Synopsis of Study Results

Name of Sponsor /Company	Daiichi Sankyo Co., Ltd.
Name of Finished Product	
Name of Active Ingredient	Memantine hydrochloride
Title of Study	Confirmatory randomized, double-blind, placebo-controlled, parallel-group study of SUN Y7017 (memantine hydrochloride) in patients with mild to moderate dementia of the Alzheimer's type
Investigators	Takashi Asada　Total 67 investigators
Study Centre(s)	Tsukuba University Hospital　Total 63 centers
Publication (reference)	None
Studied Period (Date of first subject enrolled to date of last subject completed)	October 11, 2003 to December 5, 2007
Phase of Development	Phase III
Objectives	To examine the dose-response relationship of memantine hydrochloride in mild to moderate dementia of the Alzheimer's type, determine the recommended dose, and verify the superiority to placebo, and also evaluate the safety of memantine hydrochloride.
Methodology	A double-blind, parallel-group study, comparing placebo (Group P), memantine hydrochloride 10 mg (Group L) and 20 mg (Group H)
Number of Patients (planned and analyzed)	(Planned) 180 patients per group, total 540 patients (Analyzed) Safety analysis set: 564 patients (186 in Group P, 190 in Group L, 188 in Group H) Efficacy analysis set: 557 patients (180 in Group P, 190 in Group L, 187 in Group H)
Diagnosis and Main Criteria for Inclusion	Target disease：dementia of the Alzheimer's type Inclusion criteria： • Patients diagnosed with probable Alzheimer's Disease according to the NINCDS-ADRDA criteria • Patients with an MMSE score between 10 and 23 • Patients with a CDR (Clinical Dementia Rating) score of "1=mild dementia" or "2=moderate dementia" • Patients aged 50 years or over at the time of consent Exclusion criteria： • Patients with neurodegenerative disorder with dementia of any other type than Alzheimer's type • Patients with systemic disease with dementia • Patients with significant psychological disease determined according to DSM-IV diagnostic criteria • Patients who participated in any previous clinical study of memantine hydrochloride • Patients with a history of severe drug allergy • Patients with drug dependence or alcoholism
Test Product, Dose and Mode of Administration, Batch Number	Memantine hydrochloride 10 mg or 20 mg orally once daily Batch number：3309、3310、4Y19、4Y20
Duration of Treatment	24 weeks
Reference Therapy, Dose and Mode of Administration, Batch Number	Placebo orally once daily Batch number：3306、3307、3308、4Y16、4Y18、5220、5221
Criteria for Evaluation	Efficacy endpoints Primary endpoints: ADAS-J cog., CIBIC-plus (ADCS-CGIC) Secondary endpoints: DAD, Caregiver-rated Crichton Scale , MMSE, CDR

	Safety endpoints Adverse events, adverse drug reactions
Statistical Method	Efficacy The efficacy was analyzed using the Full Analysis Set (FAS), and the primary analysis was the LOCF analysis using the FAS. The level of significance was 5% two-sided. However, in analysis using the maximum contrast method, a significace level of 2.5% (one-sided) was adopted. 1) Primary endpoints ADAS-J cog.: The change in total score from the baseline of the double-blind period to Week 24 of treatment (change in score) was calculated for each of Groups P, L, and H, with comparison of the dose responsiveness across the three groups, as well as investigation of the superiority of the memantine hydrochloride group (Groups L and H) to the placebo group. CIBIC-plus: The overall assessment (global change) at Week 24 of treatment was examined using the contrast test, with comparison of the dose responsiveness across the three groups, as well as investigation of the superiority of the memantine hydrochloride groups to the placebo group. 2) Secondary endpoints For individual total scores of the DAD, Caregiver-rated Crichton Scale, MMSE, and CDR, as the same method of ADAS-J cog. the change from the baseline of the double-blind period to Week 24 of treatment (change in score) was calculated in each treatment group, with comparison of the dose responsiveness across the three groups using contrast test, as well as investigation of the superiority of the memantine hydrochloride groups to the placebo group. Safety The incidences of adverse events and adverse reactions were calculated by treatment group, with comparison of the dose responsiveness in the incidences across the three groups using Cochran-Armitage test.
Summary - Conclusion	Efficacy As for the ADAS-J cog., the change in score of Week 24 was 1.80±0.34（Least-squares mean±SE） in Group P, 0.55±0.33 in Group L, and 1.45±0.34 in Group H. The contrast test with contrast coefficients of (−1, 0, 1) demonstrated p=0.5863 and that with (−2, 1, 1) demonstrated p=0.0785, neither of which showed significant difference. An analysis using the t-test showed statistically significant difference for Group L compared to Group P (p=0.0088). As for the CIBIC-plus, the global change at Week 24 of treatment was 4.53±1.04（Mean±SD） in Group P, 4.30±1.08 in Group L, and 4.28±0.99 in Group H. The contrast test with contrast coefficients of (−2, 1, 1) demonstrated statistically significant difference with p=0.0197, thereby confirming the dose-response relationship. An analysis using the t-test showed statistically significant differences for both Group L (p=0.0417) and Group H (p=0.0222) compared to Group P. As for the DAD, the contrast test of the change in score (LOCF analysis) with contrast coefficients of (−1, 0, 1) demonstrated p=0.6266 and that with (−2, 1, 1) demonstrated p=0.6219, neither of which showed significant difference. As for the Caregiver-rated Crichton Scale, the contrast test of the change in score with contrast coefficients of (−1, 0, 1) demonstrated p=0.0191 and that with (−2, 1, 1) demonstrated p=0.0140, thereby

	confirming the dose-response relationship. As for the MMSE, the contrast test of the change in score with contrast coefficients of (−1, 0, 1) demonstrated p=0.0006, and that with (−2, 1, 1) demonstrated p=0.0001, thereby confirming the dose-response relationship. As for the CDR-SB (CDR-Sum of the Boxes: total score for individual CDR items), the contrast test of the change in score with contrast coefficients of (−1, 0, 1) demonstrated p=0.1152, and that with (−2, 1, 1) demonstrated p=0.0582, neither of which showed significant difference. Safety The incidences of adverse events and adverse reactions did not differ across the three treatment groups.
Date of Report	Feb.14, 2011