## 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

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| **Study Title** | **Prospective, single-arm, multi-center, open-label study to investigate the efficacy and tolerability of the once daily (OD) memantine treatment.** |
| **Name of finished product** | Axura® (Merz Pharmaceuticals GmbH) |
| **Name of active ingredient** | Memantine HCl (1-amino-3,5-dimethyladamantane hydrochloride) |
| **Coordinating Investigator** | [redacted] Germany.<br>~~For a list of all investigators *see Appendix 16.1.4.*~~ |
| **Total number of study centers** | 25 centers were initiated. Subjects were screened at 21 centers. |
| **Publication (reference)** | Not applicable |
| **Study period** | Date of first enrollment: 24 OCT 2007<br>Date when the last subject completed the study: 03 DEC 2008 |
| **Phase of development** | Phase III B |
| **Objective(s)** | The study objective was to evaluate the effects of memantine treatment on communication abilities and other cognitive abilities in dementia of Alzheimer's type (DAT) patients with Mini Mental State Examination (MMSE) < 20 at screening. Additionally, tolerability data of the once daily intake of the study medication were collected and documented.<br>**Primary:**<br>To show efficacy of the memantine once daily treatment on cognitive function and communication over a period of 12 weeks.<br>**Secondary:**<br>To assess functional communication, activities of daily living [ADL], global impression, and tolerability. |

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| **Methodology** | The mean change in the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery [CERAD-NP] total score of DAT patients from baseline to week 12 was evaluated. Due to the natural course of the disease and the progressive deterioration of cognitive abilities in moderate to severe DAT patients, a decline in CERAD-NP total score over a 12-week period would be expected in moderate to severe Alzheimer's dementia [AD] patients. The primary objective of the study was to confirm that after 12 weeks OD memantine treatment, there was improvement compared to the baseline status, i.e. the mean change in the CERAD-NP total score was greater than zero. |
| **Number of subjects (planned and analyzed)** | Planned: 119 enrolled with 89 evaluable<br>Screened: 107<br>Analyzed: 97 |
| **Diagnosis and main criteria for inclusion** | **Inclusion at screening:**<br>• Signed informed consent prior to the initiation of any study specific procedures<br>• Male or female outpatients at least 50 years of age and at least 8 years of education<br>• German as mother-tongue or at least spoke the language fluently<br>• Current diagnosis of probable Alzheimer's disease consistent with NINCDS-ADRDA criteria and with DSM IV TR criteria for Dementia of the Alzheimer's type (screening visit 1 and baseline visit 2)<br>• Communication difficulties judged by a physician to be closely related to the diagnosis of Alzheimer's disease<br>• Alzheimer's disease confirmed by magnetic resonance imaging [MRI] or computer tomography [CT] scan within the past 12 months before study entry or MRI conducted at screening (screening visit 1, or confirmed by MRI conducted at screening and baseline visit 2)<br>• MMSE total score at screening visit < 20<br>• Subject had a knowledgeable and reliable carer who |

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| | accompanied the subject to all clinic visits during the course of the study<br>• Concomitant treatment in accordance to Study Protocol ~~9.4.7.1 and Appendix A~~<br>• If female, at least 2 years post menopausal or surgically sterile<br>• Sight and hearing sufficient to undertake the study-related procedures and psychometric tests without difficulty<br>• The investigator believed that the subject would be capable of completing all study-related psychometric tests during the study<br>**Exclusion (at screening visit 1 and baseline visit 2):**<br>• Evidence of clinically significant and active pulmonary, gastrointestinal, renal, hepatic, endocrine or cardiovascular system disease<br>• Recent history (within 3 months prior to screening), or currently untreated $B_{12}$, TSH, or folate deficiency, considered clinically significant<br>• Evidence (including CT/MRI results) of any clinically significant central nervous system disease other than Alzheimer's disease<br>• Current evidence of clinically significant, unstable psychiatric illness (other than symptoms associated with Alzheimer's disease) including psychotic disorders and bipolar or unipolar depression<br>• Oncological diagnosis (hematological or solid tumor) currently treated or still evidence of active disease<br>**Exclusion (at screening visit 1 only):**<br>• Modified Hachinski Ischemia score > 4 at screening<br>• History of severe drug allergy, hypersensitivity, or known hypersensitivity to amantadine and lactose<br>• Known or suspected history of alcoholism or drug abuse within the past 10 years<br>• Participation in an investigational drug study, or received treatment with an investigational drug within 90 days (or 5 half-lives, whichever was longer) prior |

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| | to the screening visit<br>• Previously treated with memantine or participation in an investigational study of memantine<br>• Presence of any disease or treatment which according to the investigator's judgment, could have interfered with the assessments of safety, tolerability, or efficacy<br>• Subject, or subject with carer, unwilling or unable to abide by the visit schedule and other study requirements<br>• Presence of any type of evident aphasia, which might have interfered with subject's communication difficulties caused by Alzheimer's disease | |
| **Investigational product** | Memantine (active ingredient: 1-amino-3,5-dimethyladamantane hydrochloride) | |
| | Dose: | week 1: 5 mg<br>week 2: 10 mg<br>week 3: 15 mg<br>week 4: 20 mg<br>weeks 5 up to week 12: 20 mg |
| | Mode of administration: | oral once daily |
| | Batch number: | 605121 |
| **Reference product** | None | |
| **Duration of treatment** | 12 weeks (4 weeks up-titration and 8 weeks main treatment period) followed by 4-week wash-out period. | |

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| **Criteria for evaluation** | |
| **Efficacy:** | **Primary efficacy endpoint:**<br>The primary efficacy endpoint is the change of the CERAD-NP total score from baseline (visit 2) to 12 weeks thereafter (visit 5). The CERAD-NP total score was calculated by addition of the following 6 subtests of the CERAD-NP test battery: Verbal Fluency, Modified Boston Naming Test (MBNT), Word List Learning, Constructional Praxis, Word List Recall, and Word List Recognition – Discriminability.<br>**Secondary efficacy endpoints:**<br>• Change in the CERAD-NP total score from baseline over time including week 16 measurement, and from end of treatment in week 12 to follow-up in week 16<br>• Change in CERAD-NP single-item subscores (Verbal Fluency, MBNT, Word List Learning, Constructional Praxis, Word List Recall, Word List Recognition – Discriminability, and Figures Recall) from baseline over time and MMSE score from screening over time<br>• Proportion of subjects who could accomplish the Trail Making Test A [TMT A] within 4 minutes over time<br>• Time for conducting the TMT A (if the test could be accomplished) over time<br>• Change in phonemic verbal fluency (S-words) score from baseline over time<br>• Change in Functional linguistic communication inventory [FLCI] score from baseline over time.<br>• Change in ADCS-$ADL_{19}$ score from baseline over time<br>• Clinical Global Impression of Change [CGI-C] score (comparison to baseline) over time. |
| **Safety:** | Adverse events [AEs], clinical chemistry and hematology, urinalysis, and vital signs. |

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| **Statistical methods** | Analysis sets included:<br>• Safety Evaluation Set [SES]: All subjects who received study medication at least once<br>• Full Analysis Set [FAS]: All subjects of the SES who had a baseline CERAD-NP total score, reached the maximum dose of 20 mg/day at week 4 after up-titration and had at least one post-baseline CERAD-NP total score measurement at weeks 4, 8 or 12<br>• Per Protocol Set [PPS]: All subjects of the FAS for whom no major protocol deviations were reported.<br><br>Efficacy analyses were performed on the FAS and PPS. Safety analyses were based on the SES.<br><br>The primary efficacy endpoint was analyzed using a one-sided single-group t-test at a significance level of 2.5%.<br><br>The null hypothesis that the mean difference between the CERAD-NP total score at week 12 and at baseline was less than or equal to 0 was tested against the alternative hypothesis of a mean difference being greater than 0. A parametric 95% confidence interval was calculated for the mean change in the CERAD-NP total score from baseline to week 12. Analysis of covariance methods were applied to investigate the impact of age, gender, center, and baseline CERAD-NP total score as covariates on the primary efficacy endpoint. |
| **Summary / conclusions**<br><br>**Efficacy results** | The efficacy results demonstrated the efficacy of memantine once daily (OD) treatment over a period of 12 weeks in the treatment of DAT patients with MMSE < 20 at screening.<br>Results for the analysis of the primary efficacy variable demonstrated that treatment with memantine OD is clinically effective in the sense of improving the cognitive status of DAT patients, as the mean CERAD-NP total score difference between visit 5 (week 12) and baseline of 5.9 (SD: 8.82) points (in the FAS) was statistically significantly greater than 0 ($p < 0.0001$, single-group one-sided t-test). The robustness of the results of the confirmatory analysis was confirmed, with $p < 0.0001$ for the Wilcoxon one-sample signed rank test. Results in the PPS were consistent with those in the FAS.<br>The mean CERAD-NP total score increased steadily at |

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| | each visit during the study, with a tailing-off observed after stopping study medication at visit 5.<br>[ANCOVA] analysis demonstrated no evident impact of age group and gender on the change of CERAD-NP total score from baseline to visit 5 (week 12). However, the numeric baseline CERAD-NP total score seemed to have an impact on this change, with higher baseline values leading to less improvement (as would be expected). A potential center effect was seen, with an outstanding improvement in CERAD-NP total score observed in pool 3 compared to all other center pools. Results of subgroup analysis of the primary efficacy endpoint were comparable to those of the ANCOVA analysis.<br>Results for the analyses of the secondary efficacy endpoints were generally similar to those of the primary endpoint. A steady improvement over time until a maximum improvement at visit 5 followed by a tailing-off at follow-up was observed for most CERAD-NP subitems, the Trail Making Test A, the Phonemic Verbal Fluency Test, and the FLCI test.<br>The results of the inter-scale correlation between the FLCI and the CERAD-NP items related to language demonstrated a notable correlation between the translated FLCI (into German language) and the CERAD-NP items related to language. The correlation was more pronounced in absolute values than in the changes from baseline and from visit 5. Correlations appeared to be stable across all visits.<br>For mean ADCS-$ADL_{19}$ score, only slight post-baseline increases could be observed. Mean ADCS-$ADL_{19}$ score was slightly higher at visit 5 (38.5 [SD: 11.22]) compared to baseline (37.8 [SD: 10.31]), with a mean difference of 0.7 (SD: 4.98) indicating a very slight improvement in the functional capabilities of the subjects. The median change from baseline was 0.0 at all visits, with the exception of visit 3.<br>The Clinical Global Impression of Severity [CGI-S] test result in observed cases at baseline was “Moderately ill” in 53 (57.6%) subjects, “Markedly ill” in 25 (27.2%) subjects, “Mildly ill” in 11 (12.0%) subjects, “Severely ill” in 2 (2.2%) subjects, and “Among the most extremely ill patients” in a single subject. No subject in this study had a CGI-S of “Normal not at all ill” or “Borderline mentally ill” at baseline. The CGI-S |

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| | test results at baseline correlated well with the CERAD-NP total score at baseline, with an increase in the severity of illness corresponding to a decrease in mean CERAD-NP total scores.<br>The CGI-C test results indicated that at visit 5 the severity of disease remained unchanged or improved to some degree in the majority of subjects. The CGI-C results at follow-up demonstrated some decline compared to the results at visit 5, with more subjects having some degree of deterioration in their severity of disease compared to baseline. |
| **Safety results** | Analysis of safety data from the 97 subjects treated in this study demonstrates that once daily memantine treatment was safe and well tolerated.<br>Treatment emergent adverse events [TEAEs] were experienced by 38 (39.2%) subjects. The most frequent TEAEs, those occurring in more than 1 subject, were fatigue (6 [6.2%] subjects), anorexia, nasopharyngitis and nausea (each in 4 [4.1%] subjects), and agitation, arthralgia, confusional state, delirium, depression, influenza, rhinitis, syncope and vertigo (each in 2 [2.1%] subjects).<br><br>The overall profile of the most frequent TEAEs in this study is not unexpected in Alzheimer's patients receiving memantine. Fatigue is a known adverse reaction to memantine. Anorexia, agitation, confusional state, delirium, and vertigo are all associated with Alzheimer's disease. Nausea and syncope are known side effects of Acetylcholinesterase inhibitors [AChEIs], which were a common concomitant medication in this study. Nasopharyngitis, arthralgia, influenza and rhinitis are not unexpected in this elderly study population.<br><br>The majority of TEAEs were mild or moderate in intensity; severe TEAEs were reported in only 5 subjects.<br>TEAEs assessed as "related to the study medication" by the investigator were reported in 13 (13.4%) subjects. Related TEAEs that occurred in more than 1 subject were fatigue, nausea, anorexia and agitation. Fatigue is a known adverse reaction to memantine, nausea is a known side effect of AChEIs, and anorexia and agitation |

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| | are associated with Alzheimer's disease.<br><br>A single subject, subject [redacted], died shortly after study termination due to acute myeloid leukaemia. The death was assessed as "not related to the study medication" by the investigator.<br><br>Treatment emergent serious adverse events [TESAEs] were experienced by 3 subjects in this study. All of these events were assessed by the investigator as "not related to the study medication".<br><br>TEAEs leading to premature discontinuation of the study were reported in 3 subjects. Only 1 of these events was assessed by the investigator "as related to the study medication" (diarrhea).<br><br>Analysis of clinical laboratory data, vital signs, electrocardiograms [ECGs], and urinalysis raised no safety concerns. |
| **Conclusion** | This study demonstrated that treatment with 20 mg memantine once daily improved functional communication and cognitive abilities in patients with moderate to severe Alzheimer's disease, with improvements seen as early as 4 weeks following the start of treatment. After a subsequent memantine wash-out period of 4 weeks, a tailing-off in efficacy was observed.<br><br>Analysis of safety data from the 97 subjects treated in this study demonstrated that once daily memantine treatment was safe and well tolerated. |