THE LANCET Neurology

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Boxer AL, Knopman DS, Kaufer DK, et al. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2013; published online Jan 2. http://dx.doi.org/10.1016/S1474-4422(12)70320-4.

Supplementary Methods

Data management. The clinical trials data management function for this study was performed by the UCSF Memory and Aging Center data management group. The multisite clinical trials management system (CTMS) was implemented using the secure, web-based, LAVA data management framework designed at UCSF and collaboratively developed and maintained by four US national Alzheimer's Disease Research Center Data Cores (funded by the US National Institutes of Health). The CRFs for the study were developed by the data management staff in coordination with the clinical leadership team (including Dr. Knopman at the Mayo Clinic and Dr. Boxer at UCSF). The data management system and multisite communication tools were administered and monitored by the data management team for the duration of the trial. The data management team worked closely with the Data Safety Monitoring Board and the study pharmacist (Dr. Fields) to ensure accurate reporting and oversight of adverse events while maintaining blinding (placebo vs. study drug) on the part of the clinical team. Data quality assurance, cleaning, and database locking were performed by the data management staff.

This was an academic study with a limited budget that did not allow for site monitors. The CTMS employed a double data entry requirement, internal logic checks, and periodic auditing by the UCSF clinical trials staff with query generation to the individual sites to maintain data quality. The UCSF clinical trials staff monitored the database and communicated with each site PI and staff by teleconference if problems were identified.

Supplementary Data

Concomittant medication use. *Antidepressant use.* 17 subjects in each group took an antidepressant medication during the study. Antidepressants that were used included (in order of frequency): fluoxetine, citalopram, escitalopram, sertraline, duloxetine, buproprion, trazodone, venlaflaxine, desvenlaflaxine, paroxetine and mirtazepine. One subject in each group took trazodone (the only SSRI with clear evidence of efficacy in FTD from a randomized, placebo-controlled trial). [1]

Antipsychotic use. One of the planned secondary analyses was to compare the number of individuals taking an antipsychotic in each group, as well the time from baseline at which the medication was started. Surprisingly, too few individuals in either group started an antipsychotic (n= 2 placebo group [risperidone 1 mg twice daily, quetiapine 25 mg daily]; n = 1 memantine group [olanzapine 5 mg daily]) to allow us to perform a formal statistical analysis.

Supplementary Reference

1. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: a randomised, controlled trial with trazodone. Dement Geriatr Cogn Disord 2004; 17:355-359.

Supplementary Table 1. Mean Differences in Outcome Measures, Adjusted for Baseline Gender

Measure	Adjusted for Gender		
	Difference	95% CI	P value
Primary outcomes			
NPI	0.8	-5.5, 7.2	0.79
CGIC	0.1	-0.3, 0.5	0.64
Secondary outcomes			
Global			
CDR-SB-FTD	0.2	-0.7, 1.2	0.61
FAQ	-1.5	-4.1, 1.2	0.27
TFLS	0.6	-2.1, 3.3	0.67
Cognitive			
MMSE	-0.1	-1.7, 1.5	0.90
EXIT25	-1.1	-3.8, 1.6	0.41
Boston Naming Test	2.9	1.4, 4.4	< 0.001
Category fluency	-0.2	-2.4, 1.9	0.82
Digits backwards	-0.2	-0.8, 0.3	0.42
Digit symbol	9.2	1.8, 16.6	0.016
Letter fluency	0.1	-1.3, 1.5	0.88
Motor			
UPDRS	-0.5	-3.4, 2.4	0.74
Tertiary outcome			
ZBI 22	1.8	-2.0, 5.7	0.35

Mean difference is placebo – memantine group.

Supplementary Table 2. Longitudinal changes from baseline

Characteristics	Placebo N = 42			Memantine N = 39		
	bvFTD	**SD**	**All**	**bvFTD**	**SD**	**All**
	N = 33	**N = 9**	**N = 42**	**N = 31**	**N = 8**	**N = 39**
NPI, mean (95% CI)	0.3 (-4.4, 5)	0.0 (-3.1, 3.1)	0.3 (-4, 4.7)	-2.4 (-6.6, 1.8)	-0.3 (-4.8, 4.2)	-1.9 (-6.1, 2.3)
CGIC, mean (95% CI)	4.8 (4.5, 5.1)	4.6 (4.3, 4.9)	4.8 (4.8, 5.1)	4.3 (3.5, 5.1)	4.6 (4.4, 4.8)	4.4 (3.7, 5.2)
CDR-SB, mean (95% CI)	1.7 (0.9, 2.6)	0.6 (-0.4, 1.5)	1.5 (0.8, 2.1)	1.6 (0.9, 2.3)	1.0 (-0.5, 2.5)	1.5 (0.9, 2.1)
FAQ, mean (95% CI)	2.9 (0.9, 4.9)	2.8 (-3.2, 8.7)	2.9 (1.0, 4.7)	4.5 (2.6, 6.4)	3.6 (-0.9, 8.2)	4.3 (2.7, 6.0)
TFLS, mean (95% CI)	-3.0 (-4.9, -1.1)	-1.7 (-5.8, 2.5)	-2.8 (-4.4, -1.1)	-4.2 (-6.7, -1.8)	-1.8 (-5.1, 1.6)	-3.7 (-5.7, -1.7)
MMSE, mean (95% CI)	-0.9 (-2.1, 0.2)	-0.7 (-1.8, 0.4)	-0.9 (-1.8, 0.0)	-1.2 (-2.8, 0.4)	-1.1 (-3.6, 1.3)	-1.2 (-2.5, 0.1)
EXIT25, mean (95% CI)	0.4 (-1.6, 2.3)	1.6 (-3.0, 6.3)	0.7 (-1.1, 2.4)	2.3 (-0.1, 4.6)	0.8 (-4.0, 5.5)	1.9 (-0.1, 3.9)
UPDRS, mean (95% CI)	2.4 (0.4, 4.4)	-2.7 (-9.1, 3.6)	1.4 (-0.7-3.4)	2.1 (-0.4, 4.5)	0.6 (-0.5, 1.6)	1.7 (-0.1-3.4)
ZBI 22, mean (95% CI)	6.4 (3.0, 9.8)	3.9 (-1.7, 9.5)	5.9 (3.0, 8.7)	3.8 (1.0, 6.7)	5.6 (1.1, 10.1)	4.2 (1.8, 6.6)
Letter fluency, mean (95% CI)	-0.4 (-1.4, 0.6)	-0.1 (-1.2, 1.0)	-0.3 (-1.1, 0.4)	-0.9 (-1.9, 0.1)	2.9 (-0.7, 6.5)	-0.1 (-1.2, 1.1)
Category fluency, mean (95% CI)	-1.5 (-3.5, 0.4)	1.8 (-5.6, 9.1)	-0.7 (-2.7, 1.3)	-0.5 (-2.5, 1.5)	-0.5 (-2.8, 1.8)	-0.5 (-1.9, 0.9)
Digit symbol, mean (95% CI)	4.1 (-3.1, 11.4)	4.5 (-4.5, 13.5)	**4.2 (-1.7, 10.1)**	-5.2 (-9.4, -1.0)	0.3 (-7.7, 8.2)	**-3.9 (-7.5, -0.3)***
Digits backwards, mean (95% CI)	-0.2 (-0.5, 0.2)	-0.2 (-1.1, 0.6)	-0.2 (-0.5, 0.2)	-0.0 (-0.5, 0.5)	0.6 (-0.4, 1.6)	0.1 (-0.3, 0.5)
Boston Naming Test, mean (95% CI)	1.0 (0.5, 1.4)	0.0 (-1.5, 1.5)	**0.7 (0.3, 1.2)**	-0.6 (-2.0, 0.9)	-5.0 (-9.0, -1.0)	**-1.4 (-2.9, 0.0)***

*Significantly different from placebo in planned ITT analysis

Supplementary Table 3. Adverse Event Summary

Number of Adverse Events, (%)	Placebo			Memantine		
	bvFTD	**SD**	**All**	**bvFTD**	**SD**	**All**
Mild	24 (64.1)	6 (85.7)	30 (66.7)	25 (92.6)	11 (68.8)	36 (83.7)
Moderate	10 (25.6)	1 (14.3)	11 (24.4)	1 (3.7)	5 (31.2)	6 (14.0)
Severe	4 (10.3)	0 (0.0)	4 (8.9)	1 (3.7)	0 (0.0)	1 (2.3)
Total, by syndrome	38 (100)	7 (100)	45 (100)	27 (100)	16 (100)	43 (100)

Supplementary Table 4. Adverse Events by System Organ Class and Preferred Term

	Placebo			Memantine		
Body Class / Preferred Term	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Any Adverse Event	30 (66.7)	11 (24.4)	4 (8.9)	36 (83.7)	6 (14.0)	1 (2.3)
Blood and Lymphatic System Disorder	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated Red Blood Cell Count	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body as Whole	1 (3.3)	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)
Fatigue	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Cognitive Disorders	0 (0.0)	1 (9.1)	0 (0.0)	5 (11.1)	1 (16.7)	0 (0.0)
Confusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Increased Confusion	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Language Problems	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	0 (0.0)	0 (0.0)
Memory Loss	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (100.0)	0 (0.0)
Eye Disorders	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Scleral Hemorrhage	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	7 (23.3)	1 (9.1)	1 (25.0)	3 (8.3)	0 (0.0)	0 (0.0)
Appetite Change	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
Constipation	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
Diverticulitis	1 (14.3)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fecal Incontinence	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Loose Stools	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
Nausea	3 (42.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oral Changes	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Supplementary Table 4. Adverse Events by System Organ Class and Preferred Term (*Continued*)

	Placebo			Memantine		
Body Class / Preferred Term	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Hepatobilliary Disorders	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated AST	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury	1 (3.3)	0 (0.0)	1 (25.0)	8 (22.2)	0 (0.0)	0 (0.0)
Abrasion	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)
Fall	1 (100.0)	0 (0.0)	1 (100.0)	5 (62.5)	0 (0.0)	0 (0.0)
Laceration	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Metabolism and Nutrition Disorders	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Appetite Change	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight Loss	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Nervous System Disorders	6 (19.8)	1 (9.1)	2 (50.0)	3 (8.3)	2 (33.3)	1 (100.0)
Back Pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (100.0)
Dizziness	1 (16.7)	1 (100.0)	0 (0.0)	1 (33.3)	1 (50.0)	0 (0.0)
Facial Weakness	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)
Increased Involuntary Movements	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
Stroke	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)

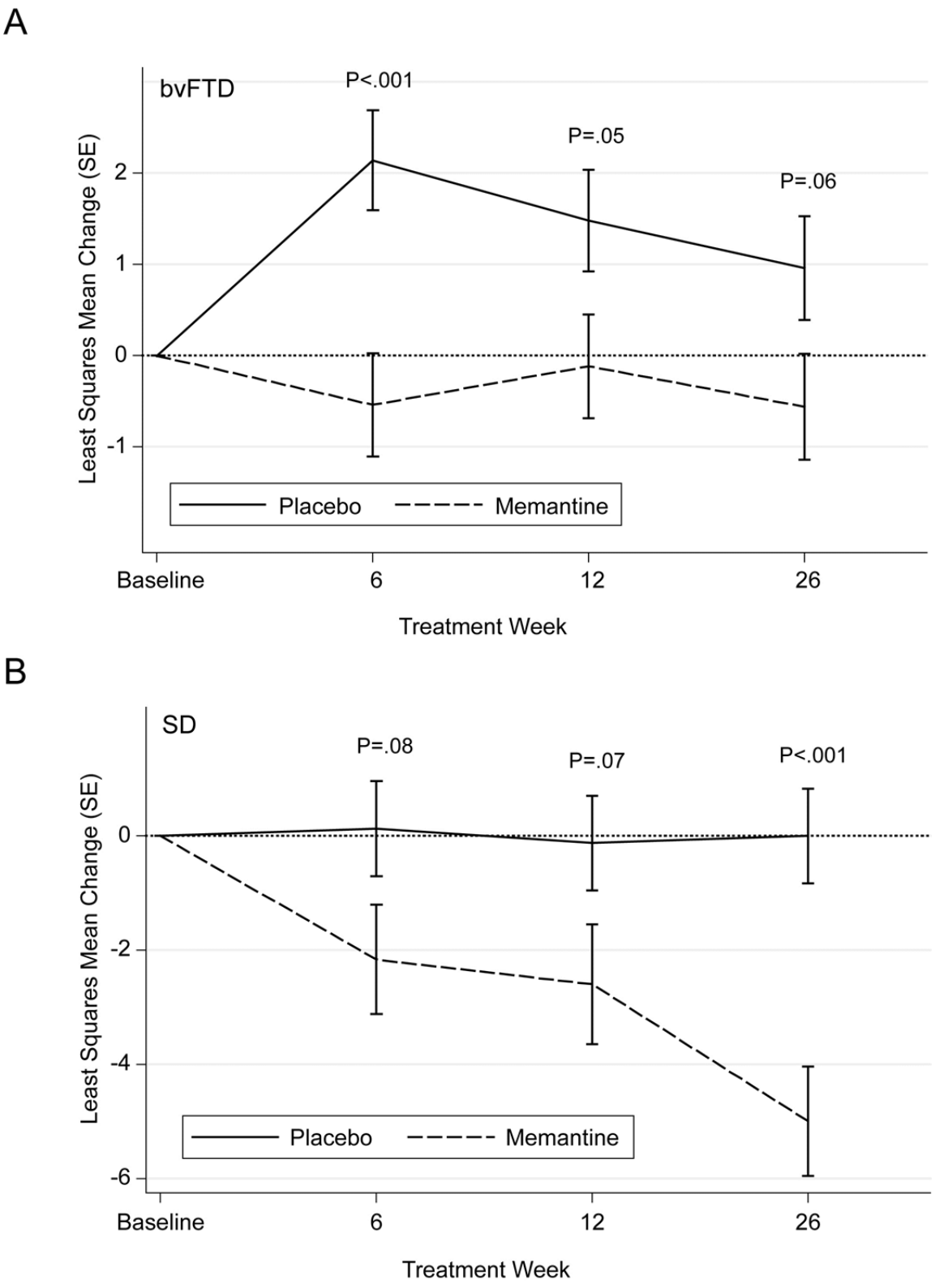
Supplementary Table 4. Adverse Events by System Organ Class and Preferred Term (*Continued*)

	Placebo			Memantine		
Body Class / Preferred Term	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Psychiatric Disorders	9 (30.0)	7 (63.6)	0 (0.0)	8 (22.2)	1 (16.7)	0 (0.0)
Agitation	1 (11.1)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Apathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Behavioral Rigidity	1 (11.1)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Dietary Changes	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Disinhibited Speech	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disorganization	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Inappropriate Sexual Behavior	0 (0.0)	4 (57.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	2 (22.2)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nightmares	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Obsessive Compulsive Symptoms	1 (11.1)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)
Somnolence	1 (11.1)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Visual Hallucinations	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Worse Behavior	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and Urinary Disorders	1 (3.3)	0 (0.0)	0 (0.0)	4 (11.1)	1 (16.7)	0 (0.0)
Nephrolithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Urinary Frequency	1 (100.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)
Urinary Incontinence	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)
Urinary Tract Infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.0)	0 (0.0)	0 (0.0)

Supplementary Table 4. Adverse Events by System Organ Class and Preferred Term (*Continued*)

	Placebo			Memantine		
Body Class / Preferred Term	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Respiratory Disorders	1 (3.3)	0 (0.0)	0 (0.0)	4 (11.1)	0 (0.0)	0 (0.0)
Cough	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)
Nasal Congestion	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)
Upper Respiratory Infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	1 (3.3)	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)
Rash	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)

Number (percentage) of adverse events of each type. For Preferred Term, the percentage is the percentage of events with that term within each Body Class. For Body Class, the percentage is the percentage of adverse events for that Body Class within all adverse events of a particular severity.



Supplementary Figure 1. Boston Naming Test Changes in bvFTD and SD groups. (A) Change from baseline in modified Boston Naming Test scores in the bvFTD group intent to treat population. **(B)** Change from baseline in modified Boston Naming Test scores in the SD group intent to treat population.