Identification and Prospective Replication of a Cognitive Biomarker for Predicting the Antidepressant Effect of ALTO-100, a Novel Pro-Plasticity Drug, in Patients with Major Depression: Results From a Large Phase 2a Study

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1. Introduction

- Up to 50% of individuals with Major Depressive Disorder (MDD) exhibit cognitive dysfunction, which is associated with worse clinical outcomes
- In MDD, hippocampal plasticity is blunted, and hippocampal volume is consistently reduced
- Reduced hippocampal volume as well as poor cognition predict greater treatment resistance
- ALTO-100 is a novel, first-in-class compound that increases neuroplasticity and promotes neurogenesis in the hippocampus, being developed for the treatment of depression
- The current study seeks to define and prospectively replicate a response-predictive biomarker for the treatment of MDD with ALTO-100

2. Study design

- Multi-site trial for treatment of MDD and/or PTSD
- Adults 18-64 years old
- Participants took ALTO-100 as monotherapy (n = 45) or adjunctive to an antidepressant (n = 78)
- 8 weeks of treatment (40 mg BID), single arm
- Total N = 243 (MDD and/or PTSD)
- N = 133 with primary MDD
- Analysis N = 123 with moderate to severe MDD (baseline MADRS ≥ 20, PHQ-9 ≥ 10)
- Biomarker developed from pre-treatment neurocognitive task performance

3. Data analysis

Discovery set:

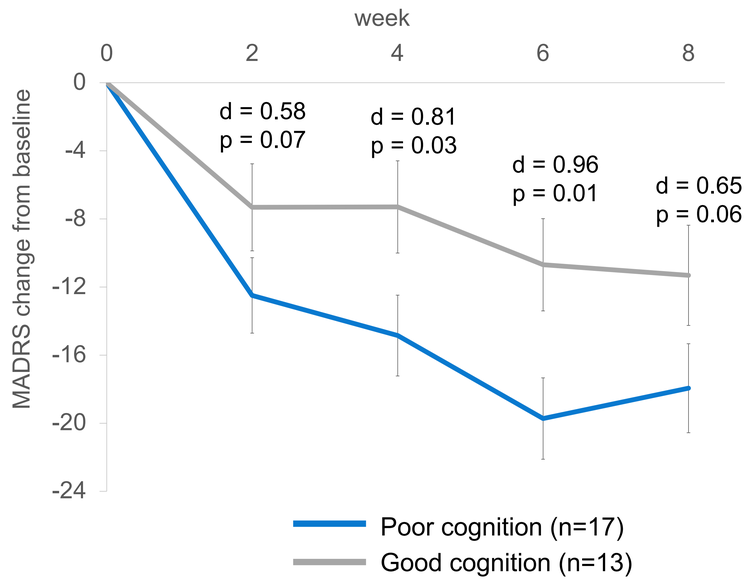
- Developed candidate poor cognition predictive marker
- Mixed Models for Repeated Measures (MMRM) used to evaluate efficacy

Test set:

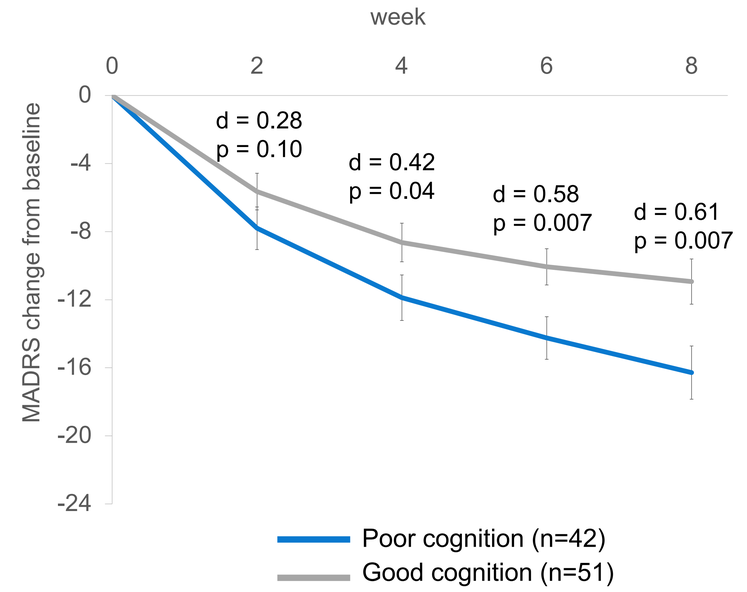
- Test data inaccessible to analysts during discovery
- After a candidate biomarker was identified, the test set was unlocked, and the biomarker prospectively tested on the remaining data
- Mixed Models for Repeated Measures (MMRM) used to evaluate clinical outcomes

	Sample size	Age (year)	Gender (male/female)	Treatment (mono/adj)	Baseline MADRS score
Discovery	30	43.37 ± 13.04	7/22	14/16	32.5 ± 5.0
Test	93	42.42 ± 14.90	27/66	31/62	29.3 ± 5.1

4. Cognitive biomarker identified in discovery set



5. Cognitive biomarker replicated in test set



★ Biomarker positive rate was between 43% and 48% in 2 separate MDD studies with cognition (total N = 280)

6. Adverse events

Dosed	Completed	Discontinued due to TEAE	At least one TEAE	With an SAE	Death
243	205 (84)	14 (5.8)	146 (60.0)	6 (2.5)	0

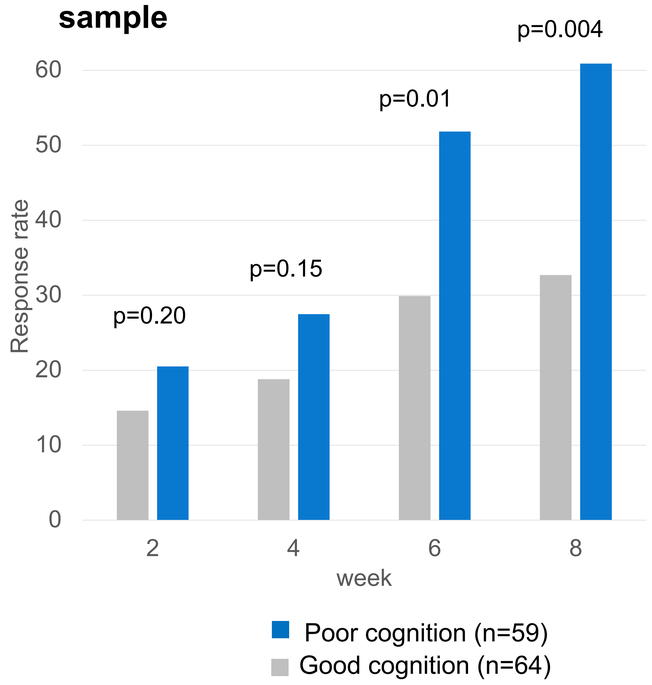
- 40.2% of the TEAEs were determined to be related to ALTO-100 by the investigator

TEAEs ≥ 5% by Preferred Term

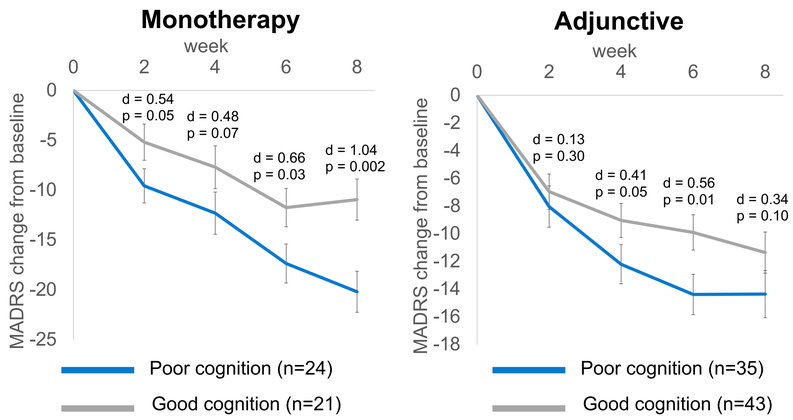
Headache	Abdominal Discomfort
40 (16)	13 (5.4)

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

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



8. Performance in monotherapy/adjunctive



9. Conclusions

- Data provides compelling evidence that ALTO-100 is more effective at treating depression in MDD with poor cognition
- Data also provides evidence that ALTO-100 is effective as both monotherapy and as an adjunctive to an existing antidepressant
- Based on these results, a prospective, biomarker-stratified, placebo-controlled phase 2b randomized efficacy study is underway (NCT05712187)

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