Clinical Study Report Synopsis for Public Disclosure

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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.

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2. SYNOPSIS

Study title	Open-label, single-arm, multi-center validation study of the ROSA-Scale (Relevant Outcome Scale for Alzheimer Patients) in patients with dementia of Alzheimer's type (DAT) treated with memantine over a 3 months period	
Name of finished product	Memantine (Axura®)	
Name of active ingredient	1-amino-3,5-dimethyladamantane hydrochloride	
Investigator(s)	[redacted] Germany	
Total number of study center(s)	47 active, qualified sites in Austria and Germany	
Publication (Reference)	Not applicable.	
Study period	Date of first enrollment:	10 DEC 2008
	Date of completion:	11 NOV 2009
Phase of development	IIIb	
Objective(s)	The primary objective of this study was to validate the ROSA-Scale content, reliability, and responsiveness for detecting changes in the symptoms of Alzheimer's disease [AD]. The secondary objective was to determine AD severity and other symptoms using the Global Deterioration Scale [GDS], the Clinical Global Impression Scale: Clinical Global Impression of Change [CGI-C], Severe Impairment Battery [SIB], Alzheimer's Disease Assessment Scale – cognitive subscale [ADAS-cog], Neuropsychiatric Inventory [NPI], Disability Assessment for Dementia [DAD], and to examine the times to perform these scales.	
Methodology	Investigator's clinical impression about the patient's stage of AD based on the caregiver's information.	
Number of patients (planned and analyzed)	Planned: 450 screened patients, at least 50 per disease stage (early, mid, and late). Analyzed: 487 patients screened (early stage: 201, mid stage: 214, late stage: 71, missing: 1), 451 patients in safety evaluation set [SES], 397 patients in full analysis set [FAS], 319 patients in per protocol set [PPS], 387 patients completed the study.	

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Diagnosis and main criteria for inclusion	**Diagnosis:** AD of all severity stages. **Main criteria for inclusion:** • Male or female inpatient or outpatient of at least 50 years of age. • The patient had a diagnosis of probable AD consistent with the National Institute of Neurological and Communicative Disease and Stroke/Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria or with the Diagnostic and Statistical Manual of Mental Disorders Text Revision [DSM IV TR] criteria for AD. • Signed informed consent prior to the initiation of any study specific procedures. • If female, patient was at least 2 years post menopausal or surgically sterile. • Sight and hearing (a hearing aid was permitted) were sufficiently good to allow the undertaking of study-related procedures and psychometric tests. • According to the investigator's opinion, the patient was capable of completing all study-related activities.	
Investigational product	Memantine (Axura®)	Active ingredient: 1-amino-3,5-dimethyladamantane hydrochloride
	Dose:	4 weeks of up-titration (5 mg once daily [o.d.] during the first week, 10 mg o.d. during week 2, 15 mg o.d. during week 3, 20 mg o.d. during week 4) and 20 mg o.d. treatment for the next 8 weeks.
	Mode of administration:	Oral
	Batch number:	080701660
Reference product	Not applicable.	

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Duration of treatment	Duration of treatment: 12 weeks • Visit [V]1 (week -1, screening visit). • V2 (day 0, baseline, start of treatment). • V3 (week 4 ± 3 days after baseline). • V4 (week 12 ± 3 days after baseline). Phone contact in week 18 ± 3 days after baseline to follow up adverse events [AEs].
Criteria for evaluation **Efficacy**	Primary variable: The primary variable was the ROSA-Scale. The objective was to validate the ROSA-Scale content, reliability, and responsiveness for detecting changes in the symptoms of AD and to analyze the data psychometrically according to the classical test theory (determination of internal consistency, test-retest reliability, construct validity, and responsiveness). Secondary variables: • GDS and CGI-C to determine AD severity and a change in severity. • SIB, ADAS-cog, NPI, DAD to assess treatment response and correlations of the ROSA-Scale with these validated scales. • Mini Mental State Examination [MMSE] as descriptive parameter. • Time for completion of all scales to assess practicability of the ROSA- and other scales.
Safety	Safety data: During the study, the following safety variables were evaluated: • AEs and serious adverse events [SAEs]. • Physical examination. • Vital signs. • Weight. • Laboratory evaluation including clinical chemistry and hematology.

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	• Urine analysis.
Statistical methods	**Efficacy analysis:** All treated patients with sufficient data available for the primary analysis were included into the FAS. The PPS was the subset of patients of the FAS without major protocol violations. Major protocol violations were defined during the data review meeting [DRM] of the study before final database lock. Scale validation was based on the FAS; other efficacy analyses were performed on both sets, the FAS and the PPS. The results of both analyses (FAS/PPS) were compared and any relevantly different outcomes or considerable deviations are described in this clinical study report [CSR]. Primary efficacy analysis: Validation and characterization of the ROSA-Scale was based on the classical test theory: factor analysis (Principal Component Method) for the development of the item structure, Cronbach's alpha for the assessment of the internal consistency, correlation coefficients for test-retest reliability and construct validity, determination of the effect size and responsiveness for the assessment of response over time. Secondary efficacy analysis: All statistical procedures performed on the secondary efficacy variables were descriptive and treated as exploratory. Descriptive summary statistics for all scales and also for pre-post differences to investigate a response over time were calculated. Descriptive subgroup analyses for different severity stages (early, mid, and late) were performed. **Safety analysis:** All patients who received study medication at least once were part of the SES. The safety analysis was based on the SES only. Safety variables with continuous outcomes (e.g., vital signs and laboratory parameters) were analyzed

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	using descriptive summary statistics. Categorical safety data and baseline characteristics (e.g., AEs and laboratory parameters with reference to normal ranges) were analyzed using frequency tables and shift tables (where appropriate).
Summary/conclusions **Efficacy results**	The factor analysis based on the principal components method identified two factors for the ROSA-Scale. Since all items had a loading higher than the pre-defined value of 0.4 for at least one factor, all ROSA-Scale items were included in the final scale. Items 1 to 6 (cognition/communication) and 12 to 16 (function/activity of daily living, quality of life, caregiver burden) were attributed to factor one. Items 7 to 11 (behavior) were attributed to factor two. The effect size between V2 and V4 based on severity-dependent weighting factors (calculated for each single severity stage) was not significantly greater than the effect size based on not severity-dependent weighting factors (calculated for all stages together). For this reason, non severity-dependent weighting factors were used for the analysis. The weighting factors of 0.2 for factor one and 0.8 for factor 2 were obtained. To ensure easy calculation of item scores and easy use of the ROSA-Scale in daily clinical practice, it was decided to implement the weighting factors of 1 for factor one and 4 for factor two. For the test-retest reliability, the data collected at V1 and V2 were highly correlated (Bravais-Pearson coefficient = 0.8915, Spearman correlation = 0.9035). For the internal consistency of the ROSA-Scale, the Cronbach's alpha was calculated as 0.8582 using baseline data. A predefined value of > 0.7 was assumed to be an acceptable correlation of all items among each other. For the construct validity, correlations between the ROSA-Scale and SIB, ADAS-cog, NPI, and DAD were assessed as being approximately in the predefined acceptable range of 0.4 to 0.6 or -0.6 to -0.4, respectively. In addition, the responsiveness index [RI] of the ROSA-Scale calculated for early, mid, and late stage severity indicated a high responsiveness. Cohen's d indicated a small effect size for mid and late stage severity.

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	The acceptability of the floor and ceiling effects of the ROSA-Scale was explored according to disease severity. Only a small ceiling effect was observed in the early stage population, not affecting acceptability. The secondary efficacy variable, the change of the ROSA-Scale total score from baseline to V3 and V4, was statistically significant improved for mid and late stage severity. Regarding the SIB total score, a statistically significant improvement for mid stage severity was revealed. The analysis of the ADAS-cog total score over time showed a statistically significant worsening for early and mid stage severity. There were neither statistically significant changes of the NPI total score and the NPI distress total score nor of the DAD total percent score. For the majority of the patients, 'minimal improvement' or 'no change' was found in the CGI-C score at week 4 and week 12 for each severity stage as well as for all stages. Most patients did not change GDS stage during the study. The majority of patients were of stage 3 and 4. The time needed for ROSA-Scale administration is shorter than the time needed for a complete assessment of cognitive, functional, and behavioral symptoms when all other scales (i.e., SIB or ADAS-cog + NPI + DAD) are administered together.
Safety results	The SES contained 451 patients. In total, 154 (34.1%) patients experienced at least one treatment emergent adverse event [TEAE]. Most TEAEs were of mild or moderate intensity, which corresponds to the previous experience gained with memantine. 77 (17.1%) patients experienced TEAEs that were assessed as 'related'. The most frequently reported 'related' TEAEs by preferred term [PT] were 'dizziness', 'vertigo', 'headache', and 'agitation'. 'Dizziness', 'vertigo', and 'agitation' are common in patients with AD as symptoms of the underlying disease. During the study, these events were mostly non-serious and of mild or moderate intensity. Treatment emergent serious adverse events [TESAEs] were reported for 38 (8.4%) patients, and for 5 (1.1%) patients the TESAEs were assessed as 'related' to study

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Conclusion	medication. During the study, the death of one (0.2%) patient was reported in combination with the TESAE 'lung edema'. This event was assessed as 'not related' to study medication. Because of 'related' TEAEs, 27 (6.0%) patients of the SES prematurely discontinued the study. No safety concerns were raised based on laboratory evaluations and vital sign results. In conclusion, the treatment with memantine was well tolerated and safe. No new safety issues were raised and the safety profile of memantine was similar to that seen in previous studies in patients with AD. The results of the current study show that the ROSA-Scale is a valid and reliable instrument for assessment of cognitive, functional and behavioral symptoms in dementia over time, which can be quickly administered in daily practice as well as in clinical trials. The current study did not raise any new safety concerns related to treatment with memantine. Reported AEs were either known for memantine or reflected common symptoms in a population of AD patients.