A 24-Week Open-Label Extension Study of Memantine in Moderate to Severe Alzheimer Disease

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Background: This study is an extension of a 28-week, randomized, double-blind, placebo-controlled study of memantine in 252 patients with moderate to severe Alzheimer disease.

Objective: To evaluate long-term memantine treatment in moderate to severe Alzheimer disease.

Design, Setting, and Patients: Open-label, 24-week extension trial. Raters remained blind to the patients’ initial study treatment. Patients (n=175) were enrolled from the previous double-blind study in an outpatient setting.

Intervention: Twenty mg of memantine was given daily.

Main Outcome Measures: Efficacy assessments from the double-blind study were continued and safety parameters were monitored.

Results: Patients who switched to memantine treatment from their previous placebo therapy experienced a significant benefit in all main efficacy assessments (functional, global, and cognitive) relative to their mean rate of decline with placebo treatment during the double-blind period (P<.05). The completion rate for the extension phase of the study was high (78%) and the favorable adverse event profile for memantine therapy was similar to that seen in the double-blind study.

Conclusion: These results extend previous findings that demonstrated the efficacy and safety of memantine in the treatment of patients with moderate to severe Alzheimer disease.

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ALZHEIMER DISEASE (AD) IS a progressive neurodegenerative disorder that afflicts millions of people worldwide. Cholinesterase inhibitors are regarded as the standard of care for the symptomatic treatment of mild to moderate AD, but there is only 1 published study on cholinesterase inhibitors that specifically included patients with more advanced AD.

Various mechanisms may contribute to neurodegeneration in AD, including glutamate-mediated excitotoxicity. While normal glutamatergic neurotransmission is required for learning and memory processes, excessive glutamatergic activity may cause neuronal dysfunction and eventually degeneration. This excitotoxic effect appears to be mediated, in part, by the N-methyl-D-aspartate receptor antagonist with rapid-gating kinetics. In 2003, memantine was approved in the United States for the treatment of moderate to severe AD and memantine is also available in the European Union and Australia.

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We previously reported results of a 28-week, double-blind, placebo-controlled trial in the United States on outpatients with moderate to severe AD. Memantine treatment resulted in significant benefits compared with placebo in global, functional, and cognitive assessments. In addition, memantine treatment of patients with moderate to severe AD receiving stable doses of donepezil was found to be safe and efficacious. Memantine treatment has also shown cognitive benefit in clinical studies on mild to moderate vascular dementia and efficacy in a study on patients who were severely demented and institutionalized.

This study evaluated the effects of memantine treatment over a longer time pe-
Efficacy measures further included a specific cognitive assessment, the Severe Impairment Battery (SIB),16,17 as well as Mini-Mental State Examination,10 Functional Assessment Staging,12 Global Deterioration Scale,11 and Neuropsychiatric Inventory.18 Efficacy assessments were conducted at initiation of the open-label extension (corresponding to the final week 28 visit of the lead-in, double-blind study) and at weeks 40 and 32.

SAFETY EVALUATION

Assessment of safety included reports of adverse events, laboratory examinations (chemistry, hematology, and urinalysis), and vital sign measurements. The World Health Organization Adverse Reaction Terminology dictionary19 was used to code adverse events.

DATA ANALYSIS

All available data for patients who entered the open-label phase were used for an observed cases analysis from week 0 to week 32, without replacement of missing data. In the protocol of the open-treatment extension period, a descriptive data analysis was planned that did not include statistical testing.

A descriptive statistical analysis was performed for the primary efficacy assessments ADCS-ADL and CIBIC-Plus, as well as for the specific cognitive instrument (the SIB), by using log sample z tests. The mean rates of change during the double-blind period (week 0-28) were compared with the mean rates of change in the open label period for the 3 assessments. All P values reported are 2-sided.

Safety analyses were performed on the safety population, which included all patients who received at least 1 dose of study medication during the open-label period.

STUDY DESIGN

All patients, including participants who had received memantine during the double-blind phase, switched directly from double-blind treatment to an initial dose of 5 mg of memantine daily and were titrated upward (weekly increases of 5 mg/d) to the maintenance dose of 20 mg/d (10 mg twice daily). This procedure maintained the blinding for the treatment assignment during the double-blind phase. Memantine tablets were administered orally for 24 weeks in the open-label phase. Patients were taken off the study medication if, in the opinion of the treating physician, continued treatment posed a potential medical risk or if patients or their caregivers withdrew consent. The study procedures were in accord with the principles in the Helsinki Declaration of 1975 and its amendments. The relevant institutional review boards approved the study protocol.

**METHODS**

**PATIENTS**

Thirty centers in the United States enrolled patients to receive open memantine treatment for 24 weeks on completion of a 28-week, double-blind phase.6 At the start of the double-blind phase, patients had to meet criteria for dementia as specified by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and for probable AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association, including a recent computerized tomographic scan or a magnetic resonance imaging scan compatible with an AD diagnosis. Furthermore, entry criteria included (1) age of 50 years or older, (2) Mini-Mental State Examination scores of 3 to 14,10 (3) Global Deterioration Scale stages 5 or 6,11 and (4) Functional Assessment Staging score of 6a or greater.12 Participants were also required to have adequate vision and hearing for neuropsychological testing and a reliable caregiver or informant.

**STUDY DESIGN**

Of 181 patients who completed the 28-week, double-blind phase, 80 patients treated with placebo and 95 patients treated with memantine opted to enter the open-label extension. Patient flow through the study is shown in Figure 1. Patients who received placebo during the double-blind phase are hereafter referred to as the PLA-MEM group, and patients who were treated with memantine in the double-blind phase are hereafter referred to as the MEM-MEM group.

Figure 1. Progression of subjects from completion of the double-blind phase to completion of the open-label extension. Asterisk indicates that some patients discontinued for multiple reasons. AE indicates adverse event.
At the baseline visit of the double-blind phase (week 0), demographic characteristics were similar for the PLA-MEM and the MEM-MEM treatment groups (Table 1). A total of 11 patients (6 PLA-MEM and 5 MEM-MEM) received, at any time during the extension period, treatment using a cholinesterase inhibitor. Furthermore, 28 patients switched to treatment using a cholinesterase inhibitor at the end of the extension study.

### EFFICACY

#### ADCS-ADL Scores

Mean changes in the ADCS-ADL score from the start of the double-blind period to the end of the open-label phase are presented in Figure 2 and Table 2.

For patients in the PLA-MEM group, switching to memantine treatment resulted in a significantly slower rate of decline during the open-label phase on the ADCS-ADL compared with the mean rate of decline during the double-blind period (weeks 0-28) ($P = .021$). The rate of decline for the MEM-MEM group, however, was faster during the open-label period than the double-blind period ($P = .035$).

#### CIBIC-Plus Ratings

The CIBIC-Plus mean ratings of change from initiation of the double-blind phase to week 52 are presented in Figure 3 and Table 2. Overall, at week 52, an identical percentage of patients (51%) treated with PLA-MEM and patients treated with MEM-MEM had a mean rating of change score of 4 or better (indicating no change or improvement from week 0).

Switching to memantine treatment significantly decreased the rate of decline on the CIBIC-Plus compared with the mean rate of placebo decline during the double-blind period ($P < .001$). The rate of decline for the MEM-MEM group during the open-label phase was also significantly slower during the open-label period than during the entire double-blind period ($P < .001$).

#### SIB Scores

The mean changes in SIB scores from weeks 0 to 52 are presented in Figure 4 and Table 2.

The rate of decline from week 28 to week 52 on the SIB for patients in the PLA-MEM group was significantly less than the projected rate of decline from the double-blind period ($P = .049$). The rate of decline for the MEM-MEM group during the open-label phase did not differ significantly from the mean rate during the double-blind memantine-treatment period ($P = .086$).

### SAFETY

The most commonly reported adverse events (AEs) during the extension study are listed in Table 3. Overall, the types of AEs reported were consistent with observations from the double-blind phase.

The majority of AEs for both treatment groups were considered either mild or moderate in severity (88% and 87% of patients, respectively). Adverse events that fulfilled criteria as serious events were reported by 27 (15%) of the 175 patients in the open-label extension (only 4 of these patients had AEs judged to be possibly related to administration of study medication). This serious event frequency was similar to that noted in the double-blind study.

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Table 1. Demographic and Clinical Characteristics for Enrolled Open-Label Population at Baseline

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>PLA-MEM (n = 80)</th>
<th>MEM-MEM (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>6 (8)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>65-74</td>
<td>29 (36)</td>
<td>31 (33)</td>
</tr>
<tr>
<td>75-84</td>
<td>38 (48)</td>
<td>46 (48)</td>
</tr>
<tr>
<td>≥85</td>
<td>7 (9)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>75.6 ± 7.15</td>
<td>75.5 ± 8.24</td>
</tr>
<tr>
<td>Male sex</td>
<td>51 (64)</td>
<td>68 (72)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>4 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>72 (90)</td>
<td>83 (87)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (5)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Modified Hachinski Ischemic Scale score (week 28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.58 ± 0.78</td>
<td>0.48 ± 0.74</td>
</tr>
<tr>
<td>Range</td>
<td>0-4</td>
<td>0-3</td>
</tr>
<tr>
<td>Week 0 MMSE score, mean ± SD</td>
<td>8.05 ± 3.65</td>
<td>7.78 ± 3.75</td>
</tr>
<tr>
<td>Week 28 MMSE score, mean ± SD</td>
<td>7.05 ± 4.67 (n = 79)</td>
<td>7.24 ± 4.85 (n = 95)</td>
</tr>
</tbody>
</table>

Abbreviations: MMSE, Mini-Mental State Examination; PLA-MEM, patients who received placebo; MEM-MEM, patients who were treated with memantine.
There were no clinically meaningful differences in changes from the study baseline (week 0) in vital signs or laboratory parameters for either of the 2 treatment groups.

**COMMENT**

This open-treatment extension provides further efficacy and safety data that add to the findings of the double-blind phase of the study. A strength of this study is the continuation of the same efficacy measures used in the double-blind phase. We were therefore able to continue to examine the clinically relevant domains that show deterioration with AD progression. During the open memantine treatment phase (weeks 28–52), observations by both clinicians and caregivers (ADCS-ADL, CIBIC-Plus) as well as a measurement of cognition (SIB) indicated that treatment initiation with memantine was effective. The benefits of memantine seen in the double-blind phase were again observed when patients treated with placebo were switched to memantine treatment in the open extension. For the patients who were randomized to memantine treatment during the double-blind phase, these clinically relevant benefits also appeared to be maintained in sum; compared with the double-blind period, decline was faster for the ADCS-ADL and slower for the CIBIC-Plus, with no significant change on the SIB. Patients who were untreated (baseline Mini-Mental State Examination scores of 0–15 in the ADCS instrument study) experienced greater mean annual declines on the SIB than both the PLA-MEM and MEM-MEM groups in this study.
Table 3. Most Frequently Reported Treatment-Emergent Adverse Events During the Open-Label Extension Phase

<table>
<thead>
<tr>
<th>Adverse Event*</th>
<th>PLA-MEM (n = 80)</th>
<th>MEM-MEM (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>15 (19)</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (6)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Aggressive reaction</td>
<td>1 (1)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Hallucination</td>
<td>0 (0)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (6)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Inflicted injury</td>
<td>5 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10 (13)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>3 (4)</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 2.

*Adverse events occurring with a frequency greater than or equal to 5% in either treatment group.

Whether open treatment extension studies show disease-modifying properties (in contrast to symptomatic effects) is often linked to the question of whether patients switching from placebo to active treatment catch up with those who continued on active treatment. Our data indicate that patients treated with PLA-MEM did not completely catch up in the ADCS-ADL or the SIB, but did nearly catch up in the CIBIC-Plus ratings. Definitive conclusions regarding this differentiation require prospective, randomized, double-blind trials.

Memantine treatment was safe and well tolerated during the course of the study and the safety profile in the open-label phase was similar in both the PLA-MEM and the MEM-MEM patient groups. Adverse events noted with the administration of memantine were consistent with previous observations, including an earlier study on patients with severe AD and vascular dementia and studies in vascular dementia. The high patient retention rate (78% overall) during this open-label study supported the good tolerability of memantine. It might be useful for future investigations to examine the efficacy of memantine in earlier stages of AD and other forms of dementia.

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