



Published in final edited form as:

Alzheimer Dis Assoc Disord. 2009 ; 23(3): 211–217. doi:10.1097/WAD.0b013e318197852f.

An Open Label Study of Memantine Treatment in Three Subtypes of Frontotemporal Lobar Degeneration

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Abstract

There are currently no FDA-approved treatments for frontotemporal lobar degeneration (FTLD). The objectives of this study were to explore the tolerability of memantine treatment in FTLD and to monitor for possible effects on behavior, cognition and function. 43 individuals who met clinical criteria for FTLD (21 with frontotemporal dementia [FTD], 13 with semantic dementia [SD] and 9 with progressive nonfluent aphasia [PA]) received 26 weeks of open label treatment with memantine at a target dose of 20 mg daily. Concurrent treatment with acetylcholinesterase inhibitors was prohibited. Cognitive and functional outcome measures included the MMSE, ADAS-cog, CDR-sum of boxes, NPI, Frontal Behavior Inventory (FBI), Executive Interview (EXIT25), Texas Functional Living Scale (TFLS), Geriatric Depression Scale (GDS) and UPDRS-motor scale. Most subjects were able to tolerate the target dose of memantine. A transient improvement was observed on the total NPI score primarily in the FTD group. Variable declines were observed on the ADAS-cog, EXIT25, FBI, NPI, TFLS and UPDRS scores. The FTD and SD groups declined on most of the cognitive and behavioral outcome measures, but remained stable on the UPDRS, whereas the PA group remained relatively stable on the ADAS-cog, NPI and TFLS, but declined on the UPDRS. Memantine was well tolerated in these subjects. Future placebo-controlled trials of memantine in FTLD are warranted and may have greater power to detect behavioral and cognitive effects if focused on the FTD and SD clinical syndromes.

Keywords

Frontotemporal dementia; semantic dementia; progressive nonfluent aphasia; memantine; open-label treatment study

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National Clinical Trial identification number: NCT00187525

John Neuhaus, PhD and Adam Boxer, MD, PhD conducted the statistical analysis.

Disclosures: ALB received research support from Forest, Elan, Wyeth and Myriad and has been a consultant for Genentech. AML is a member of speakers bureaus for Forest, Pfizer, and Schwarz and a consultant for Pfizer. BLM has been a consultant and/or speaker for Novartis, Elan, Genentech and Pfizer and received research support from Forest. The remaining authors have no financial conflict. Forest Research Institute (FRI) was not involved collection, management, analysis or interpretation of the data. FRI was not involved in preparation or approval of the manuscript, although it was given an opportunity to review the manuscript before submission. No changes were made based on this review.

Introduction

Frontotemporal lobar degeneration (FTLD) is a common cause of dementia, particularly in younger individuals with disease onset at ages less than 65. ¹ FTLD represents at least three clinical syndromes which are distinct from Alzheimer's Disease (AD). The most common, frontotemporal dementia (FTD), presents with behavioral changes and a dysexecutive syndrome, whereas the other two syndromes, semantic dementia (SD) and progressive nonfluent aphasia (PA) feature language dysfunction and variable behavioral abnormalities. ²

The clinical and pathological heterogeneity of FTLD creates particular challenges for determining optimal pharmacological management. Currently, there are no FDA-approved treatments for FTLD, although a number of medications that affect the function of specific neurotransmitter systems have been studied and may offer modest benefits for the behavioral and cognitive sequelae of this disorder. ³ There is selective vulnerability of serotonergic neurons in FTLD, and a meta-analysis of SSRI treatment studies suggests that these medications offer modest benefits for improving the behavioral symptoms of FTLD. Although commonly used to control behavior in FTLD, antipsychotic agents may be of limited utility in FTLD due to enhanced sensitivity to extrapyramidal side effects. ⁴ Less success has been reported in treating the cognitive symptoms of FTLD. Unlike AD, cholinergic neurons are relatively preserved in FTD, and studies using acetylcholinesterase inhibitors have produced mixed results. One open-label study suggested that rivastigmine was well-tolerated in FTD, ⁵ and a recent placebo-controlled study demonstrated a potential benefit of galantamine in primary progressive aphasia, ⁶ however experience from a number a FTLD-specialty clinics suggests that acetylcholinesterase inhibitors frequently worsen behavior in FTLD patients with more severe behavioral impairments. ^{1, 7}

Aberrant glutamatergic neurotransmission has been implicated in neuronal dysfunction from a variety of neurodegenerative disorders including FTLD. ^{3, 8} Memantine is an uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor that stabilizes neurobehavioral decline in moderate to severe AD, ^{9, 10} and has recently been reported to improve behavior in three FTD patients. ¹¹ Phosphorylation and degradation of the tau protein, abnormalities of which are associated with some forms of FTLD, are powerfully regulated by NMDA receptor activation. ¹²

The relative efficacy of memantine for neuropsychiatric symptoms of AD, initial experience in FTD, as well as the possible involvement of NMDA-receptor mediated cellular dysfunction in a variety of neuropathological variants of FTLD, regardless of clinical syndrome, suggests that memantine may be useful in treating the symptoms of FTLD. To investigate the effects of memantine treatment in FTLD subjects, 43 individuals who met research criteria for one of the three FTLD neurobehavioral syndromes ² were studied for 26 weeks during open-label memantine treatment with the FDA-approved dose for AD.

Methods

Study Design

This was a 26 week, open-label study of memantine HCl in tablet form. Subjects who met enrollment criteria were titrated to the maximal FDA-approved dose of memantine for Alzheimer's disease, 10mg twice daily, over a period of four weeks. Individuals who could not tolerate 20mg of memantine daily were allowed to remain on the highest tolerated dose. The primary objective of the study was to assess the tolerability of memantine in FTLD over 26 weeks of open-label treatment. The secondary objectives of the study were to explore whether memantine treatment was associated with a stabilization or improvement in the neuropsychiatric, cognitive, motor or functional impairments associated with FTLD.

Secondary outcome measures are listed in detail below. After completing the first 26 weeks of the study, all subjects were given the option to receive an additional 26 weeks of open label memantine treatment.

National Clinical Trial identification number: NCT00187525.

Patient Selection

Subjects were recruited from the Memory and Aging Center at the University of California, San Francisco, or the Department of Neurology at the University of Texas Southwestern Medical Center. All aspects of the study were approved by the Institutional Review Boards at each site.

All subjects met criteria for one of the three core FTLD clinical syndromes: FTD, SD or PA.² Age was between 40 and 80 years. Because of the relative insensitivity of the Mini Mental State Exam (MMSE)¹³ to the executive and behavioral deficits of FTLD, subjects were enrolled if they had an MMSE score greater than 15 or a clinical dementia rating (CDR)¹⁴ of less than 3. All subjects had to have a reliable informant with frequent contact who could accompany them to all study visits. Subjects with concurrent FTD and amyotrophic lateral sclerosis (ALS) were allowed to participate if they did not have bulbar symptoms that would be expected to lead to death or an inability to complete the study procedures within six months of the baseline visit. Participants had an MRI or CT scan of the brain within one year of screening consistent with an FTLD diagnosis.

Exclusion criteria

Potential participants were excluded from the study if they 1) had insufficient English fluency to complete the study procedures, 2) evidence of another neurological or psychiatric disorder which would preclude a diagnosis of FTLD; 3) had used acetylcholinesterase inhibitors, antipsychotic agents, mood stabilizers (such as lithium and valproate) or benzodiazepines (other than temazepam or zolpidem) within 4 weeks of baseline; 3) had a clinically significant medical disease within the past year; 4) had brain MRI or CT findings not consistent with an FTLD diagnosis (eg. a large cortical stroke, extensive white matter disease); 5) had other laboratory or ECG abnormalities judged to be clinically significant by the study investigators.

Procedures

Study visits included a screening visit, a baseline visit and follow up visits at weeks 4, 8, 16, 26. Although subjects were excluded if they had used antipsychotic medications within 4 weeks of baseline, participants were allowed to start (or restart) if needed after the baseline visit. Study assessments included the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog; performed at baseline, week 16 and week 26)¹⁵, the Clinical Dementia Rating scale, sum of boxes score (CDR-SOB; performed at baseline and week 26)¹⁴, the Executive Interview (EXIT25; performed at baseline and week 26)¹⁶, the Frontal Behavioral Inventory (FBI; performed at baseline and weeks 8, 16 and 26)¹⁷, the Geriatric Depression Scale (GDS; performed at baseline and week 26)¹⁸, the Mini Mental State Exam (MMSE; performed at baseline and week 26)¹³, the Neuropsychiatric Inventory, total score (NPI; performed at baseline, weeks 4, 8, 16 and 26)¹⁹, the Texas Functional Living Scale (TFLS; Performed at baseline, weeks 8, 16 and 26)²⁰ and the Unified Parkinson's Disease Rating Scale – motor (UPDRS; performed at baseline, weeks 8, 16 and 26)²¹.

Safety Assessments

Adverse event information was collected at all study visits and follow-up phone calls, including early termination visits by asking whether there were any changes in health since the last visit.

Baseline and 26 week laboratory (cell blood counts, routine chemistries, urinalysis) and ECG data were reviewed by the investigators to monitor for treatment-related changes. Adverse events were rated as mild, moderate or severe based on standard definitions.

Statistical Analysis

Baseline demographic and outcome measure values were compared with Chi square or univariate ANOVA statistics with Tukey post-hoc analysis. Changes in secondary outcomes over time and differences were explored by plotting mean \pm standard error for each FTLT subtype at each time point during which data were collected. Statistical analyses were performed using SPSS for Windows (SPSS, Chicago, Version 15).

Results

Enrolment and baseline demographics

A total of 43 subjects were enrolled in the study and 37 subjects completed 26 weeks of open-label treatment (Table 1). There were 21 subjects with FTD, 13 individuals with SD and 9 with PA. Both the FTD and SD groups were predominantly male, whereas the PA group was predominantly female (Chi-square = 9.834; $p = 0.007$). There were no differences in education or disease duration between subject groups. Three of the FTD subjects, none of the SD subjects and one of the PA subjects withdrew prior to completing 26 weeks of treatment. One FTD subject completed 26 weeks of treatment but did not return for the final study visit. Three of the withdrawals were due to AEs, one was due to a caregiver issue and one was due to worsening of disease precluding further measurements.

Adverse events

Three FTD subjects experienced mild adverse events (AE's) and one experienced a severe AE (severe constipation leading to an emergency room visit) that were judged to be possibly medication-related. Four PA subjects experienced mild AEs. There were no AEs reported in the SD group (Table 2). The most common adverse event was confusion, reported in 4 subjects.

Behavioral Scales

NPI—Baseline NPI scores differed between groups ($F[2,36]=3.194$; $p=0.054$), and were higher in the FTD group than the PA ($p=0.047$)(Table 2). A transient decrease (improvement) in the total NPI score, that was maximal at week 16 but declined to baseline at week 26, was observed when data were combined in all three groups (Figure 1A). In all subjects combined, changes from baseline were (change from baseline \pm SEM) -2.71 ± 0.85 points ($p= 0.001$; 95% CI: $-4.37,-1.04$) at 4 weeks, increased to -4.40 ± 1.43 ($p=0.002$; 95% CI: $-7.20,-1.61$) at 8 weeks; further increased to -4.76 ± 1.84 ($p=0.01$; 95% CI: $-8.36,-1.16$) at 16 weeks, but declined back to baseline at 26 weeks 0.48 ± 1.80 ($p = 0.27$; 95% CI: $-3.05, 4.01$).

FBI—At baseline, FBI scores differed between the three patient groups ($F[2,35]=3.434$, $p = 0.044$). The FTD group had a higher mean FBI score than the PA group ($p=0.036$). There was a non-significant trend towards higher FBI scores in the SD than PA groups ($p=0.128$). The longitudinal FBI data are shown in Figure 1B. For all subjects, the overall estimate of change in FBI from baseline to week 26 was 2.43 ± 1.17 ($p=0.038$, 95% CI= $0.14, 4.73$).

Cognitive Scales

ADAS-cog—There were no differences in baseline ADAS-cog scores between groups ($F [2,35]=0.13$; $p=0.878$; Table 3). The largest decline in ADAS-cog performance was observed in the SD group. From baseline to week 26, SD subjects' ADAS-cog scores increased by 8.1 ± 3.1 points ($p = 0.001$; 95%CI= $1.3, 14.9$). There was a non-significant trend towards an

increase in ADAS-cog score in the FTD group of 3.1 ± 2.3 points ($p=0.156$; 95% CI: -1.7, 7.8), whereas the PA group remained relatively stable (0.1 ± 1.1 points change, $p=0.942$, 95% CI: -2.7, 2.8).

EXIT25—There were no baseline differences in EXIT25 score between groups. The SD group declined over 26 weeks, by 4.67 ± 1.8 points ($p=0.004$, 95% CI: 1.5, 7.8; Table 3). Variable declines were observed in the FTD and PA groups.

MMSE—There were no baseline differences in MMSE ($F[2,34]=1.085$, $p=0.35$). We fitted a model that included terms for linear change in MMSE over time, diagnostic group and time by group interaction. In all subjects combined MMSE declined 2.21 ± 0.7 points over 26 weeks ($p=0.002$; 95% CI= -3.59, -0.84).

Functional/Motor Scales

CDR-SOB—There were baseline differences in CDR-SOB between the subject groups ($F[2,32]=7.388$, $p=0.002$; Table 3). The FTD group had higher (more impaired) baseline CDR-SOB scores than the PA group ($p=0.002$) and there was a non-significant trend towards a higher CDR-SOB in the FTD group than the SD group ($p=0.071$). In all subjects combined, the overall change in CDR-SOB was 0.39 ± 0.33 points ($p=0.24$, 95% CI= -0.25, 1.03; Table 3) over the course of the study.

TFLS—There were no baseline differences in TFLS score between the three groups ($p=0.475$; Table 3). The FTD and SD groups declined over time on the TFLS at a similar rate (Figure 1D). The FTD group declined by -4.4 ± 1.5 points ($p=0.022$, 95% CI: -8.59, -0.8) and the SD group declined by -4.9 ± 1.8 points ($p=0.018$, 95% CI: -8.8, -1.0) over 26 weeks. The PA subjects demonstrated variable change of -2.1 ± 2.4 points ($p=0.452$, 95% CI: -3.6, 7.9) over 6 months.

UPDRS—There were no differences in baseline UPDRS score between groups (Table 3). The PA group's UPDRS score increased by 6.4 ± 2.1 points ($p=0.003$; 95% CI = 2.05, 10.38), whereas the other two groups remained relatively stable on the UPDRS over 26 weeks (Figure 1E).

Discussion

We found that most FTLD subjects were able to tolerate 26 weeks of open-label memantine treatment. A transient improvement in total NPI score was observed over the first 16 weeks of treatment which was most apparent in the FTD group. Variable declines on most of the other secondary outcome measures were observed in each FTLD clinical subtype. The SD and FTD groups showed the greatest declines on the cognitive and functional measures but remained stable on the UPDRS, whereas the PA group remained relatively stable on the cognitive and functional measures, but declined on the UPDRS. Since this was an open-label study, it is not possible to know whether any of the changes on the outcome measures were related to memantine treatment, per se. Moreover, without a placebo group, a rigorous analysis of AE frequency was not possible. Nonetheless, the longitudinal data acquired as part of the study may prove useful in planning future FTLD clinical trials.

An unexpected finding of the study was a transient decrease (improvement) in NPI score that was maximal at week 16, but increased back to baseline by week 26 most prominently in the FTD group. At baseline, the FTD group had the highest NPI scores, and also appeared to display the largest magnitude change on the NPI. Since the NPI reflects caregiver reports of behavior and includes the degree of distress caused by these behaviors, it is highly likely that some of the observed changes were related to non-treatment related aspects of study participation such as more frequent clinic visits and placebo effect. In addition, as six of the subjects had been

on antipsychotic medication prior to study enrollment, it is possible that some of the improvement in NPI could have been due to a reduction in side effects from these medications since only two of the subjects required antipsychotic medication treatment after the baseline visit. A smaller, 26 week, open-label study of memantine in FTD and SD failed to demonstrate any improvements on the NPI, however the reported analysis was limited to comparing the first and last observations, and thus may have missed the transient change we observed.²³ A number of placebo-controlled trials of memantine for AD^{24, 25}, as well as one small case series in FTD¹¹, have demonstrated improvements in NPI score that were similar in magnitude and time course to that we observed. With these results in mind, our findings suggest that placebo-controlled efficacy studies of memantine for FTLT are warranted.

We compared longitudinal changes in behavioral, cognitive and functional scales in all three subtypes of FTLT that were measured over a relatively short time course typical of a clinical trial. For the cognitive and functional measures, the FTD and SD groups followed a similar pattern of decline, whereas the PA group remained relatively stable over the 26 weeks of follow up. In contrast, the PA group displayed a large decline on the UPDRS-motor scale, and a modest decline on the TFLS over the same time period. The striking increase in parkinsonism that we observed is consistent with the frequent association of the clinical PA syndrome with tau-related neuropathology at autopsy, often in the form of Corticobasal Degeneration or Progressive Supranuclear Palsy, syndromes often associated with atypical parkinsonism.²⁶⁻²⁸

Although this was an open-label treatment study that by definition precludes any comment about the efficacy of memantine for the symptomatic treatment of FTLT, our data provide additional rationale for conducting a randomized placebo-controlled trial of memantine in FTLT. Furthermore, these data suggest that focusing on the FTD and SD syndromes in such a trial may allow for greater power to detect an effect of memantine on the behavioral and functional decline caused by FTLT. Finally, the variable declines observed on many of the outcome measures used for this study suggest that development of more FTLT-sensitive cognitive and functional outcome measures and better operational criteria for subject inclusion and exclusion will be necessary for future large randomized controlled clinical trials in FTLT.^{29, 30}

Acknowledgments

Supported by: Forest Research Institute, K23NS408855, The John Douglas French Foundation, P50AG-03-006-01, P01AG019724, The L. Hillblom Foundation and the State of CA.

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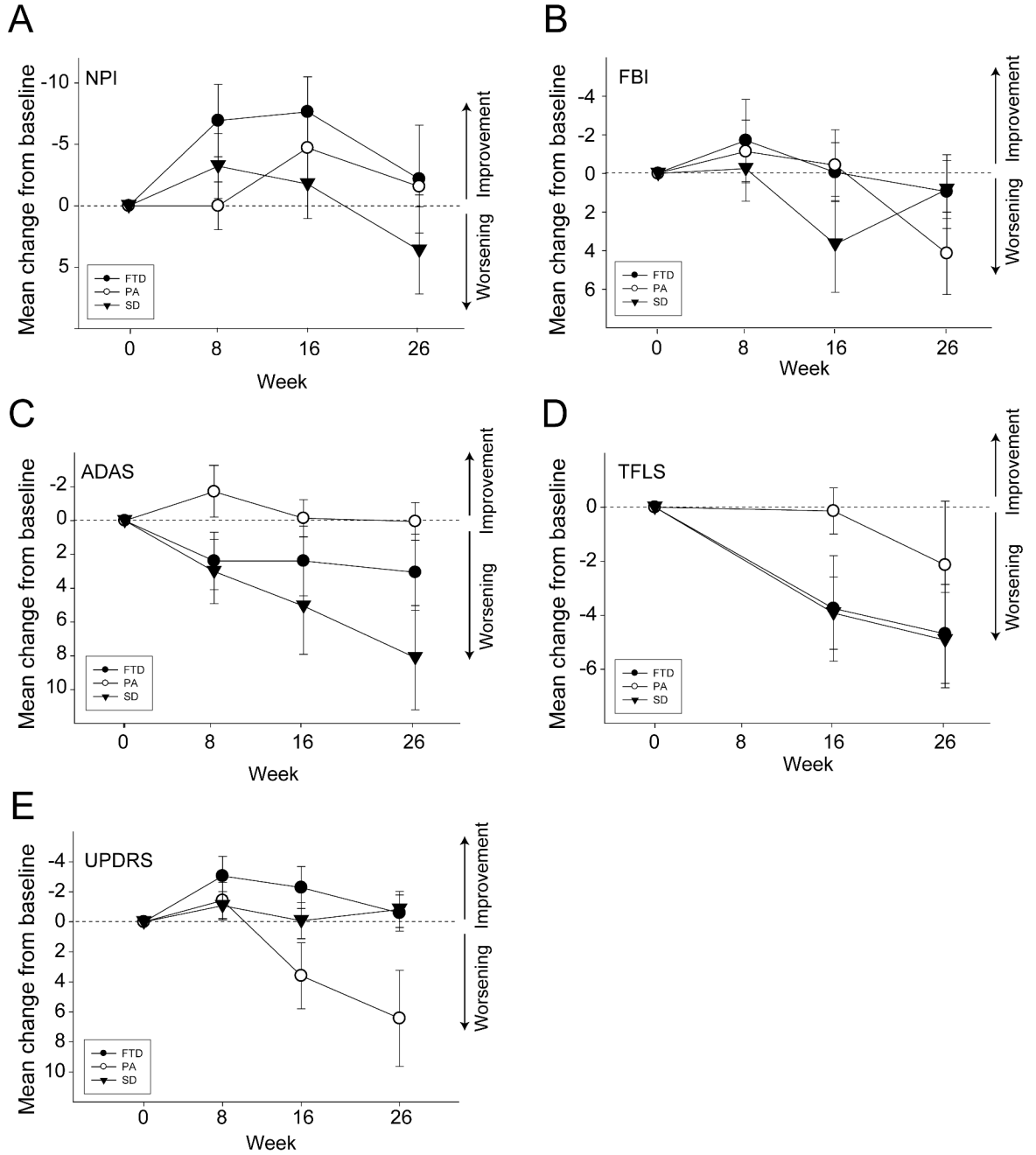


Figure 1. Longitudinal Changes in Secondary Outcome Measures

A. Mean (\pm SEM) change from baseline in Neuropsychiatric Inventory (NPI) total score in each patient group.

B. Mean (\pm SEM) change from baseline in Frontal Behavior Inventory (FBI) in each patient group.

C. Mean (\pm SEM) change from baseline on the ADAS-cog in each patient group.

D. Mean (\pm SEM) change from baseline on the ADAS-cog in each patient group.

E. Mean (\pm SEM) change from baseline on the TFLS in each patient group.

Table 1**Subject Demographics**

	FTD	SD	PA	Total
Enrolled	21	13	9	43
Age \pm SEM (yrs.)	60.3 \pm 1.8	66.3 \pm 2.1	70.1 \pm 2.4	64.2 \pm 1.3
Gender (M/F)	15/6	11/2	2/7*	28/15
Education (yrs.)	15.5 \pm 0.7	16.6 \pm 0.9	15.1 \pm 0.9	15.7 \pm 0.4
Disease duration (yrs.)	4.0 \pm 0.6	4.0 \pm 0.6	4.6 \pm 0.6	4.2 \pm 0.3
Completed 26 wks	16 [†]	13	8	37
Withdrawals	4	0	1	5
SSRI Use (Number [%])	9 (42.3)	7 (53.8)	3 (33.3)	19 (44.2)
Prior antipsychotic use	4	2	0	6
Antipsychotic started during study	1	1	0	2
Mean daily dose (mg)	20	18.5 \pm 3.0	17.5 \pm 4.0	18.6 \pm 2.3
Adverse events	4	0	4	8

* p = 0.007, Chi square;

[†] one subject completed 26 weeks of treatment but did not return for the final visit.

Table 2
Treatment Emergent Non-Serious Adverse Events

<i>Diagnosis</i>	<i>Organ System</i>	<i>Description</i>	<i>Action Taken/Outcome</i>
FTD	CNS	Mild Confusion, near-syncopal episode	None. Patient and caregiver elected to remain on 10 mg BID.
PA	CNS	Confusion, more difficulty with ADL's	Dose decreased without change in symptoms. Patient remained on 15 mg QD for the duration of study.
PA	CNS, GI	Confusion, nausea	Dose decreased to 10 mg QD. Symptoms resolved after 48 hrs.
PA	CNS, GI	Confusion, nausea, right-sided headache	Dose decreased to 15 mg QD with improvement
FTD	Immune, CNS	Allergic reaction with facial swelling, psychosis	Medication stopped. Patient withdrawn.
FTD	Immune	Rash	Medication stopped. Patient withdrawn.
PA	CNS	Excessive somnolence	Medication stopped. Patient withdrawn.

Table 3
Change in Cognitive and Functional Scores (Week 26 – Baseline)

	FTD	SD	PA	Total	P value*	Post-hoc [†]
ADAS-cog						
Baseline	19.9±4.0	22.5±3.3	21.8±3.6	21.1±2.2	0.878	
26 Weeks	23.0±4.9	30.6±4.0	21.9±3.7	25.3±3.0	0.474	
Change	3.1±2.3	8.1±3.1	0.1±1.1	4.2±1.6	0.150	
CDR-SOB						
Baseline	7.17±0.8	4.75±0.7	2.33±0.8	5.41±0.6	0.002	FTD > PA
26 Weeks	7.40±1.0	4.88±0.7	3.49±1.4	5.77±0.6	0.047	FTD > PA
Change	0.23±0.6	0.13±0.5	1.2±0.7	0.39±0.3	0.517	
EXIT25						
Baseline	14.9±2.0	13.9±2.4	16.0±3.3	14.8±1.3	0.866	
26 Weeks	15.9±2.9	18.6±2.9	14.4±3.0	16.4±1.8	0.665	
Change	0.94±1.7	4.67±1.8	-1.63±1.1	1.61±1.0	0.066	SD > FTD
FBI						
Baseline	26.5±3.6	23.5±3.4	10.3±3.4	22.3±2.5	0.044	FTD > PA
26 Weeks	28.0±3.0	24.3±4.2	16.7±5.2	24.6±2.3	0.109	
Change	1.4±1.9	0.83±1.5	5.0±2.3	1.9±1.1	0.523	
GDS						
Baseline	7.7±1.7	7.3±2.1	2.8±0.8	6.7±1.1	0.254	
26 Weeks	6.5±1.4	8.2±2.2	2.6±1.0	6.1±1.0	0.178	
Change	-1.2±1.2	0.8±1.2	-0.2±0.7	0.5±0.8	0.575	
MMSE						
Baseline	23.4±1.8	20.8±1.9	24.8±1.4	22.8±1.0	0.350	
26 Weeks	21.0±2.5	19.0±2.5	23.3±2.4	20.8±1.5	0.574	
Change	-2.4±1.1	-1.8±1.4	-1.5±1.1	2.0±0.7	0.866	
NPI						
Baseline	27.7±4.8	19.5±4.1	9.1±3.6	21.3±2.9	0.054	FTD > PA
26 Weeks	25.5±4.1	23.1±4.3	7.6±3.1	21.2±2.7	0.037	FTD > PA
Change	-2.2±4.4	3.6±3.6	-2.1±2.3	0.0±2.4	0.539	
TFLS						

	FTD	SD	PA	Total	P value*	Post-hoc [†]
Baseline	35.2±3.4	36.5±3.1	42.4±4.2	37.1±2.1	0.425	
26 Weeks	30.5±4.4	31.6±4.0	40.3±4.5	32.8±2.6	0.370	
Change	-4.4±1.5	-4.9±1.8	-2.1±2.4	-4.3±1.1	0.650	
UPDRS						
Baseline	9.2±2.1	3.3±1.1	7.2±2.4	6.8±1.2	0.090	
26 Weeks	8.6±2.8	2.4±0.8	13.6±4.1	7.5±1.7	0.046	PA > SD
Change	-0.6±1.2	-0.8±1.3	6.4±2.1	0.7±1.0	0.017	PA > SD

Mean ± SEM values shown. Bold values indicate statistical significance, ANOVA with Tukey post-hoc.

* Overall ANOVA.

[†] p < 0.05 Tukey post hoc test.