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	Number of patients planned: 175
(planned and analysed)	Number of patients analyzed:
	Full analysis set; 315
	Safety analysis set; 316
Diagnosis and main criteria	Main inclusion criteria:
for inclusion	• 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 \geq 140 mmHg and $<$ 180 mmHg, and diastolic BP
	\geq 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 \geq 140 mmHg and < 180 mmHg and diastolic BP
	\geq 90 mmHg and < 110 mmHg" and either or both of "Systolic
	$BP \ge 160 \text{ mmHg}$ " and "Diastolic $BP \ge 100 \text{ mmHg}$."
	Main exclusion criteria:
	Secondary or malignant hypertension
	Myocardial infarction or cerebrovascular disorder

· Poorly controlled diabetis Test product, dose and mode Run-in period: of administration 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 on ΔBP 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 develop		
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follows: -15.9/-12.4 mmHg in the group of patients inadequately controlled by high-dose ARB and given combination therapy with	Summary-conclusions	The adjusted mean change in BP (Systolic BP/Diastolic BP) was as
controlled by high-dose ARB and given combination therapy with	-	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		CS-866AZ; -16.8/-11.4 mmHg in the group of patients
inadequately controlled by low-dose ARB. given CS-866AZ:		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