SHORT COMMUNICATION

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Memantine for the Treatment of Alzheimer's Disease

Tolerability and Safety Data from Clinical Trials

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Abstract

Background: Memantine, a moderate-affinity, uncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors, is the first non-cholinergic agent approved for the treatment of Alzheimer's disease (AD), and the first medication approved in the US and Europe for the treatment of moderate to severe stages of the disease. The objective of this study was to analyse safety and tolerability data from phase III memantine trials and from the open-label extensions of those trials.

Method: We conducted an analysis of the pooled data for tolerability and safety from six double-blind, placebo-controlled, memantine trials with a minimum duration of 24 weeks (three trials in mild to moderate AD and three in moderate to severe AD; 20 mg/day; 2311 patients) and four open-label extensions of those trials (two in mild to moderate AD and two in moderate to severe AD; 20 mg/day, 1405 patients), for a total treatment period of up to 2 years.

Results: The analysis revealed that adverse events occurring during both short- and long-term memantine treatment were minimal, and similar in type and frequency to those reported for placebo-treated patients. The most frequently reported adverse events in placebo-controlled trials included agitation (7.5% memantine vs 12.0% placebo), falls (6.8% vs 7.1%), dizziness (6.3% vs 5.7%), accidental injury (6.0% vs 7.2%), influenza-like symptoms (6.0% vs 5.8%), headache (5.2% vs 3.7%) and diarrhoea (5.0% vs 5.6%). Discontinuations due to adverse events were similar in memantine- and placebo-treated groups (8.9% vs 9.8%, respectively).

Conclusion: Consistent with the favourable tolerability profile of memantine observed in clinical use, this analysis of pooled safety data indicates that both short- and long-term memantine treatment of patients with AD is safe and well tolerated, with an adverse event profile similar to that of placebo.

Background

Memantine, a moderate-affinity, uncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors, was the first drug to receive approval for treatment of moderate to severe Alzheimer's disease (AD) in Europe (in 2002) and the US (in 2003). (In October 2006, the cholinesterase inhibitor donepezil was also approved in the US for the treatment of severe AD.) The systematic clinical use of meman-

tine dates back to 1978, when it was registered in Germany and became popular as an all-purpose neurological tonic; in 1989, it was launched as an anti-dementia drug.[1]

Over the past 15 years, the efficacy and safety of memantine have been assessed in clinical trials of patients with various types of dementia and various degrees of disease severity.[2-9] The approval for memantine by the US FDA as a treatment option for patients with moderate to severe AD was based on its efficacy in three clinical trials in moderate to severe AD or dementia,[6,7,9] coupled with a favourable safety and tolerability profile from 57 trials in control subjects and patients with a variety of neurological conditions.[10,11] Shortly thereafter, trials in patients with mild to moderate AD were performed, and many of the key efficacy trials have been continued as open-label extension studies.

The objective of this report was to analyse safety and tolerability data collected in the six 6-month phase III memantine trials, involving patients with mild to moderate AD or moderate to severe AD. Additional data from the open-label extensions of these trials are also reported, for a total treatment period of up to 104 weeks.

Methods

The safety and tolerability data were collected from double-blind, placebo-controlled (DBPC) memantine AD trials with a minimum duration of 24 weeks and open-label extensions (OLEX) of those studies. Trial data, provided by Forest Laboratories, Inc., Merz Pharmaceuticals GmbH and H. Lundbeck A/S were current as of 11 August 2006. Our data set did not include information from a recently published Chinese trial (study 10116) involving 258 patients with moderate to severe AD,[12] or from an unpublished trial in severe AD, recently completed in Japan.[13] The data shown here represent a compilation of safety (deaths, serious adverse events [SAEs]) and tolerability (AEs, discontinuations) outcomes; no inferential statistical analysis was performed.

Results

Safety Population and Drug Exposure

The short-term safety data presented in this report originate from six DBPC memantine trials in AD;[5-7,14-16] long-term safety data are from four OLEX of five of those trials[17-21] (one OLEX

Table I. Individual study profiles

Study and study number	Duration (wk)	No. of subjects		AD severity
		PBO	MEM	
DBPC trials				
9605[6]	28	126	126	Moderate to severe
MD-01[14]	24	172	178	Moderate to severe
MD-02[7]	24	201	202	Moderate to severe
99679[15]	24	152	318	Mild to moderate
MD-10[5]	24	202	201	Mild to moderate
MD-12[16]	24	216	217	Mild to moderate
OLEX trials				
9605 OLEX[17]	24	80	95	Moderate to severe
MD-03 ABC[18]a	80	264b	296b	Moderate to severe
MD-11 ABC[19,20]c	80	160b	154b	Mild to moderate
MD-12 AB[21]	80	178b	178b	Mild to moderate

a Study MD-03 is an OLEX of trials MD-01 and MD-02.

b Number of patients who entered phase A.

c Study MD-11 is an OLEX of trial MD-10.

AD = Alzheimer's disease; **DBPC** = double-blind, placebo-controlled; **MEM** = 'memantine' for DBPC trials and 'memantine-memantine' for OLEX trials; **OLEX** = open-label extension; **PBO** = 'placebo' for DBPC trials and 'placebo-memantine' for OLEX trials.

Table II. Characteristics of Alzheimer's disease (AD) patients in double-blind, placebo-controlled memantine trials

Parameter	All		Mild to moderate AD		Moderate to severe AD	
	PBO (n = 1069)	MEM (n = 1242)	PBO (n = 570)	MEM (n = 736)	PBO (n = 499)	MEM (n = 506)
Age (y)[a]	76.1 ± 8.2	75.8 ± 8.0	75.6 ± 8.1	75.3 ± 7.6	76.7 ± 8.2	76.5 ± 8.4
Female [n (%)]	650 (60.8)	792 (63.8)	316 (55.4)	444 (60.3)	334 (66.9)	348 (68.8)
White [n (%)]	983 (92.0)	1139 (91.7)	541 (94.9)	703 (95.5)	442 (88.6)	436 (86.2)
Weight (kg)[a]	67.9 ± 14.1	67.4 ± 14.0	69.5 ± 14.3	67.8 ± 14.1	66.0 ± 13.6	66.9 ± 13.8
MMSE[a]	13.9 ± 5.1	14.4 ± 5.3	17.6 ± 3.5	17.7 ± 3.6	9.8 ± 3.2	9.5 ± 3.2
Treatment duration (days)[a]	153.2 ± 43.3	153.3 ± 44.4	156.3 ± 36.2	153.4 ± 40.7	149.7 ± 50.1	153.2 ± 49.5
Treatment duration [n (%)]						
≥1 wk	1061 (99.3)	1229 (99.0)	567 (99.5)	729 (99.0)	494 (99.0)	500 (98.8)
≥4 wk	1034 (96.7)	1200 (96.6)	556 (97.5)	716 (97.3)	478 (95.8)	484 (95.7)
≥12 wk	951 (89.0)	1108 (89.2)	524 (91.9)	665 (90.4)	427 (85.6)	443 (87.5)
≥18 wk	909 (85.0)	1064 (85.7)	509 (89.3)	643 (87.4)	400 (80.2)	421 (83.2)
≥24 wk	632 (59.1)	753 (60.6)	345 (60.5)	432 (58.7)	287 (57.5)	321 (63.4)
≥26 wk	84 (7.9)	101 (8.1)	4 (0.7)	10 (1.4)	80 (16.0)	91 (18.0)

a Mean ± SD.

MEM = memantine; **MMSE** = Mini-Mental State Examination; **PBO** = placebo.

trial enrolled patients from two of the DBPC trials; table I). Three of the DBPC trials[6,7,14] (24–28 weeks) and two OLEX trials[17,18] (24–80 weeks) enrolled patients with moderate to severe AD; three DBPC trials[5,15,16] (24–26 weeks) and two OLEX trials[19,21] (80 weeks) enrolled patients with mild to moderate AD.

Patients' baseline characteristics and the mean duration of treatment for the DBPC trials and OLEX studies are shown in tables II and III. Of the 1405 patients who received open-label memantine treatment, 1149 were treated for at least 24 weeks. Taken together, safety populations of the placebo-controlled and open-label AD studies included 1924 patients exposed to memantine for up to 104 weeks.

Across all trials, patients were well-matched for age, sex, weight and Mini-Mental State Examination (MMSE) scores between the treatment groups (tables II and III). The average (mean ± SD) ages of patients treated with placebo and memantine across all DBPC trials were 76.1 ± 8.2 and 75.8 ± 8.0 years, respectively; the average MMSE scores for placebo- and memantine-treated patients were 13.9 ± 5.1 and 14.4 ± 5.3, respectively (table II).

Adverse Events

Memantine (10–20 mg daily) was safe and well tolerated both in DBPC and in OLEX trials, with a low frequency of specific AEs. In the six DBPC trials, a similar proportion of memantine (57.2%) and placebo (57.9%) patients reported a treatment-emergent adverse event (TEAE); the most frequently reported AEs included agitation, fall, dizziness, accidental injury, influenza-like symptoms, headache and diarrhoea (table IV).

In the mild-to-moderate DBPC AD trials, no TEAEs were reported in the memantine groups with a frequency that was >5% and more than twice that of placebo. In trials in moderate to severe AD, hypertension was reported in 5.1% of memantine-treated patients and 2.2% of placebo-treated patients (table IV).

Table V lists the most frequently reported AEs in OLEX trials involving patients with either mild to moderate AD or moderate to severe AD. In all OLEX trials, 78.1% patients reported at least one TEAE, with agitation, accidental injury, fall and urinary tract infection being experienced by at least 10% of patients in all groups. Comparison of the two treatment sequences (placebo-memantine and memantine-memantine) revealed no evidence of increased risk of AEs associated with the 6 months

Table III. Characteristics of patients in open-label extensions memantine trials in Alzheimer's disease (AD)

Parameter	All			Mild to moderate AD			Moderate to severe AD		
	PBO-MEM (n = 682)	MEM-MEM (n = 723)	total (n = 1405)	PBO-MEM (n = 338)	MEM-MEM (n = 332)	total (n = 670)	PBO-MEM (n = 344)	MEM-MEM (n = 391)	total (735)
Age (y)[a]	76.5 ± 8.3	76.1 ± 8.0	76.3 ± 8.1	76.5 ± 8.5	76.0 ± 7.7	76.2 ± 8.1	76.6 ± 8.1	76.1 ± 8.2	76.3 ± 8.1
Female [n (%)]	418 (61.3)	457 (63.2)	875 (62.3)	183 (54.1)	189 (56.9)	372 (55.5)	235 (68.3)	268 (68.5)	503 (68.4)
White [n (%)]	623 (91.3)	649 (89.8)	1272 (90.5)	320 (94.7)	308 (92.8)	628 (93.7)	303 (88.1)	341 (87.2)	644 (87.6)
Weight (kg)[a]	68.7 ± 14.8	68.2 ± 14.2	68.5 ± 14.5	71.2 ± 15.3	69.1 ± 14.4	70.2 ± 14.9	66.2 ± 13.9	67.5 ± 13.9	66.9 ± 13.9
MMSE[a]	13.5 ± 5.0	13.0 ± 5.0	13.3 ± 5.0	17.2 ± 3.5	17.0 ± 3.7	17.1 ± 3.6	9.9 ± 3.2	9.6 ± 3.2	9.7 ± 3.2
Treatment duration (d)[a]	368.0 ± 196.2	362.7 ± 198.2	365.3 ± 197.2	441.8 ± 171.9	436.8 ± 179.3	439.3 ± 175.5	295.7 ± 191.7	299.8 ± 191.9	297.9 ± 191.7
Treatment duration [n (%)]									
≥1 wk	678 (99.4)	714 (98.8)	1392 (99.1)	336 (99.4)	328 (98.8)	664 (99.1)	342 (99.4)	386 (98.7)	728 (99.0)
≥4 wk	657 (96.3)	702 (97.1)	1359 (96.7)	328 (97.0)	325 (97.9)	653 (97.5)	329 (95.6)	377 (96.4)	706 (96.1)
≥12 wk	621 (91.1)	662 (91.6)	1283 (91.3)	317 (93.8)	314 (94.6)	631 (94.2)	304 (88.4)	348 (89.0)	652 (88.7)
≥18 wk	607 (89.0)	627 (86.7)	1234 (87.8)	311 (92.0)	300 (90.4)	611 (91.2)	296 (86.0)	327 (83.6)	623 (84.8)
≥24 wk	569 (83.4)	580 (80.2)	1149 (81.8)	305 (90.2)	284 (85.5)	589 (87.9)	264 (76.7)	296 (75.7)	560 (76.2)
≥26 or 28[b] wk	521 (76.4)	525 (72.6)	1046 (74.4)	295 (87.3)	271 (81.6)	566 (84.5)	219 (63.7)	245 (62.7)	464 (63.1)
≥44[b] or 48 wk	375 (55.0)	391 (54.1)	766 (54.5)	259 (76.6)	249 (75.0)	508 (75.8)	125 (36.3)	151 (38.6)	276 (37.6)
≥52 or 60[b] wk	368 (54.0)	381 (52.7)	749 (53.3)	229 (67.8)	222 (66.9)	451 (67.3)	123 (35.8)	146 (37.3)	269 (36.6)
≥78 or 80[b] wk	265 (38.9)	287 (39.7)	552 (39.3)	122 (36.1)	147 (44.3)	269 (40.1)	84 (24.4)	100 (25.6)	184 (25.0)

a Mean ± SD.

b Mild to moderate AD trials.

MEM-MEM = memantine-memantine; **MMSE** = Mini-Mental State Examination; **PBO-MEM** = placebo-memantine.

Table IV. Treatment-emergent adverse events (TEAEs) and discontinuations due to adverse events (AEs) in double-blind, placebo-controlled trials

AE	All		Mild to moderate AD		Moderate to severe AD	
	PBO (n = 1069)	MEM (n = 1242)	PBO (n = 570)	MEM (n = 736)	PBO (n = 499)	MEM (n = 506)
Pts with TEAEs [n (%)][a]						
At least 1 TEAE	619 (57.9)	710 (57.2)	299 (52.5)	371 (50.4)	341 (68.3)	345 (68.2)
Accidental injury	77 (7.2)	74 (6.0)	33 (5.8)	43 (5.8)	44 (8.8)	31 (6.1)
Agitation	128 (12.0)	93 (7.5)	39 (6.8)	35 (4.8)	89 (17.8)	58 (11.5)
Confusion	37 (3.5)	56 (4.5)	18 (3.2)	27 (3.7)	19 (3.8)	29 (5.7)
Diarrhoea	60 (5.6)	62 (5.0)	25 (4.4)	30 (4.1)	35 (7.0)	32 (6.3)
Dizziness	61 (5.7)	78 (6.3)	30 (5.3)	44 (6.0)	31 (6.2)	34 (6.7)
Fall	76 (7.1)	84 (6.8)	36 (6.3)	49 (6.7)	40 (8.0)	35 (6.9)
Headache	40 (3.7)	64 (5.2)	21 (3.7)	39 (5.3)	19 (3.8)	25 (4.9)
Hypertension	29 (2.7)	54 (4.3)	18 (3.2)	28 (3.8)	11 (2.2)	26 (5.1)
Influenza-like symptoms	62 (5.8)	74 (6.0)	35 (6.1)	47 (6.4)	27 (5.4)	27 (5.3)
Urinary incontinence	44 (4.1)	46 (3.7)	16 (2.8)	17 (2.3)	28 (5.6)	29 (5.7)
Urinary tract infection	49 (4.6)	50 (4.0)	16 (2.8)	22 (3.0)	33 (6.6)	28 (5.5)
Pts who discontinued due to AEs [n (%)][b]						
Any AE	105 (9.8)	111 (8.9)	33 (5.8)	60 (8.2)	72 (14.4)	51 (10.1)
Agitation	25 (2.3)	15 (1.2)	7 (1.2)	4 (0.5)	18 (3.6)	11 (2.2)
Confusion	5 (0.5)	11 (0.9)	0	3 (0.4)	5 (1.0)	8 (1.6)
Dizziness	6 (0.6)	7 (0.6)	2 (0.4)	6 (0.8)	4 (0.8)	1 (0.2)

a Table includes all TEAEs that occurred in at least 5% of pts in any group.

b AEs most frequently leading to discontinuation in all trials.

AD = Alzheimer's disease; **MEM** = memantine; **PBO** = placebo; **pts** = patients.

of additional memantine treatment in memantine-memantine-treated patients. Furthermore, the higher frequency of AEs observed in the OLEX studies compared with the DBPC studies (78.1% vs 57.2%) is likely accounted for by the longer duration of the studies and the increasing fragility of the patients.

Discontinuation Due to Adverse Events

In the six DBPC trials, a similar number of memantine-treated (8.9%) and placebo-treated (9.8%) patients withdrew from the trials due to AEs. Agitation was the AE most frequently associated with study discontinuation both in DBPC (1.2% memantine vs 2.3% placebo) and in OLEX (1.9% placebo-memantine vs 1.8% memantine-memantine) trials (tables IV and V).

Deaths, Serious Adverse Events, ECG Evaluations

There were no significant differences in the number of deaths or the frequency of serious AEs between patients treated with placebo and those treated with memantine in pooled studies of mild to moderate AD, moderate to severe AD or overall (table VI).

Also, in a pooled safety population of all subjects from DBPC trials who had an ECG evaluation at both baseline and at the endpoint (placebo, n = 914; memantine, n = 1086), there were no significant differences between the placebo- and memantine-treated patients in the duration of the corrected QT interval at baseline compared with at endpoint (QTc Bazett: placebo = 2.1 ± 23.0 ms, memantine = 0.5 ± 22.1 ms; mean difference = −1.6 ms, 90% CI −3.3, 0.0) [data not shown]. In addition, there were no significant differences in the frequency of potentially clinically significant post-baseline QTc inter-

Table V. Treatment-emergent adverse events (TEAEs) and discontinuations due to adverse events (AEs) in open-label extension trials

AE	All			Mild to moderate AD			Moderate to severe AD		
	PBO-MEM (n = 682)	MEM-MEM (n = 723)	total (n = 1405)	PBO-MEM (n = 338)	MEM-MEM (n = 332)	total (n = 670)	PBO-MEM (n = 344)	MEM-MEM (n = 391)	total (n = 735)
Pts with TEAEs [n (%)][a]									
At least 1 TEAE	528 (77.4)	569 (78.7)	1097 (78.1)	276 (81.7)	273 (82.2)	549 (81.9)	263 (76.5)	302 (77.2)	565 (76.9)
Accidental injury	100 (14.7)	105 (14.5)	205 (14.6)	59 (17.5)	50 (15.1)	109 (16.3)	41 (11.9)	55 (14.1)	96 (13.1)
Agitation	112 (16.4)	110 (15.2)	222 (15.8)	56 (16.6)	45 (13.6)	101 (15.1)	56 (16.3)	65 (16.6)	121 (16.5)
Dizziness	65 (9.5)	45 (6.2)	110 (7.8)	44 (13.0)	29 (8.7)	73 (10.9)	21 (6.1)	16 (4.1)	37 (5.0)
Fall	93 (13.6)	98 (13.6)	191 (13.6)	56 (16.6)	49 (14.8)	105 (15.7)	37 (10.8)	49 (12.5)	86 (11.7)
Urinary incontinence	44 (6.5)	50 (6.9)	94 (6.7)	25 (7.4)	16 (4.8)	41 (6.1)	19 (5.5)	34 (8.7)	53 (7.2)
Urinary tract infection	90 (13.2)	78 (10.8)	168 (12.0)	42 (12.4)	34 (10.2)	76 (11.3)	48 (14.0)	44 (11.3)	92 (12.5)
Pts who discontinued due to AEs [n (%)][b]									
Any AE	116 (17.0)	97 (13.4)	213 (15.2)	59 (17.5)	36 (10.8)	95 (14.2)	57 (16.6)	61 (15.6)	118 (16.1)
Accidental injury	8 (1.2)	7 (1.0)	15 (1.1)	4 (1.2)	3 (0.9)	7 (1.0)	4 (1.2)	4 (1.0)	8 (1.1)
Agitation	13 (1.9)	13 (1.8)	26 (1.9)	7 (2.1)	3 (0.9)	10 (1.5)	6 (1.7)	10 (2.6)	16 (2.2)
Dizziness	9 (1.3)	4 (0.6)	13 (0.9)	6 (1.8)	1 (0.3)	7 (1.0)	3 (0.9)	3 (0.8)	6 (0.8)
Pneumonia	7 (1.0)	7 (1.0)	14 (1.0)	4 (1.2)	3 (0.9)	7 (1.0)	3 (0.9)	4 (1.0)	7 (1.0)

a Table includes AEs that ranked as the five most frequently reported in any trial group.

b Table includes AEs leading to discontinuation that ranked as the three most frequently reported in any trial group.

AD = Alzheimer's disease; **MEM** = memantine; **PBO** = placebo; **pts** = patients.

Table VI. Deaths and serious adverse events (SAEs)

Trial	Safety population (n)		Deaths [n (%)]		Pts with at least 1 SAE [n (%)]		Number of SAEs per 100 pts	
	PBO	MEM	PBO	MEM	PBO	MEM	PBO	MEM
9605	126	126	5 (4.0)	2 (1.6)	24 (19.0)	16 (12.7)	26.2	15.1
MD-01	172	178	3 (1.7)	5 (2.8)	29 (16.9)	26 (14.6)	26.7	23.6
MD-02	201	202	2 (1.0)	1 (0.5)	20 (10.0)	25 (12.4)	15.4	21.3
MOD-SEV	**499**	**506**	**10 (2.0)**	**8 (1.6)**	**73 (14.6)**	**67 (13.2)**	**22.0**	**20.6**
99679	152	318	2 (1.3)[a]	5 (1.6)	9 (5.9)	33 (10.4)	7.2	10.7
MD-10	202	201	1 (0.5)	1 (0.5)	20 (9.9)	20 (10.0)	13.4	16.9
MD-12	216	217	2 (0.9)	3 (1.4)	28 (13.0)	27 (12.4)	21.8	18.0
MILD-MOD	**570**	**736**	**5 (0.9)**	**9 (1.2)**	**57 (10.0)**	**80 (10.9)**	**14.9**	**14.5**
All	**1069**	**1242**	**15 (1.4)**	**17 (1.4)**	**130 (12.2)**	**147 (11.8)**	**18.2**	**17.0**

a Includes one patient who died >30 days after completing the trial.

MEM = memantine; **MILD-MOD** = trials in mild to moderate Alzheimer's disease; **MOD-SEV** = trials in moderate to severe Alzheimer's disease; **PBO** = placebo; **pts** = patients.

vals (≥500 ms) and QTc interval changes from baseline (≥30 ms and ≥60 ms).

Discussion

In both short- and long-term clinical trials, memantine (10–20 mg/day) was shown to be a safe, well-tolerated drug for the treatment of AD. Across all short-term DBPC studies, the type and frequency of individual AEs and the frequency of discontinuations due to AEs were similar between patients taking memantine and those taking placebo, a conclusion also reached in two recent meta-analyses of DBPC memantine trials.[22,23] In addition, there were no significant differences in the frequency of deaths, serious AEs, or ECG abnormalities in the DBPC studies. A similar safety and tolerability profile was reported in a recently published DBPC trial of memantine in moderate to severe AD, conducted in China (n = 258).[12] In long-term studies (OLEX), there were no notable differences in the type of AEs, number of AEs, or number of discontinuations between patients switched from placebo to memantine and those who received memantine continuously throughout the study period.

The observation that there were no differences in tolerability or safety between patients treated with memantine and placebo poses a particular advantage for patients with AD, who typically become more clinically fragile as the illness progresses. This tolerability profile of memantine should lead to relatively high compliance rates in real-life settings, potentially maximizing the clinical benefits of the drug.

The favourable safety and tolerability profile of memantine, an uncompetitive antagonist of NMDA receptors (NMDARs), is usually attributed to its receptor-binding properties: low to moderate affinity, high voltage dependence, and fast on/off kinetics. For example, memantine is better tolerated than uncompetitive NMDAR antagonists with a high binding affinity, such as ketamine and MK-801.[1,24,25]

In addition, the safety and tolerability profile of memantine appears to be distinct from those of donepezil, rivastigmine and galantamine, the three cholinesterase inhibitors (ChEIs) currently used for the treatment of AD. A recent Cochrane meta-analysis stated that short-term ChEI treatment in patients with AD is "fairly well tolerated",[26] but it also revealed that, compared with placebo, the use of ChEIs was associated with a significantly higher occurrence of all withdrawals, withdrawals due to AEs, and total number of patients who experienced at least one AE. The meta-analysis also reported that the odds of experiencing several gastrointestinal AEs (e.g. anorexia, diarrhoea, nausea, vomiting) were higher among patients treated with a ChEI, compared with patients treated with placebo.[26] Available OLEX data on ChEI use suggest long-term safety profiles similar to those observed in short-term trials, with possible improvements in tolerability with increasing duration of treatment.[27-30]

The fact that memantine and the ChEIs do not interact *in vivo*[31] suggests a possibility of safe and tolerable combination therapies, which indeed has been demonstrated in several DBPC trials.[7,32,33] The non-overlapping tolerability profiles of memantine and the ChEIs should be used to maximize the benefits of treatments for AD.

Based on the data presented here, we conclude that the tolerability and safety of memantine in patients with AD is almost indistinguishable from that of placebo, which is of benefit to patients in moderate to severe stages of the illness. In addition, due to its low potential for drug-drug interactions, memantine may be particularly well suited for combination therapy.

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