Phase 3 Clinical Trial in MCI due to AD Targeting Hippocampal Hyperactivity

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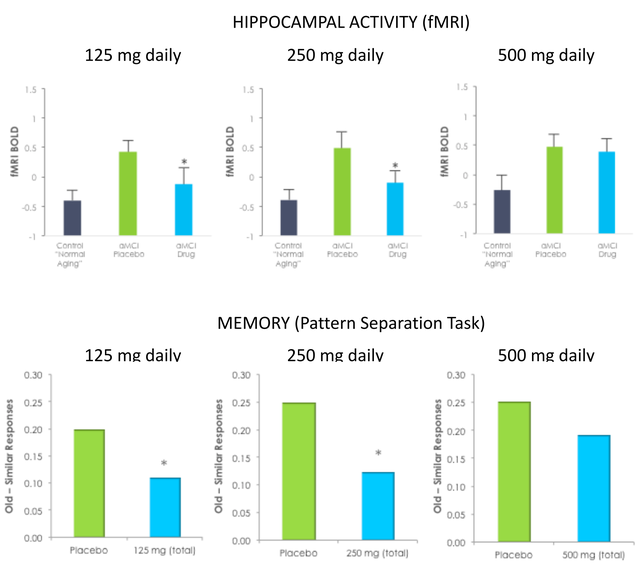
Background: There is now strong evidence from preclinical models and human patients, particularly in early stages of AD, that neuronal circuits become hyperactive contributing to neuronal pathology and brain dysfunction (recent review Busche et al. 2015; also Busche et al. 2012; Ewers et al. 2011). Many studies using functional magnetic resonance imaging (fMRI) have demonstrated that hippocampal hyperactivity is a highly consistent and characteristic signature in amnestic mild cognitive impairment (aMCI) (Bakker et al., 2012, 2015; Celone et al., 2006; Dickerson et al., 2004; 2005; Hamalainen et al., 2007; Yassa et al 2010; Ewers et al 2011 for review) and its magnitude is both significantly correlated with the extent of neuronal injury affecting AD-specific regions of the brain (Putcha 2011) and predicts subsequent cognitive decline/conversion to a dementia diagnosis (Sperling, 2007; Dickerson et al., 2008; Miller et al., 2008). Moreover, greater hippocampal hyperactivity occurs in MCI due to AD determined by PET amyloid imaging and persists in the MCI phase of the disease over a three year follow up during which time greater worsening on the Clinical Dementia Rating Scale-sum of boxes (CDRsb) is evident in MCI due to AD relative to patients with amyloid negative PET scans (Huijbers et al., 2015). These data support a novel therapeutic approach to target hyperactivity, especially in the aMCI phase of AD when hippocampal hyperactivity is most pronounced. A Phase 2 study of the atypical antiepileptic levetiracetam in patients with aMCI used hippocampal hyperactivity for target engagement and to assess the functional significance of reducing hyperactivity. Levetiracetam demonstrated therapeutic efficacy for reduction of hyperactivity in a low dose range that concurrently improved memory task performance in aMCI patients (Bakker et al. 2012; 2015). Based on a close parallel in the amount of drug exposure required for efficacy in both preclinical studies and MCI patients (plasma level µg/mL), AGB101 was formulated as an extended release once-a-day medication and is now supported by the FDA for use in the Phase 3 trial to test its efficacy on slowing progression in patients with MCI due to AD.

Study Design: A multicenter, randomized, double-blind, placebo-controlled study will evaluate the efficacy and safety of AGB101 (low-dose levetiracetam, 220 mg, extended release tablet) on slowing progression of amnestic mild cognitive impairment due to Alzheimer's disease. A total of 830 subjects will be randomized (415/treatment group). Participants who meet criteria for enrollment with MCI due to AD will be treated with AGB101 or placebo in a 78-week protocol. The primary efficacy evaluation will be the change in CDR-SB from baseline to 78 weeks. Secondary cognitive and functional efficacy assessments will include both MMSE and FAQ. Biomarkers for neuronal injury including entorhinal cortex thinning and volume and hippocampal volume will be evaluated in structural MRI assessments. Subjects enrolled with MCI due to AD will have amnestic mild cognitive impairment as defined by: (1) MMSE scores between 24 and 30, inclusive; (2) A memory complaint reported by the subject or their study partner that is verified by the study partner; (3) Abnormal memory function documented by an education adjusted score on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-Revised; (4) A Clinical Dementia Rating Scale (CDR) score of 0.5; Memory Box score of ≥ 0.5; (5) General cognitive and functional performance sufficiently preserved that a diagnosis of Alzheimer's dementia cannot be made at the time of the screening visit and essentially preserved activities of daily living; and (6) Florbetapen PET brain scan positive for amyloid. In addition to the screening and the baseline visit, the protocol will consist of 3 major visits and 3 minor visits during the 78-week study. This study will be conducted at approximately 89 study sites in seven countries (US, Canada, France, Germany, UK, Spain, Poland). Worldwide Clinical Trials, a contract research organization, will oversee operational aspects of this study on behalf of AgeneBio, Inc., the sponsor of the study.

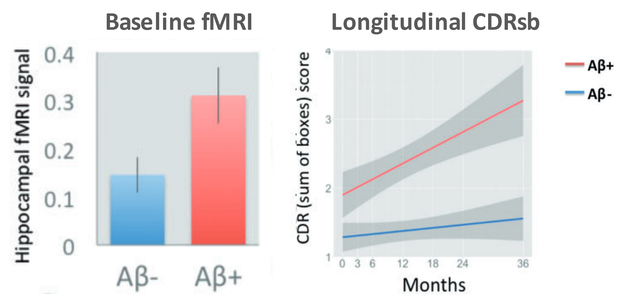
Conclusion: The Phase 3 trial of AGB101 represents a novel treatment approach to address the hippocampal overactivity in the earliest symptomatic phase of Alzheimer's disease, with potential to slow progressive decline in this population at high risk for AD dementia.

Low, but not high dose, AGB-101 attenuates hippocampal overactivity and improves memory in a pattern separation task (Bakker et al 2012, 2015)



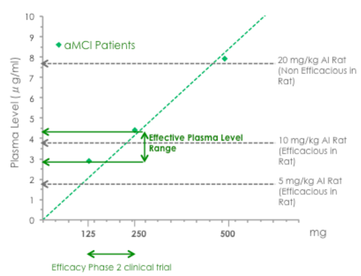
- Low doses (125-250 mg daily) attenuate hippocampal overactivity and improve pattern separation.
- A high dose (500 mg daily) fails to improve either measure.

Hippocampal Overactivity and progression on CDR-SB in Amyloid Positive MCI Patients (Huijbers et al., 2015)



The bar graph on the left shows greater hippocampal overactivity in patients with MCI due to AD (as defined by amyloid imaging) compared to MCI (amyloid negative) patients. That overactivity persisted for 36 months (not shown). The graph on the right shows greater progression of CDRsb in MCI due to AD (amyloid positive).

Efficacious exposures similar in Memory-impaired Aged Rats and aMCI patients. Ineffective exposures also similar.

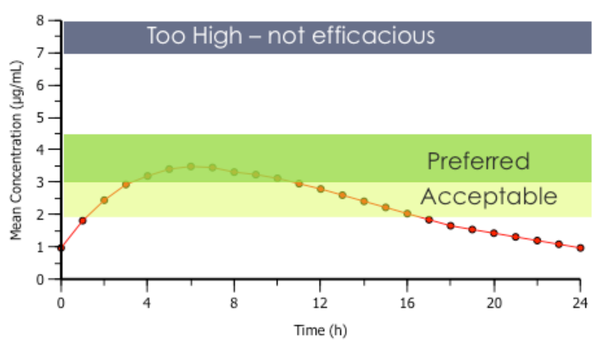


	Observed Efficacy (µg/mL)
Age-Impaired Rats	1.9 – 3.9
aMCI	2.9 – 4.4

	No Efficacy (µg/mL)
Age-Impaired Rats	7.8
aMCI	7.9

Steady State Formulation Goals:
- Preferred range based on aMCI between 2.9 and 4.4 µg/mL
- Acceptable range based AI rats and aMCI between 1.9 and 4.4 µg/mL

AGB101 (220 mg) Extended Release Simulated Steady State Dose PK profile (Fed)



220 mg formulation meets Preferred Range Goals
- Exposures maintained between 2.9 and 4.4 ug/mL for 7-8 hours; above 1.9 for 14 hours. Approved by FDA for use in Phase 3

HOPE4MCI

HOPE4MCI Study

- Enrollment criteria well defined and consistent with earlier clinical studies
- Diagnosis of aMCI
- Logical memory impairment (Wechsler LM)
- Positive PET scan with florbetapen F18 injection (beta-amyloid scan)
- Subjects: patients randomized to AGB101 (220 mg of levetiracetam) or placebo (once-daily dosing)
- Treatment duration: 18 months
- Trial size: 830 (415 per arm)
- Retention should not be affected by drug-related adverse events

Efficacy	Endpoints/ Outcomes Measures
Primary Efficacy Clinical	Change in Clinical Dementia Rating - Sum of Boxes (CDR-SB)
Key Secondary Biomarker	Neuronal injury as measured by change in entorhinal cortex atrophy using structural MRI
Additional Secondary Outcomes Clinical	FAQ (functional), MMSE (cognitive), BPS-O (neuropsychological)

SUMMARY / CONCLUSIONS

- AGB101 reduces hippocampal overactivity and improves hippocampal task related memory function
- AGB101 (220 mg) is a novel extended release formulation of levetiracetam
  - Suitable for once-daily dosing
  - Maintains exposures needed for efficacy in Phase 2 POC MCI study and in animal models
  - Does not exceed efficacious exposures
- Phase 3 Trial designed to ensure progression in CDR-SB over the 18 month trial
- End-of-Phase 2 Meeting with the FDA completed in June 2016

- We gratefully acknowledge partial support from NIH R01AG048349 to Johns Hopkins University (PIs: MA and MG) and from ADDF PACT (PI: SRL).

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