SYNOPSIS

Name of Sponsor/Company	Daiichi Sankyo Co., Ltd.
Name of Finished Product	Memary®
Name of Active Ingredient	Memantine hydrochloride
Title of Study	Clinical Study of SUN Y7017 (Memantine Hydrochloride) in Combination with Donepezil Hydrochloride in Patients with Moderate to Severe Alzheimer's disease.
Investigators	Taira Oe, and 175 other investigators
Study Centre(s)	Department of Neuropsychiatry, Oe Hospital, and 142 other centers
Publication (reference)	・ Geriat. Med. 2016; 54(11): 1147-1158 ・ Geriat. Med. 2017; 55(2): 232
Studied Period	Date of informed consent of the first subject: 28 Feb 2012 Date of final observation: 10 Mar 2016
Phase of Development	Phase 4
Objectives	To evaluate the efficacy and safety of memantine hydrochloride at an oral dose of 20 mg once daily for 24 weeks in patients with moderate to severe Alzheimer's disease receiving treatment with donepezil hydrochloride in a placebo-controlled, double-blind, parallel-group study design.
Methodology	Study design: Multicenter, randomized, double-blind, placebo-controlled, parallel-group comparative study
Number of Patients (planned and analyzed)	Planned:500 Analyzed:546
Diagnosis and Main Criteria for Inclusion	Diagnosis:Patients with moderate to severe AD who has been taking cholinesterase inhibitors. Inclusion Criteria: 1. Patients diagnosed with dementia of Alzheimer's type on the DSM-IV-TR and probable Alzheimer' disease on NINCDS-ADRDA diagnostic criteria. 2. Patients diagnosed with Alzheimer's disease on CT or MRI intracerebral scans. 3. Patients with MMSE score between 1 and 14. 4. Patients receiving cholinesterase inhibitors continuously before the start of the screening period. Annotation; donepezil hydrochloride must be taken for at least 4 weeks before the start of the screening period. Age: 50 years old or more

	Sex: Both Exclusion Criteria: 1. Patients with a coexisting dementia other than Alzheimer's disease. 2. Patients with serious neuropathy complications. 3. Patients with musculoskeletal diseases that will hamper conduct of tests and observations in the present study. 4. Others, patients deemed not suitable to take part in the present study by the investigator.
Test Product, Dose and Mode of Administration, Batch Number	The starting dose is 5mg once daily. The dose should be increased in 5mg increments per week to 20mg Batch Number: ・ Memantine hydrochloride 5 mg tablet (S7017F1S10T01, RR-1011, ZJ-2013) ・ Memantine hydrochloride 10 mg tablet (S7017F1S10T02, ZK-0011, ZK-0020)
Duration of Treatment	12-week run-in period (Period 1) and 24-week double-blind period (Period 2)
Reference Therapy, Dose and Mode of Administration, Batch Number	The placebo is administered once daily. Batch Number: ・ Memantine hydrochloride 5 mg tablet placebo (S7017F1S10T03, Y7017F1H12T01, Y7017F1H13T01) ・ Memantine hydrochloride 10 mg tablet placebo (S7017F1S10T04, S7017F1S10T05, Y7017F1H12T02, Y7017F1H13T02, Y7017F1H13T03)
Criteria for Evaluation	・ Efficacy ➢ Primary endpoint ✧ Evaluation of cognitive function (Changes in the SIB-J score from baseline score (Week 24 - Week 0)) ➢ Secondary endpoints ✧ Evaluation of behavioral and psychological symptoms of dementia and Evaluation by caregiver (Changes in the Behave-AD score or Crichton score from baseline score (Week 24 - Week 0))
Statistical Method	・ The efficacy analysis was performed by imputing missing data using the last observation carried forward (LOCF)

	approach using the FAS. As the analysis of efficacy, the analysis of covariance (ANCOVA) on the changes in the SIB-J score (Week 24 – Week 0) in the FAS (LOCF) was performed with the score at Week 0 and daily dose of donepezil hydrochloride as covariates and treatment group as an independent factor at a significance level of 0.05 (two-sided) to verify the superiority of memantine hydrochloride at an oral dose of 20 mg once daily for 24 weeks over placebo. The adjustedmean and the 95% confidence interval (CI) of differences (memantine hydrochloride group – placebo group; the same hereinafter) were calculated. ・ For secondary endpoint, the same analyses were performed as in the primary endpoint. ・ The changes in the SIB-J score at Week 24 – Week 0 in the FAS (LOCF) were also analyzed using the Wilcoxon rank sum test at a significance level of 0.05 (two-sided). ・ Additional analyses was performed on the subject with MMSE score between 5 and 14 points (at the start of the double-blind period) ・ The incidence of adverse events was calculated by treatment group. Adverse drug reaction data were similarly analyzed. Adverse event terms were converted based on the Medical Dictionary for Drug Regulatory Activities terminology (MedDRA). Adverse event data were classified by system organ class (SOC) and by preferred term (PT).
Summary - Conclusion	・ No statistically significant difference in the changes in the SIB-J score (Week 24 – Week 0) was found at Week 24 in the ANCOVA (p=0.2437); however, the point estimate of the changes in the SIB-J score was higher in the memantine hydrochloride group than in the placebo group at all measurement time points. The results of the normality test on the changes in the SIB-J score (Week 24 – Week 0) revealed that the changes in the SIB-J score (Week 24 – Week 0) in this study were not normally distributed. ・ No statistically significant difference in the changes in the SIB-J score (Week 24 – Week 0) was found in the analysis using the Wilcoxon rank sum test (p=0.0563), which does not

	require the assumption of normal distribution, either; however, the P value was smaller than that obtained in the ANCOVA. ・ In the analysis of the secondary endpoints, no statistically significant differences were found in the changes in total score of Behave-AD, which is the BPSD rating scale, and the total score of the Crichton Geriatric Behavioural Rating Scale between the treatment groups. ・ As a result of the explorative analysis, a statistically significant difference in the changes in the SIB-J score (Week 24 – Week 0) was found in the subgroup of MMSE score between 5 and 14 points, which is the same patient population as in Japanese and overseas confirmatory studies in the development stage (Study IE3501 and Study MEM-MD-02, etc.) (p = 0.0165: Wilcoxon rank sum test), which indicated that combination therapy inhibited the reduction in cognitive function as in Study MEM-MD-02. ・ No clear differences in the incidence or onset trend of adverse events or serious adverse events reported in this study were found between the treatment groups. Common adverse drug reactions reported in the memantine hydrochloride group (combination group) were known adverse reactions to memantine hydrochloride used as monotherapy, and none of the results indicated signs etc. suggesting new safety concerns about memantine hydrochloride used in combination with donepezil hydrochloride.
Date of Report	15, Dce, 2017