LP102 Effects of the p38α kinase inhibitor neflamapimod on the basal forebrain, assessed by structural MRI, in Alzheimer's disease (AD)

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BACKGROUND

The p38α kinase inhibitor neflamapimod acts on molecular mechanisms underlying cholinergic degeneration, including reducing the expression of BACE1, and restores number & morphology of Basal Forebrain Cholinergic Neurons (BFCNs) in Ts2 transgenic mice [1]. In addition, in a phase 2a clinical-study in dementia with Lewy bodies (DLB), neflamapimod improved BFCN-associated clinical outcomes [1].

Recently, MRI-based volumetry (as a measure of atrophy) of the Nucleus basalis of Meynert (NbM) within the basal forebrain has been correlated to clinical outcomes in AD, PD and DLB [2-5]. Herein, we retrospectively assessed MRI scans obtained in a previously reported phase 2a pilot clinical study of neflamapimod in AD [6], utilizing analytic techniques to assess NbM volume that were not available when the study was conducted.

OBJECTIVES

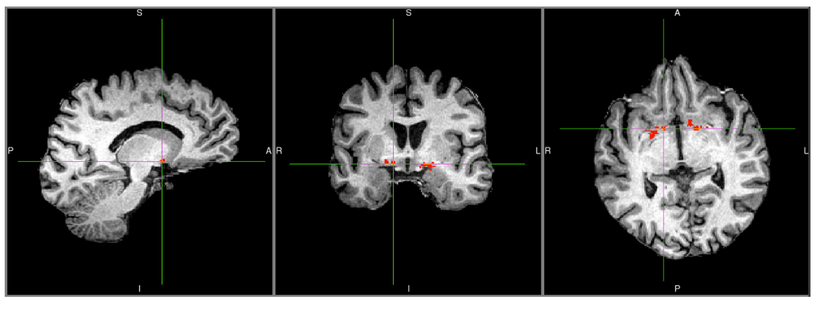
To evaluate the effect of neflamapimod on basal forebrain cholinergic degeneration in AD, as assessed by structural MRI.

PARTICIPANTS AND METHODS

Blinded longitudinal study of neflamapimod in patients with amyloid-PET documented early AD (MMSE 20-28). Study design and main results have been published [6].

Structural (3D T1 Isotropic) MRI was obtained before, and after 12 weeks treatment (n=14 participants). NbM volume was assessed using a probabilistic atlas [7] and followed over time.

Example: NbM based on probabilistic mask shown in red

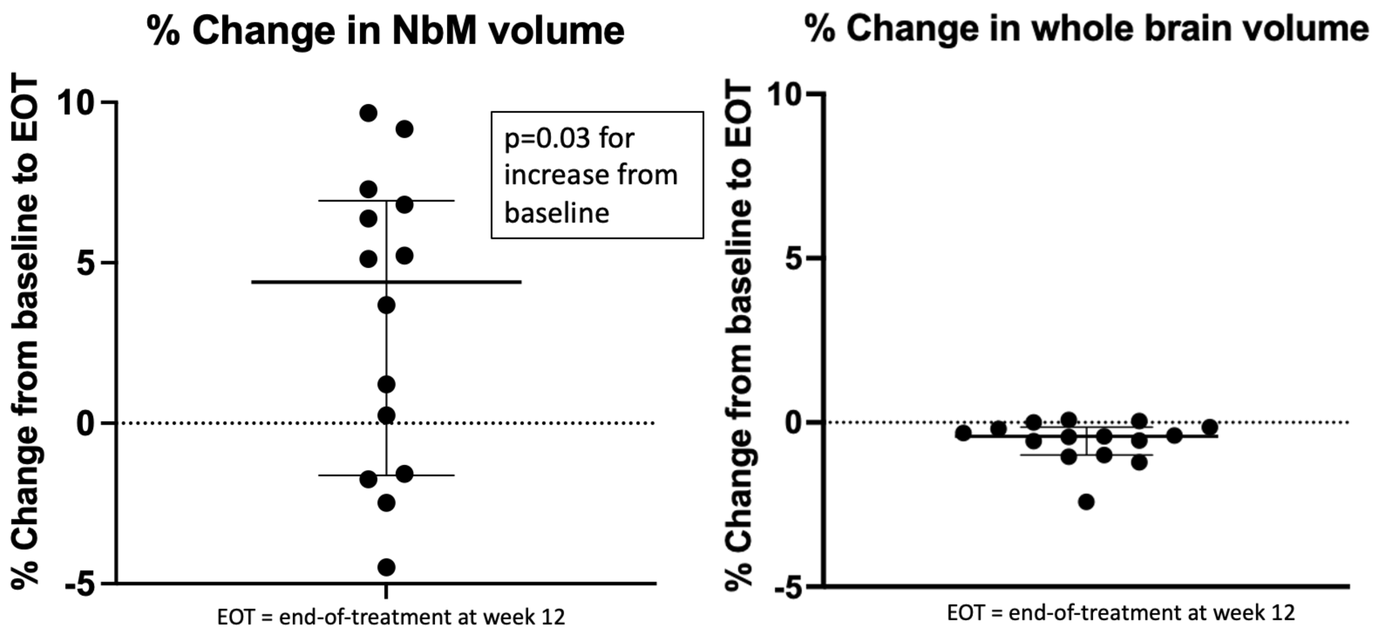


KEY FINDINGS - CONCLUSIONS

- NbM volume by MRI has potential as a biomarker to assess therapeutic effects on the basal forebrain
- Neflamapimod treatment is associated with increasing NbM volume, suggesting p38α kinase inhibition positively impacts the cholinergic degenerative process in AD
- Further evaluation of the potential effect of neflamapimod on the basal forebrain, as assessed by structural MRI, in placebo-controlled clinical trials in AD and other diseases in which the basal forebrain is impacted (e.g., dementia with Lewy bodies) is warranted

DATA -RESULTS

At baseline, mean Nucleus basalis of Meynert (NbM) volume within the basal forebrain was 353(SD=33) mm^3. At the end-of-treatment, NbM volume increased significantly from baseline (p=0.03, Wilcoxon signed rank test), with a median 4.5% (Interquartile Range, IQR: -1.6, +6.9%) increase for the study overall, and 8 of 14 participants showing >3% increase in NbM volume. As previously reported, global brain volume was decreased by a median 0.4% (IQR: -1.0%, -0.1%).



DISCUSSION

In contrast to our results, in longitudinal studies of untreated subjects with early AD there is an annual percentage *decrease* in NbM volume of 0.5-1.0% [8,9]. That neflamapimod could reverse NbM atrophy is in line with the preclinical results in Ts2 mice, in which neflamapimod reversed the neurodegenerative phenotype in the basal forebrain [1]. In addition, in a separate clinical trial in AD [10], neflamapimod compared to placebo significantly lowered CSF levels of total tau, a reported CSF biomarker of NbM atrophy [11]. Moreover, there is evidence from animal models and from postmortem human brain studies suggesting that many cholinergic neurons are depleted of phenotypic markers, shrink, and persist in an atrophic state in early AD (rather than die), allowing for the possibility of reversal of the atrophic state with drug treatment[12].

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