Clinical Study Report Synopsis for Public Disclosure

This Clinical Study Report Synopsis is provided to the public for informational purposes only in accordance with legal requirements. Being part of the clinical study report it had been prepared according to legal/regulatory requirements and best practice at the time of study completion.

The study listed may include information about approved and non-approved uses, doses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Patients should always seek medical advice before making any decisions on their treatment. Healthcare professionals should always refer to the specific prescribing information approved for the patient's country or region.

Page numbering in the Clinical Study Report Synopsis may be inconsistent due to the fact that it is part of a comprehensive clinical study report. Information not relevant for the Clinical Study Report Synopsis is crossed-out. Information in the Clinical Study Report Synopsis may have been redacted (blacked out) to fulfill legal requirements (e.g. statutory obligations on protection of personal data) or to protect commercially confidential information of Merz Pharmaceuticals GmbH.

2 SYNOPSIS

Study identifier MRZ 90001-2267 / 1

Title of study

Prospective, randomized, double-blind, placebo-controlled, multicenter study to investigate the efficacy and safety of 10mg memantine in the treatment of memory, concentration or attention problems (subjective cognitive impairment) in the absence of dementia.

Investigator, study sites

The study was performed in Germany (11 active centers) and the United Kingdom (UK) (6 active centers). [redacted]

Publication (reference)

None to date.

Study period:	First subject enrolled:	29 Nov 2010	**Phase:** 2
	Last subject enrolled:	12 Sep 2011	

Objectives

Primary objective:

To investigate the efficacy and safety of 10mg/day memantine in comparison to placebo in the treatment of memory, concentration, or attention problems (subjective cognitive impairment) in the absence of dementia.

Secondary objectives:

To investigate the efficacy of 10mg memantine in comparison to placebo measured by the CogState computer-based neuropsychological test battery (C-NTB), Everyday Cognition 39 (ECog39), and Hospital Anxiety and Depression Scale (HADS).

Study design and methodology

This was a prospective, double-blind, randomized, placebo-controlled, multicenter study with parallel group design. Overall, 297 male and female subjects with complaints of subjective memory, concentration, or attention problems were randomly assigned to one of two treatment groups, i.e., memantine group versus placebo group, in a 1:1 ratio at visit 2 (day 0).

A daily single dose of 10mg or the respective placebo was administered to each subject starting at visit 2 (day 0). The active treatment period lasted 12 weeks followed by a 4 week safety observation period.

Number of subjects planned

A total of 300 subjects with 150 subjects receiving memantine 10mg and 150 subjects receiving placebo were planned to be recruited. At least approximately 100 subjects were planned to be recruited in memory clinics in the UK and Germany and at least approximately 100 subjects were planned to be recruited by non specialist outpatient sites in UK and Germany.

Diagnosis and main criteria for inclusion

Male and female elderly subjects, ≥50 and ≤80 years of age, with subjective worsening of memory, concentration or attention problems for longer than 6 months were enrolled into this study. Subjects could confirm that a relative or friend had noticed the memory, concentration or attention problems of the subject.

The subjects had to have a "Patient Global Impression Severity" (PGI-S) score of ≥ 3 (at least moderate), a MiniCog score of 3 or more and had to experience the memory, concentration or attention problems at least four times per week.

Excluded were subjects with memory, concentration or attention problems that interfered with basic daily activities, subjects with significant neurological disease or major psychiatric disorder, epilepsy or history of epileptic fits, severe or acute mental illness, significant systemic illness, such as cancer, kidney failure, severe hepatic impairment, uncontrolled diabetes, diagnosed pulmonary, gastrointestinal, hepatic, endocrine, untreated vitamin B12, thyroid stimulating hormone or folate deficiencies, sleep apnea, concurrent use of medication that could have affected cognition or taking any medications that are contra-indicated in combination with memantine. Subjects with heart attack, heart failure, arrhythmia or carotid stenosis, history of stroke or transient ischemic attacks within the last 6 months were also excluded.

Test product

Investigational medicinal product: memantine

Dosage: 10mg film-coated lactose-free tablets (1 tablet/day).

Active ingredients: memantine-HCl (-amino-3,5-dimethyladamantane hydrochloride).

Route of administration: Oral either in the morning or in the evening but at the same time every day.

Batch number: 00204

Reference product

Reference product: Placebo

Dosage: Film-coated tablets matching 10mg memantine tablets.

Active ingredients: None.

Route of administration: Oral either in the morning or in the evening but at the same time every day.

Batch number: 4424201

Duration of study treatment

During the study five visits were conducted: screening visit 1 (day -7 to -2), baseline visit 2 (day 0), visit 3 (week 4), visit 4 (week 12), visit 5/follow-up (week 16). Study treatment was given from baseline to visit 4.

Criteria for evaluation

Efficacy evaluations

Primary efficacy variable

"Patient Global Impression of Change" (PGI-C) at visit 4, which measured the subjective change of the symptoms in comparison to before treatment on a seven point scale analogous to a clinical global impression scale.

Secondary efficacy variables

- PGI-C at visit 3 and visit 5
- Change from baseline (visit 2) to visit 3, 4, and 5 in single items measured by C-NTB (CogState Battery)
- Change from baseline (visit 2) to visit 4 in ECog39 domain score and total score
- Change from baseline (visit 2) to visit 4 in HADS score.

Pharmacodynamic evaluations

Not applicable.

Pharmacokinetic evaluations

Not applicable.

Safety evaluations

Safety variables

Blood pressure, incidence rates of adverse events (AEs), serious adverse events, AEs with fatal outcome and AEs leading to discontinuation.

Other evaluations

Other variables

Further summaries included the subject dispositions, incidence of protocol deviations, demographic data and other baseline characteristics, incidence of previous and concomitant therapies and the treatment compliance.

Statistical methods

The primary efficacy variable was defined as PGI-C at visit 4. The primary efficacy analysis was the statistical comparison between the placebo group and the memantine group at visit 4 in the Full Analysis Set (FAS) where missing values were imputed using the last observation carried forward (LOCF) approach. The group comparison was performed by the use of an analysis of covariance (ANCOVA) model, with treatment group, PGI-S at screening, gender, age, education, and pooled center as factors. Additionally, the p-value of the two sided t-test testing the null hypothesis that the least square mean difference is zero was provided. For this proof-of-concept study alpha was set to 0.1. Sensitivity analyses of the results were also based on the Per-Protocol Set (PPS) and observed cases.

Furthermore a reduced ANCOVA model, a Cochran-Mantel-Haenszel test with modified ridit scores stratified by pooled centers and a responder analysis using a logistic regression model (response defined as any improvement in PGI-C) was performed.

The change in CogState C-NTB from baseline to visit 4 was analyzed descriptively using an ANCOVA model analog to the primary efficacy endpoint. All further secondary efficacy variables were analyzed descriptively using summary statistics.

All safety variables were analyzed descriptively on the Safety Evaluation Set.

Interim analysis

No interim analysis was planned or performed.

Summary of results

Study subjects

Overall, 371 subjects were screened and 297 subjects were randomized (memantine 10mg: 145 subjects; placebo: 152 subjects). Of those randomized 2 subjects (1 memantine 10mg group and 1 placebo group) were not treated and discontinued prior to receiving any study treatment.

Overall, 264 subjects (88.9%) completed the study; 129 subjects (89.0%) in the memantine 10mg group and 135 subjects (88.8%) in the placebo group. A total of 33 randomized subjects discontinued the study (including the 2 subjects who discontinued prior to receiving any treatment); 16 subjects (11.0%) from the memantine 10mg group and 17 subjects (11.2%) from the placebo group. For those subjects who discontinued, AEs were the most frequent reason for discontinuation, which occurred in 22 subjects (66.7%); 11 subjects (68.8%) in the memantine 10mg group and 11 subjects (64.7%) in the placebo group.

The 295 randomized and treated subjects were included in the SES, 273 subjects were included in the FAS and 248 subjects in the PPS.

The SES consisted of 180 women (61.0%) and 115 men (39.0%), all white, except for 1 Asian in the memantine group, with a mean (SD) age of 65.3 (8.15) years (range: 50 to 80 years; median 66.0 years). The mean (SD) years of subject education was 12.7 (3.29) years (range: 6 to 27 years; median 12 years).

Efficacy results

A summary of the main study efficacy results is presented for the FAS (LOCF) in the following table.

Main Study Efficacy Results – FAS (LOCF)

	Placebo N=139	Memantine 10mg N=134
Patient Global Impression of Change (PGI-C)		
L.S. mean PGI-C score at visit 4 (week 12)	3.54	3.68
Mean PGI-C score at visit 3 (week 4)	3.6	3.7
Mean PGI-C score at visit 4 (week 12)	3.5	3.7
Mean PGI-C score at visit 5/follow-up (week 16)	3.5	3.7
PGI-C Score at visit 3 (week 4)		
1 = Very much better	1 (0.7)	1 (0.7)
2 = Much better	6 (4.3)	6 (4.5)
3 = A little better	40 (28.8)	36 (26.9)
4 = No change	88 (63.3)	83 (61.9)
5 = A little worse	4 (2.9)	7 (5.2)
6 = Much worse	0	0
7 = Very much worse	0	1 (0.7)
PGI-C Score at visit 4 (week 12)		
1 = Very much better	0	2 (1.5)
2 = Much better	12 (8.6)	13 (9.7)
3 = A little better	54 (38.8)	36 (26.9)
4 = No change	66 (47.5)	66 (49.3)
5 = A little worse	6 (4.3)	13 (9.7)
6 = Much worse	1 (0.7)	3 (2.2)
7 = Very much worse	0	1 (0.7)
PGI-C Score at visit 5/follow-up (week 16)		
1 = Very much better	2 (1.4)	1 (0.7)
2 = Much better	16 (11.5)	8 (6.0)
3 = A little better	41 (29.5)	36 (26.9)
4 = No change	66 (47.5)	72 (53.7)
5 = A little worse	8 (5.8)	14 (10.4)
6 = Much worse	3 (2.2)	2 (1.5)
7 = Very much worse	0	0
CogState Computer-Based Neuropsychological Test Battery		
Detection Task (lower score=better performance)		
L.S. mean change from baseline to visit 4 (week 12)	0.01	0.00
Mean change from baseline to visit 3 (week 4)	-0.05	0.00
Mean change from baseline to visit 4 (week 12)	0.02	0.01
Mean change from baseline to visit 5/follow-up (week 16)	-0.02	-0.01

Table continues on the next page.

Main Study Efficacy Results – FAS (LOCF) continued

	Placebo N=139	Memantine 10mg N=134
Identification Task (lower score=better performance)		
L.S. mean change at visit 4 (week 12)	0.00	0.00
Mean change from baseline to visit 3 (week 4)	-0.02	-0.01
Mean change from baseline to visit 4 (week 12)	0.01	-0.01
Mean change from baseline to visit 5/follow-up (week 16)	0.00	-0.01
One-Card Learning Task (higher score = better performance)		
L.S. mean change from baseline to visit 4 (week 12)	0.02	0.02
Mean change from baseline to visit 3 (week 4)	0.02	0.01
Mean change from baseline to visit 4 (week 12)	0.02	0.02
Mean change from baseline to visit 5/follow-up (week 16)	0.02	0.03
One Back Task (higher score = better performance)		
L.S. mean change from baseline to visit 4 (week 12)	0.02	0.03
Mean change from baseline to visit 3 (week 4)	0.02	0.03
Mean change from baseline to visit 4 (week 12)	0.03	0.03
Mean change from baseline to visit 5/follow-up (week 16)	0.05	0.06
Groton Maze Learning Task (lower score=better performance)		
L.S. change from baseline to visit 4 (week 12)	-3.82	-4.33
Mean change from baseline to visit 3 (week 4)	-3.2	-0.7
Mean change from baseline to visit 4 (week 12)	-3.4	-2.6
Mean change from baseline to visit 5/follow-up (week 16)	-4.4	-6.1
Continuous Paired Associated Learning Task (lower score=better performance)		
L.S. mean change from baseline to visit 4 (week 12)	1.51	0.67
Mean change from baseline to visit 3 (week 4)	-2.7	0.2
Mean change from baseline to visit 4 (week 12)	0.0	-0.0
Mean change from baseline to visit 5/follow-up (week 16)	-3.9	-4.7
ECog39 (lower score=better performance)		
Mean change from baseline to visit 4 (week 12) in:		
Total score	-0.2	-0.2
Memory	-0.3	-0.3
Language	-0.2	-0.2
Visual	-0.1	-0.1
Planning	-0.2	-0.1
Organizing	-0.1	-0.1
Divided	-0.2	-0.3
HADS Score (lower score=better performance)		
Mean change from baseline to visit 4 (week 12) in:		
Anxiety	-0.2	-0.0
Depression	-0.1	-0.3

~~Source: Tables 14.2.1.1, 14.2.1.3, 14.2.1.7, 14.2.2.1, 14.2.2.3, 14.2.2.5, 14.2.3.1, 14.2.3.3, 14.2.4.1 and 14.2.4.3~~

Patient Global Impression of Change (PGI-C)

For the FAS (LOCF), ANCOVA analysis showed that the L.S. mean difference from placebo in PGI-C at visit 4 (week 12) was 0.15 (90% CI: -0.02 to 0.32); this difference was not statistically significant (p=0.157). Therefore, the primary study objective to show superiority of memantine 10mg over placebo was not met. No notable differences in mean PGI-C scores were observed between the treatment groups at any timepoint. The mean PGI-C score in the total population was 3.7 at visit 3 (week 4) and 3.6 at visit 4 (week 12) and visit 5/follow-up (week 16). ANOVA analysis with treatment group and pooled center as factors indicated similar non-statistically significant findings to the ANCOVA analysis. At visit 4 (week 12), approximately half of all subjects in both treatment groups reported no change in PGI-C scores and all remaining subjects experienced improvements in scores (mainly a little better), except for 13% of subjects in the memantine 10mg group and 5% of subjects in the placebo group who experienced a worsening in scores (mainly a little worse).

Logistic regression analysis of PGI-C response rates (LOCF) at visit 4 (week 12) indicated that subjects in the memantine 10mg group were less likely (odds ratio [OR] = 0.68; 90% CI: 0.45 to 1.03) to have a response to treatment than those in the placebo group. The included factors and covariates of gender, age, education and the regions East Germany, South Germany and North UK were shown to have no statistically significant effect on PGI-C response rate. The region of North Germany was shown to have a statistically significant effect on PGI-C response rate (p=0.014) although no conclusions can be drawn from this finding.

Reduced logistic regression analysis of PGI-C response rates with treatment group and pooled center included as factors indicated similar findings to the full logistic regression analysis; statistically significant findings were observed for the intercept (p=0.012) and the region of North Germany (p=0.005) for the FAS (LOCF) at visit 4 (week 12) although no real conclusions can be drawn from this.

CogState Computer-Based Neuropsychological Test Battery

Mean changes in CogState C-NTB (LOCF data) from visit 2 (baseline) to visit 3 (week 4), visit 4 (week 12) and visit 5 (week 16/follow-up) indicated no notable differences from placebo in the memantine 10mg group for any task. Similarly, ANCOVA analysis of changes in the primary outcome measures of CogState C-NTB (LOCF data) from visit 2 (baseline) to visit 4 (week 12) indicated no statistically significant differences from placebo for any task although numerically slightly better results were observed for the memantine 10mg group for all tasks.

Detection Task

For the detection task, a correct response rate of 96% was achieved in each treatment group at visit 4/ week 12 (LOCF). The mean time to complete the task was 2.60 $\log_{10}$ ms in each group, indicating a marginal worsening from visit 2 (baseline) to visit 4 (week 12) of 0.01 $\log_{10}$ ms and 0.02 $\log_{10}$ ms in the memantine 10mg group and placebo group, respectively.

No notable trends in task completion were observed over time. ANCOVA analysis indicated no L.S. mean change (0.0 $\log_{10}$ ms) in the memantine 10mg group and a non-statistically significant L.S. mean worsening of 0.01 $\log_{10}$ ms in the placebo group from visit 2 (baseline) to visit 4 (week 12).

Identification Task

For the identification task, a correct response rate of 96% was achieved in each treatment group at visit 4/week 12 (LOCF). The mean time to complete the task was 2.74 $\log_{10}$ ms in both treatment groups, indicating a marginal improvement from visit 2 (baseline) to visit 4 (week 12) of 0.01 $\log_{10}$ ms in the memantine 10mg group and marginal worsening of 0.01 $\log_{10}$ ms in the placebo group. No notable trends in task completion were observed over time. ANCOVA analysis indicated no L.S. mean change (0.0 $\log_{10}$ ms) in either treatment group from visit 2 (baseline) to visit 4 (week 12).

One-Card Learning Task

For the one-card learning task, a correct response rate of 68% and 67% was achieved in the memantine 10mg and placebo group, respectively, at visit 4/week 12 (LOCF). The mean Arcsine proportion of correct responses was 0.97 in both groups, indicating a marginal improvement from visit 2 (baseline) to visit 4 (week 12) of 0.02 in both groups. An improvement in one-card learning task results from visit 2 (baseline) was observed in the memantine 10mg group over time (0.01 at visit 3 [week 4], 0.02 at visit 4 [week 12], and 0.03 at visit 5/follow-up [week 16]) whereas no such trend was seen in the placebo group (0.02 at all visits). ANCOVA analysis indicated L.S. mean improvements of 0.02 in both treatment groups from visit 2 (baseline) to visit 4 (week 12); however, these changes were not statistically significant.

One-Back Task

For the one-back task, a correct response rate of 91% and 90% was achieved in the memantine 10mg and placebo group, respectively, at visit 4/week 12 (LOCF). The mean Arcsine proportion of correct responses was 1.33 in both treatment groups indicating a marginal improvement from visit 2 (baseline) to visit 4 (week 12) of 0.03 in both groups. An improvement in one-back task results from visit 2 (baseline) was observed in both treatment groups over time: memantine 10mg group (0.03 at visits 3 and 4 [weeks 4 and 12], and 0.06 at visit 5/follow-up [week 16]) vs. placebo group (0.02 at visit 3 [week 4], 0.03 at visit 4 [week 12], and 0.05 at visit 5/follow-up [week 16]).

ANCOVA analysis indicated no L.S. mean improvements of 0.03 in the memantine 10mg group and 0.02 in the placebo group from visit 2 (baseline) to visit 4 (week 12); however, these changes were not statistically significant.

Groton Maze Learning Task

For the Groton maze learning task, the mean number of errors was 55.1; 53.8 in the memantine 10mg group and 56.5 in the placebo group at visit 4/week 12 (LOCF), indicating a mean improvement from visit 2 (baseline) to visit 4 (week 12) of 2.6 in the memantine 10mg group and 3.4 in the placebo group. An improvement in Groton Maze learning task results from visit 2 (baseline) was observed in both treatment groups over time: memantine 10mg group (0.7 at visit 3 [week 4], 2.6 and visit 4 [week 12] and 6.1 at visit 5/follow-up [week 16]) vs. placebo group (3.2 at visit 3 [week 4], 3.4 at visit 4 [week 12], and 4.4 at visit 5 [week 16]). ANCOVA analysis indicated L.S. mean improvements of 4.33 in the memantine 10mg group and 3.82 in the placebo group from visit 2 (baseline) to visit 4 (week 12); however, these changes were not statistically significant.

Continuous Paired Associated Learning Task

For the continuous paired associated learning task, the mean total error was 43.8; 42.9 in the memantine 10mg group and 44.6 in the placebo group at visit 4/week 12 (LOCF), indicating no mean change (0.0) from visit 2 (baseline) to visit 4 (week 12) in either treatment group. An improvement from visit 2 (baseline) in continuous paired associated learning task scores was observed in the placebo group at visit 3/week 4 (2.7) and in both treatment groups at visit 5/follow-up/week 16 (memantine 10mg group: 4.7 vs. placebo group: 3.9). A slight worsening in score was observed in the memantine 10mg group from visit 2 (baseline) to visit 3/week 4 (0.2). ANCOVA analysis indicated L.S. mean worsening of 0.67 in the memantine 10mg group and 1.51 in the placebo group from visit 2 (baseline) to visit 4 (week 12); these changes were not statistically significant.

Analysis of CogState C-NTB data with data not satisfying integrity criteria revealed general similar findings to those described above for the main efficacy population.

ECog39 Total and Domain Scores

No notable differences were observed between the treatment groups with regard to ECog39 total and domain scores at visit 4/week 12 (LOCF) for the FAS. The mean total and domain scores was approximately 2 in all treatment groups at visit 4 (week 12) indicating questionable or occasional problems.

The mean ECog39 total score improved by 0.2 in both treatment groups from visit 2 (baseline) to visit 4 (week 12). Mean improvements in ECog39 domain scores of 0.1 to 0.3 were observed in both treatment groups from visit 2 (baseline) to visit 4 (week 12). Memory scores improved by 0.3, language scores improved by 0.2, and visual and organizational scores improved by 0.1 in both treatment groups.

Planning scores improved by 0.1 in the memantine 10mg group vs. 0.2 in the placebo group, while divided scores improved by 0.3 in the memantine 10mg group vs. 0.2 in the placebo group.

Hospital Anxiety and Depression Scores

No notable differences were observed between the treatment groups with regard to HADS scores at visit 4/week 12 (LOCF) for the FAS. The mean anxiety score was 5.7 in the memantine 10mg group and 5.9 in the placebo group at visit 4/week 12 (LOCF), indicating no mean change from visit 2 (baseline) in the memantine 10mg group (0.0) and a mean improvement from visit 2/baseline (0.2) in the placebo group. The mean depression score was 3.7 in the memantine 10mg group and 3.8 in the placebo group at visit 4/week 12 (LOCF), indicating a mean improvement from visit 2 (baseline) of 0.3 in the memantine 10mg group vs. 0.1 in the placebo group.

Safety results

Slightly more subjects in the memantine 10mg group reported TEAEs (75 subjects, 52.1%) compared with the placebo group (66 subjects, 43.7%) as shown in the table below. No notable differences were observed between the 2 treatment groups with regard to the frequency and type of AE reported with the exception of nervous system disorders, psychiatric disorders and skin and subcutaneous disorders. Nervous system disorders occurred in 19 subjects (13.2%) in the memantine 10mg group and 25 subjects (16.6%) in the placebo group; these included headache, which occurred less frequently in the memantine 10mg group (8 patients, 5.6%) than in the placebo group (13 patients, 8.6%) and dizziness, which occurred slightly more frequently in the memantine 10mg group (7 patients, 4.9%) than the placebo group (4 patients, 2.6%). Psychiatric disorders occurred more frequently in the memantine 10mg group (14 subjects, 9.7%) than in the placebo group (9 subjects, 6.0%), of which anxiety was the most common TEAE (memantine 10mg group: 6 subjects, 4.2%; placebo group: 1 subject, 0.7%), followed by depression (memantine 10mg group: 3 subjects, 2.1%; placebo group: 0 subjects). Skin and subcutaneous disorders less frequently in memantine 10mg group (4 subjects, 2.8%) than the placebo group (13 subjects, 8.6%); pruritus was the most common TEAE (memantine 10mg: 1 subject, 0.7%; placebo group: 3 subjects, 2.0%).

However, most nervous system disorders (i.e. headache and dizziness), psychiatric disorders (including anxiety and depression) and skin and subcutaneous disorders (including pruritus) were considered not related to treatment. Overall, the most frequent TEAEs (regardless of causality) by preferred term were headache and nasopharyngitis.

Overall summary of treatment emergent adverse events (safety evaluation set)

	Placebo (N=151)		Memantine 10mg (N=144)	
	n	(%)	n	(%)
Number (%) of subjects with:				
Any TEAE	66	(43.7)	75	(52.1)
Any related TEAE	25	(16.6)	27	(18.8)
Any serious TEAE	1	(0.7)	2	(1.4)
Any related serious TEAE	0		0	
Any TEAE leading to discontinuation[a]	10	(6.6)	11	(7.6)
Any related TEAE leading to discontinuation	7	(4.6)	9	(6.3)
Any fatal TEAE	1	(0.7)	0	
Any related fatal TEAE	0		0	

Note: Related = related to treatment (treatment-related)

[a] The number of patients with AEs leading to discontinuation in the placebo group differs from the number of patients (10 vs. 11) ~~in Table 14.1.1.3~~ as only treatment-emergent AEs are presented in this table; Subject [redacted] discontinued due to a non-treatment emergent AE.

~~Source: Table 14.3.2.1~~

Overall, related TEAEs were comparable between both treatment groups; 27 subjects (18.8%) in the memantine 10mg group had a treatment-related TEAE compared with 25 subjects (16.6%) in the placebo group. The most frequent treatment-related TEAEs by preferred term were headache, dizziness, insomnia and fatigue, which occurred at low incidences of 4% or less in the placebo group, and 3% or less in the memantine group.

No notable differences were observed between the treatment groups with regard to frequency and types of severe TEAEs experienced, and most TEAEs were mild or moderate in intensity. Severe TEAEs were reported for 1 subject (0.7%) in the memantine 10mg group and 3 subjects (2.0%) in the placebo group. There was no trend in the type of severe TEAE reported and all were single events.

Serious TEAEs were reported for 2 subjects (1.4%) in the memantine 10mg group (1 subject with epiploic appendagitis, and 1 subject with depression) and 1 subject (0.7%) in the placebo group (death, peri-operative peritoneal damage, peritonitis, small intestinal obstruction, vomiting, endotoxic shock, pneumonia, and post-operative vomiting). None of the serious TEAEs were considered treatment-related by the investigator. The epiploic appendagitis was reported 2 days after the subject had discontinued study drug (due to increased blood pressure). The epiploic appendagitis in Subject [redacted] resolved after treatment with antibiotics ~~(Section 16.2, Listing 14.3.3.2).~~

The depression of Subject [redacted] was considered a recurrence of the subject's underlying concomitant disease of depression. Study drug was discontinued and the depression resolved after treatment with mirtazapine.

The investigator reported that the cause of death of Subject [redacted] in the placebo group was due to incompetent operative and post-operative management leading to peritonitis and toxic shock and ischemia of the bowel.

In total, 11 subjects (7.6%) in the memantine 10mg group had a TEAE that led to discontinuation compared with 10 subjects (6.6%) in the placebo group. Headache, restlessness, dizziness and fatigue were the most common TEAEs leading to discontinuation. More subjects in the placebo group discontinued due to headache (4 subjects, 2.6%) compared to the memantine 10mg group (1 subject, 0.7%). Three subjects (2.0%) discontinued the placebo group and no subjects discontinued the memantine 10mg group because of restlessness. There were no other differences between the treatment groups in the frequency and types of TEAEs that led to discontinuation. Most TEAEs that led to discontinuation were single events in either or both treatment groups.

There were no other clinically significant safety findings during the study.

Conclusions

Efficacy

- No statistically significant or clinically relevant difference from placebo in PGI-C scores was observed for the memantine 10mg group in this study; most subjects reported no change or slight improvements in PGI-C scores from visit 2 (baseline) to visit 4 (week 12).

- CogState C-NTB, ECog39 and HADS scores were generally supportive of the primary efficacy finding indicating no notable effects with memantine 10mg treatment compared with placebo.

Safety

- Memantine compared to placebo was safe and well-tolerated. There were no overall notable differences between memantine 10mg and placebo in the incidence of TEAEs and types of TEAEs reported.

- There was a low incidence of subjects with serious TEAEs: 1.4% (2 subjects) in the memantine 10mg group and 0.7% (1 subject in the placebo group who died). No treatment-related serious TEAEs were reported.

- Overall, the safety profile of memantine in this study did not deviate from previous conducted studies in other indications.