Synopsis – Study 11018

Title of Study A randomised, double-blind, placebo-controlled, 6-month study of the efficacy and safety of memantine in patients with Parkinson's Disease Dementia or Dementia with Lewy Bodies
Investigators 30 investigators at 30 centres in 8 countries *Signatory investigator* – Murat Emre, Professor, MD, Department of Medicine, Istanbul University, Istanbul, Turkey
Study Centres 30 centres – 2 in Austria, 4 in France, 3 in Germany, 3 in Greece, 4 in Italy, 6 in Spain, 4 in Turkey, and 4 in the United Kingdom
Publication Emre M and the 11018 study investigators. *A Randomised, Double-blind, Placebo-controlled, 6-Month Study of the Efficacy and Safety of Memantine in Patients with Parkinson's Disease Dementia (PDD) or Dementia with Lewy Bodies (DLB)*. Poster at the 13th Congress of the European Federation of Neurological Societies (EFNS), Florence, Italy, 12-15 September 2009.
Study Period *First patient first visit* – 31 January 2007 *Last patient last visit* – 23 December 2008
Objectives To explore the efficacy and safety of memantine compared to placebo over a 6-month period, in outpatients with a diagnosis of Parkinson's Disease Dementia or Dementia with Lewy Bodies, with a mild to moderate severity
Methodology • This was an interventional, multi-national, multi-centre, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study. • Following screening, the patients were randomised (1:1) to 24 weeks of treatment with placebo or memantine and stratified according to diagnosis of DLB or PDD. Patients randomised to memantine were up-titrated by weekly increments of 5 mg over a 4-week dose escalation period. The target dose of 20 mg/day was administered at the start of the fourth week, and maintained for the rest of the study. • Efficacy data were collected at baseline, Weeks 4, 12, and 24 (except for Unified Parkinson's Disease Rating Scale [UPDRS] data, which was only collected at baseline and Week 24. At Week 12, only UPDRS part III data was collected). • Safety data were collected at baseline, Weeks 4, 12, 16, and 24. • A Safety Follow-up Visit was scheduled for 4 weeks after completion or withdrawal from the study.

Number of Patients Planned and Analysed

- 200 patients were planned for enrolment: a minimum of 80 in the DLB group and 80 in the PDD group
- Patient disposition is tabulated below:

	Memantine		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	98		101		199	
Patients treated (all-patients-treated set [APTS]):	96		99		195	
Patients completed	80	83.3	79	79.8	159	81.5
Patients withdrawn	16	16.7	20	20.2	36	18.5
All-patients-treated set DLB [APTS-DLB]):	34		41		75	
Patients completed	27	79.4	31	75.6	58	77.3
Patients withdrawn	7	20.6	10	24.4	17	22.7
All-patients-treated set PDD [APTS-PDD]):	62		58		120	
Patients completed	53	85.5	48	82.8	101	84.2
Patients withdrawn	9	14.5	10	17.2	19	15.8
Primary reason for withdrawal:						
Adverse events	11	11.5	12	12.1	23	11.8
Lack of efficacy	1	1.0	1	1.0	2	1.0
Non-compliance with study protocol	0	0.0	1	1.0	1	0.5
Withdrawal of consent	4	4.2	6	6.1	10	5.1
Analysis sets:						
APTS	96		99		195	
APTS-DLB	34		41		75	
APTS-PDD	62		58		120	
Full-analysis set (FAS)	93		97		190	
Full-analysis set for the DLB population (FAS-DLB)	33		41		74	
Full-analysis set for the PDD population (FAS-PDD)	60		56		116	

Main Inclusion Criteria

Outpatients ≥50 years of age who:

- had a current diagnosis of probable DLB according to the third report of the DLB consortium or a current diagnosis of Parkinson's Disease according to the clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank and a current diagnosis of PDD according to DSM-IV-TR™ criteria
- had mild to moderate dementia, defined as a Mini Mental State Examination (MMSE) total score ≥10 and ≤24 at screening and at baseline
- had a modified Hoehn & Yahr score ≤III while "ON"
- had a magnetic resonance imaging (MRI) or computerised tomography (CT) scan within the past 12 months with results consistent with the diagnosis of either DLB or PDD and not suggestive that the symptoms of dementia were more likely to be attributable to another cause (such as vascular dementia)

Investigational Medicinal Product, Dose and Mode of Administration, Batch Numbers

Memantine – 20 mg/day; tablets, orally; batch Nos. 31690C01/R412-221 (5 mg) and 41130/R408-754 (10 mg)

Duration of Treatment

24 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number

Placebo – tablets, orally; batch No. 31689C01

Efficacy Assessments

- Global – Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC)
- Behaviour – Neuropsychiatric Inventory (NPI)
- Function – Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL_{23})
- Motor function – UPDRS and UPDRS part III
- Caregiver burden – Zarit Burden Interview (ZBI)
- Cognition – Boston Naming Test (BNT), Benton Facial Recognition Test (BFRT), Benton Judgement of Line Orientation (BJLO), Simple (SRT) and Choice (CRT) Reaction Time, Digit Ordering Test (DOT), Brief Extended Verbal Paired Associates (VePAL), Alzheimer's Disease Assessment Scale – Cognitive subscale – Orientation Test (ADAS-cog-OT), Verbal Recall and Recognition Test (VRRT), Controlled Oral Word Association Test (COWAT), Category Fluency Test (CFT), Alternating Categories Test (ACT), Trails Making Test (TMT), CogState Set Shifting Test (CASST), Ten-point Clock-Drawing Test (10-CDT), Stroop Interference Test (congruent [SIT-C] and incongruent [SIT-I] conditions)

Safety Assessments

Adverse events (AEs), vital signs, and weight

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all randomised patients who took at least one dose of investigational medicinal product (IMP)
  - *all-patients-treated set for the DLB population* (APTS-DLB) – all randomised patients with DLB who took at least one dose of IMP
  - *all-patients-treated set PDD for the PDD population* (APTS-PDD) – all randomised patients with PDD who took at least one dose of IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-baseline assessment of at least one efficacy outcome
  - *full-analysis set for the DLB population* (FAS-DLB) – all patients in the APTS-DLB who had at least one valid post-baseline assessment of at least one efficacy outcome
  - *full-analysis set for the PDD population* (FAS-PDD) – all patients in the APTS-PDD who had at least one valid post-baseline assessment of at least one efficacy outcome
- No primary endpoint was defined; all analyses are considered exploratory.
- The efficacy analyses were performed on the FAS, FAS-DLB, and FAS-PDD, using both last observation carried forward (LOCF) and observed cases (OC). ADCS-CGIC was analysed by analysis of variance (ANOVA). All other efficacy assessments were evaluated by the change from baseline variable, using analysis of covariance (ANCOVA). Treatment and centre were included as factors in all models, and for the efficacy assessments with a baseline assessment, baseline score, patient population (DLB or PDD), and baseline-by-population interaction were also included in the models. The treatment-by-population interaction was evaluated in the FAS analyses. The ADCS-CGIC was further analysed using the Cochran-Mantel-Haenszel (CMH) test, stratified for centre and disease population.
- Cognition was analysed using change from baseline in the individual cognitive scale scores, the domain (executive, attention, memory, language, and visuospatial) composite scores, and the total composite score (the sum of all domain scores).
- Due to the different structures of the cognitive scales, each raw score was standardised. In order to create dimensionless raw scores, each scale-specific score (on an individual basis) was standardised at each visit by subtracting the analysis set (FAS-PDD or FAS-DLB) sample mean score at baseline from the raw score and dividing the difference by the sample standard deviation at baseline. In order to adjust for different numbers of scales within specified cognitive domains, as well as for the scale score correlation within patients, the domain scores were standardised by dividing the domain score by the disease-specific domain sample standard deviation at baseline for the composite score. For domain and composite analyses, cognitive scales were modified in a manner such that higher scores always represent better performance.

Demography of Study Population

- All but one of the patients were Caucasian, 45% of them were women, and the mean age at baseline was 73.5 years (range: 52 to 92 years). There was a slightly higher proportion of men in the placebo group than in the memantine group (58% *versus* 53%), and there were more men than women in the DLB population (59% *versus* 41%.
- At screening, there were no clinically relevant differences between the treatment groups in age, height, weight, body mass index (BMI), medical, psychiatric or neurological history, Hoehn & Yahr, UPDRS, or MMSE scores, or with respect to the use of concomitant medication.
- In the PDD population, patients in the memantine group had had a diagnosis of Parkinson's disease (PD) for approximately 1 year shorter than patients in the placebo group at screening. The time between diagnosis of PDD and PD was also approximately 1 year shorter in the memantine group than in the placebo group.

Efficacy Results

- Overall, memantine-treated patients improved more on the ADCS-CGIC than did placebo-treated patients. This improvement was statistically significant at Week 24 for patients with DLB, and at Week 12 for patients with PDD.

ACGS-CGIC score (FAS, OC, ANOVA) Patient population	Week	Memantine		Placebo		Difference from Placebo
		n	Mean	n	Mean	
DLB+PDD	12	86	3.3	88	3.8	-0.5**
	24	79	3.4	78	3.7	-0.3
DLB	12	30	3.3	38	3.7	-0.4
	24	27	3.1	31	3.8	-0.8*
PDD	12	56	3.3	50	3.9	-0.6**
	24	52	3.5	47	3.6	-0.1

* p<0.05; ** p<0.01 *versus* placebo

- A statistically significantly higher proportion of memantine-treated patients at Week 12, and a numerically higher proportion of memantine-treated patients at Week 24 showed improvement or stabilisation on the ADCS-CGIC than did placebo-treated patients. This effect was more pronounced in the DLB population at Week 24, while memantine-treated patients in the PDD population showed significant improvement only at Week 12.

ACGS-CGIC grouped categories (FAS, OC, CMH) Patient population		Improvement				No Change				Deterioration			
		Memantine		Placebo		Memantine		Placebo		Memantine		Placebo	
	Week	n	%	n	%	n	%	n	%	n	%	n	%
DLB+PDD	12**	49	57	34	39	30	35	34	39	7	8	20	23
	24	44	56	39	50	23	29	17	22	12	15	22	28
DLB	12	15	50	15	40	13	43	13	34	2	7	10	26
	24	15	56	14	45	7	26	5	16	5	18	12	39
PDD	12*	34	61	19	38	17	30	21	42	5	9	10	20
	24	29	56	25	53	16	31	12	26	7	14	10	21

* p<0.05; ** p<0.01 *versus* placebo

Efficacy results (continued)

- Overall, memantine-treated patients improved more on the NPI at Week 12 than did placebo-treated patients. Memantine-treated patients with DLB improved statistically significantly more (by 5.9 points; LOCF) on the NPI at Week 24 than did placebo-treated patients. Memantine treatment did not cause significant improvement on the NPI in patients with PDD.

Change from baseline NPI total score (FAS, OC, ANCOVA) Patient population	Week	Memantine		Placebo		Difference from Placebo
		n	Mean	n	Mean	
DLB+PDD	12	86	-3.7	90	-0.6	-3.2*
	24	80	-3.1	79	-1.0	-2.1
DLB	12	30	-4.6	39	0.6	-5.2
	24	27	-6.2	31	-1.1	-5.1^
PDD	12	56	-2.5	51	-0.1	-2.4
	24	53	-2.0	48	-0.7	-1.3

* p=0.051; ^ p<0.05 (LOCF) *versus* placebo

- Memantine-treated patients with DLB improved statistically significantly more at Week 24 than did placebo-treated patients on the NPI single items hallucinations, appetite/eating disorder, delusions, and sleeping/night-time behaviour.
- There were no statistically significant differences in mean change from baseline between the memantine and placebo groups in the ADCS-ADL_{23}, UPDRS, UPDRS part III scale scores in either the DLB+PDD, DLB, or PDD populations.
- Memantine-treated patients in the DLB+PDD and PDD populations improved statistically significantly more at Week 12 in ZBI total and role strain scores than did placebo-treated patients.
- Memantine-treated patients in the entire patient population (DLB+PDD) improved more than placebo-treated patients at Week 24 on the BFRT (visuospatial) and at Week 12 on the COWAT (executive) cognitive scales. In addition, memantine-treated patients with DLB improved more than placebo-treated patients at Week 24 on the SIT-C and 10-CDT (executive) cognitive scales, as did memantine-treated patients with PDD at Week 12 on the COWAT and SIT-I (executive) scales. However, since a reverse trend was found in favour of placebo for some measures (and for some time-points within measures) the results of the cognitive score analysis should be interpreted with caution.

Safety Results

- The adverse event incidence is summarised below:

	Memantine		Placebo	
	n	(%)	n	(%)
Patients treated	96		99	
Patients who died	3		3	
Patients with serious AEs (SAEs)	14	14.6	10	10.1
Patients with AEs	46	47.9	43	43.4
Patients with AEs leading to withdrawal	11	11.5	12	12.1
Total number of AEs	111		93	
Total number of SAEs	27		17	

- Three patients in each treatment group died. The incidence of SAEs was slightly higher in memantine group (14 patients [15%]) than in the placebo group (10 patients [10%]). In both treatment groups and in both disease subpopulations, *nervous system disorders* was the SOC with the highest incidence of SAEs. There were no other apparent trends regarding the deaths and other SAEs except that they reflected the frail, demented, and elderly population being studied.
- The incidence of adverse events was slightly higher in the memantine group (48%) than in the placebo group (43%); the difference was seen in the DLB population. In the memantine group, the incidence of adverse events was higher in the DLB population (53%) than in the PPD population (45%). In placebo-treated patients, the incidence of adverse events was slightly lower (41%) in the DLB population than in the PDD population (45%). Given the patient population and the duration of the study, the incidence of adverse events was low.
- The SOCs with the highest incidences (≥10%) of adverse events were *nervous system disorders* (memantine: 27%; placebo: 13%) and *psychiatric disorders* (memantine: 8%; placebo: 12%). The adverse event with the highest incidence in *nervous system disorders* was *somnolence* (memantine: 5%; placebo: 3%). The adverse events in *psychiatric disorders* were distributed across many different symptoms.
- In the memantine group, the adverse events with an incidence ≥5% comprised *fall* (9%) and *somnolence* (5%). *Somnolence* is known to be associated with memantine treatment. In the placebo group, the incidence of *fall* (8%) was similar to that in the memantine group; no other adverse events had an incidence ≥5%. In the DLB population, *somnolence* was only seen in the memantine group; furthermore, *gastroenteritis viral* (9%, 3 patients) and *pain in extremity* (6%, 2 patients) also had an incidence ≥5% in the memantine group.
- A total of 13 patients (14%) in the memantine group and 7 patients (7%) in the placebo group had one or more *severe* adverse events. None of the severe adverse events were reported in more than 2 patients in either treatment group. Similar incidences of *severe* adverse events were reported in the two disease populations. In the memantine group, 5 patients had *severe*, *related* adverse events (*fall* [SAE], *cerebrovascular accident* [SAE], *Parkinsonism*, *somnolence*, and *hallucination*). In the placebo group, 1 patient had a *severe*, *related* adverse event (*fall* [SAE]).
- A total of 11 patients (11%) in the memantine group and 12 patients (12%) in the placebo group had adverse events contributing to withdrawal. In both treatment groups, the incidence was higher in the DLB population (memantine: 15%; placebo: 17%) than in the PDD population (memantine: 10%; placebo: 9%).
- In the memantine group, the SOC with the highest incidence of adverse events contributing to withdrawal was *nervous system disorders* in both disease populations. In the placebo group, the SOC with the highest incidence of adverse events contributing to withdrawal was *psychiatric disorders* for the DLB population and *nervous system disorders* for the PDD population. No adverse event contributing to withdrawal was reported in more than 2 patients.
- No clinically relevant changes from baseline in vital signs, weight, or BMI were seen during the study.

Conclusions

- This study suggests that memantine is beneficial in the treatment of patients with mild to moderate DLB or PDD. Memantine-treated patients had a better treatment outcome in terms of global and behavioural measures, compared to placebo-treated patients, and larger proportions of memantine-treated patients improved or stayed unchanged in their global status. These findings were more pronounced in patients with DLB.
- Memantine is effective in the treatment of specific behavioural disturbances known to be problematic in DLB and PDD, namely, hallucinations, appetite/eating disorder, delusions, and sleeping/night-time behaviour.
- Although statistically significant differences were detected on individual cognitive scales, no clear beneficial treatment effect in favour of memantine was found on cognition at Week 24 based on the individual scales. Furthermore, due to the large number of missing observations and the limitations associated with alternative appropriate imputation methods, no firm conclusions could be drawn from the overall cognitive composite scores.
- Memantine was safe and well tolerated in patients with DLB as well as in patients with PDD.

Date of the Report

16 December 2009

This study was conducted in compliance with the principles of *Good Clinical Practice*.