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Memantine and Functional Communication in Alzheimer's Disease: Results of a 12-Week, International, Randomized Clinical Trial

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Abstract. Post hoc analyses suggest that memantine treatment may provide communication-related benefits in patients with Alzheimer's disease (AD). In this 12-week, international, randomized, double-blind, placebo-controlled trial of memantine (10 mg bid), the functional communication abilities of patients with AD (MMSE range: 10–19) were assessed using the Functional Linguistic Communication Inventory (FLCI; primary measure). Two combined subscales (Social Communication and Communication of Basic Needs) from the American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults (ASHA FACS; secondary measure) were administered to caregivers. Treatment-emergent adverse events were also recorded. After 12 weeks, memantine-treated patients ($n = 133$) demonstrated a non-significant improvement on the FLCI (placebo: −0.6; memantine: 0.7; $p = 0.070$, LOCF) and a significant improvement on the ASHA FACS (placebo: −5.3; memantine: 0.5; $p = 0.022$), compared with placebo-treated patients ($n = 124$). Memantine had a low incidence of adverse events. In patients with moderate AD, memantine treatment improved functional communication, as recognized by caregivers.

Keywords: Alzheimer's disease, American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults (ASHA FACS), communication, drug therapy, Functional Linguistic Communication Inventory (FLCI), language, memantine, randomized controlled trial

INTRODUCTION

Communication is central to all human activities and interactions. Individuals with Alzheimer's disease (AD) lose particular communication abilities during the mild, moderate, and severe stages of the disease [1]. Communication deficits in the

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moderate stage of AD include problems with word-finding, confrontation naming, and verbal fluency [1–4]. In addition, increasing impairment is observed in "functional communication," which the American Speech-Language-Hearing Association (ASHA) defines as "the ability to receive or to convey a message, regardless of the mode, to communicate effectively and independently in a given environment" [5, 6]. The inability of patients to communicate effectively may lead to adverse behaviors such as agitation and aggression, which can result in significant stress and burden for caregivers [7, 8].

In AD clinical trials, outcome measures typically include instruments that measure cognition, functional abilities, global status, and behavior; however, instruments that measure specific deficits in language and functional communication have rarely been used. Nevertheless, post hoc analyses suggest that the therapies approved for the treatment of AD may improve patients' functional communication across the severity spectrum of the disease. For example, a retrospective, pooled analysis of four 26-week trials of rivastigmine, a cholinesterase inhibitor (ChEI), demonstrated that rivastigmine-treated patients with mild to moderate AD improved significantly on the language domain of the AD Assessment Scale-cognitive subscale (ADAS-cog), compared with their placebo-treated counterparts [9]. Similarly, in patients with moderate to severe AD, post-hoc analyses suggest that treatment with memantine, an uncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors, is associated with significantly better performance than placebo on the language domain of the Severe Impairment Battery (SIB) [10, 11], as well as on individual items involving language and communication from the SIB, the AD Cooperative Study-Activities of Daily Living scale (ADCS-ADL; 19-item version), and the Behavioral Rating Scale for Geriatric Patients (BGP) [12]. Furthermore, in an international, randomized, double-blind, placebo-controlled trial in patients with moderate to severe AD, an extended-release memantine formulation was associated with significant benefits on the prospectively defined measure of verbal fluency, compared with placebo [13]. Also, in studies of individuals suffering from post-stroke aphasia, ChEIs [14] as well as memantine [15] have been associated with improvements in communication abilities. Finally, a recent open-label trial in patients with moderate to severe AD demonstrated that once-daily memantine treatment was associated with significant improvement in functional communication after 12 weeks [16].

The purpose of this randomized, double-blind, placebo-controlled trial was twofold: 1) to prospectively examine the effects of memantine treatment on functional communication in patients with moderate AD, and 2) to evaluate the utility of the Functional Linguistic Communication Inventory (FLCI) [17] and the Functional Assessment of Communication Skills for Adults (ASHA FACS) scale [18], two measures of functional communication, as assessment tools in a randomized clinical trial in AD.

MATERIALS AND METHODS

Trial design

This 12-week trial (MEM-MD-71; NCT00469456) began recruiting in April 2007, with the first patient visit on May 24, 2007. The last patient visit occurred on November 4, 2008. Participants were recruited from 25 centers: 14 in Australia, 8 in South Africa, and 3 in New Zealand. The 265 participants (male and female, $\geq$50 years of age) were native English speakers who had a diagnosis of probable AD, according to criteria set forth by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), a Mini-Mental State Examination (MMSE) [19] score of 10–19 at both Screening (Week 2) and Baseline (Week 0), and computed tomography (CT) or magnetic resonance imaging (MRI) results within the past 12 months consistent with this diagnosis. Concurrent treatment with a ChEI was permitted but not required; in those receiving ChEI therapy, a stable dose of a single ChEI was required for at least 3 months prior to study entry and throughout the study. Subjects were required to pass a physical examination, clinical laboratory evaluation, and electrocardiogram (ECG) at Screening (Visit 1); they also had to be ambulatory or ambulatory-aided, with vision and hearing capabilities sufficient for compliance with testing procedures. Females were required to be surgically sterile or postmenopausal for at least 2 years. All subjects were required to have a knowledgeable and reliable caregiver who spoke English and could accompany the patient to all visits. Caregivers were required to spend sufficient time with the patients that they could accurately describe changes in the patients' cognitive, functional, and language abilities.

Exclusion criteria included clinically significant and active pulmonary, gastrointestinal, renal, hepatic, endocrine, or cardiovascular system disease

or cancer; evidence of psychiatric or neurologic disorders other than probable AD; dementia complicated by other organic brain disease or predominant delusions; clinically significant deficiency in vitamin B_{12} or folate; Hachinski Ischemic Score [20] >4 at Screening; hypertension (sitting systolic blood pressure [SBP] > 180 mm Hg; diastolic blood pressure [DBP] > 100 mm Hg); hypotension (sitting SBP < 90 mm Hg; DBP < 50 mm Hg); history of alcoholism or drug abuse within 5 years prior to Screening; evidence of impaired kidney function or severe renal impairment; prior treatment with memantine, participation in a memantine clinical trial, or hypersensitivity to amantadine or rimantadine; participation in an investigational drug study or treatment with an investigational drug within 30 days (or 5 half-lives, whichever is longer) of Screening; likely institutionalization during the trial; any other condition that, in the opinion of the investigator, would make the patient or caregiver unsuitable for the study. Patients taking unapproved concomitant medications at any point throughout the trial were required to be discontinued from the trial. Written informed consent was provided by the patient (if possible) or legally authorized representative, as well as the patient's caregiver. This trial was approved by Institutional Review Boards (IRBs) at each participating site in Australia, and by the Central IRB in New Zealand and South Africa.

Interventions

This study was a randomized, double-blind, placebo-controlled trial in which participants were required to complete up to 2 weeks of open-label, placebo-only treatment immediately prior to Baseline, after which they were randomly assigned to treatment with either memantine (10 mg bid) or placebo (1 : 1 ratio). The Statistical Programming department at Forest Research Institute (FRI) generated a list of patient randomization codes, identifying each patient by randomization number and treatment assignment. Randomization numbers were assigned sequentially at each study site as each patient entered the study. A hard copy of the randomization list was maintained and stored in a secure area by Drug Safety Surveillance at FRI. Medication corresponding to the randomization numbers, which included an identifying tear-off panel for the patient's medication accountability form, was provided to each study site.

Patients assigned to double-blind memantine treatment were titrated in weekly increments of 5 mg, reaching the maximum, target dose of 10 mg bid at the beginning of Week 4. Placebo-treated patients were given tablets identical in number and appearance to those containing memantine. All actively treated patients were required to reach the target dose, and dosage modifications were not permitted for patients experiencing dose-limiting adverse events. After completion of the trial, all patients were provided up to 6 months of open-label memantine treatment.

Outcome measures

Efficacy

The primary outcome measure was the mean change from Baseline on the FLCI [17], a direct, performance-based tool designed to assess functional communication in patients with moderate to severe AD. The instrument, which takes approximately 30 minutes to complete, evaluates 10 areas: greeting and naming, answering questions, writing, sign comprehension and object-to-picture matching, word reading and comprehension, reminiscing, following commands, pantomime, gesture, and conversation. Approximately half of the items included in the FLCI were derived from a research battery used in a five-year longitudinal study of 91 patients with AD; the other items were added later to further assess the effects of the disease on functional communication [17]. The combined set of items was administered to a standardization sample of 40 patients with AD. The FLCI has demonstrated the ability to differentiate between patients in moderately severe (mean MMSE 6.8; bladder-incontinent but not bedridden), severe (mean MMSE 1.5; bowel- and bladder-incontinent but not bedridden), and very severe (mean MMSE 0.0; bowel/bladder-incontinent and bedridden) stages of AD [2, 17]. The measure demonstrates high test-retest reliability and has been validated [17] against the Arizona Battery for Communication Disorders of Dementia (ABCD), a standardized test of linguistic communicative function in patients with AD [21]. The score range for the FLCI is 0–87, with higher scores indicating higher levels of functioning [17]. FLCI assessments were completed at Screening, Baseline, and Weeks 4, 8, and 12 (Endpoint).

The secondary outcome measure was the mean change from Baseline on two combined subscales from the ASHA FACS: Social Communication (SC) and Communication of Basic Needs (CBN) [18, 22]. The ASHA FACS, used by speech-language pathologists in the United States and other countries [18, 22], is a caregiver rating scale that was designed to assess functional

communication skills in a wide variety of patients with disorders of speech, language, and cognitive communication. It was initially validated for use in dementia and shown to correlate significantly with MMSE scores in a sample of 15 patients (coefficient for the total score: 0.716; $p < 0.01$) [22]; subsequently, in a sample of 108 Brazilian subjects with mild AD ($n = 32$), moderate AD ($n = 25$), and elderly control subjects without dementia ($n = 51$), the Portuguese version of the scale demonstrated good sensitivity (75.0%) and specificity (82.4%), with high internal consistency (Cronbach $\alpha = 0.955$), test-retest reliability (interclass $r = 0.995$; $p < 0.001$), inter-examiner reproducibility (interclass $r = 0.998$; $p < 0.001$) and criterion validity when correlated with ADAS-cog ($r = -0.69$; $p < 0.001$) [5]. The total ASHA FACS takes approximately 20 min to complete and evaluates 4 areas: social communication, communication of basic needs, daily planning, and reading/writing/number concepts. The score range for the total ASHA FACS is 0–301, with higher scores indicating higher levels of functioning; the combined score range for the two ASHA FACS subscales (SC and CBN) utilized as the secondary outcome measure in this study is 0–196, with higher scores indicating higher levels of functioning. The ASHA FACS was administered at Screening, Baseline, and Weeks 4, 8, and 12 (Endpoint). The ASHA FACS total score was utilized as an additional outcome measure.

Another additional outcome measure was the Clinical Global Impression of Change (CGI-C) [23], an assessment performed by the clinician through direct observation of the patient, with separate input from the caregiver. CGI-C ratings range from 1 (very much improved) to 7 (very much worse); a score of 4 indicates no clinically relevant change. The CGI-C was assessed at Weeks 4, 8, and 12 (Endpoint). Additional protocol-specified CGI measures were used to assess global change in social interaction and communication.

Two additional measures, the Oral Production Test (OPT) and the Caregiver Perceived Burden Questionnaire (CPBQ) were administered at Baseline and Week 12 (Endpoint). The OPT, a component of the Neuropsychological Assessment Battery [24], evaluates a patient's speech output and fluency while describing a picture of a family scene. The CPBQ [8], an exploratory measure that was not analyzed as a part of this report, is designed to assess the quality of a patient's speech, social interaction and awareness, and ability to manage daily activities as it affects the caregiver.

Safety and tolerability

Clinical laboratory determinations, a standard 12-lead electrocardiogram (ECG), and a physical examination were performed at Screening; vital signs, including weight, were performed at Screening and all study visits. Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were recorded at all post-Screening study visits. The number (percentage) of patients with potentially clinically significant post-Baseline values of vital sign parameters were tabulated by treatment group.

Data analysis

The Safety Population consisted of all randomized patients who took at least one dose of double-blind study medication. The Intent-to-Treat (ITT) Population consisted of all patients in the Safety Population who had at least one post-Baseline assessment of the primary efficacy parameter, the FLCI. Primary and secondary outcomes were analyzed by comparing least squares mean differences (LSMD) at Endpoint in the two study groups (ITT population), using the last observation carried forward (LOCF) approach for imputation of missing data. Supporting analyses were based on the observed cases (OC) approach, as well as on a mixed-effects model with repeated measures (MMRM; FLCI only). A two-way ANCOVA model was used for these analyses, with treatment group and study center as factors and Baseline value as covariate. CGI data were analyzed using a Cochran-Mantel-Haenszel test, controlling for study center and using modified ridit scores. All tests were two-sided, with $\alpha = 0.05$.

Sample size

Since clinical data regarding an expected treatment effect of the FLCI were not available, and since the FLCI and SIB are similar in score range and type of assessment, the sample size was estimated based on pooled data from the Severe Impairment Battery (SIB) from 3 previously completed memantine studies (memantine: 249; placebo: 277) [25–27]. In this pooled sample, a mean $\pm$ SD treatment difference of 2.91 ± 7.81 points in favor of memantine was observed at Week 12. Using this estimate, a minimum of 125 patients per group were determined to be required to detect a similar treatment effect with a power greater than 80%, using a two-sided, two sample *t*-test at a significance level of 0.05.

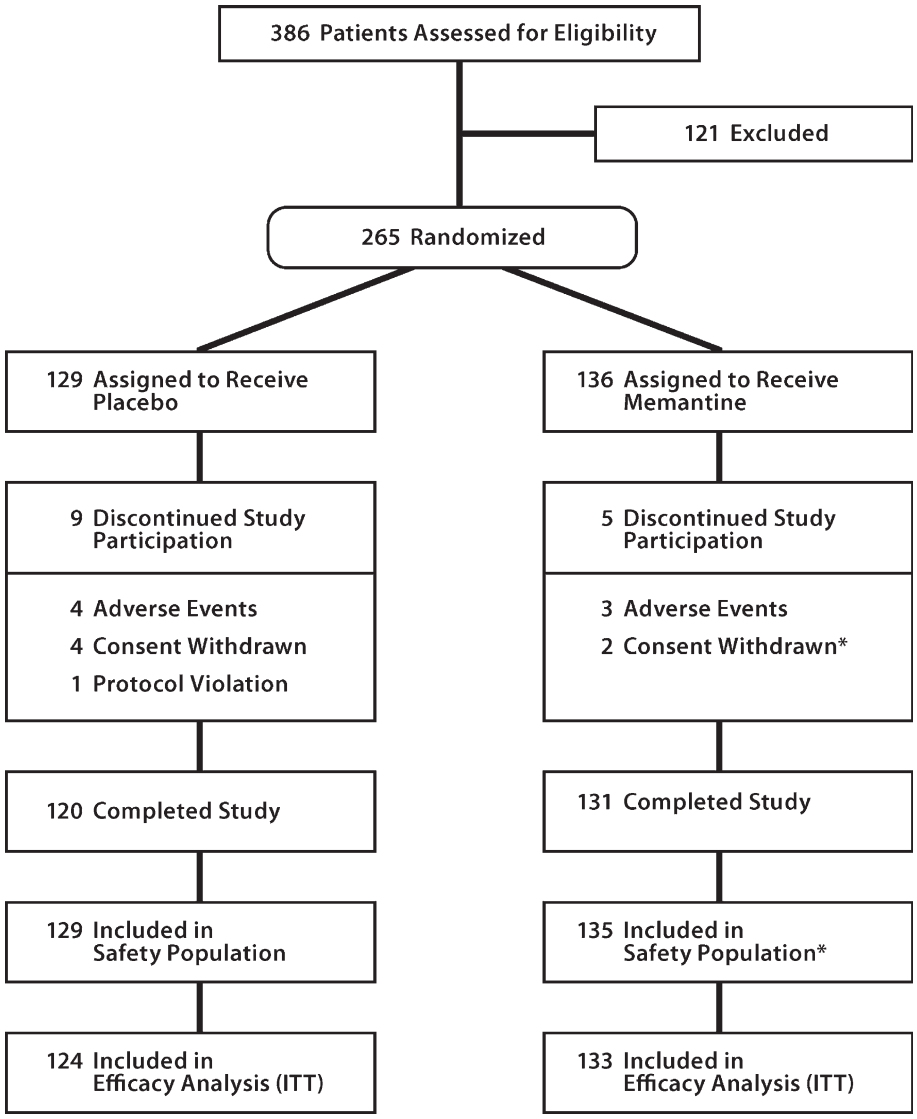

Fig. 1. Study flow.
One patient in the memantine group discontinued the trial without receiving study medication (withdrew consent) and was not included in the Safety Population. ITT indicates Intent-to-Treat Population.

RESULTS

Patients

The trial flow diagram is presented in Fig. 1. A total of 129 and 136 patients were randomized to receive placebo and memantine, respectively, with 120 (93.0%) and 131 (96.3%) completing the trial; four participants in the placebo group and three in the memantine group discontinued due to AEs (Fig. 1). The demographic and clinical characteristics of the study population are shown in Table 1. Placebo and memantine groups were well matched at Baseline. No clinically significant differences were noted.

Efficacy

Primary outcome measure: FLCI

Memantine treatment showed a non-significant improvement over placebo on the FLCI at Week 12 (LOCF: $p = 0.070$; OC: $p = 0.184$), with statistically significant differences in favor of memantine at Week 4 (LOCF/OC: $p = 0.028$) and Week 8 (LOCF: $p = 0.015$; OC: $p = 0.023$) (Fig. 2A, Table 2). The MMRM

Table 1
Summary of baseline patient characteristics (safety population)

Parameter	Placebo ($n = 129$)	Memantine ($n = 135$)
Age, years*	75.1 ± 8.7 [53–92]	74.8 ± 8.1 [52–94]
Women, *n* (%)	74 (57.4)	80 (59.3)
White, *n* (%)	118 (91.5)	122 (90.4)
Weight, kg*	69.2 ± 13.9 [39.9–107.3]	68.1 ± 13.2 [35.0–114.0]
Education, years*	11.3 ± 3.0 [0–18]	11.7 ± 2.9 [5–24]
MMSE score*	16.0 ± 2.5 [10–20]†	15.7 ± 2.7 [10–19]
Concomitant ChEI treatment, *n* (%)		
Donepezil	39 (30.2)	44 (32.6)
Galantamine	27 (20.9)	27 (20.0)
Rivastigmine	2 (1.6)	1 (0.7)

*Mean ± standard deviation [range].
†One randomized patient with an MMSE score of 19 at Screening scored a 20 at Baseline. ChEI indicates cholinesterase inhibitor; MMSE indicates Mini-Mental State Examination.

analysis indicated a statistically superior performance of the memantine group at Week 8 ($p = 0.022$) and across the entire trial (LSMD [95% CI]: 1.3 [0.2, 2.40]; $p = 0.021$).

Secondary outcome measure: ASHA FACS subscales

Caregivers of memantine-treated patients reported significantly better patient communication, compared with caregivers of placebo-treated patients, on the combined ASHA FACS subscales of SC and CBN at Weeks 12 (LOCF: $p = 0.022$; OC: $p = 0.033$) and 8 (LOCF: $p = 0.008$; OC: $p = 0.006$) (Fig. 2B, Table 2).

Additional outcome measures: CGI-C, ASHA FACS total score, and OPT

Memantine treatment was associated with a greater proportion of patients who showed an overall improvement (CGI-C<4) at Week 12, versus placebo-treated patients (LOCF: 39.1% vs. 28.2%, $p = 0.033$; OC: 39.1% vs. 28.6%, $p = 0.031$) (Fig. 3; Table 2). At Week 12, memantine treatment was not associated with significantly higher response rates than placebo on CGI Social Interaction or CGI Communication, although a significant effect of memantine was seen at Week 8 on both measures (Social Interaction, LOCF: $p = 0.041$; OC: $p = 0.036$; Communication, LOCF: $p = 0.006$; OC: $p = 0.005$). Similar to the ASHA FACS subscales of SC and CBN, the ASHA-FACS total score also demonstrated that caregivers of memantine-treated patients experienced significantly better patient communication than caregivers of placebo-treated patients at Week 12 (LOCF: $p = 0.010$; OC: $p = 0.013$). No significant difference between groups was observed on the OPT at Week 12 (LOCF: $p = 0.185$; OC: $p = 0.099$)

Safety and tolerability

Four (3.1%) placebo-treated patients and three (2.2%) patients treated with memantine discontinued the trial due to an AE (Fig. 1). Overall TEAEs are summarized in Table 3. The TEAE profile was similar between the two groups; dizziness, restlessness, and headache were the only TEAEs reported by ≥2.0% patients, and that were higher in the memantine group (Table 3). A total of 13 (10.1%) patients in the placebo group and four (3.0%) patients in the memantine group experienced an SAE, none of which was judged related to the study drug. No patients in the memantine group died during the trial; one (0.8%) patient in the placebo group died. Potentially clinically significant (PCS) adverse events that occurred in more memantine-treated patients than placebo-treated patients were a weight increase of ≥7% (2.3% vs. 0%), a weight decrease of ≥7% (2.3% vs. 0%), and a diastolic blood pressure measurement of ≥180 mm Hg that also represented a change of at least 20 mm Hg over Baseline (1.5% vs. 0%).

DISCUSSION

This study, to our knowledge, is the first published prospective, double-blind, placebo-controlled study examining the benefits of an anti-dementia agent on communication abilities in patients with AD. Memantine treatment was found to be numerically superior to placebo for the primary efficacy parameter of this study, the FLCI score change at Week 12, but the treatment difference failed to reach statistical significance. Caregivers of memantine-treated patients reported significantly improved patient communication (OC and LOCF) compared with caregivers of

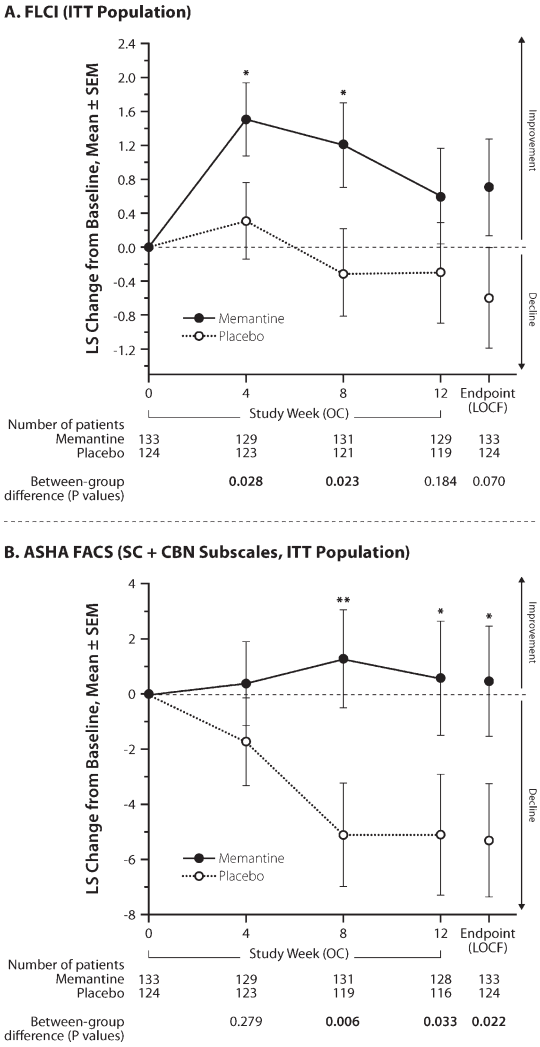

Fig. 2. A) Compared with placebo, memantine did not significantly improve functional communication at study Endpoint, as assessed using the FLCI, although the effect was significantly in favor of memantine at Weeks 4 and 8. B) Memantine treatment significantly improved functional communication compared with placebo at study Endpoint and Weeks 8 and 12, based on an assessment of caregivers, using the CBN and SC subscales of the ASHA FACS. ASHA FACS indicates the American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults scale; CBN, Communication of Basic Needs subscale; FLCI, Functional Linguistics Communication Inventory; ITT, Intent-to-Treat; LOCF, last observation carried forward; LS, least squares; MMRM, mixed-effects model with repeated measures; OC, observed cases; SC, Social Communication subscale; SEM, standard error of the mean. *$p < 0.05$; **$p < 0.01$; bold P values indicate those attaining statistical significance.

placebo-treated patients on the ASHA FACS subscales, from Week 8 onward (Fig. 2). A significant difference was also observed between the groups at Week 12 on the global outcome measure, and a higher percentage of patients treated with memantine improved when compared with patients receiving placebo (Fig. 3). In addition, memantine treatment was associated with a low incidence of adverse events (only dizziness and restlessness were notably higher in the memantine-treated group), suggesting that memantine use in this patient population was not limited by adverse events.

These results are consistent with other prospective and post hoc analyses of communication in patients with AD treated with memantine. Schmitt et al. [11] reported that memantine was associated with significantly better performance than placebo on the language domain of the SIB in a trial of patients with moderate to severe AD concurrently taking a ChEI [26], and several other post hoc analyses have demonstrated evidence of memantine-treated patients significantly outperforming placebo-treated patients on a variety of language- and communication-based subscales [10, 28]. Similarly, significant benefits of memantine versus placebo were seen on the prospectively defined measure of verbal fluency in patients with moderate to severe AD from a randomized, double-blind, placebo-controlled trial of extended-release memantine [13]. Post hoc analyses of the ChEIs donepezil [29, 30] and rivastigmine [9] have also demonstrated a superiority of drug treatment over placebo on domains of language in patients with AD. Interestingly, a post-hoc analysis of our data revealed no significant treatment-by-AChEI-usage interaction on the FLCI ($p = 0.9497$; LOCF) or ASHA FACS ($p = 0.1335$; LOCF) at study Endpoint across both groups.

Although several post hoc analyses of language and communication abilities have been performed on data obtained in antidementia drug trials [9, 11, 13, 28, 29], to our knowledge this study is unique in that it is the only prospective, randomized, double-blind, placebo-controlled trial to utilize a language and communication instrument as the primary outcome measure. The choice of one patient-based (FLCI) and one caregiver-based (ASHA FACS) outcome measure offered complementary insights into patients' communication abilities. Both the FLCI [2, 17] and the ASHA FACS [5, 22] have been validated for use in patients with AD, and ASHA FACS scores (Portuguese version) have been shown to correlate significantly with ADAS-cog scores in both individuals with AD ($r = -0.69$, $p < 0.001$) and in age-matched controls ($r = -0.63$, $p < 0.001$) [5]. A recent open-label trial of memantine, which was designed in part to complement this study, also investigated FLCI performance in patients with moderate to severe AD [16]. In that trial, once-daily (20 mg) memantine treatment was associ-

Table 2
Summary of efficacy (week 12, ITT population, LOCF)

Parameter	Baseline score*		Week 12 (Endpoint)			
	Placebo ($n=124$)	Memantine ($n=133$)	Placebo† ($n=124$)	Memantine† ($n=133$)	LSMD [95% CI]	p value
FLCI	67.8 ± 11.3	68.7 ± 11.1	-0.6 ± 0.6	0.7 ± 0.6	1.3 [−0.1, 2.8]	0.070‡
ASHA FACS (SC+CBN)	137.8 ± 28.1	134.7 ± 30.2	-5.3 ± 2.1	0.5 ± 2.0	5.9 [0.9, 10.9]	0.022‡
			Participants, n (%)			
CGI-C						
Improvement (Scores 1–3)	NA	NA	35 (28.2)	52 (39.1)	NA	
No Change (Score 4)	NA	NA	43 (34.7)	45 (33.8)	NA	0.033§
Worsening (Scores 5–7)	NA	NA	46 (37.1)	36 (27.1)	NA	

*Mean ± SD. †Least Squares Mean Difference ± SEM. ‡Based on Analysis of Covariance (ANCOVA; see **Materials and Methods**); §P value for the 7-category outcome measure; based on a Cochran-Mantel-Haenszel test (see **Materials and Methods**). CGI-C is a measure of change from Baseline; therefore, Baseline values are not applicable. ASHA FACS indicates the American Speech-Language-Hearing Association - Functional Assessment of Communication Skills for Adults scale; CBN, Communication of Basic Needs; CGI-C, clinical global impressions of change; CI, confidence interval; FLCI, Functional Linguistic Communication Inventory; ITT, Intent-to-Treat; LOCF, last observation carried forward; LSMD, least squares mean difference; NA, not applicable; SC, Social Communication; SD, standard deviation; SEM, standard error of the mean.

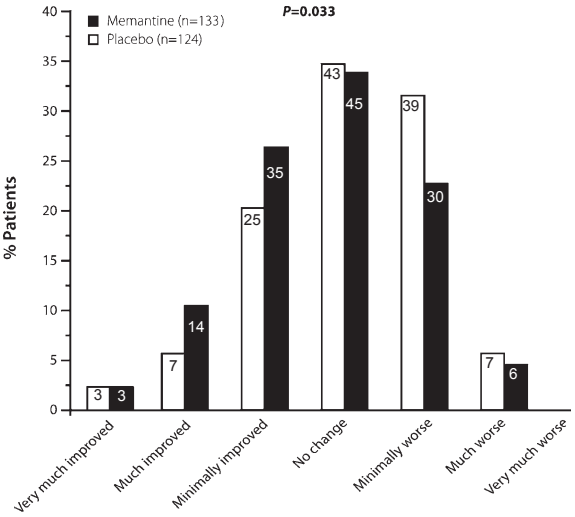

Fig. 3. Clinical Global Impression of Change at Week 12 (ITT Population; LOCF).
Patients treated with memantine performed significantly better on the CGI-C than those treated with placebo. Numbers inside the bars indicate numbers of patients that were scored to each category. p values were obtained using a Cochran-Mantel-Haenszel test. ITT indicates Intent-to-Treat; LOCF, last observation carried forward.

Table 3
Summary of treatment-emergent adverse events (safety population)*

TEAE	Placebo ($n=129$)	Memantine ($n=135$)
Any TEAE	64 (49.6)	66 (48.9)
Dizziness	2 (1.6)	7 (5.2)
Upper respiratory tract infection	5 (3.9)	4 (3.0)
Fall	4 (3.1)	4 (3.0)
Hypertension	4 (3.1)	4 (3.0)
Edema, peripheral	4 (3.1)	3 (2.2)
Headache	2 (1.6)	3 (2.2)
Restlessness	0 (0.0)	3 (2.2)
Diarrhea	5 (3.9)	2 (1.5)
Nausea	3 (2.3)	2 (1.5)
Agitation	4 (3.1)	0 (0.0)
Syncope	3 (2.3)	0 (0.0)

*Data [n (%)] include all treatment-emergent adverse events (TEAEs) experienced by at least 2.0% of patients in either treatment group.

ated with significant improvement on the FLCI after 12 weeks [16], an effect that persisted after a 4-week washout period. It should be noted, however, that the open-label study cannot be directly compared with our study since it was unblinded and did not include a placebo comparator.

The outcome of our trial is consistent with the communication-related measures from other trials in AD; however, the interpretation of our results may be limited due to the modest sample size, a short duration of treatment (12 weeks), and the exploratory use of 2 instruments not commonly utilized in AD trials. In addition, the clinical relevance of a treatment difference (LSMD) of 1.3 points on the FLCI, and of 5.9 points on the ASHA FACS in a population of patients with AD is unknown.

CONCLUSIONS

In patients with moderate AD, memantine is a well-tolerated treatment option that may be associated with improvements in functional communication skills, particularly as recognized by caregivers. In addition, the FLCI and ASHA FACS, used here for the first time

in a randomized clinical trial of AD, may be useful tools for assessing communication-related declines and treatment benefits in patients with AD.

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