A Biomarker-Based Enrichment Strategy for Neuropsychiatric Drug Development: Examples from Two Ongoing Phase 2b Studies

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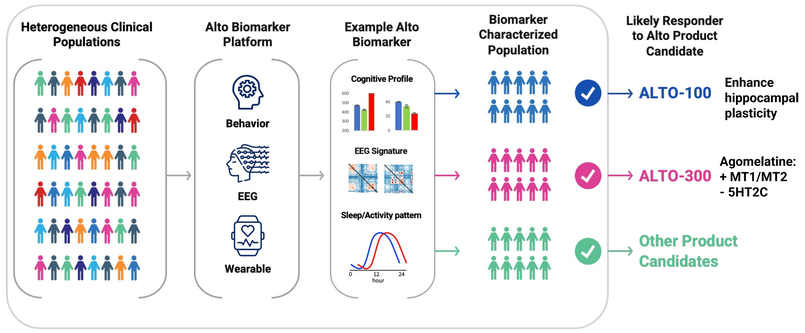
1. Why precision psychiatry?

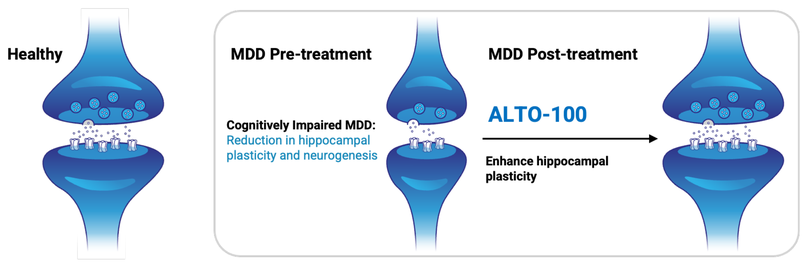
- Traditional drug development → ↓ effect size, ↑ variability
- Precision psychiatry matches right drug with right patient…

- …by identifying predictive biomarkers.

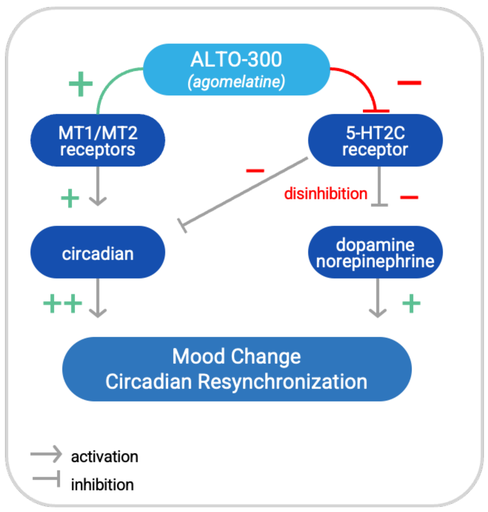


2. Novel mechanisms of action

- ALTO-100 enhances hippocampal plasticity



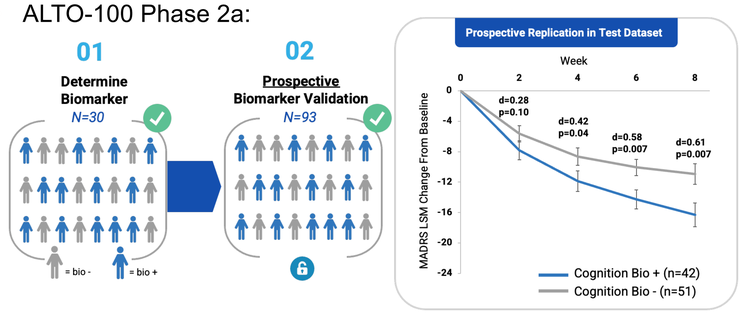
- ALTO-300 is a melatonin receptor (MT1/MT2) agonist and serotonin receptor (5HT2C) antagonist



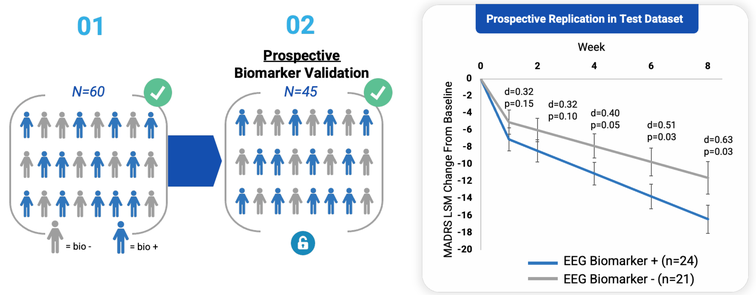
3. Biomarker identification in open-label studies

- Large open-label studies were used to identify predictive biomarkers for ALTO-100 and ALTO-300.
- Machine learning model is trained on a discovery set of participants for initial identification of predictive biomarkers.
- An independent test set is used to test for biomarker replication

- ALTO-100 Phase 2a:



- ALTO-300 Phase 2a:

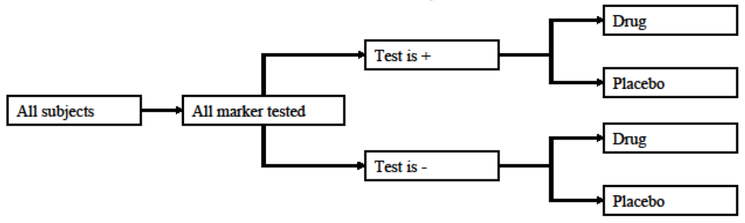


4. Safety data from Phase 2a studies

Drug	Discontinued due to TEAE	At least one TEAE	With an SAE	Death
ALTO-100 (n = 243)	14 (5.8%)	146 (60%)	6 (2.5%)	0
ALTO-300 (n = 239)	12 (5.0%)	172 (72%)	6 (2.5%)	0

5. Biomarker enrichment strategy (FDA guidance)

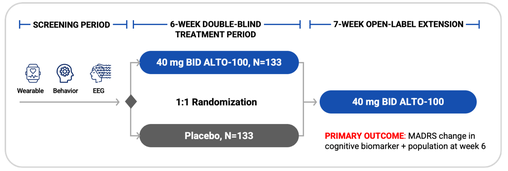
- After biomarker identification, placebo-controlled efficacy must be assessed in patients positive for the biomarker
- FDA framework for enrichment designs:



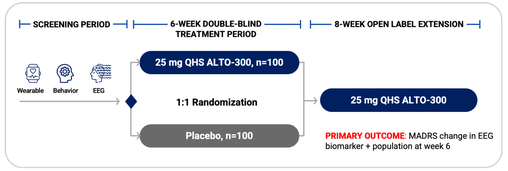
(figure taken from Enrichment Strategies for Clinical Trials to Support Determination of Human Drugs and Biological Products: Guidance for Industry, US Dept. of HHS, FDA, CDER, CBER, March 2019)

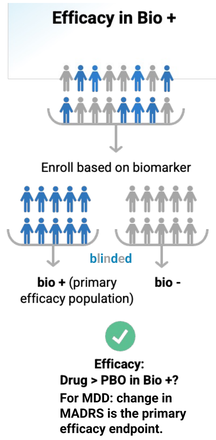
7. Enrichment-based study designs in ongoing phase 2b trials, powered in patients with the biomarker

- ALTO-100-201



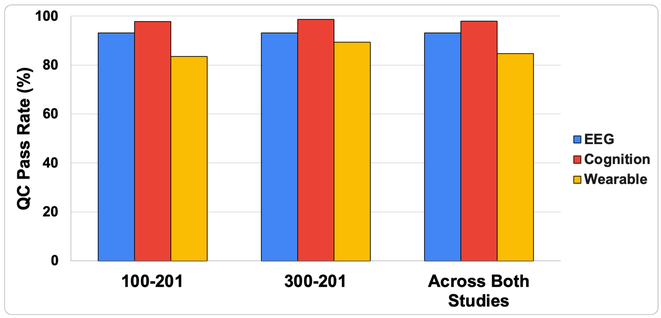
- ALTO-300-201





8. Biomarker quality control pass rates are high

- Quality control (QC) pass rates for biomarker assessments were all >80%, and >90% for EEG and cognition-based biomarkers.
- Of note, most sites lacked prior EEG experience
- Biomarker status assessed in < 24 hours to stratify enrollment and is blinded to sites, participants, and Alto clinical staff.



9. Conclusions

- Precision psychiatry approaches can increase drug efficacy signals during development
- Separate discovery and test dataset analyses in large Phase 2a studies can identify and confirm enrichment biomarkers for patient selection
- Both ALTO-100 and ALTO-300 were well tolerated
- Enrichment-based study designs are utilized in ongoing Phase 2b studies to assess primary outcome efficacy in patients with the biomarker (outcomes in those without the biomarker are qualitatively assessed and not powered)
- Strong quality control pass rates for baseline biomarker data demonstrate feasibility of large biomarker-driven clinical trials, important for potential Phase 3 and commercialization

10. Acknowledgments

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