

## Magnetic resonance imaging and neuropsychological results from a trial of memantine in Alzheimer's disease

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### Abstract

**Background:** This study was designed to assess changes in brain volume and cognitive abilities in memantine-treated patients with Alzheimer's disease (AD) by using an exploratory, single-arm, delayed-start design.

**Methods:** Cholinesterase inhibitor-treated patients with AD (N = 47; Mini-Mental State Examination score range: 15–23) were enrolled in an observational lead-in period (weeks: 1–24), followed by an open-label period of add-on memantine treatment (weeks: 25–48). The patients underwent magnetic resonance imaging at weeks 0 (baseline), 24 (immediately before memantine initiation), and 48 (endpoint), and a battery of neuropsychological tests at weeks 0, 24, 28, 36, and 48. The primary outcome measure was the annualized rate of change (%) in total brain volume (TBV) between the two study periods. Data were analyzed using paired *t*-tests.

**Results:** There were no statistically significant differences in the rates of change in TBV, ventricular volume, or left hippocampal volume between the study periods; however, the memantine treatment period was associated with a significantly slower right hippocampal atrophy ( $-5.5\% \pm 12.0\%$  vs  $-10.8\% \pm 7.2\%$ ;  $P = .038$ ). Memantine treatment was also associated with superior performances on the Boston Naming Test ( $P = .034$ ) and the Trail Making Test, Part B ( $P = .001$ ), but also with a higher number of errors (i.e., repetitions and intrusions) on the California Verbal Learning Test. Memantine was found to be safe and well tolerated.

**Conclusions:** In this study, no difference in the rates of TBV change between the two periods was observed; however, memantine treatment was found to be associated with slowing of right hippocampal atrophy, and with improvement on one test of executive functioning as well as a test of confrontation naming ability. Trials using structural magnetic resonance imaging and a delayed-start design may be a feasible option for the assessment of treatments for AD.

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### Keywords:

Memantine; Alzheimer's disease; Magnetic resonance imaging; Neuropsychological testing; Open-label; Multi-center; Clinical trial; Single-arm delayed-start design; Hippocampal volume change; Total brain volume

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### 1. Introduction

Current therapies approved for the treatment of Alzheimer's disease (AD) include three cholinesterase inhibitors (ChEIs; donepezil, galantamine, and rivastigmine),

as well as memantine, an uncompetitive antagonist of *N*-methyl-D-aspartate receptors. All four drugs have been shown to provide symptomatic benefits in clinical trials [1,2], whereas evidence of neuroprotective effects (e.g., the ability to slow neurodegeneration) has been gathered primarily from preclinical models of the disease [3,4].

In preclinical studies, memantine has been shown to improve cognitive performance in animal models of AD [5–7], reduce amyloid burden [7,8], and prevent neurotoxicity induced by  $\beta$ -amyloid peptides [9,10] or otherwise mediated by different types of glutamatergic receptors [10–12]. On the basis of these data, it can be hypothesized that memantine treatment may slow the rate of progression of AD in humans, which would be a clinical indicator of a neuroprotective effect of the drug.

Because of the slow progression of the disease and large variance in the rate of structural and functional changes between subjects, trials aimed at demonstrating delayed disease progression typically require large sample sizes and a study duration of a year or more [13]. Such trials are very expensive and difficult to perform; therefore, there is considerable interest in designing shorter trials that can be performed with smaller sample sizes. Because of the correlation between neuronal loss and cognitive decline [14–16], serial structural magnetic resonance imaging (MRI), which has a low test-retest error rate [17], has been proposed as a surrogate measure for the progression of AD. Although brain atrophy as measured by MRI is not yet validated as an outcome measure in clinical trials for AD, quantitative evaluations of structural changes could conceivably be used as evidence of biological effects during phase II clinical drug development, and as evidence of disease modification or as support for clinical measurements in phase III regulatory trials [13].

Because serial MRI captures an objective structural change, it is reasonable to postulate that imaging studies circumvent many sources of error that are inherent in the instruments used for neuropsychological evaluation. Therefore, imaging trials could be particularly well suited to designs in which subjects are observed during two subsequent periods (e.g., before and after treatment), in which the rates of change between the two periods are compared (i.e., in studies in which participants act as their own controls). Such an approach can be termed a “single-arm, delayed-start” design, to differentiate it from the more common “randomized start” studies, which consist of placebo and treatment groups that begin therapy at different times [13,18]. In a single-arm, delayed-start study, the absence of the placebo group is partly compensated for by the availability of pretreatment information for each patient, which serves as an internal control and allows for paired comparisons (and therefore for a reduction in sample size for the same statistical power).

The goal of this exploratory, proof-of-concept study was twofold: first, to characterize the progression of AD using volumetric MRI and cognitive outcome measures (and thus to investigate the feasibility of a single-arm, delayed-start design with brain-volumetric endpoints), and second,

to examine the effect of memantine treatment on brain atrophy and cognitive decline in patients with AD who are concurrently receiving stable treatment with a ChEI.

## 2. Methods

Patients were screened at 10 sites in the United States, and randomization occurred at nine. One site contributed 20 patients to the safety population; the other sites contributed 2 to 9 patients each. The protocols and consent forms for this study were approved by the Institutional Review Boards of the enrolling sites, and written informed consent was provided by a caregiver and either the patient or a legally authorized representative.

### 2.1. Inclusion criteria

All patients were required to have a knowledgeable and reliable caregiver. Participants included male and female outpatients who were at least 50 years old, had a diagnosis of probable AD (NINCDS-ADRDA [National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association] criteria [19], supported by an MRI scan), and a Mini-Mental State Examination (MMSE) [20] score in the range of 15 to 23. At baseline (week 0), all participants had been receiving stable ChEI therapy for a minimum of 3 months, and they showed no abnormalities on physical examination, blood/urine analyses, or electrocardiogram. Because of recruitment difficulties, the initial MMSE range of 15 to 20 was expanded to 15 to 23.

### 2.2. Exclusion criteria

Patients were excluded for the following reasons: having dementia complicated by DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) axis I disorders, other organic disease, or predominant delusions; a Modified Hachinski Ischemic Score of  $>4$  at baseline; therapy with more than one ChEI; severe renal impairment; previous treatment with or hypersensitivity to memantine, amantadine, or rimantadine; claustrophobia or other conditions that would obstruct the successful completion or interpretation of an MRI scan; or a high likelihood of nursing home placement within 12 months from baseline.

### 2.3. Trial design

This study was a phase IV, multicenter, single-group, open-label trial, consisting of an observational lead-in period of ChEI treatment (weeks: 1–24) followed by a period of combined memantine–ChEI treatment (weeks: 25–48) (Fig. 1). The memantine dose was titrated in increments of 5 mg, once weekly for 4 consecutive weeks, ultimately reaching a target dosage of 20 mg/d at the beginning of week 28.

For all primary and secondary outcome measures, the rate of change during the memantine treatment phase was compared with the rate of change during the observational

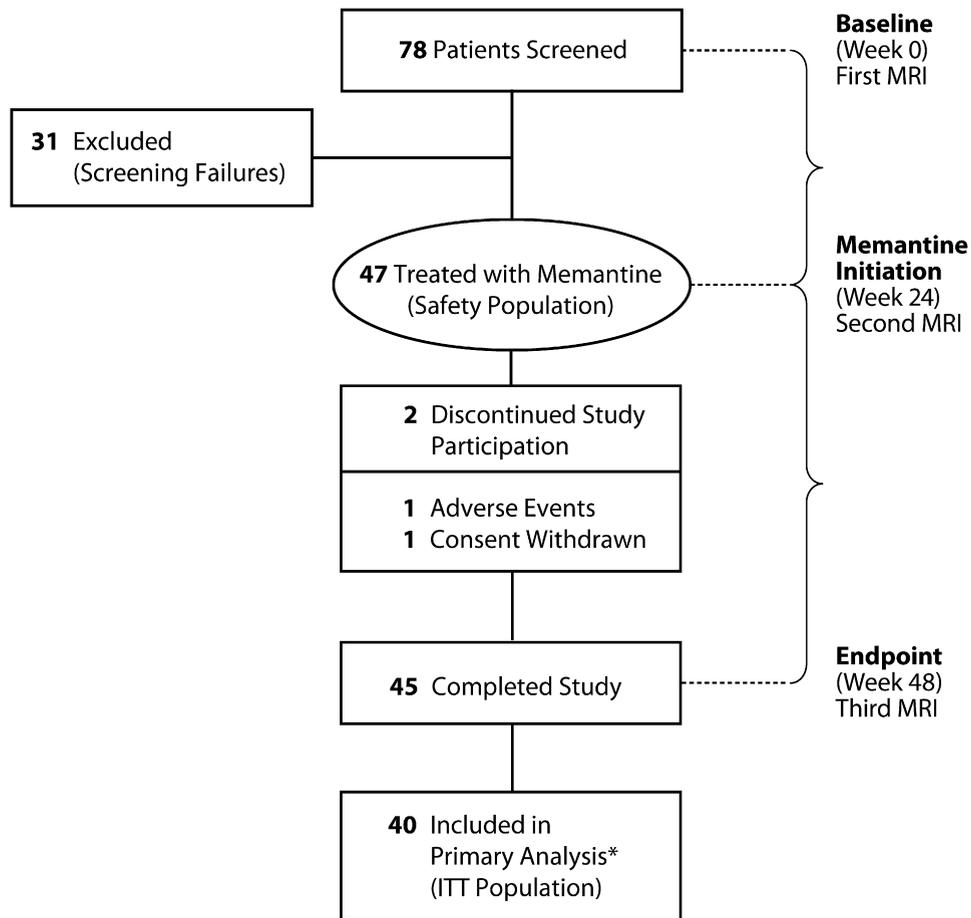


Fig. 1. Study flow. The safety population comprised all patients who took a minimum of one dose of memantine; the ITT population comprised all patients in the safety population who had obtained a well-validated and reliable value on a minimum of one MRI outcome measure. \*Five patients who completed the study did not have a well-validated and reliable value in at least one MRI outcome measure (i.e., total brain atrophy, ventricular volume enlargement, or hippocampal atrophy) in both study periods. ChEI indicates cholinesterase inhibitor; ITT, intent-to-treat; MRI, magnetic resonance imaging.

phase. The primary outcome was the annualized rate of change in total brain volume (TBV), whereas the secondary MRI outcomes were the annualized rates of change in total ventricular volume (VV), left hippocampal volume (LHV), and right hippocampal volume (RHV). All protocol-based volumetric efficacy measures were relative, expressed as percent volume change per year; absolute annualized volume changes ( $\text{cm}^3/\text{yr}$  for TBV and VV;  $\text{mm}^3/\text{yr}$  for LHV and RHV) were analyzed post hoc.

#### 2.4. MRI scans and atrophy assessment

Brain scans were obtained by means of 1.5 T scanners, manufactured by Siemens (New York City, NY), General Electric (Fairfield, CT), or Philips (Andover, MA), using the following sequences: Siemens, coronal 3D  $T_1$ -weighted magnetization-prepared rapid gradient echo; General Electric, spoiled gradient recalled echo; and Philips, turbo field echo. For each patient, all three scanning sessions were performed using the same scanner. TBV atrophy and VV enlargement measurements were performed using a

co-registration and subtraction technique developed by Synarc [21,22]; hippocampal volumes were traced using the semi-automated, atlas-based method of Hsu et al [23]. The TBV atrophy measurements followed a standard protocol and an automated procedure for the final calculation of the boundary shift integral. Scans performed at baseline (week 0) and at endpoint (week 48) were registered (aligned) with the scans performed at the end of the observational phase (week 24). These registrations ensured that all time points were within the same range as the week 24 scan when performing the boundary shift integral [21,22].

#### 2.5. Neuropsychological outcomes

Performance on a battery of neuropsychological tests, all considered to be secondary outcomes, was assessed at weeks 0, 24, 28, 36, and 48; for all tests, higher scores indicated better performance. The battery of tests comprised the MMSE [20], the short form of the California Verbal Learning Test (CVLT) [24], the Trail-Making Test (TMT) Parts A and B [25], the Symbol-Digit Modalities Test [26], the short form

of the Token Test [27], the 16-item version of the Reporter's Test [28], the Boston Naming Test (BNT) [29,30], the Controlled Oral Word Association Test [31], and the Category Fluency Test [31].

### 2.6. Safety and tolerability

Physical examination, blood and urine analysis, and electrocardiogram were performed at baseline. Vital signs and adverse events (AEs) were recorded at weeks 0, 4, 12, 24, 28, 36, and 48. AEs were also recorded throughout the study. An AE was considered to be treatment-emergent if it emerged or worsened in severity after the first dose of memantine (week 25).

### 2.7. Trial populations

The safety population consisted of all patients who took a minimum of one dose of memantine. The intent-to-treat (ITT) population consisted of all patients in the safety population who obtained a well-validated and reliable value on a minimum of one MRI outcome measure in each of the two study periods.

### 2.8. Sample size calculations

Because of the exploratory nature of this study, no sample size calculations were performed.

### 2.9. Statistical analysis

For each assessment tool, protocol-based analyses included descriptive statistics, comparison of change during the ChEI-only phase (weeks: 1–24) to change during the ChEI-memantine phase (weeks: 25–48), and the Spearman correlation between MRI-based and neuropsychological changes. The comparisons were based on the observed cases within the ITT population and were conducted using a paired *t*-test at a significance level of  $\alpha = 0.05$ . In addition, exploratory post hoc analyses of volumetric data were performed, consisting of (a) a comparison of absolute annualized brain volume changes ( $\text{cm}^3/\text{yr}$  for TBV and VV;  $\text{mm}^3/\text{yr}$  for LHV and RHV) between the two study periods and (b) an autoregressive first-order model of brain volume changes, performed to detect rates of change during memantine treatment that deviated from the rate expected, based on changes during the observational phase [32,33]. Post hoc treatment of neuropsychological data included analysis of an average time required to connect two points (s/point) on Parts A and B of the TMT (paired *t*-test). Finally, for statistically significant MRI and neuropsychological outcomes, effect sizes (Cohen's *d*) were calculated [34].

Because several volumetric and neuropsychological parameters were non-normally distributed, all outcome measures were also analyzed using the nonparametric Wilcoxon signed-rank test.

Because of the exploratory nature of this trial, no corrections for multiple comparisons were performed for either protocol-based or post hoc analyses.

## 3. Results

### 3.1. Study population

A total of 45 patients (95.7%) completed the trial (Fig. 1). Characteristics of the safety population ( $n = 47$ ) at baseline are summarized in Table 1; the characteristics of the ITT population ( $n = 40$ ) were not significantly different from those of the safety population.

### 3.2. Efficacy

#### 3.2.1. MRI-based outcome measures

The addition of memantine had no significant effect on TBV, VV, or LHV (Fig. 2, Table 2), either in the comparison of the rates of volume change between the two study periods or in the autoregressive analysis of expected versus actual volume changes. The annualized rate of atrophy (% change) of the right hippocampus was significantly lower during the memantine treatment period as compared with the observational period ( $-5.47\%$  vs  $-10.80\%$ ;  $P = .038$ , two-sided paired *t*-test; Fig. 2, Table 2), which was also observed in a post hoc analysis of absolute volume changes ( $-88.30 \pm 165.91 \text{ mm}^3$  vs  $-177.21 \pm 129.95 \text{ mm}^3$ ;  $P = .021$ ). In addition, a post hoc autoregressive analysis suggested that the right hippocampal atrophy during the memantine treatment period was significantly slower than the rate that would be expected based on the atrophy observed during the observational period (% change:  $P = .008$ ; absolute change:  $P = .003$ ; data not shown). Finally, an additional post hoc analysis suggested that, during the observational period, the RHV

Table 1  
Summary of patient characteristics at baseline\*

Age, years <sup>†</sup>	75.3 ± 7.6
Women, n (%)	30 (63.8)
Race, n (%)	
White	40 (85.1)
Black	6 (12.8)
Other	1 (2.1)
Weight, kg <sup>†</sup>	69.8 ± 15.8
Education, years <sup>†</sup>	12.0 ± 2.3
Handedness, n (%)	
Right	41 (87.2)
Left	6 (12.8)
MMSE score <sup>†</sup>	19.1 ± 2.2
MMSE range	15–23
Concomitant ChEI treatment, n (%)	
Donepezil	34 (72.3)
Galantamine	11 (23.4)
Rivastigmine	2 (4.3)

Abbreviations: ChEI, cholinesterase inhibitor; MMSE, Mini-Mental State Examination.

\* Safety population, N = 47.

<sup>†</sup> Mean ± standard deviation.

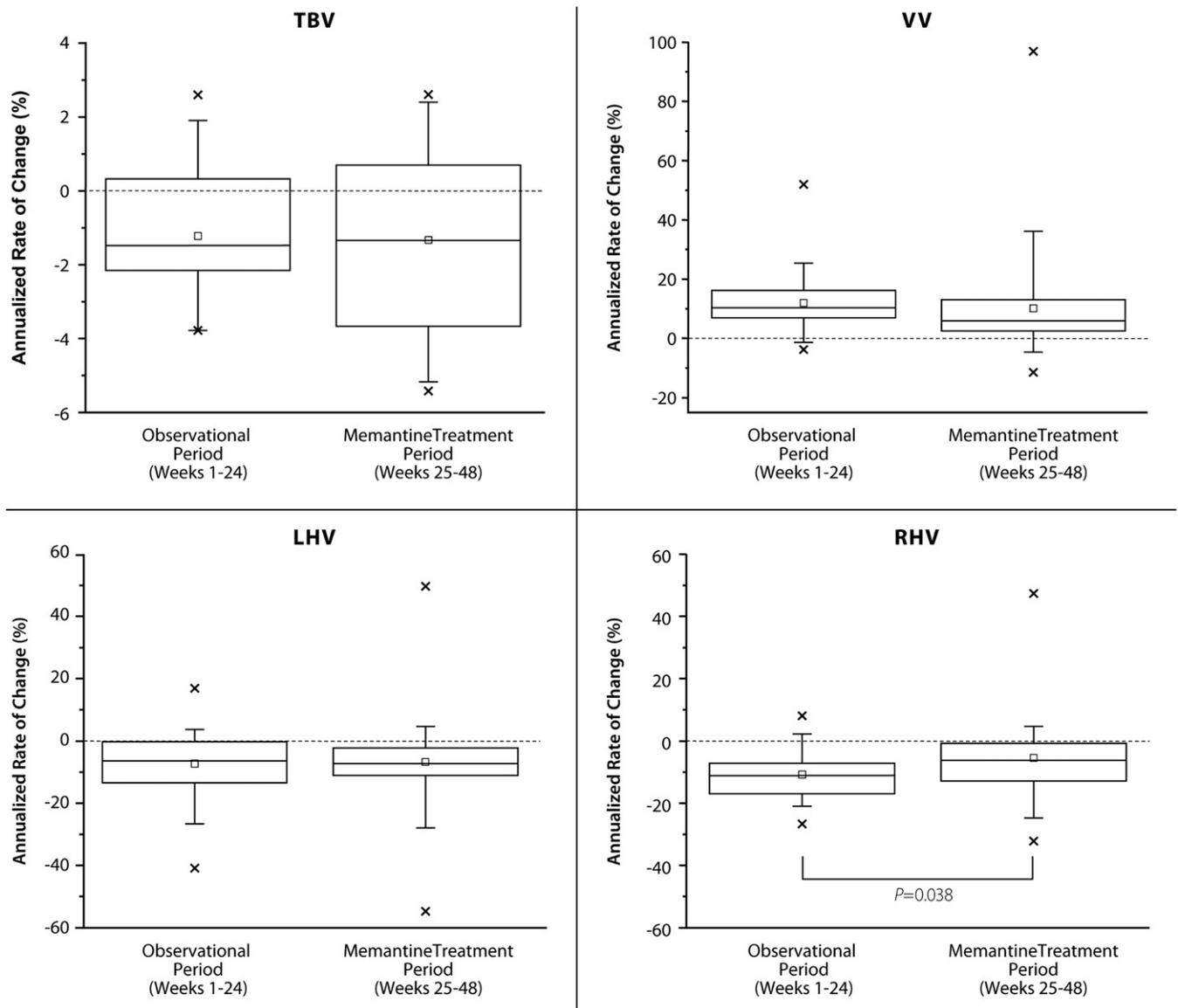


Fig. 2. Brain volume changes during observational and memantine-treatment periods. The addition of memantine significantly slowed the atrophy rate of the right hippocampus, but did not affect the rate of change in TBV, VV, or LHV. In the box charts, the “x” signs denote first percentile/minimum and 99th percentile/maximum values, respectively; lower and upper bar whiskers denote fifth and 95th percentiles, respectively; lower and upper box limits denote 25th and 75th percentile, respectively; middle line denotes 50th percentile (median). The small square ( $\square$ ) denotes the mean value. LHV indicates left hippocampal volume; RHV, right hippocampal volume; TBV, total brain volume; VV, total ventricular volume.  $P$  value was obtained using a two-sided paired  $t$ -test.

may have declined faster than the LHV (Table 2), because the mean ( $\pm$  SD) difference in atrophy rates ( $-3.17\% \pm 12.9\%$ ) approached statistical significance ( $P = .074$ ,  $t$ -test). However, during the memantine treatment period the difference in atrophy rates was smaller and not close to the significance level, with left hippocampal atrophy occurring nominally faster ( $1.58\% \pm 10.76\%$ ;  $P = .379$ ). The analysis of absolute volume changes yielded similar results (data not shown).

A post hoc power calculation of the RHV indicated that at a significance level of 0.05, the power to detect an effect size of 0.25 with 40 patients (and with 95% confidence) was about 34%; 120 patients would be required to detect

that effect size with that degree of confidence with a power of 80%.

### 3.2.2. Neuropsychological outcome measures

Analysis of the neuropsychological outcome measures (Table 3) revealed that the addition of memantine was associated with a significant improvement in both the number of points connected on the TMT, Part B ( $P = .001$ ), and the number of correct responses on the BNT ( $P = .034$ ). A post hoc analysis demonstrated that memantine treatment was also associated with a shorter average duration needed to connect points in Part B of the TMT; however, the difference between treatment periods was not statistically

Table 2  
MRI-based outcome measures: annualized volume change\*

Outcome measure	Annualized change (% volume/yr)			P value (effect size) <sup>†</sup>
	Observational period (weeks: 1–24)	Memantine treatment period (weeks: 25–48)	Mean difference (95% CI)	
Total brain volume	−1.10 ± 1.53 (n = 33) <sup>‡</sup>	−1.36 ± 2.40 (n = 33) <sup>‡</sup>	−0.25 (−1.41, 0.90)	0.657
Total ventricular volume	11.89 ± 9.80 (n = 38) <sup>‡</sup>	9.79 ± 17.21 (n = 38) <sup>‡</sup>	−2.27 (−6.65, 2.10)	0.299
Left hippocampal volume	−7.63 ± 10.47 (n = 40) <sup>‡</sup>	−7.05 ± 14.16 (n = 40) <sup>‡</sup>	0.58 (−6.60, 7.76)	0.871
Right hippocampal volume	−10.80 ± 7.23 (n = 40) <sup>‡</sup>	−5.47 ± 11.96 (n = 40) <sup>‡</sup>	5.33 (0.32, 10.34)	0.038 (0.34)

Abbreviations: CI, confidence interval.

P values were obtained from two-sided paired *t*-tests.

\* Values are expressed as percentage changes, mean ± standard deviation (observed cases). Positive values indicate volume increase, whereas negative values indicate volume decrease.

<sup>†</sup> Effect sizes were calculated for items demonstrating significant differences between treatment groups.

<sup>‡</sup> Number of patients in the intent-to-treat population who had reliable MRI scans of brain area in both phases of the study.

significant ( $P = .064$ ). Post hoc analyses also revealed that the memantine treatment period was associated with significantly increased errors on the CVLT (total repetitions, Trials 1–4 [ $P = .038$ ] and total intrusions, long-delay/short-delay/free recall [ $P = .015$ ]).

### 3.2.3. Controlling for non-normally distributed outcome values

Although the protocol-based method for analyzing the volumetric and neuropsychological outcomes was the *t*-test, several items demonstrated a non-normal distribution. Nonparametric reanalysis of all outcome measures (Tables 2 and 3) using the Wilcoxon signed-rank test yielded identical results, that is, all items that were significant using *t*-test analysis were also significant using the Wilcoxon signed-rank test, and no additional items showing significant differences between groups were observed (data not shown).

### 3.2.4. Correlations between changes observed using MRI and neuropsychological tests

To determine whether the neuropsychological changes observed during the memantine treatment phase were associated with altered rates of change on MRI measures, correlations between volumetric and cognitive changes were investigated (Spearman's coefficient). Improvement (i.e., increase in the number of points connected) on the TMT Part B correlated with slower left hippocampal atrophy ( $r = 0.383$ ;  $P = .040$ ) and a concomitant slowed increase in VV ( $r = -0.489$ ;  $P = .008$ ). In addition, a positive correlation was observed between worsening (i.e., decrease in number of correct responses) on the Category Fluency Test and accelerating atrophy of the entire brain ( $r = 0.386$ ;  $P = .029$ ).

### 3.3. Safety and tolerability

A total of 24 (51.1%) patients experienced a treatment-emergent AE while taking memantine (Table 4). Two

patients (4.3%) experienced one serious AE each (sprained ankle, sick sinus syndrome); the latter patient was the only participant to discontinue the trial because of an AE. No patients in the safety population died during the trial.

## 4. Discussion

### 4.1. Summary

This study demonstrated that it is feasible to enroll patients and successfully complete a delayed-start trial in AD, using the rate of TBV change (assessed using MRI) as the primary outcome measure. The study did not show a significant difference in total brain atrophy rates between the periods of ChEI-only and memantine-ChEI treatment, but it showed a significantly slower right hippocampal atrophy and a significantly better performance on the BNT and Part B of the TMT during the memantine-ChEI phase compared with the ChEI-only period. Taking into consideration all the analyses, these data support the assumption that memantine treatment may alter the progression of AD.

### 4.2. Trial design

This trial was a hypothesis-generating, proof-of-concept study, intended to primarily show the feasibility of a design in which patients serve as their own controls. Our approach—in which structural and functional changes over a 6-month lead-in period were compared with changes over the subsequent 6-month treatment period—was adopted because we believed it would offer several advantages over the design of a typical randomized, placebo-controlled trial in AD. Single-arm, delayed-start trials are simpler to recruit for and conduct due to the absence of the randomization step (and with it, a requirement for high coordination between the research centers), and only the patients need to be blinded to treatment. Additionally, fewer

Table 3  
Summary of neuropsychological outcomes\*

Outcome measure	Score immediately before memantine initiation		Mean score change				
	n	Week 24 <sup>†</sup>	n	Weeks 1–24 (ChEI only) <sup>†</sup>	Weeks 25–48 (ChEI + Mem) <sup>†</sup>	Difference <sup>‡</sup>	P-value (effect size) <sup>§</sup>
MMSE	40	19.1 ± 3.7	40	−0.15 ± 2.40	0.48 ± 3.32	0.63 (−0.78, 2.03)	.374
CVLT							
Trials 1–4	40	14.7 ± 5.7	40	−1.08 ± 4.62	0.30 ± 4.28	1.38 (−1.13, 3.88)	.274
Short delay recall	40	2.2 ± 2.4	40	−0.13 ± 1.70	−0.10 ± 1.68	0.03 (−0.93, 0.98)	.958
Long delay recall	40	1.0 ± 1.9	40	0.15 ± 1.25	0.15 ± 1.27	0.00 (−0.70, 0.70)	1.000
Yes/No recognition	40	18.9 ± 4.2	40	−0.30 ± 3.76	0.43 ± 4.21	0.73 (−1.49, 2.94)	.511
Repetitions (total number, Trials 1–4)*	40	0.7 ± 1.2	40	−0.18 ± 1.74	0.75 ± 2.05	0.93 (0.05, 1.80)	.038 (0.34) <sup>¶</sup>
Intrusions (long-delay/short-delay/free recall)*	40	0.9 ± 1.26	40	−0.35 ± 1.78	0.78 ± 1.66	1.13 (0.23, 2.02)	.015 (0.41) <sup>¶</sup>
Trail-Making Test							
Part A (number of points connected)	40	24.6 ± 2.4	39	−0.15 ± 2.67	0.03 ± 3.00	0.18 (−1.54, 1.90)	.834
Part B (number of points connected)	28	10.6 ± 7.3	25	−3.80 ± 4.95	1.88 ± 4.72	5.68 (2.63, 8.73)	.001 (0.59) <sup>¶</sup>
Part A (s/point)	39	4.8 ± 3.9	39	0.3 ± 3.8	0.1 ± 3.8	−0.14 (−2.45, 2.17)	.904
Part B (s/point)	25	56.2 ± 72.6	25	26.9 ± 70.5	−27.2 ± 72.2	−54.1 (−111.7, 3.5)	.064
SDMT							
Number of completed boxes	38	19.8 ± 9.6	38	−0.97 ± 6.40	−0.79 ± 6.99	0.18 (−3.57, 3.94)	.921
Token Test							
Number of correct answers	40	12.4 ± 3.1	40	−1.20 ± 3.09	−0.45 ± 3.40	0.750 (−1.11, 2.61)	.420
Reporter's Test							
Number of correct responses	40	12.9 ± 2.8	40	−0.35 ± 3.19	−0.60 ± 3.10	−0.25 (−1.89, 1.39)	.759
Boston Naming Test							
Number of correct responses	40	22.7 ± 5.8	40	−0.88 ± 2.75	0.73 ± 3.05	1.60 (0.13, 3.07)	.034 (0.35) <sup>¶</sup>
COWAT							
Total	39	19.6 ± 7.3	39	0.26 ± 6.43	2.33 ± 5.26	2.08 (−1.21, 5.36)	.208
Letter F	39	6.9 ± 3.8	39	−0.15 ± 3.05	1.18 ± 2.89	1.33 (−0.33, 3.00)	.113
Letter A	39	5.1 ± 3.7	39	0.28 ± 2.82	0.49 ± 2.09	0.21 (−1.13, 1.54)	.758
Letter S	39	7.6 ± 5.0	39	0.13 ± 3.48	0.67 ± 3.03	0.54 (−1.26, 2.34)	.548
Category Fluency Test	39	8.4 ± 4.2	39	0.33 ± 3.53	−0.28 ± 2.68	−0.62 (−2.28, 1.05)	.460

Abbreviations: ChEI, cholinesterase inhibitor; CI, confidence interval; COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; Mem, memantine; SDMT, Symbol-Digit Modalities Test; MMSE, Mini-Mental State Examination.

\* Observed cases; higher scores indicate higher levels of functioning for all tests except CVLT repetitions and intrusions. For clarity, the mean values for errors and/or incorrect responses that were not significantly different between groups were excluded (Trail-Making Test, Boston Naming Test, COWAT, Category Fluency Test, SDMT, CVLT false positives).

<sup>†</sup> Mean ± standard deviation.

<sup>‡</sup> Mean (95% CI).

<sup>§</sup> Effect sizes were calculated for items demonstrating significant differences between treatment groups.

<sup>¶</sup> P-values indicating significance at the .05 level (two-sided paired *t*-tests).

participants are needed because of a generally smaller variability of measurements; a study with MRI-based outcomes requires 2–10 times fewer participants to achieve the same statistical power as a study with outcomes based on neuropsychological tests [35–37].

#### 4.3. Results of MRI

The MRI data from this study indicate that 6 months of treatment with memantine (20 mg/d) significantly reduced atrophy of the right hippocampus but had no discernible effect on the other brain volumetric measures. This finding was further supported by post hoc autoregressive analyses, showing that the atrophy rate of the RHV during the memantine treat-

ment period was significantly slower than what would be expected based on the rate of atrophy during the preceding 24 weeks. Sensitivity analyses, in which outliers were removed, also yielded significant results for the RHV (data not shown).

The mean annualized hippocampal atrophy, obtained over the first (observational) 6 months of our study (an average atrophy rate of 9.22% for the combined hippocampal volume; Table 2) is higher than that obtained in some earlier studies. For example, a mean atrophy rate of 3.3% was obtained by both Jack et al [35] and the Alzheimer's Disease Neuroimaging Initiative [37], and a recent meta-analysis of longitudinal hippocampal volume changes showed a mean annualized hippocampal atrophy rate of 4.66% (95% CI: 3.92–5.40) in patients with AD [38]. However,

Table 4  
Treatment-emergent adverse events (TEAEs)\*

Adverse event	Memantine/ChEI (n = 47)
Any TEAE	24 (51.1)
Hypercholesterolemia	3 (6.4)
Arthralgia	2 (4.3)
Decreased appetite	2 (4.3)
Depression	2 (4.3)
Diarrhea	2 (4.3)
Fatigue	2 (4.3)
Headache	2 (4.3)
Nausea	2 (4.3)
Somnolence	2 (4.3)
Urinary tract infection	2 (4.3)
Vomiting	2 (4.3)

\* Data: n (%) include all adverse events experienced by at least two (4.3%) patients (safety population).

according to a recent meta-analysis of controlled MRI studies in patients with either mild cognitive impairment or AD [39], most previous studies recruited patients who were less severely affected than those recruited in our trial, and hippocampal atrophy rates in AD tend to increase with increasing disease severity (e.g., volume loss effect sizes of 1.3 and 1.7 correspond to MMSE values of  $>22$  and  $\leq 22$ , respectively [39]). Therefore, the atrophy rates observed in our study can reasonably be expected to exceed those observed in studies involving patients who were less affected by the disease. In addition, methodologies for measuring brain volume may differ between studies, thereby making direct comparisons problematic.

As mentioned previously, our study found a significant effect of memantine on the atrophy rate of the right, but not the left, hippocampus. Typically, studies report aggregated rather than lateralized hippocampal data; of 28 studies included in the meta-analysis by Shi et al [39], only 11 (39.2%) reported separate data for each side. Across all such studies, greater atrophy was consistently found in the left hippocampus [39]. In contrast, during the first 6 months of our study (i.e., before memantine treatment; Table 2), atrophy occurred nominally faster in the right hippocampus than in the left, with the difference between the two rates approaching statistical significance (right,  $10.80\% \pm 7.23\%$ ; left,  $7.63\% \pm 10.47\%$ ;  $P = .074$ ). During the memantine treatment period, the difference between left and right hippocampal atrophy rates was smaller, with the left side undergoing atrophy nominally faster (right,  $5.47\% \pm 11.96\%$ ; left,  $7.05\% \pm 14.16\%$ ;  $P = .379$ ).

The reasons for this inverse asymmetry of right and left hippocampal atrophy during the observational period as compared with what has been observed in previous studies [39] are unclear, as are the reasons for the differential effect of memantine during the treatment phase; however, factors such as the stage of disease or type of pharmacological intervention may be involved. There is also a possibility that memantine exerts a stronger effect on the right hippocampus than on the left. Interestingly, a double-blind, placebo-con-

trolled trial of donepezil in patients with AD also showed significant effects on the RHV but not the LHV (see below) [40]. To resolve this issue, more studies examining the relationship between the asymmetry of hippocampal atrophy, the severity of AD, and the treatment effects of antidementia medications are needed.

#### 4.4. Results of neuropsychological tests

As compared with the observational period, the period of memantine treatment was associated with an improved performance on the BNT and Part B of the TMT, but also with a higher number of errors (i.e., repetitions and intrusions) on the CVLT (Table 3). Neuropsychological data from other clinical trials of memantine involving patients with mild to moderate AD have similarly shown inconsistent results. For example, post hoc [41] and protocol-based analyses from the MEM-MD-10 trial (mean MMSE score: 17.3) [42] demonstrated a significant benefit of memantine on the total score and domains of language and memory of the Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-cog). Conversely, trial MEM-MD-12 (mean MMSE score: 16.9), which, similar to our study, included patients receiving concurrent ChEI treatment, showed no overall advantage of memantine on this measure [43]. It is difficult to correlate score changes from a global assessment of cognition, such as the ADAS-cog, with changes on more in-depth assessments such as those in the battery of neuropsychological tests used in this trial. Also, it is possible that the tests of specific cognitive domains are not sensitive enough to assess this level of impairment, especially given the small sample size used in this study.

#### 4.5. Correlation between the MRI-based and neuropsychological test results

Although this study demonstrated a few statistically significant correlations between brain atrophy rates and neuropsychological test performance during the memantine treatment phase (see Results section), the majority of the correlations were not significant, and the clinical relevance of those that were significant is unclear. It is possible that memantine treatment exerts differential effects on different brain regions, and that our choice of neuropsychological tests was not adequate to simultaneously capture both structural and functional changes. For example, spatial memory, which is presumably mediated by the right hippocampus, was not specifically tested in this trial. In addition, because MRI has a greater power than neuropsychological tests to detect changes [35], it is possible that what appears to be a discrepancy between volumetric results and neuropsychological test results are actually statistical in nature, and that a higher correlation between results might be detected in a larger sample of patients. It should be noted that a previously conducted trial with a somewhat larger sample size ( $N = 52$ ) demonstrated a significant correlation between

cognitive performance and the atrophy of the total brain, but not of the hippocampus [44].

#### 4.6. AD treatment and brain atrophy: other studies

To date, only a few randomized, double-blind, placebo-controlled trials in AD have used structural MRI as an outcome measure. Two of those trials involved memantine (20 mg/d), and neither of them demonstrated significant differences between treatment groups in MRI measures after 52 weeks [45,46]. However, in the smaller trial ( $N = 36$ ), the overall hippocampal atrophy rate was nominally slower in the memantine group than in the placebo group [45], whereas in the larger trial ( $n = 278$ ), patients in the placebo group demonstrated a slower than expected annualized rate of atrophy (1.6%), which was similar to the rate observed in the memantine group (1.5%) [46]. Two imaging trials have also been performed using donepezil. In one trial [40], patients treated with 5 to 10 mg/d donepezil for 24 weeks ( $n = 34$ ) demonstrated a mean  $\pm$  SD annualized increase in RHV ( $1.4\% \pm 16.0\%$ ), whereas those in the placebo group ( $n = 33$ ) showed a volume decrease ( $-7.6\% \pm 12.0\%$ ;  $P < .02$ ). In this study, donepezil-treated patients also had a slowed rate of decline in LHV, although the effect did not reach statistical significance ( $-1.7\% \pm 15.0\%$  vs  $-7.8\% \pm 10.5\%$ ;  $P = .09$ ) [40]. In the other donepezil study, a prospective cohort of patients treated with donepezil (5 mg/d) for 52 weeks ( $n = 49$ ) was compared with matched historical controls ( $n = 93$ ) [47]. The mean annualized rate of hippocampal atrophy was significantly slower in the donepezil cohort than in the historical control group ( $-3.8\% \pm 2.8\%$  vs  $-5.0\% \pm 2.5\%$ ;  $P = .008$ ). Structural imaging has also been used in randomized, placebo-controlled trials of investigational medications for AD, including an 18-month trial of bapineuzumab, in which no significant differences in TBV or VV changes were seen between the groups [48]; a 78-week trial of tramiprosate that showed no between-group differences in the primary analysis, but showed a treatment effect on hippocampal volume in favor of tramiprosate in an adjusted model ( $P = .011$ ) [49]; and a 12-month trial of AN1792 that unexpectedly showed a significant TBV decrease, significant VV increase, and nonsignificant hippocampal volume loss in patients who responded to the antibody, as compared with nonresponders [50]. All these studies, involving both approved and investigational therapies, point to the complexity of interpreting brain volume changes in patients with AD.

#### 4.7. Study limitations

Several limitations should be taken into account when interpreting the results of our trial. First, although our sample size may have been sufficient for the detection of volumetric outcomes [35–37], it might have been too small for the detection of changes on the neuropsychological tests. In addition, the duration of treatment in the trial may have

been insufficient to detect effects of memantine on both types of outcome measures. Both measures may also have inherent limitations, as the MRI-based outcomes have not yet been validated in dementia trials, and the neuropsychological test results may have been influenced by practice effects; however, previous studies of cognition in patients with AD have shown little or no practice effects in patients at all levels of impairment [51]. The absence of a parallel placebo arm in our study makes it impossible to detect treatment effects under circumstances of accelerating atrophy, as in the Alzheimer's Disease Neuroimaging Initiative study [37], in which case a constant atrophy rate would actually indicate an improvement. Finally, outcome measures that are presumably sensitive to right hippocampal activity (eg, tests involving spatial memory, such as the Visual Reproduction subtest from the Wechsler Memory Scale [52]), were not included in this study; future studies involving lateralized hippocampal changes should include one or more such measures.

## 5. Conclusions

The results of this proof-of-concept study support the feasibility of single-arm, delayed-start trials with MRI-based endpoints for the evaluation of disease-modifying treatments. Our results provide indications that memantine may contribute to some alteration of the disease progression in patients with AD; however, the small sample size, lack of a placebo-treated comparison group, and the possibility that the trial duration was too short to detect functional changes preclude any definitive conclusions. Because of the results of this proof-of-concept study, we recommend that additional, expanded versions of this trial type be considered.

## Acknowledgments

The authors wish to acknowledge E. Malca Resnick, Ph.D., formerly with Forest Research Institute (FRI), who participated in study conceptualization/design and initial trial conduct. Also from FRI, medical monitors Heikki Hakkarainen, M.D., and Allison Mann, M.D., provided medical oversight, and Michael Tocco, Ph.D., coordinated the publication process and provided editorial assistance. Vojislav Pejović, Ph.D., and Michael L. Miller, Ph.D., from Prescott Medical Communications Group, provided medical writing, editorial support, and manuscript coordination. Forest Laboratories, Inc. sponsored this trial and provided financial, material, and statistical support.

The following were members of the Memantine MD-15 Study Group: S. Flitman, Xenoscience, Inc., Phoenix, AZ; M.L. Gordon, North Shore-Long Island Jewish Health System, Manhasset, NY; S. Kapoor, Bayview Research Group, Los Angeles, CA; C. Kohlenberg, Independent Psychiatric Consultants, SC, Waukesha, WI; M. Levy\*, Behavioral Medical Research, Staten Island, NY; E. Pfeiffer, USF

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