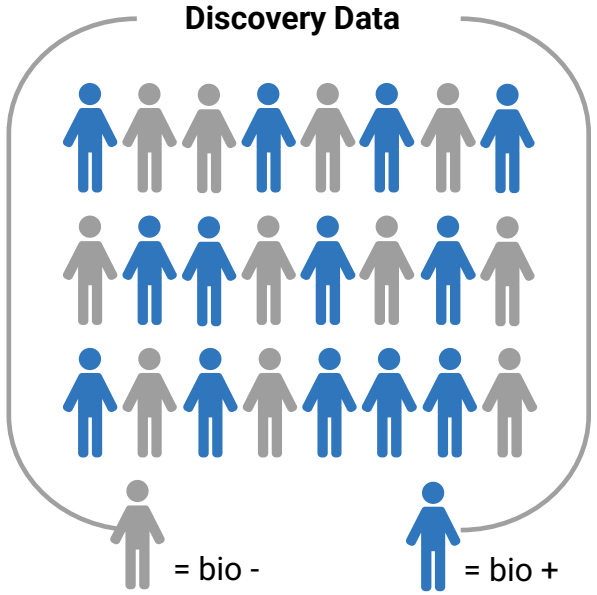
EEG MACHINE LEARNING STRATEGY

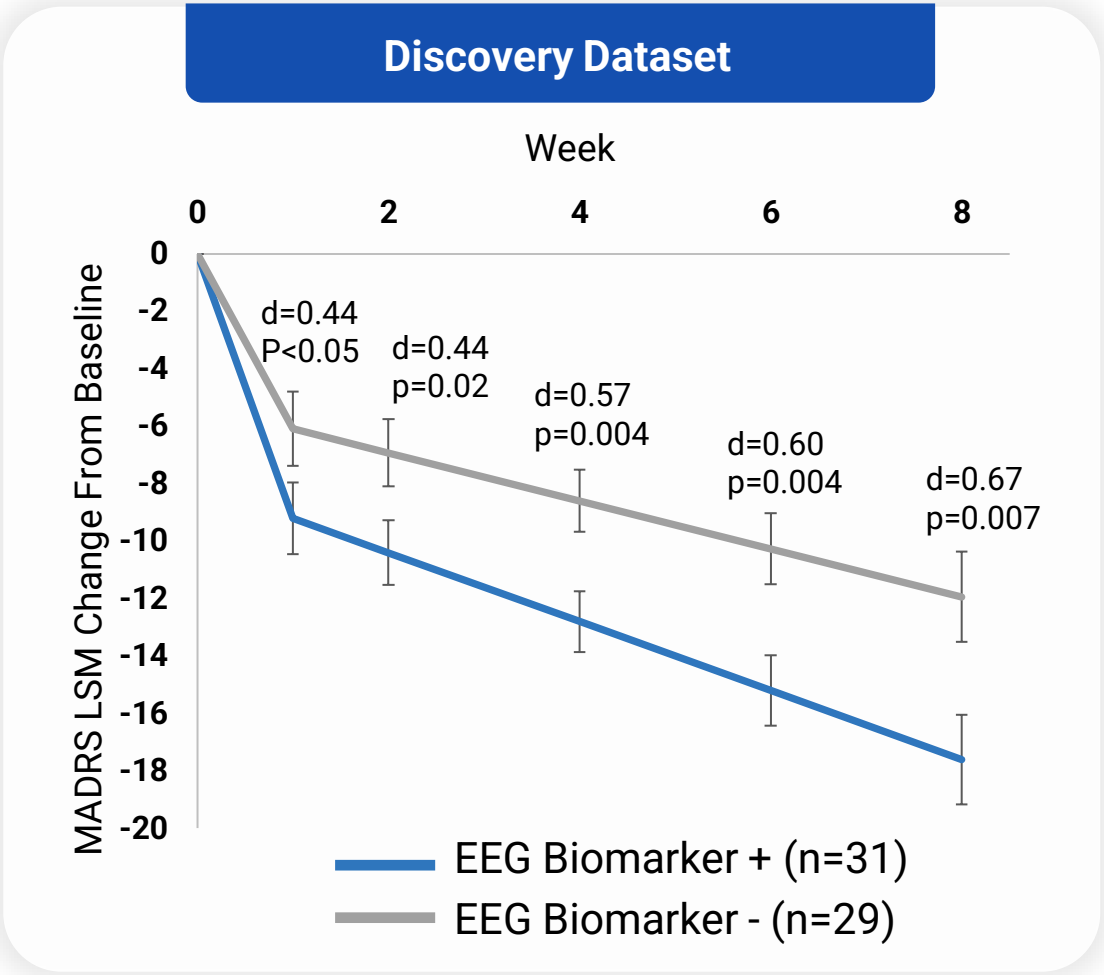


IDENTIFICATION OF EEG BIOMARKER

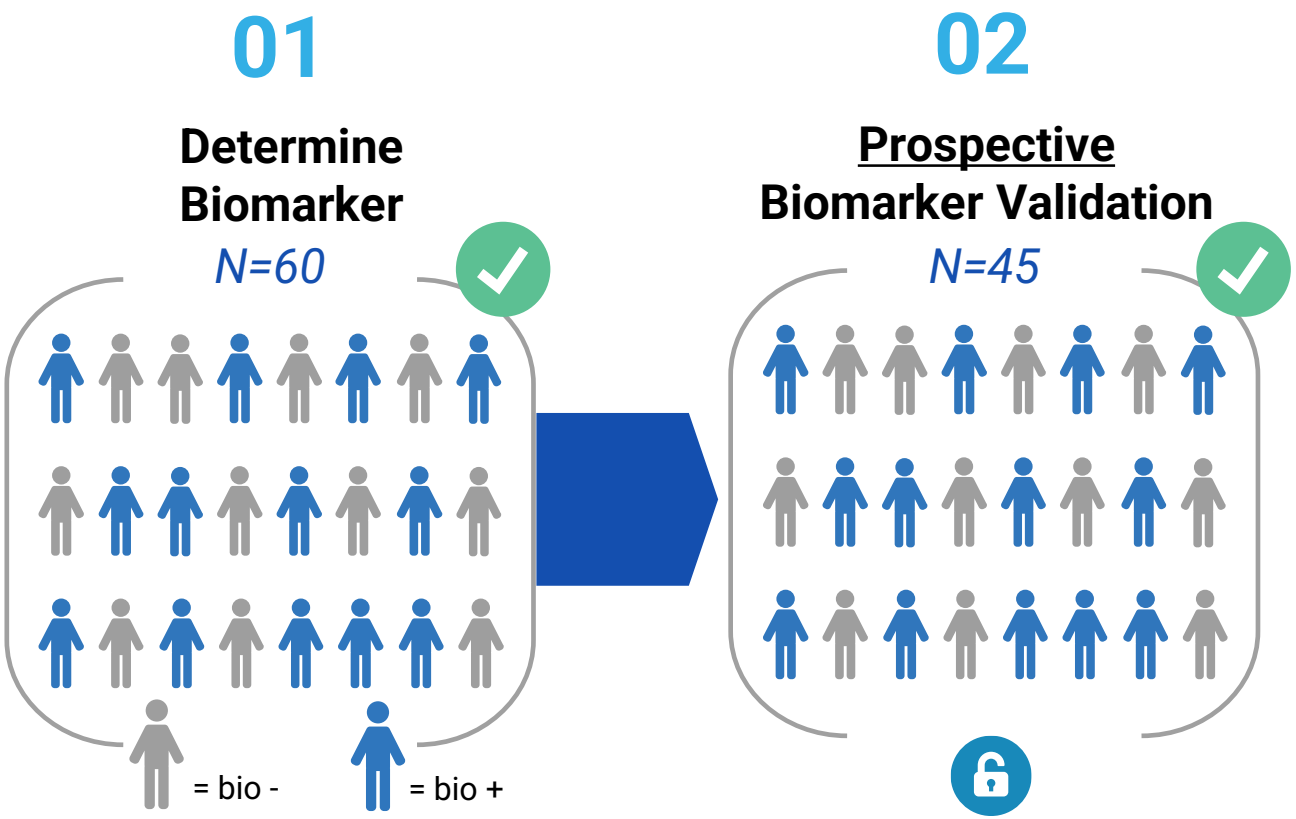
01

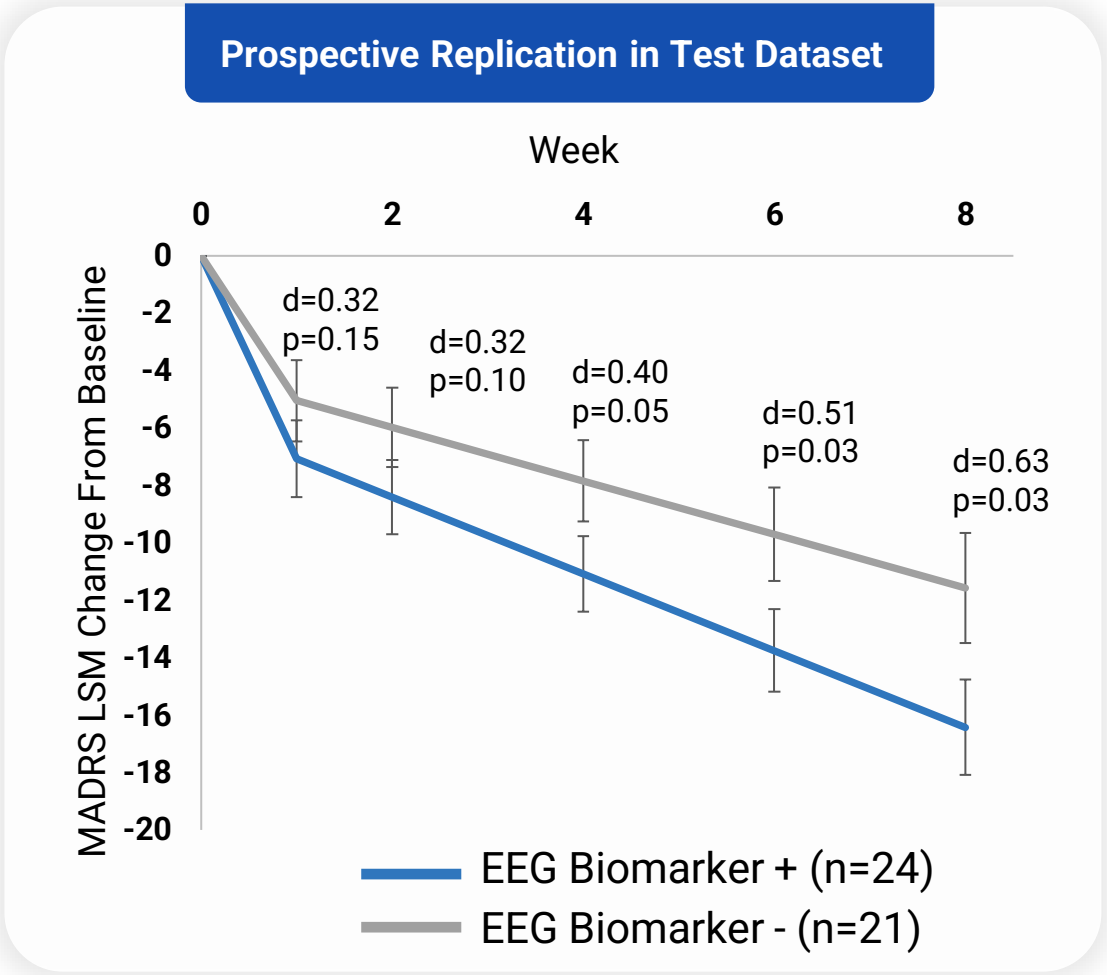
Determine Biomarker





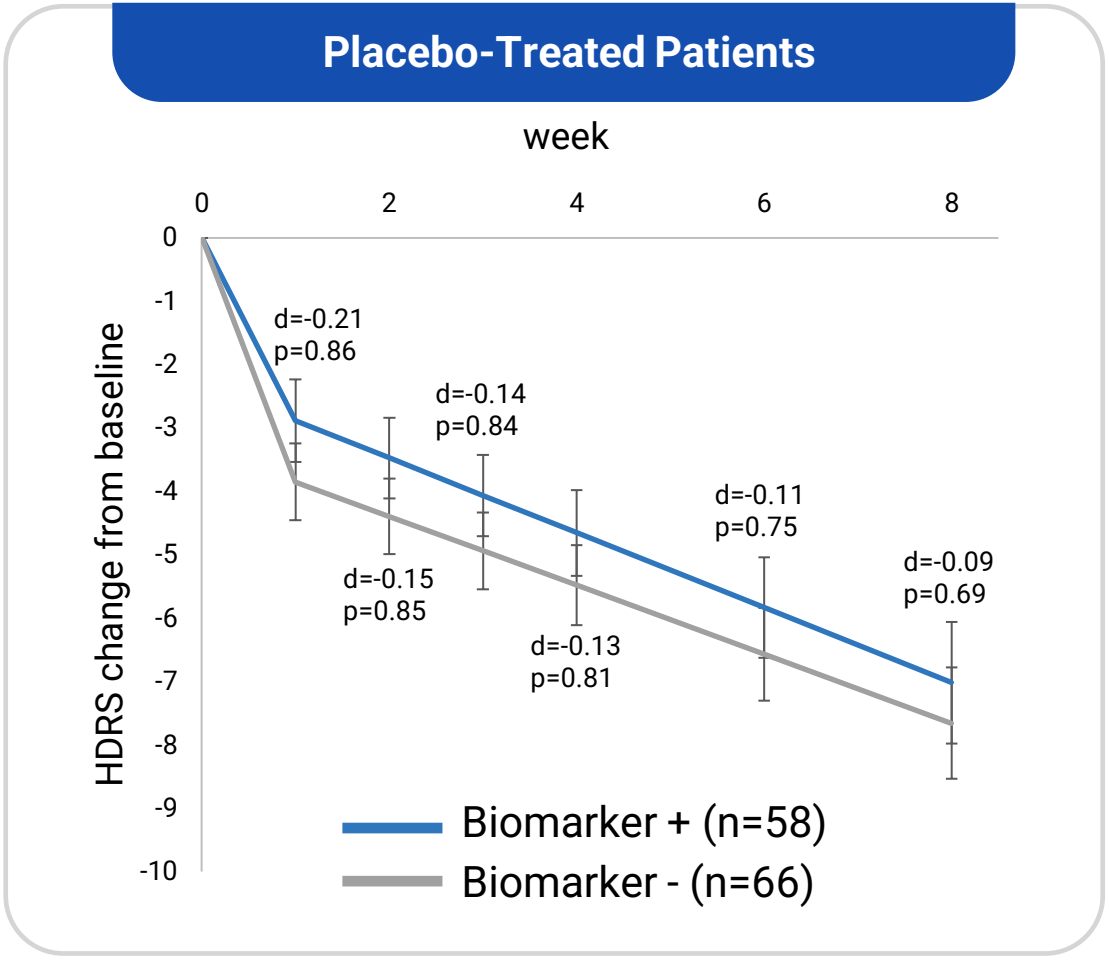
PROSPECTIVE TESTING OF EEG BIOMARKER AS PREDICTIVE OF RESPONSE

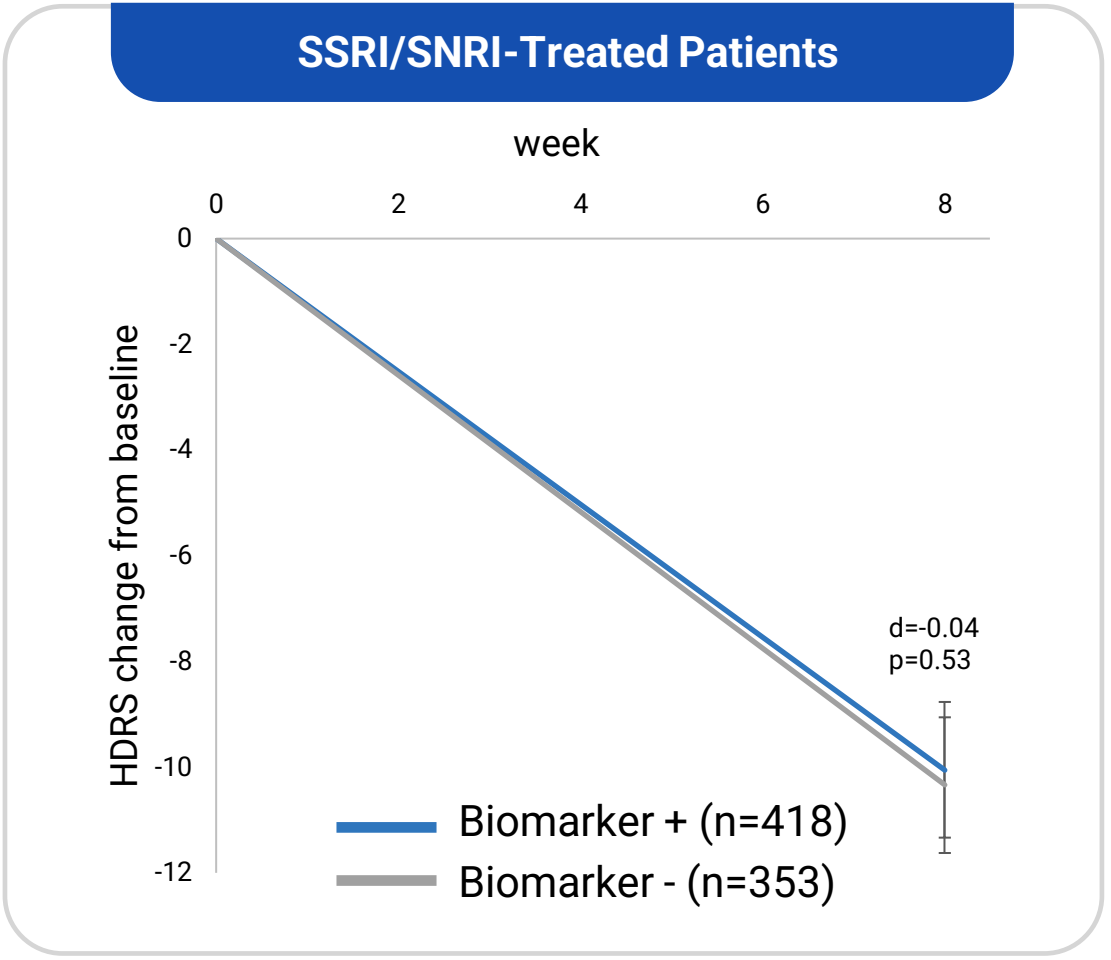




1. IDENTIFIED EEG SIGNATURE AS PREDICITVE
2. PROSPECTIVELY LABEL PATIENTS AS BIO+/-

EEG MODEL PREDICTION IS SPECIFIC TO ALTO-300





ALTO-300 DEMONSTRATED A FAVORABLE TOLERABILITY PROFILE

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

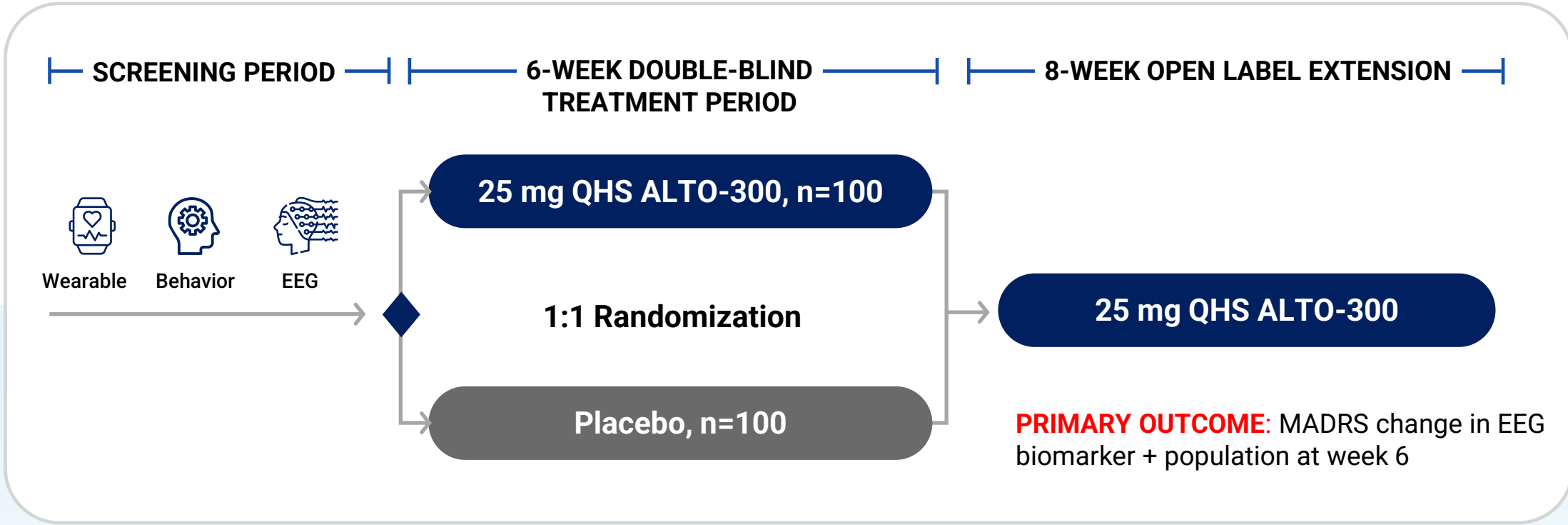
Note: participants may have had more than one AE

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)

ONGOING PHASE 2B BIOMARKER-GUIDED TRIAL IN MDD



- **Adjunctive** treatment to an existing antidepressant with an insufficient response
- **Includes participants with and without the biomarker** and randomization stratified by biomarker status
- Site-based and decentralized – **sites and participants blinded to biomarker status**
- Primary MDD but allows co-morbid anxiety disorders and PTSD

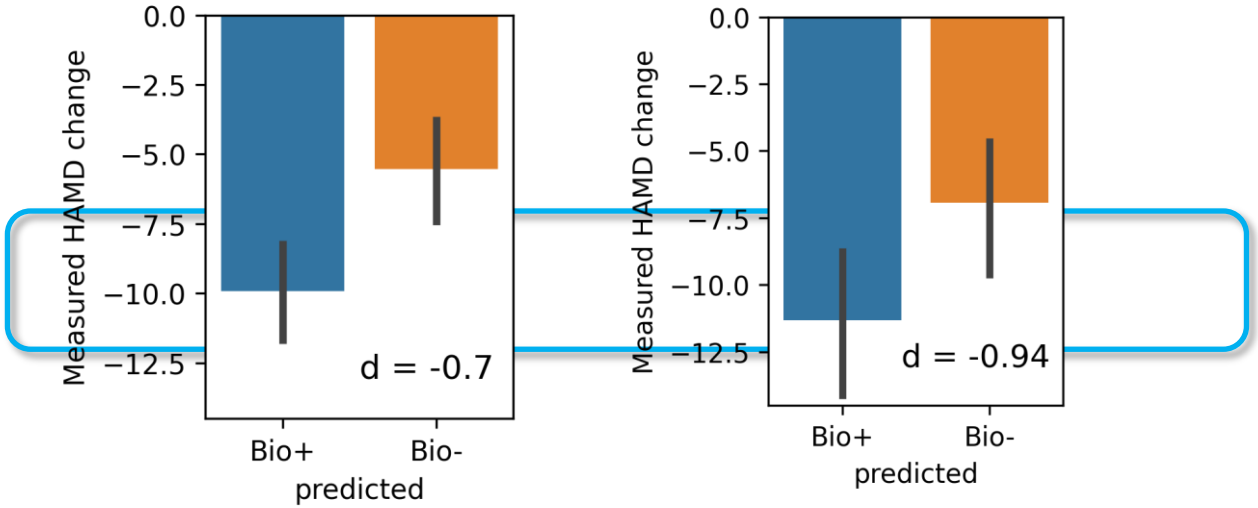
EEG-BASED SSRI RESPONSE PREDICTION BIOMARKER

DISCOVERY AND PROSPECTIVE REPLICATION OF AN SSRI BIOMARKER

Open-Labelled Study

Discovery

Biomarker + vs − (median split)



(MMRM analysis)

- N=93 open label SSRI
- 8 weeks treatment
- 19-channel EEG

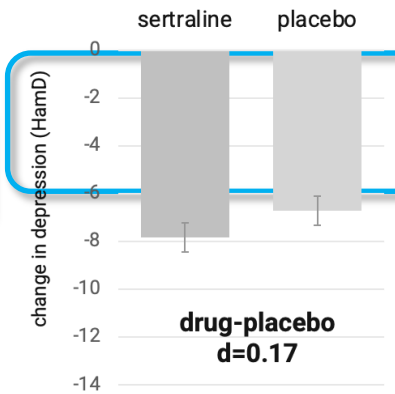
Replication

Biomarker + vs − (median split)

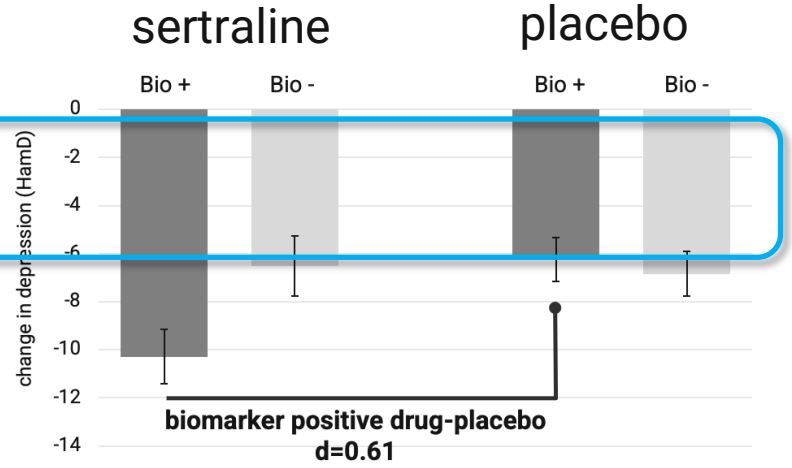
- N=42 open label SSRI
- Generalizes across specific SSRIs

Placebo-Controlled Study

All-comer



Biomarker-stratified



Wang et al. Prediction of Antidepressant Response Using Machine Learning and Resting State EEG. ACNP 2022