SYNOPSIS

Name of sponsor/company	Daiichi Sankyo Co., Ltd.
Name of finished product	REZALTAS® COMBINATION TABLETS LD・COMBINATION TABLETS HD
Name of active ingredient	CS-866AZ (Olmesartan medoxomil/Azelnidipine)
Title of study	Add-on, open-label, phase III study of CS-866AZ
Study centre(s)	Sixteen sites in Japan
Publication (reference)	J. Clin. Therap. Med. **26**: 47-62, 2010
Studied period	July 2006 to March 2008
Phase of development	Phase III
Objectives	1) and 2) were assessed in patients with essential hypertension that was inadequately controlled by monotherapy with olmesartan medoxomil (OLM) or azelnidipine (AZL): 1) Efficacy and safety of 12-week co-administration of OLM and AZL 2) Safety of 1-year co-administration of OLM and AZL
Methodology	A multicenter, open-label study
Number of patients (planned and analysed)	Number of patients planned: 180 Number of patients analyzed: Full analysis set; 208 Safety analysis set; 210
Diagnosis and main criteria for inclusion	Main inclusion criteria: ・ Age ≥20 years ・ Baseline BP during the monotherapy period was stable and fulfilled the criterion: "systolic BP ≥ 140 mmHg and < 180 mmHg, and diastolic BP ≥ 90 mmHg and < 110 mmHg." ・ The 24-hour BP determined by ambulatory blood pressure monitoring (ABPM) during the monotherapy period met the criterion: "systolic BP ≥ 135 mmHg and diastolic BP ≥ 80 mm Hg." Main exclusion criteria: ・ Secondary or malignant hypertension ・ Myocardial infarction or cerebrovascular disorder ・ Night-shift workers
Test product, dose and mode of administration	Monotherapy period : AZL 8 mg tablet, OLM 10 mg tablet, AZL 16 mg tablet, OLM 20 mg tablet

	Co-administration period: Co-administration of OLM 20 mg tablet and AZL 16 mg tablet (OLM 20 mg/AZL 16 mg below), Co-administration of OLM 10 mg tablet and AZL 8 mg tablet (OLM 10 mg/AZL 8 mg below). If sitting BP did not reach the target sitting BP, the dose was increased to OLM 20 mg/AZL 16 mg. Study drugs were administered orally once a day after breakfast.
Duration of treatment	Monotherapy period, 6 weeks; Co-administration period, 52 weeks
Reference therapy	None
Criteria for evaluation	Efficacy (primary and main secondary endpoint): The difference between sitting BP (systolic BP and diastolic BP) during the monotherapy period and that of the co-administration period (ΔBP) Safety: Adverse events (occurrence or exacerbation of subjective symptoms/objective findings and abnormal changes in clinical laboratory values)
Statistical method	Efficacy (primary and main secondary endpoint): A linear model analysis was performed on ΔBP at the co-administration period with the dose during the monotherapy period and BP during the same period as factors. Also the adjusted mean of ΔBP and its 95% confidence interval were calculated for each of the dose during the monotherapy period to assess the effect of the co-administration compared to that of monotherapy. Safety: The number and percentage of patients who developed adverse events (AEs) with a possible causal relationship to the study drug and all AEs were determined.
Summary-conclusions	The changes from baseline to weeks 12 and 52 in seated blood pressure [systolic blood pressure/diastolic blood pressure (SBP/DBP)] were -15.7/-11.8 mmHg and -17.6/-13.0 mmHg, respectively, in the group of patients with hypertension inadequately controlled by OLM 20 mg and given OLM/AZL. Similarly, the changes in the group of patients inadequately controlled by OLM 10 mg and given OLM/AZL, were -15.7/-9.1 mmHg and -19.6/-12.7 mmHg, respectively. The changes were -16.6/-10.9 mmHg and -18.4/-12.5 mmHg, respectively, in the group who were inadequately controlled by AZL 16 mg and given co-administration therapy with OLM/AZL; and -19.3/-11.5 mmHg and -21.5/-13.4 mmHg, respectively, in the group who were

	inadequately controlled by AZL 8 mg and given OLM/AZL. The above results demonstrated the good antihypertensive effect of the 12-week and 52-week (long-term) combination therapy with OLM and AZL in the groups of patients with hypertension that was inadequately controlled by monotherapy with either OLM or AZL. In terms of safety, there was no increase in either the type or the incidence of clinically important adverse events during the long-term combination therapy with OLM and AZL. The dose titration from OLM 10 mg/AZL 8 mg to OLM 20 mg/AZL 16 mg did not cause any safety problems. Based on these results, combination therapy with OLM and AZL was well tolerated, showed a good antihypertensive effect, and maintained the antihypertensive effect during long-term use in patients with essential hypertension that was inadequately controlled by monotherapy with OLM or AZL. In conclusion, combination therapy with OLM and AZL might be a useful option in patients whose hypertension is inadequately controlled by monotherapy.
Date of report	October 14, 2010