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# Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for combination therapy

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## Abstract

**Introduction:** Memantine and cholinesterase inhibitors potentially offer additional benefits in Alzheimer's disease (AD) when used together. This study assessed the efficacy and safety of combination treatment with memantine added to stable donepezil in patients with moderate to severe AD, and in a subset with moderate AD.

**Methods:** Post hoc meta-analyses of data combined from two 24-week, randomised, double-blind, placebo-controlled trials of memantine 20 mg/day versus placebo, added to a stable cholinesterase inhibitor, were conducted. Data were included for all patients receiving donepezil 10 mg/day with Mini-Mental State Examination (MMSE) scores < 20 ( $n = 510$ ). Efficacy was assessed using measures of cognition, function, and global status. Furthermore, marked clinical worsening, defined as concurrent deterioration from baseline in the three main efficacy domains, and safety, measured by treatment-emergent adverse events, were assessed. Analyses were performed for patients with moderate to severe AD (MMSE 5-19; MOD-SEV subgroup), and also for patients with moderate AD (MMSE 10-19; MOD subgroup;  $n = 367$ ).

**Results:** At week 24, in the MOD-SEV subgroup, patients receiving memantine added to donepezil significantly outperformed those receiving placebo added to donepezil in measures of cognition ( $P < 0.0001$ ), function ( $P = 0.02$ ), and global status ( $P = 0.010$ ), with standardised mean differences (SMDs) of 0.36, 0.21, and 0.23, respectively (all last observation carried forward). Similarly, in the MOD subgroup, significant benefits were observed for cognition ( $P = 0.008$ ), function ( $P = 0.04$ ) and global status ( $P = 0.008$ ), with SMDs of 0.28, 0.21, and 0.28, respectively. Significantly fewer patients receiving memantine added to donepezil showed marked clinical worsening than those receiving placebo added to donepezil, in both subgroups (MOD-SEV: 8.7% versus 20.4%,  $P = 0.0002$ ; MOD: 5.9% versus 15.0%,  $P = 0.006$ ). The incidence of adverse events was similar between treatment groups.

**Conclusions:** These results support and extend previous evidence that combination treatment with memantine added to stable donepezil in patients with moderate AD, and in those with moderate to severe AD, is associated with significant benefits in reducing 24-week decline in cognition, function and global status. Combination treatment produces substantially reduced rates of marked clinical worsening, has good safety and tolerability, and generates effect sizes that are both statistically significant and clinically meaningful.

## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which patients typically lose cognitive faculties, struggle to carry out activities of daily living (ADLs), and experience behavioural and neuropsychiatric

problems. At present, AD cannot be cured, any improvements produced by pharmacotherapy are often temporary, and no treatments have been demonstrated to be disease-modifying. Consequently, alleviating symptoms, and delaying or reducing clinical worsening (that is, symptom progression), without modifying the underlying pathophysiology, are realistic and meaningful treatment goals [1] that can be termed disease-course-modifying effects [2]. Achieving these goals allows patients to spend

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more time in the milder, more functional, stages of AD than they would without treatment [1].

Memantine, an uncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) glutamate receptors, is approved in the EU and US for the treatment of patients with moderate to severe AD (Mini-Mental State Examination [MMSE] [3] score < 20). Donepezil, a cholinesterase inhibitor (ChEI), is approved for the treatment of mild to moderate AD in the EU, and for mild, moderate, and severe AD in the US and some other countries. As monotherapy, both memantine and donepezil have demonstrated efficacy for treating the symptoms of AD within their respective approved indications [4-12]. In addition, the incidence of clinical worsening, as defined by concurrent deterioration in three domains (cognitive, functional, and global) over time, is reduced by memantine treatment in patients with moderate to severe AD [6], and by donepezil treatment in patients with mild to moderate AD [13].

Since memantine and donepezil have different and complementary mechanisms of action, together they potentially offer additional benefits to the patient [14]. Pharmacokinetic and pharmacodynamic data in healthy volunteers provided initial evidence that memantine and donepezil may be safely used in combination [15]. The addition of memantine to stable ChEI therapy has also been associated with a good safety profile in patients with AD [16,17].

Two 24-week, randomised, double-blind, placebo-controlled trials (RCTs) have investigated the efficacy and safety of memantine 20 mg/day in combination with a ChEI. The first, MEM-MD-02, assessed the efficacy of administration of memantine (10 mg twice daily) versus placebo in patients with moderate to severe AD (MMSE 5-14;  $n = 404$ ) receiving stable donepezil therapy [16]. Relative to placebo, memantine produced significant benefits in all four key symptom domains of AD, namely, cognition, function, behaviour, and global status [16]. The second RCT, MEM-MD-12, assessed the efficacy of administration of memantine (20 mg once daily) versus placebo in patients with mild to moderate AD (MMSE 10-22;  $n = 433$ ) taking a stable dose of any approved ChEI therapy [17]. In this trial, the only potential signal of benefit for memantine treatment over placebo (effect size estimate 0.118 in favour of memantine;  $P = 0.184$ ) was observed for the cognitive measure (AD Assessment Scale-cognitive subscale, ADAS-Cog), but the trial was not adequately powered to detect with statistical significance, an effect size smaller than 0.325 [17]. In both studies, combination therapy with memantine added to a ChEI was well-tolerated [16,17].

In addition to the lack of power to detect effect sizes smaller than 0.325, two possible explanations were provided by Porsteinsson and colleagues for the discrepancy

in findings between MEM-MD-02 and MEM-MD-12: the difference in baseline disease severity, and the difference in permitted ChEIs [17]. In the present study, data from both RCTs are combined, and the hypothesis that low power and baseline heterogeneities caused the divergent results between MEM-MD-02 and MEM-MD-12, and potentially obscured significant memantine treatment-related benefits in patients with moderate AD, is tested. In a post hoc meta-analysis and subgroup analysis approach, these data are used to assess the efficacy of memantine 20 mg/day versus placebo in patients receiving stable doses of donepezil (10 mg/day) in two subgroups: moderate to severe AD (MMSE 5 to 19), and moderate AD (MMSE 10 to 19).

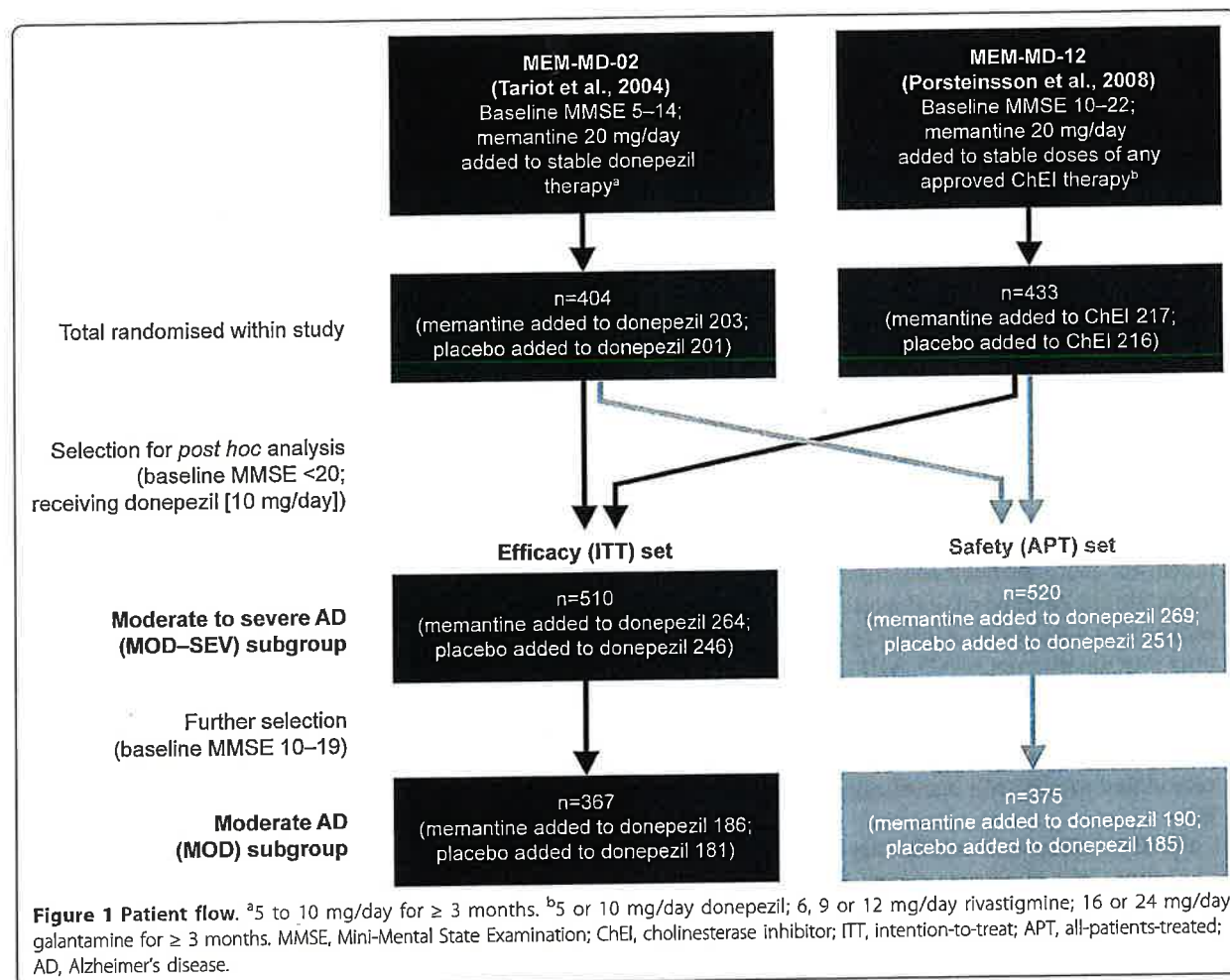
The rationale for choosing these patient subgroups (subpopulations) were that they represent the current approved indication of memantine in the EU (moderate to severe AD), and the overlap of the approved memantine and donepezil indications in the EU (moderate AD). As is commonly done in clinical trials, the MMSE was used as a subpopulation staging surrogate measure to delineate mild (MMSE  $\geq 20$ ) from moderate (MMSE 10 to 19) and severe (MMSE < 10) stages of AD. Finally, since donepezil was the most commonly used ChEI in these trials, ChEIs other than donepezil were excluded, and analysis was restricted to patients receiving 10 mg/day of donepezil to minimise heterogeneity and any potential effects of underdosing.

Therefore, the analyses in this study of patients with AD with MMSE < 20 taking stable donepezil 10 mg/day consist of: 1) meta-analyses to compare the efficacy of memantine versus placebo across individual domains of AD; 2) pooled analyses to compare the efficacy of memantine versus placebo in reducing the occurrence of marked clinical worsening, and 3) pooled analyses to assess the tolerability profile of memantine versus placebo.

## Methods

### Study design and patients

Figure 1 depicts data flow for study inclusion and subgroup analysis. Studies were selected for inclusion if they fulfilled the criteria of: phase III RCTs of patients with a diagnosis of AD and treated with memantine 20 mg/day added to stable ChEI; a double-blind observation period of at least 24 weeks, and a majority of patients receiving stable treatment with donepezil. Two studies met the inclusion criteria (MEM-MD-02 and MEM-MD-12), both of which were performed in multiple centres in the US [16,17]. Study approval was granted by the local Institutional Review Board (IRB) at each trial site, and written informed consent was obtained from each study participant if possible, and either the caregiver or a legally acceptable representative (if different from the caregiver) before initiation of study-specific procedures according to IRB protocols [16,17].



Full details of individual study design and patient inclusion criteria for MEM-MD-02 and MEM-MD-12 have been presented previously [16,17]. In summary, the patient inclusion criteria were similar: 50 years of age or older; diagnosis of probable AD according to the NINCDS-ADRDA criteria; a brain magnetic resonance imaging or computed tomographic scan within 12 months consistent with a diagnosis of probable AD; and treatment with a ChEI for at least 6 months with a stable dosing regimen for at least 3 months. The individual clinical study inclusion criteria differed in the required baseline MMSE score (see Figure 1) and the allowed ChEI (only donepezil use in MEM-MD-02; any ChEI in MEM-MD-12). In both studies, patients treated with memantine received a fixed total dose of 20 mg/day.

Selection was restricted to patients receiving stable treatment with donepezil 10 mg/day. Two subgroups of patients were analysed: the MOD to SEV subgroup of patients with moderate to severe AD (MMSE < 20, range 5 to 19), conforming to the approved indication

of memantine in the EU, and the MOD subgroup of patients with moderate AD (MMSE 10 to 19), conforming to the overlap of the approved memantine and donepezil indications in the EU.

#### Trial registration

The data were obtained from the sponsors of the original trials; trial registration was not relevant to these two studies since both studies were completed before July 1, 2005; MEM-MD-02 was completed by June 2002, and MEM-MD-12 was completed by March 2003 [16,17].

#### Efficacy measures

Cognition was assessed using the Severe Impairment Battery (SIB) [18–20] in study MEM-MD-02 (patients with moderate to severe AD) and the ADAS-Cog [21] in study MEM-MD-12 (patients with mild to moderate AD). In both studies, function was assessed using the AD Cooperative Study - Activities of Daily Living scale (ADCS-ADL) [22,23]. The 23-item version (ADCS-ADL<sub>23</sub>) was used in

MEM-MD-12, and the 19-item version (ADCS-ADL<sub>19</sub>), developed specifically for patients with moderate to severe AD [23], was used in MEM-MD-02. Global status was assessed using the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) [24,25].

An individual domains meta-analysis was performed for each subgroup. This required data from the different cognitive and functional rating scales within the same domain to be combined across the selected trials. Consequently, the outcome measures for this meta-analysis were change from baseline to endpoint (week 24) in cognition (SIB/ADAS-Cog score), function (ADCS-ADL<sub>19</sub>/ADCS-ADL<sub>23</sub> score), and global status (CIBIC-Plus score).

Data from both studies were pooled in clinical worsening analyses, a form of responder analysis in which response is defined not by improvement but by worsening [6]. The criteria used to define clinical worsening were based on concurrent worsening in the cognitive, functional and global domains from baseline to endpoint (week 24) [6]. Marked clinical worsening was defined as a decline of  $\geq 4$  points on ADAS-Cog or  $\geq 5$  points on SIB, plus any decline on ADCS-ADL<sub>19</sub>/ADCS-ADL<sub>23</sub> and CIBIC-Plus [6]. This definition is intended to represent the average natural cognitive decline observed in patients with moderate to severe AD over 6 months, and can be considered as clinically significant cognitive worsening [6].

Finally, safety and tolerability were assessed in a pooled analysis of adverse events (AEs), including both the total incidence of AEs, and the AEs with an incidence  $\geq 5\%$  in either treatment group.

#### Statistical analysis

All analyses were performed using SAS<sup>®</sup> 9.2 and RevMan 5 software. Efficacy was analysed in the intention-to-treat (ITT) set, defined as all patients who were randomised to, and received at least one dose of, either placebo or memantine, and who completed at least one post-baseline assessment in the cognitive (SIB/ADAS-Cog) or functional (ADCS-ADL<sub>19/23</sub>) domains. Analyses were conducted at week 24 using the last observation carried forward (LOCF) approach for missing data, and also for observed cases (OC).

For the individual studies in the meta-analyses, standardised effect sizes for each outcome measure were calculated as the standardised mean difference (SMD) of the change from baseline to endpoint. The overall standardised effect size for each outcome measure was calculated using the inverse-variance method. Per convention, we use Cohen's guidelines to serve as operational definitions to qualitatively interpret the magnitude of effect sizes as follows: 0.2 is small, 0.5 is medium, and 0.8 is large [26]. Effect sizes of magnitude 0.2 or larger are considered clinically significant

in the context of general medical therapeutics [26], and are also clinically noticeable in the context of AD therapeutics [27]. The meta-analyses were conducted using the fixed-effect model. Overall effect was tested using the Z-statistic. Statistical testing for heterogeneity was based on chi squared tests and the *I*-squared summary statistic; heterogeneity between studies was considered for *P*-values  $< 0.10$ , or *I*-squared  $> 50\%$ . The pooled analyses of clinical worsening included patients in the ITT set who had an assessment on all three efficacy scales.

Safety was assessed in the all-patients-treated (APT) set, defined as all patients who were randomised to, and received at least one dose of, either placebo or memantine. Significance was calculated using Fisher's exact test; *P*-values  $< 0.05$  were considered statistically significant.

## Results

### Study population

A total of 510 patients with moderate to severe AD (MOD-SEV subgroup; MMSE 5 to 19) (339 from MEM-MD-02, and 171 from MEM-MD-12; 264 receiving memantine added to donepezil, and 246 receiving placebo added to donepezil) were included in the ITT set. Of these, 367 patients (186 receiving memantine added to donepezil, and 181 receiving placebo added to donepezil) were part of the MOD subgroup (MMSE 10 to 19) (Figure 1). As expected, other than baseline MMSE score, there were no clinically relevant differences between treatment groups in terms of baseline demographics (Table 1).

### Excluded patient population characteristics

Table 2 shows the baseline characteristics for the 327 patients (mean baseline MMSE 18.0) originally enrolled in MEM-MD-02 (65 of 404 patients) or MEM-MD-12 (262 of 433 patients) who did not meet inclusion criteria for this study and were excluded from the efficacy analysis. Of the excluded patients who were part of the ITT set, 130 (all from MEM-MD-12; 90 receiving donepezil and 40 receiving a ChEI other than donepezil) met exclusion criteria for mild-stage AD (a baseline MMSE score of  $\geq 20$ ); there were no significant differences in baseline MMSE between patients randomised to memantine ( $n = 63$ ; MMSE = 21.1) or placebo ( $n = 67$ ; MMSE = 21.0). A further 100 patients from the ITT set (all from MEM-MD-12) met baseline MMSE criteria for moderate AD (MMSE 10 to 19) but were excluded for receiving a ChEI other than donepezil; these patients also had no significant differences in baseline MMSE between those randomised to memantine ( $n = 47$ ; MMSE 14.1) or placebo ( $n = 53$ ; MMSE 15.0). Finally, 81 patients from the ITT set (56 from MEM-MD-02 and 25 from MEM-MD-12) were excluded for taking a dose of donepezil less than 10 mg/day.

**Table 1 Baseline patient demographics and MMSE scores (ITT set)**

Characteristic	MOD-SEV subgroup <sup>a</sup>		MOD subgroup <sup>b</sup>	
	Memantine added to donepezil (n = 264)	Placebo added to donepezil (n = 246)	Memantine added to donepezil (n = 186)	Placebo added to donepezil (n = 181)
Female	155 (58.7)	151 (61.4)	114 (61.3)	110 (60.8)
Age, mean (SD) years	75.1 (8.5)	75.8 (8.5)	75.9 (8.4)	76.4 (8.2)
Caucasian	236 (89.4)	230 (93.5)	166 (89.2)	171 (94.5)
Black	10 (3.8)	6 (2.4)	5 (2.7)	4 (2.2)
Asian	3 (1.1)	1 (0.4)	3 (1.6)	1 (0.6)
Other	15 (5.7)	9 (3.7)	12 (6.5)	5 (2.8)
MMSE score, mean (SD)	11.9 (3.9)	11.7 (3.7)	13.9 (2.5)	13.4 (2.6)

Data are number (%) unless otherwise specified. <sup>a</sup>Moderate to severe Alzheimer's disease (AD) (MMSE 5 to 19 at baseline), receiving donepezil (10 mg/day). <sup>b</sup>Moderate AD (MMSE 10 to 19 at baseline), receiving donepezil (10 mg/day). MMSE, Mini-Mental State Examination; ITT, intention-to-treat.

#### Efficacy in individual domains of AD (meta-analyses)

After 24 weeks of treatment, patients in the MOD-SEV subgroup receiving memantine added to donepezil showed significantly better efficacy across all examined domains of cognition, function, and global status than patients treated with placebo added to donepezil. The overall standardised effect sizes for memantine versus placebo were: 0.36 ( $P < 0.0001$ ) for cognition, 0.21 ( $P = 0.02$ ) for function, and 0.23 ( $P = 0.010$ ) for global status (all LOCF; see Figure 2a). OC analyses produced similar results for statistical significance and standardised effect sizes. There was no sign of heterogeneity in either LOCF or OC analyses.

Treatment with memantine added to donepezil was also associated with significant clinical benefits in the MOD subgroup. The overall standardised effect sizes for memantine versus placebo were: 0.28 ( $P = 0.008$ ) for cognition, 0.21 ( $P = 0.04$ ) for function, and 0.28 ( $P = 0.008$ ) for global status (all LOCF; see Figure 2b). In OC analyses, memantine treatment was associated with statistical significance only for the global status measure, but similar overall standardised effect sizes were observed. There was no sign of heterogeneity in either LOCF or OC analyses.

#### Efficacy in reducing the occurrence of marked clinical worsening

In the MOD-SEV subgroup, 23/263 patients receiving memantine added to donepezil (8.7%) showed marked clinical worsening compared to 50/245 patients receiving placebo added to donepezil (20.4%), a significant difference of 11.7% ( $P = 0.0002$ ; LOCF) (Figure 3a). The OC analysis produced a similar result (8.5% versus 18.9%;  $P = 0.003$ ).

In the MOD subgroup, 11/185 patients receiving memantine added to donepezil (5.9%) showed marked clinical worsening compared to 27/180 patients receiving placebo added to donepezil (15.0%), a significant difference of 9.1% ( $P = 0.006$ ; LOCF) (Figure 3b). Again, the OC analysis produced a similar result (5.9% versus 12.6%;  $P = 0.047$ ).

#### Safety and tolerability - incidence of adverse events

The incidence of AEs over 24 weeks was similar between the patients treated with memantine added to donepezil versus placebo added to donepezil (Table 3). In the MOD-SEV subgroup, the most common AEs with an incidence  $\geq 5\%$  in patients treated with memantine added to donepezil were: dizziness, agitation, confusional state, diarrhoea, and nasopharyngitis (Table 3). In the MOD subgroup, the most common AEs with an incidence  $\geq 5\%$  in patients treated with memantine added to donepezil were: dizziness, diarrhoea, falls, and urinary tract infection (Table 3). In both severity subgroups, the frequency of agitation was statistically significantly lower in patients treated with memantine added to donepezil compared with patients treated with placebo added to donepezil (Table 3). There were no other statistically significant differences between treatment groups for AEs with an incidence  $\geq 5\%$ .

#### Discussion

##### Efficacy

This study combined efficacy data for 510 patients with AD and MMSE  $< 20$  from the two 24-week, phase III RCTs of memantine 20 mg/day added to stable donepezil (MEM-MD-02 and MEM-MD-12). It yielded SMD effect sizes in favour of combination treatment with memantine added to stable donepezil (versus placebo added to stable donepezil) that were in the clinically significant 0.2 to 0.4 range for all efficacy domains (Figure 2).

Study MEM-MD-02, which observed significant benefits for memantine over placebo in cognition, function, and global status, considered generally the same population of patients as the present study (MMSE 5 to 14, receiving stable donepezil therapy) [16,28,29]. Consequently, the data from MEM-MD-02 contributed favourably to the results of this meta-analysis. Regarding study MEM-MD-12 [17], only the data for the patients with moderate AD and who were taking donepezil 10 mg/day were included.

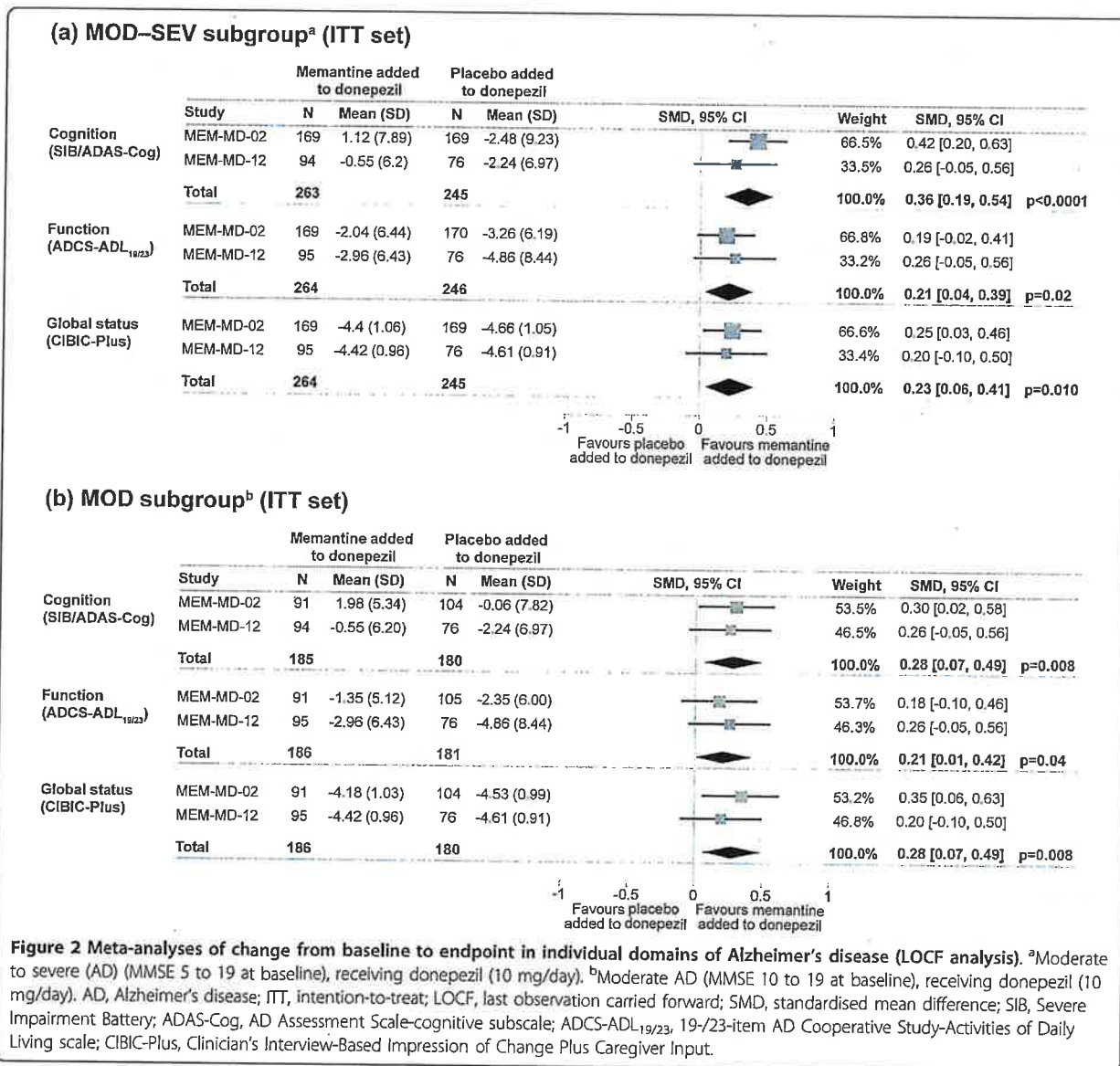
**Table 2 Baseline characteristics of patients excluded due to any reason<sup>a</sup>**

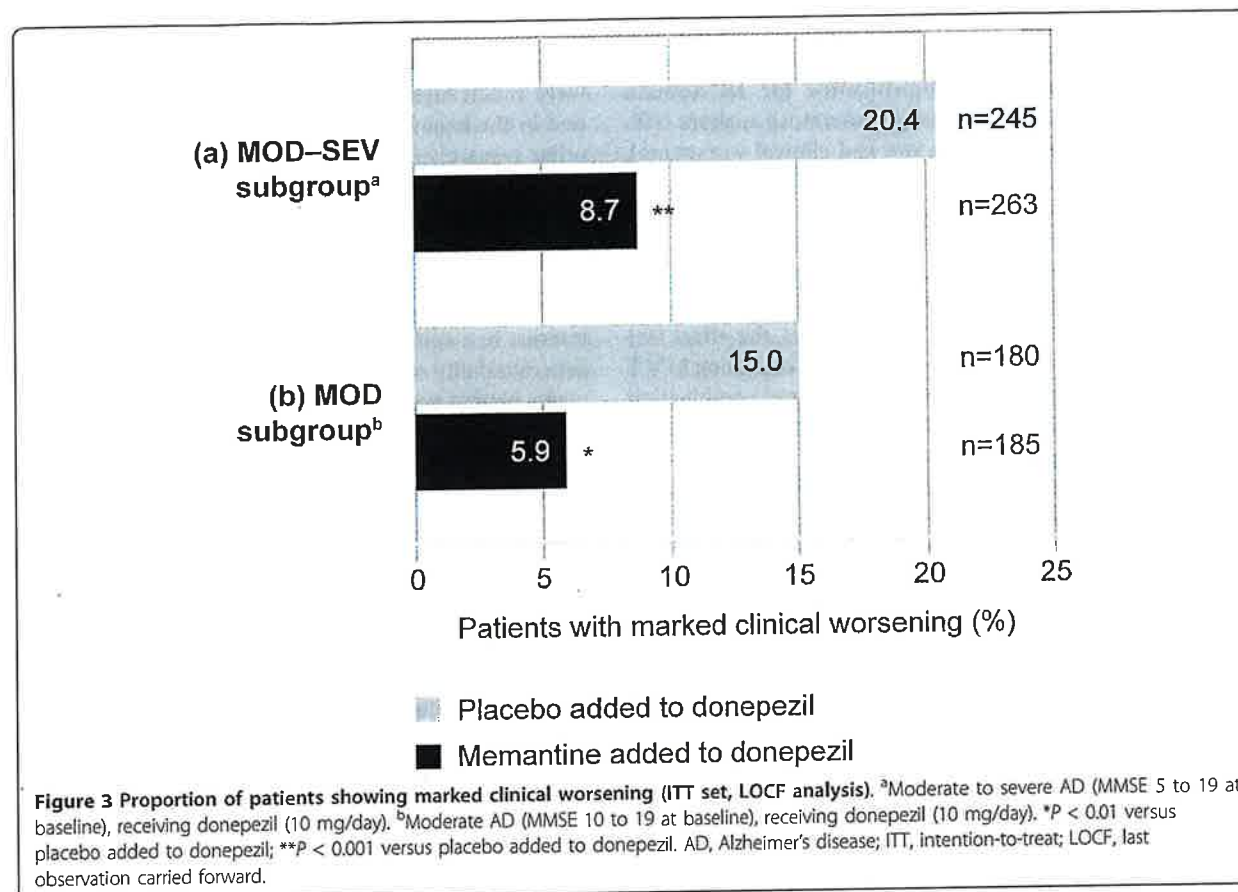
Characteristic	All excluded patients	
	Memantine (n = 156)	Placebo (n = 171)
Female	91 (58.3)	92 (53.8)
Age, mean (SD) years	75.4 (7.3)	75.7 (8.7)
Caucasian	147 (94.2)	162 (94.7)
Black	4 (2.6)	3 (1.8)
Asian	0 (0.0)	1 (0.6)
Other	5 (3.2)	5 (2.9)
MMSE score, mean (SD)	17.9 (4.0)	18.0 (3.6)

Data are number (%) unless otherwise specified. <sup>a</sup>Exclusion criteria were mild Alzheimer's disease (MMSE  $\geq$  20 at baseline), receiving a cholinesterase inhibitor other than donepezil, or receiving donepezil at a dose < 10 mg/day. MMSE, Mini-Mental State Examination.

In this particular subpopulation, benefits in cognition, function and global status of similar magnitude to those observed for patients in MEM-MD-02 were observed; these data demonstrated statistical significance when combined in this meta-analysis with data from the MEM-MD-02 study. These results support the hypothesis that low power and heterogeneities due to baseline ChEI treatment and disease severity may have significantly contributed to the apparently divergent results previously observed between the studies MEM-MD-02 and MEM-MD-12; these differences may have obscured the significant benefits of adding memantine to stable donepezil treatment in patients with moderate AD.

The results observed in these meta-analyses are comparable to those reported in previous meta-analyses for the





benefits of memantine monotherapy over placebo [30,31]. The overall standardised effect sizes in the cognitive domain are 0.36 in the present analysis (MOD-SEV subgroup; LOCF), 0.26 in Winblad *et al.* (OC) [30] and 0.29 in Doody *et al.* (LOCF) [31]. Results found here are also

comparable to previous findings in the domains of function and global status [30,31]. A major difference between this study and those previously reported is that patients in the present analysis were already receiving symptomatic benefits from donepezil, and thus the benefits observed for

**Table 3 Adverse events with an incidence  $\geq$  5% in either treatment group over 24 weeks (APT set)**

Adverse event	MOD-SEV subgroup <sup>a</sup>		MOD subgroup <sup>b</sup>	
	Memantine added to donepezil (n = 269)	Placebo added to donepezil (n = 251)	Memantine added to donepezil (n = 190)	Placebo added to donepezil (n = 185)
Patients with AEs	206 (76.6)	186 (74.1)	144 (75.8)	136 (73.5)
Dizziness	20 (7.4)	19 (7.6)	17 (8.9)	16 (8.6)
Agitation	17 (6.3)*	29 (11.6)	9 (4.7)*	19 (10.3)
Confusional state	15 (5.6)	6 (2.4)	-	-
Diarrhoea	14 (5.2)	21 (8.4)	12 (6.3)	14 (7.6)
Nasopharyngitis	14 (5.2)	6 (2.4)	-	-
Falls	11 (4.1)	15 (6.0)	10 (5.3)	11 (5.9)
Urinary tract infection	-	-	10 (5.3)	8 (4.3)
Depression	-	-	6 (3.2)	11 (5.9)

Data are number (%). <sup>a</sup>Moderate to severe AD (MMSE 5 to 19 at baseline), receiving donepezil (10 mg/day). <sup>b</sup>Moderate AD (MMSE 10 to 19 at baseline), receiving donepezil (10 mg/day). \*P < 0.05 versus placebo added to donepezil. APT, all-patients-treated; AE, adverse event; '-' denotes AEs with an incidence < 5% in both treatment groups in the respective severity subgroup.

memantine treatment here are over and above those produced by donepezil alone. Also notable is that LOCF analyses yielded statistical significance for all domain measures (cognition, function, global status), analyses (efficacy in individual domains, marked clinical worsening), and groups/subgroups (MOD-SEV, MOD) (eight out of eight LOCF comparisons favoured combination therapy at  $P < 0.05$ ), whereas OC analyses yielded statistical significance ( $P < 0.05$ ) favouring combination therapy in six of eight analyses (the exceptions being cognition and function in the MOD subgroup). Nonetheless, the effect size estimates for the magnitude of clinical effects using LOCF and OC analyses were similar, and favoured combination therapy in each case. Taken together with the observation that the MOD subgroup contains only approximately two-thirds the sample size of the MOD-SEV group, and would therefore be more sensitive to the adverse effects of reductions in power from an OC analysis (compared to an LOCF analysis), these observations further support the hypothesis that lack of power, along with differences in baseline severity and ChEI type, substantially contributed to the absence of significant findings in the original MEM-MD-12 study.

While longer-term observational clinical cohort studies also support the clinical effectiveness of combination therapy above and beyond stable ChEI monotherapy [32-34], the recently published 52-week, randomised, placebo-controlled DOMINO-AD study in patients with moderate to severe AD (mean baseline standardised MMSE = 9.1), receiving stable donepezil therapy for at least 6 weeks, and whose clinician was considering a change in drug treatment, did not report similar effects [35]. This was an important study that had substantial methodological limitations, which may have particularly affected reliability and validity of results regarding detecting potential group differences over the full course of the 52-week study; these limitations included a study re-design due to delayed and insufficient recruitment, subsequently not meeting re-adjusted sample size requirements, high and imbalanced attrition causing non-ignorable missing data, and reporting of mixed effects modelling results based on difference testing, as opposed to equivalence testing, performed without a posteriori power analysis (when required sample sizes were not achieved). Overall, these limitations may have substantially biased towards null results and resulted in inadequate power to demonstrate significant differences between groups, particularly between donepezil monotherapy and memantine added to donepezil. Yet, despite these limitations, the overall results provide further evidence to support the benefits of donepezil continuation, and of memantine treatment despite discontinuation of donepezil. Though controversial and open to interpretation, potential signals of efficacy for the addition of

memantine to donepezil therapy, as reflected in the initial 30 weeks of the study (during which the patient numbers were much higher compared to week 52 assessment), and in the behavioural domain, have been postulated by other researchers, or reported in the study, and warrant further secondary analysis [35,36]. Additionally, while scientific, methodological and practical considerations preclude direct comparison or inclusion of DOMINO-AD data in the current study, which was designed to assess a different hypothesis, this would be of great future interest in a suitably designed study that would broaden generalisability of findings to a wider and more heterogeneous patient population across two continents.

Long-term observational clinical cohort studies performed in naturalistic settings with prospectively collected data show similar patterns to RCTs, and demonstrate Level II grade, generalisable evidence that favours combination treatment over monotherapy, and monotherapy over placebo/no anti-dementia medication treatment [32-34]. Long-term combination therapy with memantine added to a ChEI has, in the clinical setting, been observed to significantly reduce cognitive and functional decline, and to delay time to nursing home admission compared to ChEI monotherapy and to standard care without a ChEI or memantine [32,33]. Furthermore, the benefits of combination therapy increase with time on treatment, and are sustained for years [32]. The latter observation is further supported by Rountree and colleagues who found that benefits of treatment with a ChEI and/or memantine significantly increased with treatment persistence and were observable across multiple symptom domains and stages of disease, including moderate and severe AD [37]. Finally, the recent REAL.FR cohort study, which followed 686 patients with mild to moderate AD in 16 specialised memory clinics in France (89% used ChEI monotherapy at baseline, 26% used ChEI and memantine combination therapy by year 4), reported significantly less decline in this cohort over 4 years compared to untreated historical cohorts [38].

#### Clinical worsening

In the MOD-SEV subgroup, the occurrence of marked clinical worsening in patients receiving memantine added to donepezil was less than half that of those receiving placebo added to donepezil (8.5% versus 18.9%;  $P = 0.003$ ; OC; MMSE 5 to 19). This rate is similar to the rate reported in patients receiving any concurrent ChEI (donepezil, galantamine, or rivastigmine) previously reported in a pooled clinical worsening analysis using data from the same two studies (9.8% versus 18.3%;  $P < 0.01$ ; OC; MMSE 5 to 19) [6]. In the present study, the occurrence of marked clinical worsening in the MOD subgroup was also observed to be less than half for those treated with