

Erratum

Memantine Treatment in Patients with Mild to Moderate Alzheimer's Disease: Results of a Randomised, Double-Blind, Placebo-Controlled 6-Month Study

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Abstract. Memantine is a moderate affinity, uncompetitive NMDA receptor antagonist currently approved for the treatment of moderate to severe Alzheimer's disease (AD). A 24-week, double-blind, placebo-controlled, study (Study 99679) conducted in Europe evaluated the efficacy and tolerability of 20 mg/day memantine in patients with mild to moderate AD. Patients were randomised to either memantine or placebo in a 2:1 ratio. Efficacy was primarily assessed as change from baseline in ADAS-cog and CIBIC-plus score. Of 470 patients randomised and treated (memantine, $n = 318$; placebo, $n = 152$), 85% and 91% completed the study. Memantine-treated patients showed statistically significant improvement relative to placebo at weeks 12 and 18, and numerical superiority at week 24 on both efficacy scales. The lack of significance at week 24 was attributed to an unexpectedly high placebo response. Memantine was well tolerated with an adverse event profile similar to placebo. The data presented support the efficacy of memantine in mild to moderate AD.

Keywords: Memantine, Alzheimer's disease, mild to moderate, NMDA receptor

INTRODUCTION

Alzheimer's disease (AD) is a chronic illness with progressive neurodegeneration and dementia. It has been estimated that AD affects approximately 1% of the population aged between 65 and 69 years and up to 20% of those aged above 85 years [8,11,14]. Clinically, AD is characterised by progressive decline in cognitive as well as functional capacities and a corresponding increase in the burden on caregivers. Pathological features of AD include extracellular amyloid

plaques containing the amyloid- β protein and intraneuronal neurofibrillary tangles consisting of hyperphosphorylated tau protein, leading to loss of synapses as well as neuronal cell death. In addition to these structural changes, there are anatomic as well as functional changes in a number of neurotransmitter systems associated with cognition, including the glutamatergic and cholinergic pathways [3,32].

At present, the pharmacotherapy of mild to moderate AD is dominated by acetylcholinesterase inhibitors (AChEIs), which enhance central cholinergic neurotransmission. Although AChEIs have modest but measurable benefits, a number of patients have tolerability problems or contra-indications to members of this class of drugs. Given the multiple deficits in neurotransmission observed in AD, no pharmacological agent tar-

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getting a single biochemical pathway can reasonably pretend to provide a major symptomatic improvement. Thus, there is a strong need for additional pharmacological treatment options in the management of the early stages of AD. One potentially useful agent in this context is memantine. Memantine is the first drug in a new class of dementia therapies that act on the glutamatergic system via antagonism of the N-methyl-D-aspartate (NMDA) receptor. Memantine has been approved for the treatment of moderate to severe AD in both Europe and the US.

Memantine is a moderate affinity, uncompetitive NMDA receptor antagonist with strong voltage-dependency and rapid blocking/unblocking kinetics [18]. These pharmacological features allow memantine to block the pathological sustained activation of the receptor hypothesised to occur in AD, while rapidly leaving the NMDA receptor channel during normal physiological activation, for example, during learning and memory formation [12,18,27,38]. Placebo-controlled studies have demonstrated efficacy and safety of memantine monotherapy in moderate to severe AD outpatients as well as in severely demented nursing home patients [25,26,37]. In clinical studies in patients receiving ongoing treatment with an AChEI, memantine/AChEI has been shown to be superior to placebo/AChEI in the treatment of moderate to severe AD [33], as well as showing some benefits in patients with mild to moderate AD [Porsteinsson et al., in press]. Recently published monotherapy study in mild to moderate AD reported significant benefits of memantine also in these patients [20]. Furthermore, two multicentre, placebo-controlled studies in mild to moderate vascular dementia provide evidence that memantine may ameliorate cognitive symptoms in earlier stages of dementia [17,35]. In the light of these findings, the present study sought to investigate the efficacy and safety of memantine in patients with mild to moderate AD.

MATERIALS AND METHODS

Study design

This randomised, double-blind, parallel-group, placebo controlled, fixed-dose study of memantine in patients with mild to moderate AD included 65 primary care centres in 12 countries (Austria, Belgium, Denmark, Finland, France, Greece, Lithuania, the Netherlands, Poland, Spain, Sweden and United Kingdom). The study was conducted in accordance with the prin-

ciples of *Good Clinical Practice* and the *World Medical Association Declaration of Helsinki* (1964) and its amendments and subsequent clarifications. The relevant local ethics committees approved the study and written informed consent was obtained from patients and caregivers before enrolment. Due to ethical considerations (availability of efficient symptomatic drugs for AD in the majority of countries), a majority of investigators required to minimise patient exposure to placebo. Therefore, eligible patients were randomised in a 2:1 ratio to 3 weeks of up-titration and 21 weeks of treatment with memantine (20 mg/day) or placebo, respectively. Dosing of memantine was initiated with 5 mg/day and titrated up with weekly steps to 20 mg/day (10 mg twice daily) according to the current Summary of Product Characteristics. The first patient first visit was in May 2002 and the last patient last visit was in September 2003. H. Lundbeck A/S funded the study and was involved in planning the design, the protocol and data analysis along with the author(s). The data are stored at H. Lundbeck A/S.

Patients

Patients who fulfilled the diagnosis of probable AD according to National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria [15] and with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for dementia of the Alzheimer's type, including a computer tomography or magnetic resonance imaging of the brain within the previous 12 months with results consistent with such diagnosis were eligible for inclusion if they were an outpatient of either sex, more than 50 years old and had a baseline MMSE total score between 11 and 23 (extremes included) [6]. Furthermore, the patients should have had a reliable and knowledgeable caregiver who could accompany the patient to all clinic visits during the study. Patients with vascular dementia, dementia or clinically significant neurological disease other than Alzheimer's disease, major depressive disorder or a score greater than 4 on the modified Haskins Ischemic Rating Scale [30] were excluded. Patients with clinically significant coexisting medical conditions or laboratory abnormalities were also excluded, as were patients receiving specific concomitant medications (anticonvulsants, antiparkinson agents, classical and depot antipsychotics, anxiolytics, hypnotics, non-SSRI antidepressants, cholinesterase inhibitors or any other investigational product). When used previously to in-

clusion, cholinesterase inhibitors were discontinued at least 30 days prior to the screening visit. SSRIs, estrogens, antiinflammatory drugs, β -blockers, insulin and H₂ blockers were allowed if dose and medication had been stable for at least 3 months and were kept stable during the study. Vitamin E, Coenzyme Q and atypical antipsychotics (risperidone ≤ 2 mg/day, olanzapine ≤ 10 mg/day or quetiapine ≤ 100 mg/day) were allowed if dose and medication had been stable for at least 30 days and kept stable during the study. Atypical antipsychotics were not to be taken 3 days before a visit. Only non-opioid analgesics could be administered chronically.

A patient was withdrawn from the study if the randomisation code for that patient was broken, or if consent to participate was withdrawn for the patient or caregiver. A patient could also be withdrawn from the study if: they had a serious adverse event (SAE: death, life-threatening condition, hospitalisation), the caregiver became unavailable, the patient was lost to follow-up, or the patient was placed in a nursing home.

Primary efficacy variables

Patients were assessed at screening, at baseline and 4, 12, 18 and 24 weeks after the start of double-blind treatment. The pre-specified primary efficacy variables were change from baseline on Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) total score [29] at week 24 and Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus) total score [24] at week 24. The ADAS-cog is an 11-item scale assessing cognitive domains of memory, language, orientation, reasoning, and praxis. Scores range from 0 to 70 with lower scores indicating less impairment. Its use in measuring changes in cognition in mild to moderate AD has been extensively validated [16,19,34]. The CIBIC-Plus is used to assess treatment effects on overall clinical status in AD, based on an independent comprehensive interview with the participant and caregiver by an experienced rater/clinician. Scores on the CIBIC-Plus range from 1 (marked improvement) to 7 (marked worsening). A score of 4 represents no change. The CIBIC-Plus score is assigned at all post-baseline visits relative to a global assessment of disease severity made at baseline. Given the multi-lingual nature of this study, translated versions of this scale were used to match the native language at the location of each centre.

Secondary efficacy variables

Secondary efficacy measures included Neuropsychiatric Inventory (NPI) [4] and the 23-item Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL₂₃) scale [9]. Patients were assessed on the NPI and the ADCS-ADL₂₃ at baseline and weeks 12 and 24. The NPI is a 12-item, caregiver interview-based instrument designed to assess frequency and severity of behavioural symptoms in dementia patients. The NPI provides both a total score (ranging from 0 to 144) as well as scores for each of its 12 items; higher scores reflect greater symptom severity. For each item, the frequency and severity of each behaviour is measured. The ADCS-ADL₂₃ for mild to moderate AD patients consists of 23 items used to assess basic and instrumental activities of daily living (ADLs). Most ADL items are comprised of a series of hierarchical sub-questions, with possible scores ranging from 0 to 78 reflecting the complete loss of ability to perform the ADL to the highest level of independent performance. Higher scores indicate better performance. The ADCS-ADL₂₃ was administered as an interview with the caregiver and assessed ADL over the previous four weeks.

Power and sample size calculations

The sample size calculation was based on the success criterion of the medication having an effect on the primary efficacy variables applying a 5% significance level for each analysis. Assuming an effect size of 0.43 for ADAS-cog total scores, 0.49 for CIBIC-plus rating and a sample size of 400 patients (133 in the placebo group and 267 in the memantine group), the study had a power of 88% to detect a significant difference between the treatments.

Rater training was undertaken to increase inter-rater reliability. Only personnel that had actively participated in rater training sessions prior to enrolment of patients were allowed to rate patients. The rater who scored the CIBIC-plus was blinded to the results of the other efficacy assessments. The same rater was to score the patient throughout the study if possible. The training materials for efficacy assessment were translated for the raters and back-translated and medically verified.

Allocation to treatment

The study products were tablets of identical appearance, taste and smell. Patients were assigned to 24-weeks of double-blind treatment with memantine or placebo in a 2:1 ratio. The details of the randomisation series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes. At each study centre, sequentially enrolled patients were assigned the lowest randomisation number available. All study personnel and participants were blinded to treatment assignment for the duration of the study.

Primary efficacy assessments

The following populations were considered in the statistical analyses: the all patients treated set (APTS), which consisted of all randomised patients who took at least one dose of study product and was identical with the safety population (a total of 470 patients; 318 treated with memantine and 152 treated with placebo). The full analysis set (FAS) consisted of all patients in the APTS who had at least one valid post-baseline assessment of both primary efficacy parameters (a total of 461 patients; 310 treated with memantine and 151 treated with placebo) and the 24 week completers set (CS24) consisted of all patients in the FAS who took randomised study product up to week 24 and were assessed on both primary efficacy parameters at the 24 week visit (a total of 403 patients; 268 treated with memantine and 135 treated with placebo). The primary efficacy variables (ADAS-cog and CIBIC-plus change from baseline in the CS24) were analysed using analysis of covariance (ANCOVA) with treatment and centre as factors and the relevant baseline value as a covariate. Two-sided hypothesis testing was performed at the 5% significance level. Results were summarised using the least squares mean (LS mean) for each treatment group with corresponding standard errors.

Secondary efficacy assessments

The secondary efficacy variables (change from baseline in NPI and ADCS-ADL₂₃ in the CS24) were analysed using ANCOVA with treatment and centre as factors and the relevant baseline value as a covariate. They were analysed per visit for both observed cases (OC) and last observation carried forward (LOCF). Two-sided hypothesis testing was performed at the 5% significance level.

As a sensitivity analysis, the CIBIC-plus was analysed at the last visit using the Cochran-Mantel-Haenszel (CMH) test stratifying by centre.

The proportions of responders based on the CS24 were analysed per visit using Fisher's Exact test. Responders were defined as patients showing marked improvement in cognitive function (change in ADAS-cog ≤ -4) and global improvement or stabilisation (CIBIC-plus ≤ 4). No interim analyses were performed. SAS version 6.12 (SAS institute, Cary, NC) was used for all analyses.

Safety and Tolerability Assessments

The safety population was identical to the APTS. Safety and tolerability were evaluated on the basis of adverse events (AEs), clinical laboratory safety data, vital signs, ECGs and weight. AE data and vital signs were collected at every visit; clinical laboratory safety data and ECGs were assessed at screening and week 24. A final safety assessment was made 30 days after the last assessment of double-blind treatment. For safety analyses, an AE occurring during the double-blind treatment period was considered a treatment-emergent AE (TEAE) if it was not present prior to the start of the double-blind medication or if it was present at baseline but increased in severity during the double-blind treatment period. The incidence of individual TEAEs was compared between treatment groups using Fisher's Exact test.

RESULTS

Patient disposition, demographics and baseline characteristics; Study 99679

A total of 470 patients were randomised and treated (memantine: 318, placebo: 152; Table 1). Of these patients, 268 (84%) in the memantine group and 135 (89%) in the placebo group were included in the CS24. The two groups were comparable with respect to proportion of women/men and age. Women constituted 65% of the patients and the mean age was 74 years (ranging from 54 to 89 years). The two treatment groups were also comparable with respect to the severity of AD at baseline. The mean MMSE total scores were 18.6 ± 3.3 for memantine and 18.9 ± 3.2 for placebo treated patients. The mean ADAS-cog total scores at baseline were 25.9 ± 10.4 for the memantine and 24.9 ± 9.7 for placebo treated patients. This is in-

Table 1
Disposition, demographics and mean baseline scores

	Memantine	Placebo
Disposition		
Patients randomised: n	318	152
Patients treated (APTS): n	318	152
Patients withdrawn: n (%)	47 (15)	14 (9)
Full analysis set (FAS): n (%)	310 (97)	151 (99)
Patients completed: n (%)	271 (85)	138 (91)
Completers set (CS24): n (%)	268 (84)	135 (89)
Demographics		
Female: n (%)	206 (65)	91 (60)
Mean age (years) \pm SD	74.0 \pm 7.4	73.3 \pm 6.9
Mean weight (kg) \pm SD	65.8 \pm 12.2	66.2 \pm 11.5
Caucasian: n (%)	318 (100)	152 (100)
Baseline scores		
Mean MMSE score \pm SD	18.6 \pm 3.3	18.9 \pm 3.2
Mean ADAS-cog score \pm SD	25.9 \pm 10.4	24.9 \pm 9.7
Previous AChEI usage: n (%)	121 (38)	54 (36)

dicative of a population with mild to moderate AD. The proportions of patients previously treated with AChEIs were 38% in the memantine group and 36% in the placebo group.

The proportion of patients who withdrew from the study was low: 15% of the patients in the memantine group versus 9% in the placebo group (Fig. 1). The most common reasons for withdrawal were AEs (9% in the memantine group versus 4% in the placebo group) and withdrawal of consent (2.5% in the memantine group versus 2% in the placebo group). No trends were seen in the AEs that resulted in withdrawal. In the memantine group, 4 patients withdrew due to dizziness and 3 patients withdrew due to depression. In the placebo group, none of the AEs leading to withdrawal were reported by more than one patient.

Efficacy of memantine; Primary endpoints

The effect of memantine compared to placebo in the CS24 on the ADAS-cog and CIBIC-plus scales is shown in Fig. 2 and Table 2. The scores for memantine-treated patients on both the ADAS-cog and CIBIC-plus scales were numerically better than those for placebo treated patients at all post-baseline assessments. Statistically significant separation in favour of memantine was seen at weeks 12 and 18 on both scales. However, on the predefined primary efficacy endpoint (i.e., at week 24), the difference in favour of memantine was not statistically significant. Nevertheless, memantine-treated patients showed a mean improvement of 1.93 points at week 24 on the ADAS-cog scale as compared to a 1.08 points improvement in placebo-treated patients.

The proportion of patients who responded to treatment was numerically greater in the memantine group compared to the placebo group at all assessments (Fig. 3, Table 3). Statistically significant separation in favour of memantine was seen at weeks 12 and 18.

Efficacy of memantine; Secondary endpoints

The effect of memantine compared to placebo in the CS24 on the NPI and ADCS-ADL₂₃ scale is shown in Table 2. The NPI total score improved in both treatment groups over time but there was no statistically significant difference between the memantine and placebo group. Likewise, no significant difference between the memantine and placebo group was detected in the ADCS-ADL₂₃ total score.

Safety and tolerability

Approximately half of all patients experienced TEAEs. The incidence of TEAEs was similar in both treatment groups and was very low given the patient population and the duration of study. The adverse events with an incidence of 4% in either group are summarised in Table 4. In both treatment groups, the majority of the TEAEs were considered by the investigator to be mild to moderate.

A total of 8 patients died during the study or within 30 days after the last dose of study drug (one during screening, 5 during double-blind memantine treatment, one during double-blind placebo treatment and one placebo-treated patient after withdrawal). None of the events leading to death were considered related to treatment. A total of 42 patients had SAEs after the

Table 2
Results of the efficacy parameters by study week on the CS24 (OC)

Outcome measure	Week	Memantine		Placebo		Difference from placebo	
		N	Change from baseline	N	Change from baseline	Mean [95% CI]	ANCOVA p-value
ADAS-cog	4	267	-1.71	135	-1.61	-0.10 [-0.98, 0.78]	0.827
	12	268	-2.46	135	-0.70	-1.76 [-2.69, -0.83]	0.000
	18	266	-2.26	135	-0.98	-1.29 [-2.33, -0.25]	0.016
	24 ^a	268	-1.93	135	-1.08	-0.85 [-2.02, 0.32]	0.156
CIBIC-plus	4	266	3.94	134	3.95	-0.01 [-0.16, 0.14]	0.896
	12	267	3.90	134	4.11	-0.21 [-0.40, -0.02]	0.033
	18	268	3.99	135	4.27	-0.28 [-0.49, -0.06]	0.012
	24 ^a	268	4.12	135	4.19	-0.07 [-0.30, 0.15]	0.523
ADCS-ADL ₂₃	12	268	-0.67	135	-0.19	-0.48 [-1.80, 0.85]	0.480
	24	267	-1.99	134	-2.08	0.09 [-1.52, 1.70]	0.912
NPI	12	268	-1.37	135	-1.02	-0.35 [-1.96, 1.26]	0.671
	24	267	-1.45	134	-2.73	1.28 [-0.50, 3.05]	0.159

^aPrespecified primary efficacy endpoint.

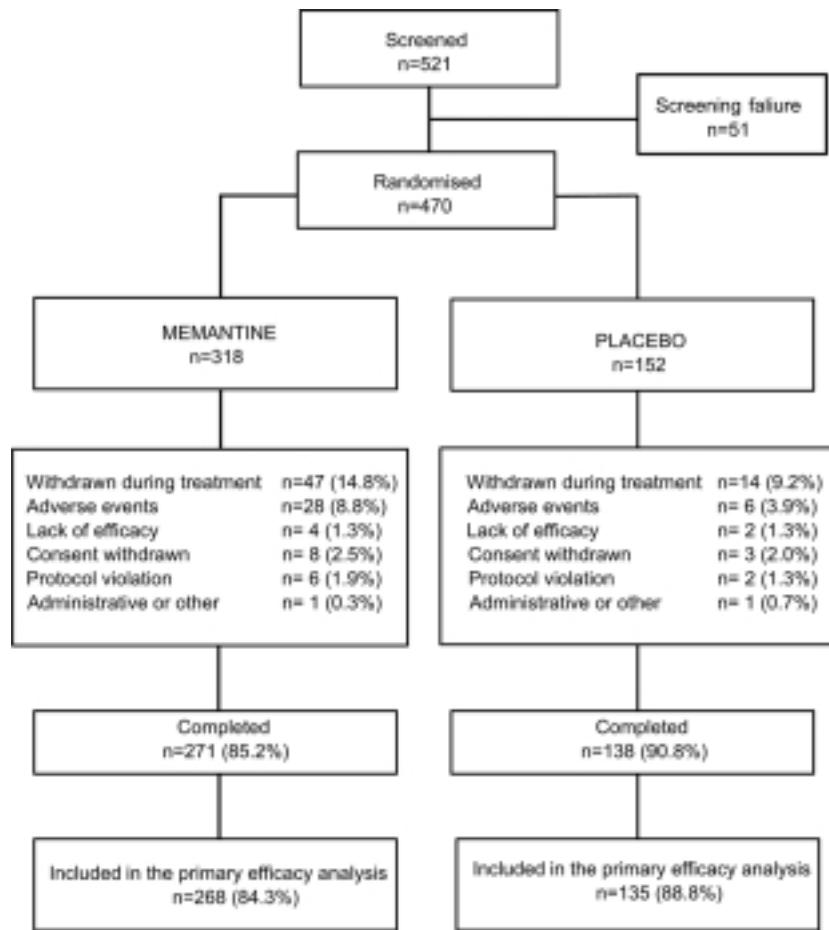


Fig. 1. Patient disposition.

start of the treatment (10% in the memantine group and 6% in the placebo group). SAEs reported in 2 or more participants in either memantine or placebo group were

accidental injury (memantine: 5, placebo: 0), depression (memantine: 3, placebo: 0), pneumonia (memantine: 2, placebo: 1), cerebral haemorrhage (meman-

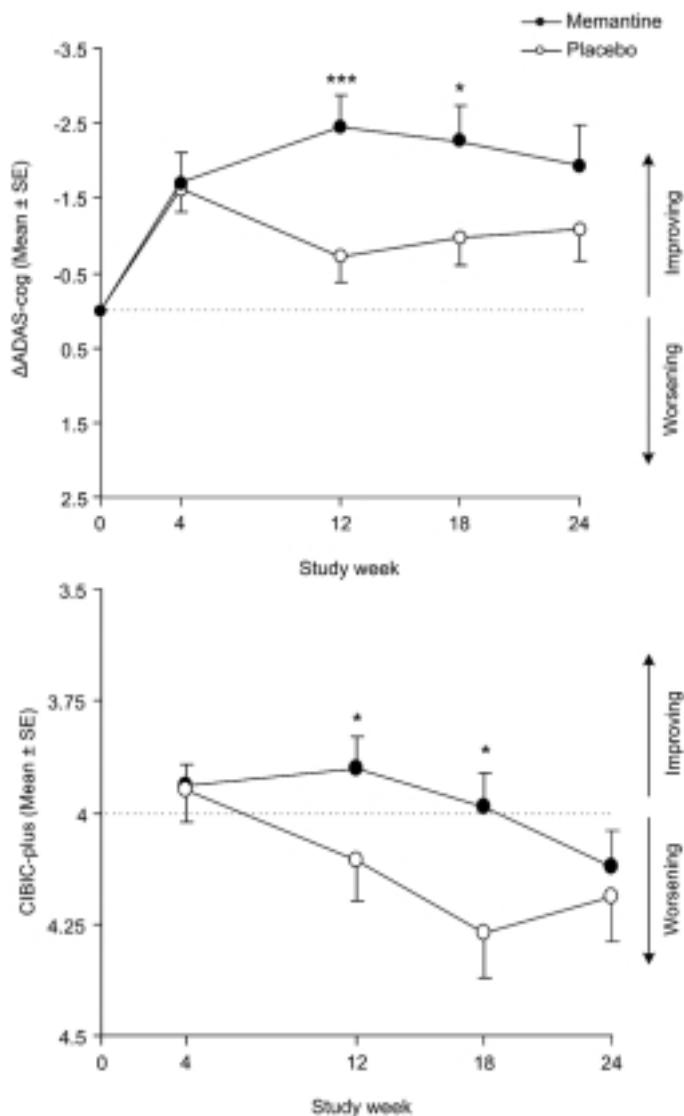


Fig. 2. Results of the primary efficacy parameters (ADAS-cog change from baseline score and CIBIC-plus total score) for memantine and placebo based on the CS24. Error bars indicate standard error (SE). * $p < 0.05$, *** $p < 0.001$ compared to placebo (ANCOVA).

tine: 2, placebo: 0), abdominal pain (memantine: 2, placebo: 0) and myocardial infarction (memantine: 2, placebo: 1). Three patients had an SAE that was considered by the investigator to be possibly or probably related to treatment. These events were fall, accidental injury and agitation (all belonging to the memantine group). The remaining SAEs were all considered to be unrelated to treatment.

The incidence of potentially clinically significant laboratory values, vital signs and ECG values was low. There were no clinically meaningful differences between treatment groups in the mean change from base-

line to endpoint for laboratory tests, vital signs, weight or ECG parameters.

DISCUSSION

The present placebo-controlled, 6-month study (99679) in outpatients with mild to moderate AD indicates that memantine is safe and well tolerated. The pattern of adverse events in the memantine group was similar to that experienced by the patients in the placebo group. The high study completion rate in the memantine group (around 85%) and the low level of ad-

Table 3
Proportion of responders by study week based on the CS24 (OC)

Week	Memantine		Placebo		Fisher's Exact test p-value
	n	Responders ^a (%)	n	Responders ^a (%)	
4	265	22.3	134	20.1	0.700
12	267	30.0	134	15.7	0.002
18	266	30.1	135	20.0	0.032
24	268	31.3	135	25.2	0.246

^aResponders were defined as patients showing marked improvement in cognitive function (change in ADAS-cog ≤ -4) and global stabilisation or improvement (CIBIC-plus ≤ 4).

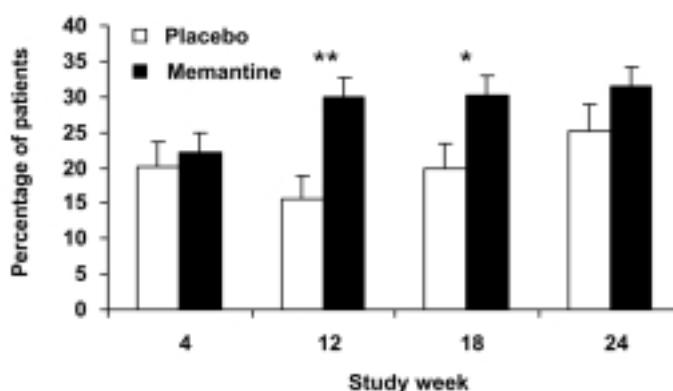


Fig. 3. Proportion of responders in patients treated with memantine or placebo based on the CS24. Responders were defined as patients showing marked improvement in cognitive function (change in ADAS-cog ≤ -4) and global stabilisation or improvement (CIBIC-plus ≤ 4). * $p < 0.05$, ** $p < 0.01$ compared to placebo (Fisher's Exact test).

verse events observed in this study are consistent with previous studies demonstrating an excellent safety and tolerability profile of memantine in AD [25,26,20,33].

On the primary efficacy variables (ADAS-cog and CIBIC-plus) memantine separated from placebo early on and was statistically superior to placebo at study weeks 12 and 18 on a 95% significance level. Although numerically superior, the benefit of memantine was not statistically significant at the predefined primary efficacy endpoints, i.e., change from baseline on ADAS-cog total score and CIBIC-plus total score at study week 24. Memantine treatment was associated with significant and clinically relevant cognitive improvements above baseline throughout the entire study indicating an overall maintenance of cognitive function from study start to end point. This conclusion is supported by the fact that the analysis was made on the CS24 and not based on a LOCF approach where early drop-outs may falsely indicate a maintenance of cognitive function given the degenerative nature of this disease. Other studies in mild to moderate AD or vascular dementia have shown that memantine is efficacious in reducing the deterioration assessed by the ADAS-cog [17,20,35].

Table 4
Treatment-emergent adverse events (TEAEs) with an incidence of $\geq 4\%$ in one of the treatment groups in the APTS

Preferred term	Memantine (n = 318) %	Placebo (n = 152) %
Patients with TEAEs	56.0	52.6
Headache	5.7	2.0
Dizziness	5.3	3.9
Accidental/inflicted injury	5.0	5.3
Rhinitis	4.4	4.6
Agitation	1.6	4.6

The lack of statistically significant results for the primary efficacy analyses at study week 24, after being statistically significantly superior to placebo at study week 12 and 18, was unexpected. This lack of a statistically significant difference may be attributed to an atypical placebo response, that is, the placebo group did not deteriorate over the 24 weeks study period as expected for this patient population. The patients receiving placebo showed an unexpected *improvement* on both primary efficacy scales late in the study.

There are several published placebo-controlled clinical studies in dementia using a similar patient population that support the notion that the observed placebo

response of the present study was indeed unusual [20, 23]. In a recent published study, the effect of 1-year treatment with the anti-inflammatory agent rofecoxib was tested in 692 patients with mild to moderate AD and a gradual decline relative to baseline was observed during the study [23]. After 24 weeks of treatment the mean deterioration in the placebo group on the ADAS-cog scale was around 2.2 points which is similar to the degree of deterioration observed in the earlier placebo-controlled studies with AChEIs [5,28,29,31]. This is in clear contrast to the 1.08 points *improvement* seen in this study.

The reason for this unusual placebo response was investigated but neither compromised blinding, vascular comorbidity, previous AChEI treatment nor concomitant medication could account for the observed effect. An analysis to investigate the treatment-by-centre interaction identified a heterogeneous treatment effect over centres ($p = 0.056$) for the CIBIC-plus scores.

A measured point difference between placebo- and drug-treated patients on a quantitative scale may not necessarily represent a clinically meaningful improvement. Responder analyses (rates of individual response) are often performed as an indication of the clinical relevance of a treatment.

Responder rates were significantly better in the memantine group compared to the placebo group at study weeks 12 and 18, but not at week 24. This finding is noteworthy for two reasons. First, the current study was not powered to show a statistically significant separation on categorical data. Second, it is unusual for a single study in mild to moderate AD to show a statistically significant difference from placebo using a conservative dual-responder criterion. The lack of statistical significance at week 24 can be attributed to an increase in the number of placebo responders. The number of memantine responders remained generally stable.

Previous studies have provided evidence that memantine is efficacious in moderate to severe AD [25,26, 33,37]. The results presented and discussed in this paper extend these findings by indicating that modulation of NMDA receptor-mediated neurotransmission is also an attractive approach in the treatment of mild to moderate AD especially when taken together with recently published results of another mild to moderate AD study [20]. The efficacy of memantine across all severity stages of AD is consistent with previous findings indicating the presence of glutamatergic abnormalities at all stages of this disease [7,10,21].

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