Evidence that neflamapimod has a beneficial effect on basal forebrain atrophy assessed by MRI in dementia with Lewy bodies

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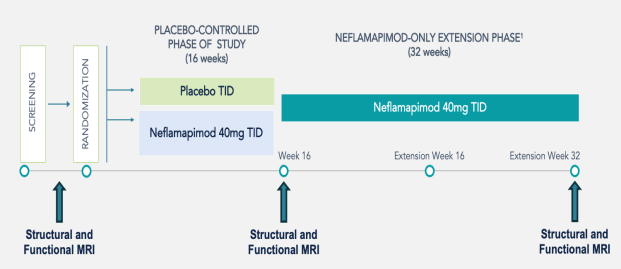
Introduction and Background

Neflamapimod, an oral p38a kinase inhibitor, targets molecular mechanisms underlying cholinergic degeneration and in preclinical studies basal forebrain cholinergic loss. In phase 2a and 2b ("RewinD-LB") trials, neflamapimod significantly slowed clinical progression in dementia with Lewy bodies (DLB), a disorder characterized by loss of basal forebrain cholinergic neurons. To evaluate MRI's potential to assess treatment effects on the basal forebrain, MRI scans were obtained from a subset of RewinD-LB participants.

Methods

A total of 159 participants with dementia with Lewy bodies (CDR-SB 0.5 or 1.0) by consensus clinical criteria were enrolled using consensus clinical criteria in a 16-week randomized, placebo-controlled period, followed by a 32-week neflamapimod-only extension. Structural and functional MRI were performed at baseline, week 16, and week 48 in the 25 participants from the UK and the Netherlands. Volumes of the left and right basal forebrain (BF) and nucleus basalis of Meynert (NbM)—the major cholinergic cluster within the BF—were quantified.

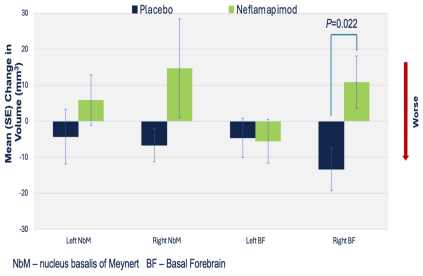


N=10 placebo, 8 Neflamapimod during placebo-controlled phase
N=11 during the extension

Results and Conclusions

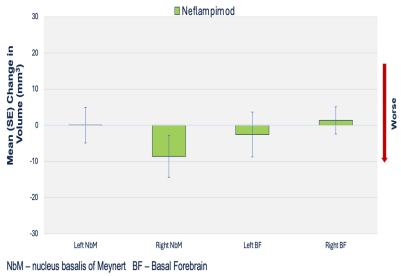
During the placebo-controlled phase neflamapimod treatment was associated with improvement (p=0.022) in right basal forebrain volume compared to placebo. No significant group differences were observed for other volumetric measures. At the end of the extension, compared to the start of the extension, there was a minor trend towards improvement in right basal forebrain volume (+1.4 mm^3, 95% CI -6.4, +9.2) associated with improved right BF–default mode network static functional connectivity (p = 0.019 for increase from baseline). Combined with the prior results in AD, the findings provide compelling evidence that neflamapimod has a beneficial impact on basal forebrain atrophy in DLB and support MRI as a tool to assess treatment effects on cholinergic degeneration

Change from Baseline in NbM or Basal Forebrain Volume Baseline During the 16-Week Duration Placebo-Controlled Phase



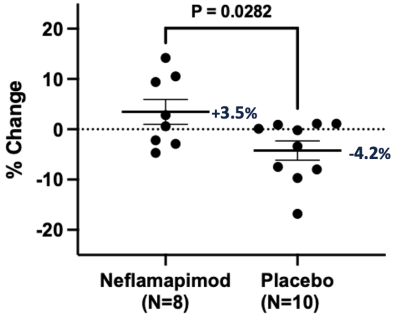
NbM – nucleus basalis of Meynert BF – Basal Forebrain

Change in NbM or Basal Forebrain Volume from Start to End of 32-Week Neflamapimod Only Extension

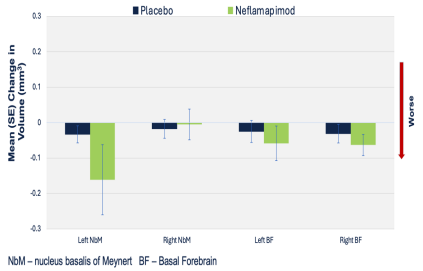


NbM – nucleus basalis of Meynert BF – Basal Forebrain

% Change in Right Basal Forebrain Volume Over 16 Weeks

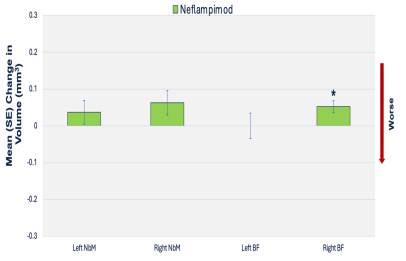


Change from Baseline in Static Functional Connectivity to Default Mode Network (DMN) During the 16-Week Duration Placebo-Controlled Phase



NbM – nucleus basalis of Meynert BF – Basal Forebrain

Change in Static Functional Connectivity to Default Mode Network (DMN)from Start to End of 32-Week Neflamapimod Only Extension



NbM – nucleus basalis of Meynert BF – Basal Forebrain

*P=0.019 for change from baseline

Correlation of rBF-DMN Functional Connectivity and Change in CDR-SB During the Extension