**Supplementary Materials**



**Supplementary Figure 1.** Change from baseline in BEHAVE-AD-FW symptom domains. A) Mean change from baseline to Week 52 in BEHAVE-AD-FW symptom domains in total study population. Error bars represent SEM. B) Mean change from baseline to Week 52 in BEHAVE-AD-FW symptom domains in *post hoc* analyses in behaviorally impaired study subpopulation. Error bars represent SEM. BEHAVE-AD-FW, Behavioral Pathology in Alzheimer’s Disease Frequency-Weighted Severity Scale; BL BHV, baseline BEHAVE-AD-FW.

**SUPPLEMENTAL METHODS**

*Patient selection*

 With the exceptions listed below, treatment with antidepressants, antipsychotics, anxiolytics/hypnotics or anti-Parkinson’s agents (≤2 weeks), anticonvulsants (≤4 weeks), anticholinergics/antihistaminics (≤2 weeks), opioid drugs (≤1 week), cyclobenzaprine and dextromethorphan (≤1 week), and sympathomimetics were not permitted.

 Any AChEI was permitted, except for any regimen including donepezil 23 mg, due to potential for poor tolerability, and patients were to remain on the same dosing regimen of background treatment throughout the study. The following antidepressants stable for ≥6 months before screening were permitted: citalopram (≤20 mg daily), escitalopram (≤10 mg daily), paroxetine (≤30 mg daily), sertraline (≤100 mg daily) and trazodone (≤100 mg daily). The following antipsychotics stable for ≥4 weeks before screening were permitted: risperidone (≤1.5 mg/day), quetiapine (≤100 mg/day), olanzapine (≤5 mg/day) and aripiprazole (≤10 mg/day). The following anxiolytics/hypnotics stable for ≥2 weeks before screening were permitted: benzodiazepines of short or intermediate half-life, including lorazepam (≤3 mg/day) and alprazolam (≤2 mg). Low doses of triazolam, temazepam, or oxazepam, zolpidem (≤5 mg/day), zopiclone (≤7.5 mg/day), eszopiclone (≤2 mg/day), trazodone (≤50 mg/day, at bedtime), or zaleplon (≤5 mg/day) were permitted for anxiety or sleeping disorders.

*Structural MRI measurements*

 Image processing for voxel-based morphometry (VBM) comprised within-subject co-registration, segmentation, normalization to a study-specific template using a diffeomorphic registration algorithm with modulation to preserve the total amount of signal from each region, and smoothing with a Gaussian kernel of 8 mm full width at half maximum [1]. All VBM pre-processing and statistical analyses were performed using the Statistical Parametric Mapping software package (SPM12) implemented in Matlab. Further, to evaluate treatment effects on atrophy of local brain volumes in regions associated with AD, hippocampal volumes, total brain volume and ventricular volume were computed at screening and after 12 months of treatment. For this, the inverse of the spatial normalization parameters obtained using the diffeomorphic registration algorithm were applied to the Automated Anatomical Labeling (for hippocampal volume) and Neuromorphometrics atlas (for ventricular volumes) to bring them into the individual subject’s space. A sum of overlap voxels (converted into mm3) was then computed between the individual segmented gray matter/cerebrospinal fluid maps and the corresponding anatomical labeling atlas using an approach proposed elsewhere [2]. Total brain volume was computed as the sum of binarized gray matter and white matter probability maps obtained in the segmentation step (converted into liters).

*Schedule of assessments*

 Visits occurred at screening, baseline, and Weeks 1, 2, 3, 4, 8, 12, 18, 24, 30, 36, 44, and 52. Telephone interviews were conducted at Weeks 1, 3, and during the follow-up period, and a final clinic visit occurred 12 weeks following the last dose. ADAS-Cog11 and ADCS-ADL were performed at baseline and Weeks 12, 24, 36, and 52. BEHAVE-AD-FW and AES were assessed at baseline and Weeks 12, 24 and 52. ADCS-CGIC was assessed at baseline and Weeks 24 and 52. AEs were monitored at every visit, and MRI scans were obtained at baseline and Week 52.

*Statistical analysis*

 The null hypothesis for each of the two active dose groups was: “The difference in change from baseline for active dose versus placebo is zero.” A sample size of 118 patients per group (a total of 354 for three groups) was selected assuming a one-sided alpha of 0.1 for the probability to reject the null hypothesis of no efficacy. With 118 patients per arm, the power was at least 80% to reject the null hypothesis of no treatment difference and assumed a true treatment difference of at least 2.23 points, corresponding to an effect size of 0.28. To account for potential attrition due to patient withdrawal, 181 patients were randomized to placebo, 181 patients to sembragiline 1 mg and 180 patients to sembragiline 5 mg.

**REFERENCES**

[1] Ashburner J (2007) A fast diffeomorphic image registration algorithm. *Neuroimage* **38**, 95–113.

[2] Aleman-Gomez Y, Melie-García L, Valdés-Hernandez P (2006) IBASPM: toolbox for automatic parcellation of brain structures. In *12th Annual Meeting of the Organization for Human Brain Mapping*.