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	Phase III Study of CS-866AZ
Study centre(s)	Seventeen sites in Japan
Publication (reference)	J. Clin. Therap. Med. **26**: 63-79, 2010
Studied period	August 2007 to February 2008
Phase of development	Phase III
Objectives	The efficacy and safety of 12-week administration of CS-866AZ were assessed in "patients with essential hypertension that was inadequately contralled by monotherapy with angiotensin II receptor blocker (ARB) or calcium channel blocker (CCB)" and in "patients with grade II essential hypertension."
Methodology	An open-label, uncontrolled, optional dose-titration, multicenter study
Number of patients (planned and analysed)	Number of patients planned: 175 Number of patients analyzed: Full analysis set; 315 Safety analysis set; 316
Diagnosis and main criteria for inclusion	Main inclusion criteria: ・ Age ≥20 years ・ Satisfied 1. or 2. below 1. Baseline BP during the run-in period (on monotherapy with an ARB or a CCB) was stable and fulfilled the criterion: "systolic BP ≥ 140 mmHg and < 180 mmHg, and diastolic BP ≥ 90 mmHg and < 110 mmHg." 2. Baseline BP during the run-in period (not taking any antihypertensive drug) was stable and fulfilled the criterion: "Systolic BP ≥ 140 mmHg and < 180 mmHg and diastolic BP ≥ 90 mmHg and < 110 mmHg" and either or both of "Systolic BP ≥ 160 mmHg" and "Diastolic BP ≥ 100 mmHg." Main exclusion criteria: ・ Secondary or malignant hypertension ・ Myocardial infarction or cerebrovascular disorder

	・ Poorly controlled diabetis
Test product, dose and mode of administration	Run-in period: Monotherapy with a low/high-dose ARB alone or a low/high-dose CCB alone No antihypertensive drug was administered in patients with grade II essential hypertension Treatment period: High-dose ARB or high-dose CCB group: CS-866AZ-20/16 (20/16 mg below) was administered. Low-dose ARB or low-dose CCB group, grade II essential hypertension group: CS-866AZ-10/8 (10/8 mg below) was administered. If sitting BP did not reach the target sitting BP, the dose was titrated to 20/16 mg. Study drugs were administered orally once a day after breakfast.
Duration of treatment	Run-in period, 4 weeks; Treatment period, 12 weeks
Reference therapy	None
Criteria for evaluation	Efficacy (primary endpoint): The difference between sitting BP (systolic BP and diastolic BP) during the run-in period and that at the end of treatment (ΔBP) Safety: Adverse events (occurrence or exacerbation of subjective symptoms/objective findings and abnormal changes in clinical laboratory values)
Statistical method	Efficacy (primary endpoint): A linear model analysis was performed onΔBP between the value during the run-in period and that at the end of treatment with the treatment group and BP during the run-in period as factors. Also the adjusted mean of ΔBP and its 95% confidence interval were calculated for each treatment group to assess the antihypertensive effect of the study drug administration. Safety: The number and percentage of patients who developed AEs with a possible causal relationship to the study drug and all AEs were determined.
Summary-conclusions	The adjusted mean change in BP (Systolic BP/Diastolic BP) was as follows: -15.9/-12.4 mmHg in the group of patients inadequately controlled by high-dose ARB and given combination therapy with CS-866AZ; -16.8/-11.4 mmHg in the group of patients inadequately controlled by low-dose ARB, given CS-866AZ;

	-10.9/-9.0 mmHg in the group of patients inadequately controlled by high-dose CCB and given CS-866AZ; -17.4/-12.0 mmHg in the group of patients inadequately controlled by low-dose CCB, given CS-866AZ; and -23.0/-16.0 mmHg in the group of patients with grade II hypertension given CS-866AZ. The antihypertensive effect was also increased after dose titration from CS-866AZ 10/8 mg to CS-866AZ 20/16 mg. In terms of safety, there was no increase in the incidence of clinically important adverse events during the administration of 10/8 mg or 20/16 mg, or after dose titration from 10/8 mg to 20/16 mg. Based on the above results, the OLM/AZL combination formulation, which has components with different mechanisms of antihypertensive effect (ARB and CCB), was found to enable a safe and good antihypertensive effect and to be a useful therapeutic alternative for patients with essential hypertension that was inadequately controlled by monotherapy with ARB or CCB, and for patients with stage II essential hypertension.
Date of report	October 14, 2010