HOPE4MCI Trial: First Trial Targeting Reduction of Hippocampal Overactivity to Treat Mild Cognitive Impairment due to Alzheimer's Disease with AGB101

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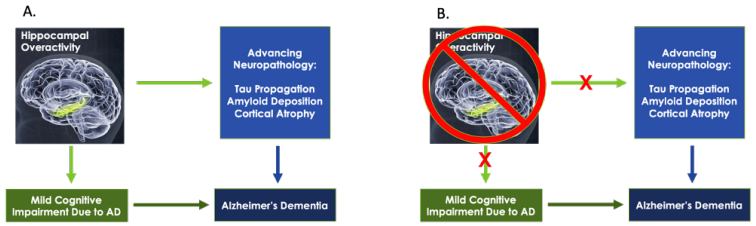


Figure 1: A. Schematic demonstrating the critical role of hippocampal overactivity in the MCI due to AD and in driving pathology leading to Alzheimer's dementia. B. A POC study with AGB101 demonstrated that reduction in hippocampal overactivity reduced memory symptoms in MCI. Ongoing late-stage trial with AGB101 is evaluating impact on advancing neuropathology and progression to AD dementia.

Background: Evidence from preclinical models and human patients demonstrates that neuronal circuits become hyperactive in prodromal AD contributing to the accumulation of Alzheimer's pathology and subsequent cognitive decline. Such data support the hypothesis that neural overactivity in the medial temporal lobe/hippocampus is a critical driver of AD neuropathology, including the deposition of amyloid and spread of tau along connectional pathways. AGB101 (low dose levetiracetam) demonstrates efficacy on a range of molecular, synaptic, electrophysiological, functional and behavioral endpoints across models and species. In a Phase 2 study measuring hippocampal activity during a pattern separation memory test in patients with aMCI, AGB101 normalized hippocampal activity and improved performance on this specific memory assessment of hippocampal function. The HOPE4MCI trial is investigating the effects of AGB101 (220 mg) vs placebo in patients with MCI due to AD.

The objective of the study is to assess the efficacy of AGB101 (low-dose levetiracetam, 220 mg, extended-release tablet) compared to placebo in subjects with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) using Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores as the sole primary outcome. A substudy will evaluate the location and amount of tau pathology using MK-6420 PET imaging at baseline and end of protocol and p-tau-217 at end of protocol (Wu et al., 2016; Berron et al., 2019; Huijbers et al., 2019; Palmqvist et al., 2020).

Methods:
This is a multicenter, randomized, double-blind, placebo-controlled, 78-week, fixed-dose study evaluating AGB101 versus placebo as a treatment for slowing the progression of MCI due to AD.
Inclusion criteria: Subjects must meet the following inclusion criteria at screening:
1) Subjects between 55 and 85 years old
2) Have MCI due to AD consistent with the NIA-AA criteria: MMSE (24-30); CDR (0.5); Impaired delayed recall on the ISLT; essentially preserved ADLs
3) Evidence of an amyloid-positive PET scan

Results:
The HOPE4MCI trial is currently underway. Sites are currently enrolling in the US and Canada. Up to date subject demographics, screen failure information, safety and dropout information will be presented at the meeting.

Conclusions:
HOPE4MCI represents the first and only late-stage clinical trial targeting the reduction of hippocampal overactivity for slowing the progression of MCI due to AD.

The HOPE4MCI trial is supported, in part, by R01AG061091 to RM and R01AG048349 to MG.

Study Design

Enrollment criteria well defined and consistent with earlier clinical studies
- **Diagnosis of aMCI**
- **Objective memory impairment in delayed recall (ISLT)**
- **Positive amyloid PET scan**

Subjects: patients randomized to AGB101 (220 mg of levetiracetam) or placebo (once-daily dosing)

Treatment duration: 18 months

Trial size: 160 (80 per arm)

Retention should not be affected by drug-related adverse events

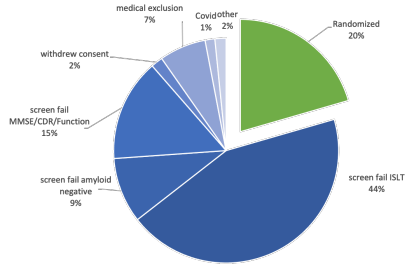
Primary Endpoint: CDR-SB

Secondary Clinical Endpoints: MMSE (cognitive), FAQ (functional), BPS-O (neuropsychological)

Secondary Imaging Biomarkers:
- **Entorhinal Cortex Atrophy (neuronal injury)**
- **[18F]MK-6240; p-tau217 (tau progression)**
- **fMRI (hippocampal overactivity)**

Study Site Map

Reasons for Screen Failure



Subjects meeting ISLT criteria 70% are amyloid positive

Enrolled Subjects - Baseline Demographics

Endpoint	Measure
Randomized / Screen Failed / In progress	147 / 733 /14
Age	72.9 (range: 55-85)
Gender	55% Male; 45% Female
Race	95.9% White; 3.4% Black/African American; 0.7% American Indian/Alaska Native
Ethnicity	83% Nonhispanic or Latino; 17% Hispanic or Latino
Screening ISLT	-2.16 ± 0.61
Baseline CDR-SB	2.7 ± 1.0
Screening MMSE	26.2 ± 1.6
Baseline MMSE	26.0 ± 2.1
Baseline FAQ	7.4 ± 5.3

Summary

- HOPE4MCI is underway
- First and only clinical trial targeting hippocampal overactivity
- Enrolled population indicative of late MCI due to AD
  - Baseline consistent with recent MCI/prodromal AD studies
- Screen fail predominantly due to strict ISLT criteria – predictive of amyloid positivity
- Well tolerated

References

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