Brain Hippocampal Volume and Cortical Thickness in Early Alzheimer's Disease Subjects with APOE4/4 and APOE3/4 Genotypes: Baseline Data from Phase 2 Biomarker Study with Oral Anti-Amyloid Agent ALZ-801

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Background

Hippocampal volume (HV) and cortical thickness (CT) are established volumetric magnetic resonance imaging (vMRI) biomarkers in Alzheimer's disease (AD) trials. Several anti-amyloid antibodies have shown brain atrophy, and no slowing of hippocampal or cortical atrophy. The vMRI measures in these studies have not been reported by APOE4 genotype. ALZ-801, an oral brain-penetrant inhibitor of amyloid oligomer formation is being evaluated in:

- Ongoing APOLLOE4 Phase 3 study in APOE4/4 homozygotes with Early AD.
- Ongoing Phase 2 study in APOE4/4 homozygotes (HM) and APOE3/4 heterozygotes (HT) focusing on MRI, CSF and plasma biomarkers in Early AD patients.
- In the Phase 2 study, we compared baseline HV and CT between HM and HT.
- These data can inform selection of primary imaging biomarkers for Phase 3 studies in APOE4 homozygotes and heterozygotes.

Methods

We analyzed data from the ongoing Phase 2 biomarker study (NCT04693520) which enrolled Early AD subjects (MMSE 22-30, CDR-G 0.5 or 1), who will receive ALZ-801 for 2 years and provide serial MRI. Of 131 screened subjects, 110 clinically eligible subjects had baseline MRI. All vMRI analyses were conducted by Bioclinica per published methods (Abushakra, 2020).

- Cortical thickness was measured using FreeSurfer, and Mayo AD signature ROI (Jack, 2017) was calculated.
- Baseline HV and average CT (Mayo Index) were correlated with age and MMSE in each APOE4 subgroup using Pearson's correlations.

Demographics & Baseline MRI Measures

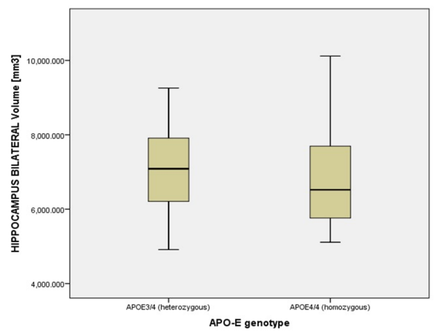
Baseline Demographics, Total HV, and Average Cortical Thickness were Similar between HM and HT

Criteria	Homozygotes (n=35)	Heterozygotes (n=75)
Age (years)	68.5	67.5
MMSE	26.5	26.0
Gender (M/F)	18M /17F	41M/ 34F
Hippocampal vMRI (mean mm± SD)	6786 ± 1207†	7092 ± 990
Cortical Thickness vMRI (mean mm^3± SD)	2.733 ± 0.168*	2.675 ± 0.198

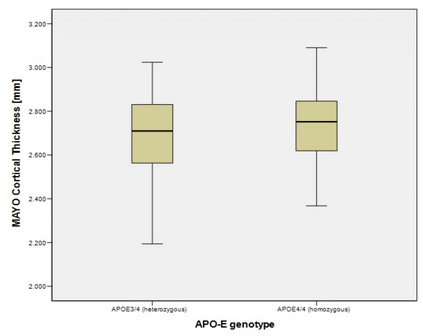
Comparison of HM vs. HT
†HV NS p = 0.112 based on two-tailed t-test
*CT NS, p= 0.196 based on two-tailed t-test

Baseline Hippocampal Volume & Cortical Thickness in HM vs. HT

Baseline HV not Significantly Different



Baseline CT not Significantly Different



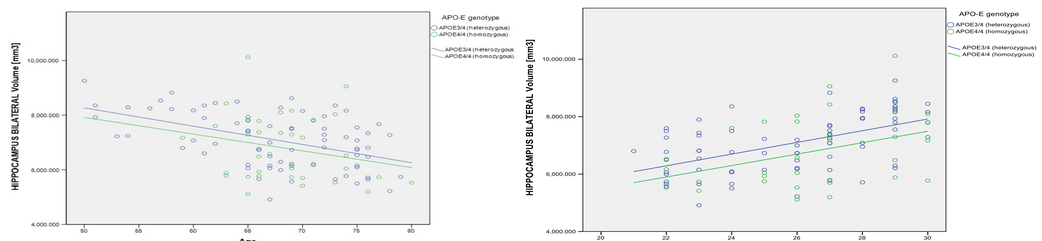
Correlation Analyses: MRI Measures vs. Age & MMSE

2 x 2 Correlation Analysis	All Subjects (n-110)	Homozygotes (n=35)	Heterozygotes (n=75)
HV vs Age	p= 0.01	NS	P<0.001
HV vs. MMSE	p= 0.01	P< 0.02	P<0.001
Cortical Thickness vs Age	p= 0.01	NS	P< 0.001
Cortical Thickness vs MMSE	p= 0.01	p<0.02	P< 0.001

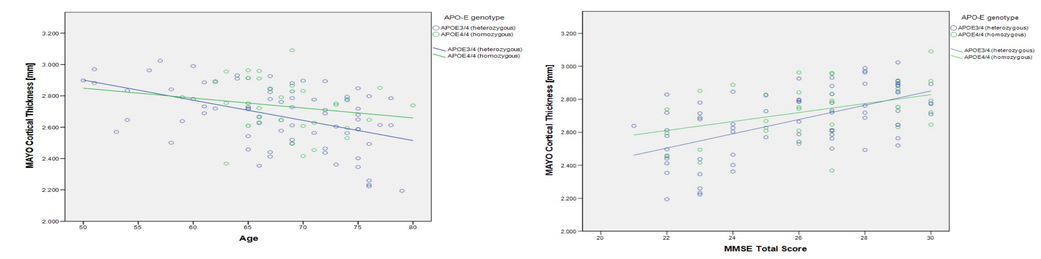
Statistics: Pearson correlation two-tailed
Significant
Not significant

Cross Sectional Analyses of HV and CT by Age & MMSE

Hippocampal Volume vs. Age and MMSE



Cortical Thickness vs. Age and MMSE



Conclusions

- The active agent in ALZ-801, tramiprosate, selectively blocks formation of soluble Aβ oligomers (Kocis, 2017 and Hey, 2018), and has shown promising efficacy in APOE4/4 AD subjects (Abushakra, 2017) with favorable safety and without the complications of brain vasogenic edema (Abushakra, 2016).
- APOE4/4 homozygotes and APOE3/4 heterozygotes at similar stage of AD did not show significant differences between baseline HV and CT measures.
- Cross-sectional analyses in APOE4/4 homozygotes show that both HV and CT correlated modestly with MMSE (R=0.41 & 0.40, both p<0.02), but not with age (R=-0.24 & -0.12, p=NS).
- In heterozygotes both HV and CT correlated strongly with MMSE (R=0.55 & 0.58, both p<0.001), and with age (R=-0.49 & -0.47, both p<0.001).
- APOE3/4 heterozygotes showed seemingly more prominent cortical thinning with advanced age and AD severity, than APOE4/4 subjects.
- In a planned Phase 3 trial in APOE3/4 heterozygotes, CT may be an optimal imaging biomarker to evaluate ALZ-801 effects on brain atrophy.