Identification and Prospective Replication of an EEG Biomarker for Predicting the Antidepressant Effect of ALTO-300 in Patients With Major Depression: Results From Large Phase 2a Studies

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1. Introduction

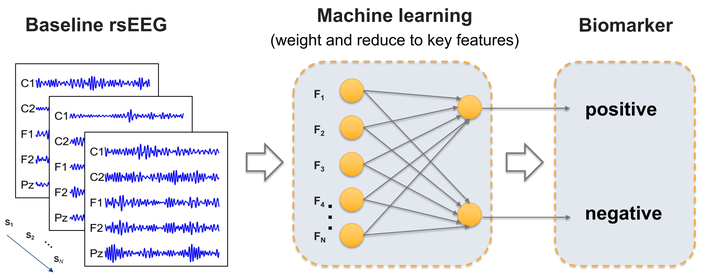
- The heterogeneity of major depressive disorder (MDD) often results in limited antidepressant efficacy
- Objective biomarkers could help identify likely responders, improving treatment outcomes
- ALTO-300 is an investigational small molecule with a unique pharmacological profile
- We used machine learning to analyze resting state electroencephalography (rsEEG) data to predict ALTO-300 treatment response in patients unresponsive to standard antidepressants (discovery set)
- We then prospectively tested whether biomarker prediction of clinical outcome replicated in a locked independent test data set from the same study (test set)

2. Study design

Two MDD trials with near identical designs (one is site-based, other is decentralized), analyzed as one study

- Adults 18-74 years old
- Adjunctive to a stable antidepressant with inadequate response (<50% symptom improvement)
- Once daily dosing for 8 weeks, single arm
- Clinical assessments at baseline, weeks 1, 2, 4, 6, 8
- rsEEG during screening, weeks 2 & 8
- 45% of EEGs done at-home through home visit by decentralized site staff
- N=239 enrolled in 14 months across in-clinic and decentralized sites; N=110 with rsEEG at baseline
- Analysis N=105 with moderate to severe MDD (baseline MADRS ≥ 20, PHQ-9 ≥ 10)

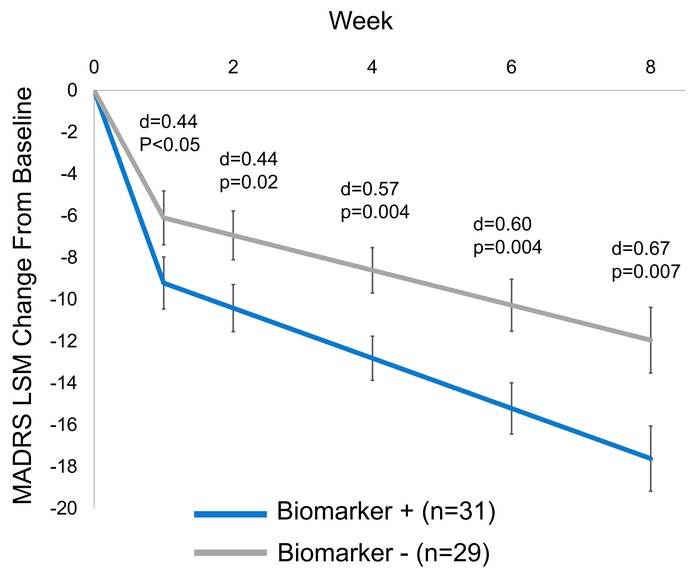
3. Data analysis



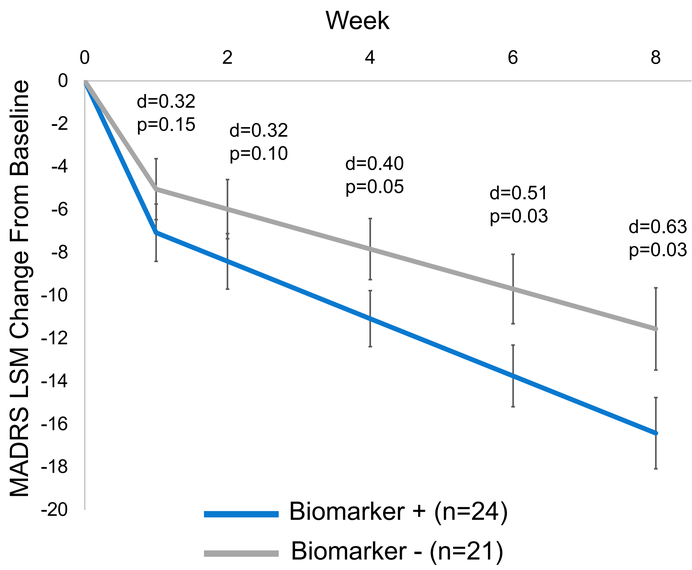
- Only baseline rsEEG was analyzed
- In the discovery set, a baseline rsEEG biomarker was developed to predict change in MADRS scores
- After the candidate biomarker was identified, the test set was unlocked to determine replication of the treatment outcome prediction
- Mixed Models for Repeated Measures (MMRM) was used to evaluate clinical outcomes

	Sample size	Age (year)	Gender (male/female)	Baseline MADRS score
Discovery	60	41.3 ± 15.5	15/45	28.2 ± 5.1
Test	45	43.1 ± 14.6	8/37	27.4 ± 4.9

4. rsEEG biomarker identified in discovery set



5. rsEEG biomarker replicated in test set



★ Biomarker positive rate were between 46% and 61% in 5 separate MDD studies with EEG (total N = 1801)

6. Adverse events

Dosed	Completed	Discontinued due to TEAE	At least one TEAE	With an SAE	Death
239	198 (82.8%)	12 (5.0%)	172 (72%)	6 (2.5)	0

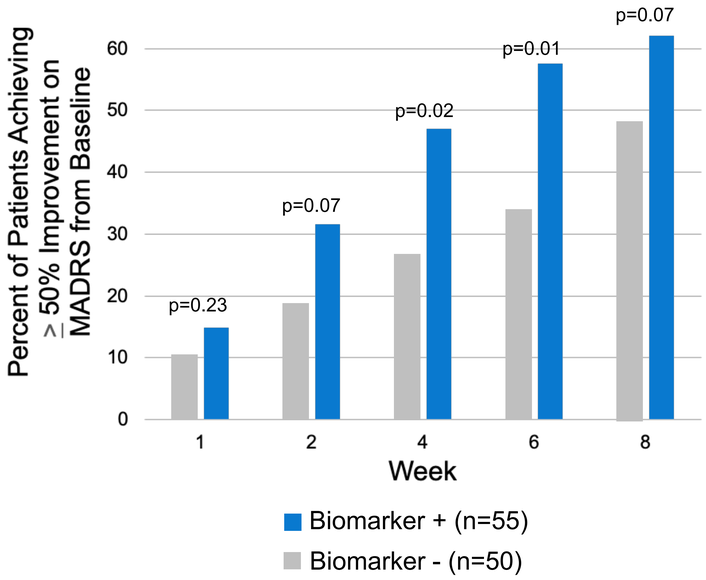
35.7% of the TEAEs were determined to be related to ALTO-300 by the investigator

TEAEs ≥ 5% by Preferred Term

Headache	Nausea	Dyspepsia	Insomnia	COVID-19	Rash (10 due to wearable)
35 (15%)	18 (7.5)	15 (6.3)	15 (6.3)	14 (5.9)	12 (5.0)

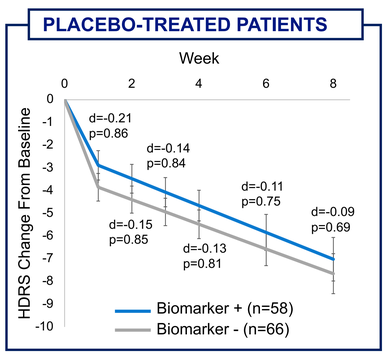
TEAE: Treatment Emergent Adverse Event; SAE: Serious Adverse Event

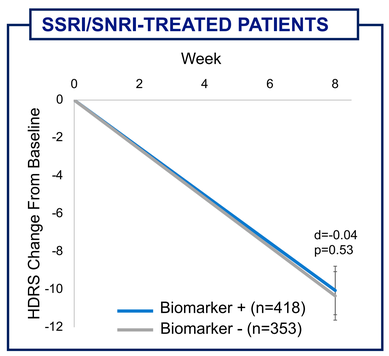
7. Response rate (≥ 50% improvement) in overall sample



8. Biomarker is specific to ALTO-300

Apply the ALTO-300 EEG biomarker to:





9. Conclusions

- ALTO-300 shows significantly enhanced MDD treatment response in patients with a machine learning-identified rsEEG biomarker compared to those who do not have the biomarker.
- Based on these results, a prospective, biomarker-stratified, placebo-controlled Phase 2b randomized efficacy study is underway (NCT05922878).

10. Acknowledgments

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