Cerebrospinal Fluid Biomarkers 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

The new diagnostic framework for AD requires evidence of beta amyloid (Aβ) and tau pathology, ± neurodegeneration (A/T/N scheme, Jack 2018). Core AD CSF biomarkers: Aβ42/40 and p-tau, become abnormal before the appearance of amyloid/tau on PET scans, and are useful for patient selection and evaluation of drug effects.

ALZ-801, an oral, brain-penetrant, inhibitor of amyloid oligomer formation, in development as a disease modifying agent is being evaluated in:

- Ongoing APOLLOE4 Phase 3 study in Early AD subjects with APOE4/4 genotype.
- Ongoing Phase 2 biomarker study in Early AD subjects with APOE4/4 homozygous and APOE3/4 heterozygous genotypes.
- The Phase 2 trial completed enrollment and will evaluate effects of ALZ-801 on CSF and plasma biomarkers of Aβ & tau pathologies, microglial and astrocyte activation, and synaptic and axonal injury.
- We compared baseline CSF biomarkers of APOE4/4 homozygotes (HM) to APOE3/4 heterozygotes (HT) who fulfilled same clinical criteria of Early AD.

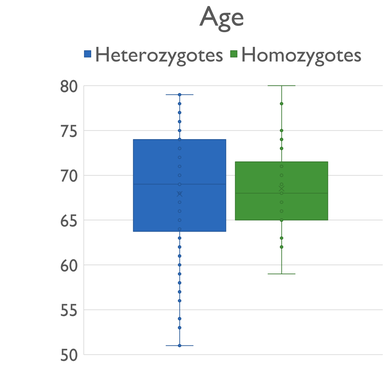
Methods

The ALZ-801 Phase 2 biomarker study ongoing at 7 sites in the Czech Republic and the Netherlands, enrolled Early AD subjects (MMSE 22-30, CDR-G 0.5 or 1) with either APOE4 HM or HT genotypes. Enrollment required a prior positive amyloid PET or CSF biomarkers fulfilling A+/T+ criteria. Subjects receive 265 mg BID ALZ-801 over 2 years and undergo assessments of CSF, plasma, MRI, and cognitive tests:

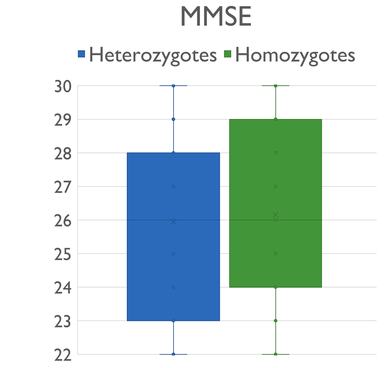
- The primary fluid biomarker endpoint is CSF p-tau$_{181}$ reduction at 2 years
- This CSF dataset includes all screened subjects who provided CSF for inclusion
- Biomarker analyses performed at the Laboratory (Dr. Blennow, Molndal, Sweden)
- Biomarkers were analyzed using Lumipulse (Fujirebio assay)
- CSF enrollment criteria were: Aβ42 ≤ 610 pg/ml with ratio of Aβ42/40 x10 ≤ 0.61, and p-tau$_{181}$ ≥ 60 pg/ml
- CSF values (pg/ml) were analyzed with descriptive statistics and compared between HM & HT using parametric and non-parametric tests and 1-tail p-values
- Of 131 screened subjects, 110 provided baseline MRI (analyses by Bioclinica) and 108 provided baseline CSF samples included in this analysis

Demographics

Age and MMSE



P = 0.65 based on two-tailed t-test assuming equal variances

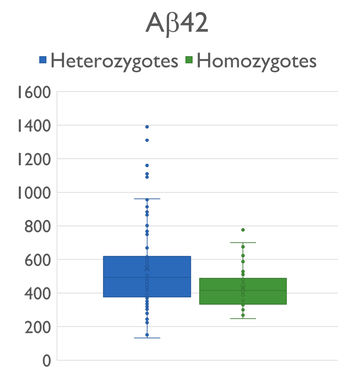


P = 0.71 based on two-tailed t-test assuming equal variances

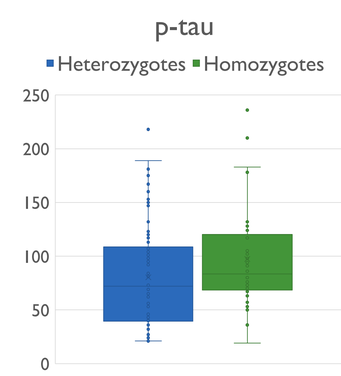
NS differences in age, MMSE, gender observed

Results

CSF Aβ and pTau$_{181}$ Baseline Biomarkers in Early AD



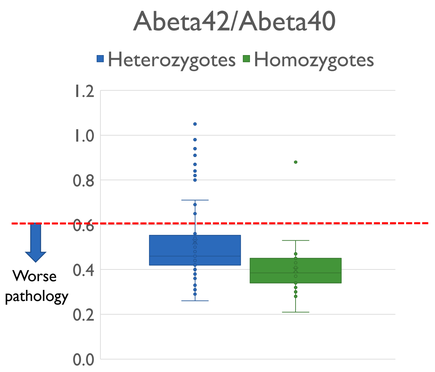
P = 0.0072 (one-tailed t-test)



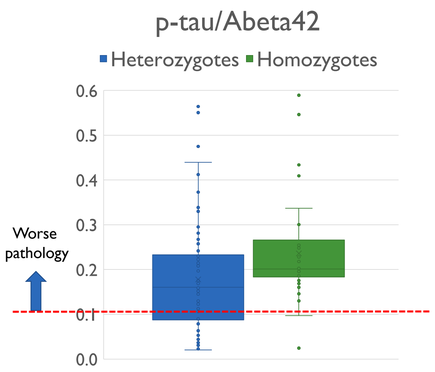
P = 0.045 (one-tailed t-test)

Baseline AD Biomarkers in Enrolled Homozygotes & Heterozygotes

At Similar Clinical Stage HM more Enriched with Aβ Pathology

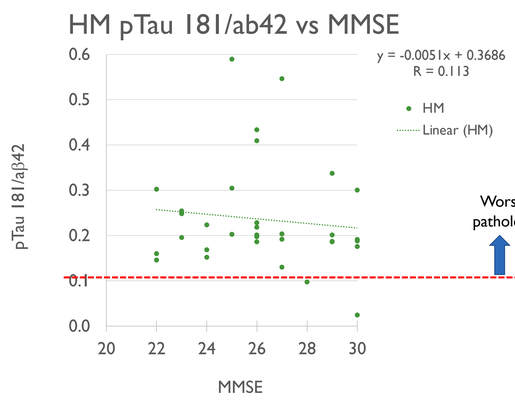


P = 0.00037 (one-tailed t-test)

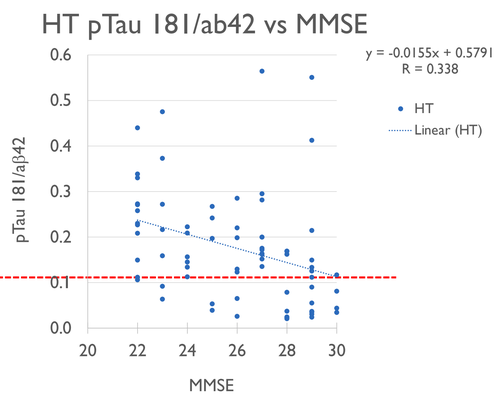


P = 0.011 (one-tailed t-test)

P-Tau/Ab42 vs MMSE (HM vs HT)



Worse pathology



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).
- Analysis of 108 Early AD patients enrolled in Phase 2 biomarker study evaluating ALZ-801 oral tablet showed significant baseline differences in CSF biomarker profiles between APOE4/4 homozygotes and APOE3/4 heterozygotes.
- >97% of homozygotes had abnormal p-tau/Aβ42 levels, thereby validating selection of this patient population for the ALZ-801 Phase 3 study.
- Approximately 1/3 of heterozygotes had negative CSF biomarkers, indicating the necessity of using biomarkers to identify A+/T+ subjects in trials.
- These biomarker analyses show a distinct phenotype of APOE4/4 AD subjects, who have higher p-tau/Aβ42 ratios than heterozygotes and appear to accumulate a high burden of amyloid and tau pathologies at the pre-MCI stage.
- These data support selection of APOE4/4 homozygotes, a population enriched in Aβ pathology, for the APOLLOE4 Phase 3 trial of ALZ-801 in Early AD.