
In AD, the primary neuropathological change include neurofibrillary tangles and extracellular neuritic plaques. These plaques primarily contain amyloid-B peptide. There is evidence that either aberrant AB production or clearance is an early component in the pathogenesis of AD. Bapineuzumab is a humanized anti-amyloid-beta monoclonal antibody in development for treatment of AD. In preclinical trials, the murine form has been shown to bind fibrillar, oligomeric and monomeric forms of AB and reduce the amount of AB in the brain and improve memory in transgenic mice that overproduce AB amyloid. In phase 2 trials involving patients with mild to moderate AD, patients were received bapineuzumab vs placebo had greater reduction in amyloid on PET amyloid imaging and reduced CSF tau suggesting target interaction and attenuation of neurodegeneration.

Methods: Study was conducted to evaluate the efficacy of IV bapineuzumab vs placebo in patients with mild to moderate AD. Two double-blind randomized, placebo controlled, phase 3 trials were conducted with patients with mild-to-moderate AD to determine efficacy and safety of bapineuzumab.

One study involved 1121 carrier of apolipoprotein E (APOE) 4 allele and other involving 1331 noncarriers. The trials were multicenter, randomized, double-blind, placebo-controlled, parallel group studies. Carrier study included 170 US sites and noncarrier study was conducted at 218 site in US, Canada, Germany and Austria. Patient were 55 yo to 88 yo, met criteria for AD and had MRI’s c/w AD and MMSE 16 to 26.

Objectives: Evaluate efficacy of bapineuzumab vs placebo by measuring change from baseline to week 78:

1. ADAS 11 item cognitive subscale and Disability Assessment for Dementia scale. Also obtained MMSE, Neuropsychological Test Battery, Clinical Dementia Rating-Sum of Boxes, Dependence Scale.
2). PET substudy at baseline, week 45 and week 71.
3). CSF tau assessed at baseline and week 71.
4). MRI participants had scanning at baseline and 13 week intervals through week 71. Looking at whole brain volume from baseline to week 71.

Bapineuzumab or placebo was administered by IV infusion to carriers of APOE at dose of 0.5mg/kg. Non carriers received either bapineuzumab or placebo at 0.5mg/kg or 1.0mg/kg every 13 weeks up to 6 infusion with final assessment at 78 weeks. A 2mg/kg dose was discontinued due to safety concerns noted on amyloid imaging w/effusion and edema. Randomization was stratified according to use of cholinesterase inhibitors vs memantine and baseline MMSE (16 to 21 and 22 to 26), participation in substudy, copy number APOE 4,

Carrier study: 1121 patient were randomized and received one dose of study drug 673 randomly assigned to 0.5mg/kg, 448 placebo. In the efficacy analysis 1090 carriers were included.

Noncarrier study: 1331 randomized and received one dose study drug, 337 0.5mg/kg, 329 1.0mg/kg , 141 2mg/kg-eliminated and received 1.0mg/kg. 524 placebo. In efficacy analysis 1114 noncarriers were included. (Table 1 baseline characteristics).

Results: Carrier group: 75% in placebo and 69% in treatment group completed the study. Noncarrier group 71% in placebo, 70%. 68% and 67% completed the study in 0.5mg/kg, 1mg/kg and 2mg/kg completed the study. More patients in treatment arm withdrew due to side effects 11% vs 7.6% in carrier, noncarrier 9.5%, 8.8%, 13.5%.

** Figure 1 and Table 2: There was no significant difference between groups in primary outcomes.

At week 78 , there was no significant change from baseline to week 78 in ADAS-cog 11 and DAD scores were -0.2 (P=0.80) and -1.2 (P=0.34) respectively. In the noncarrier study, ADAS cog 11 and DAD scores were -0.3 (P=0.64) and 2.8 (P=0.07) at 0.5mg/kg dose and 0.4 (P=0.62) and 0.9 (P=0.55) with 1.0mg/kg dose.

Biomarker outcome:

PET scanning: no significant change found in standardized uptake value ratio in the 5 cortical areas of interest: anterior cingulate cortex, posterior cingulate cortex, frontal cortex, lateral temporal cortex and parietal cortex.
CSF Tau: In carriers on Bapineuzumab, a significant reduction in tau was observed at week 71 where there was an increase in tau with placebo. Among noncarriers, no significant between group difference in tau was observed in the treatment arms.

Volumetric MRI: Among carriers and noncarriers there was no significant difference in annual rate of brain loss.

Safety: In carrier group 92.6% in treatment group and 88.8% in placebo group reported ADR. Noncarrier group: 88.7%, 88.8% and 90.8% in the 0.5mg/kg, 1.0mg/kg and 2.0mg/kg reported ADR compared to 88.7% in placebo group. (Table 3).

****Major safety finding: In carrier group amyloid-related imaging abnormalities with effusion and edema was identified among patients receiving bapineuzumab (15.3%) which increased with dose and APOE 4 allele number (11.4% heterozygotes, 27.3% homozygotes). In the noncarrier group, same abnormalities were found in 4.2% 0.5mg/kg, 9.4% 1.0mg/kg and 14.2% 2.0mg/kg. This abnormality occurred early in treatment with Bapineuzumab. Majority of patients were asymptomatic for this finding. Among carriers, fatal adverse event occurred in 1.1% placebo group and 2.2% in treatment group. Neoplasm was the most common ADR which led to death in the treatment group (0.9%). Among noncarriers, fatal events occurred in 1.3% placebo, 1.2% 0.5mg/kg, 2.1% 1.0mg/kg and 3.5% 2.0mg/kg. Neoplasm leading to death occurred in 0.4% placebo and treatment patients.

Conclusion: Bapineuzumab did not improve clinical outcomes in patients with Alzheimers disease despite differences biomarkers observed in carriers. No differences were seen in ADAS-cog 11, DAD, Clinical Dementia Rating Scale, Neuropsychological Test Battery, MMSE. Treatment doses of bapineuzumab was limited by finding of amyloid related imaging abnormalities with effusion and edema especially at higher doses and number APOE 4 alleles.