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2. SYNOPSIS

Name of Sponsor: Daiichi Sankyo Europe GmbH	Individual Trial Table Referring to Module 5.3.5.1 of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: CS-866CMB(E)		
Name of Active Ingredient: Olmesartan medoxomil + hydrochlorothiazide		

Title of Study: Efficacy and Safety of Olmesartan Medoxomil/Hydrochlorothiazide Combination 20/25 mg versus 40/25 mg in Moderately to Severely Hypertensive Patients Not Adequately Controlled by Olmesartan Medoxomil 40 mg Monotherapy (Protocol CS866CM-B-E302, EudraCT Number 2006-003876-28)

Investigators: [redacted]

Study Centre(s): 92 principal investigators screened patients at clinical sites in Europe (8 in Belgium, 17 in Germany, 12 in the Netherlands, 17 in Poland, 19 in Russia, 10 in Slovakia, and 9 in the Ukraine).

Publication (reference): None

Study Period:	**Phase of Development**:
First patient in: 05 December 2006 Last patient out: 07 May 2008	Phase III

Objectives:

The primary objective was to compare the efficacy in lowering mean trough sitting diastolic blood pressure (dBP) between olmesartan medoxomil (OM)/hydrochlorothiazide (HCTZ) 20/25 mg versus 40/25 mg, in those patients inadequately controlled on OM 40 mg monotherapy, assessed by conventional blood pressure (BP) measurements, after 8 weeks of double-blind treatment, as compared with baseline.

The secondary objectives were:

1. To evaluate the efficacy of OM/HCTZ 20/25 mg versus 40/25mg, by measuring the change in mean trough sitting dBP, after 4 weeks (Visit 5) of double-blind treatment, using conventional BP measurements, compared with baseline (Visit 4, Week 8).
2. To evaluate the efficacy of OM/HCTZ 20/25 mg versus 40/25 mg, by measuring mean trough sitting systolic blood pressure (sBP), after 4 weeks (Visit 5) and after 8 weeks (Visit 6) of double-blind treatment, using conventional BP measurements, compared with baseline (Visit 4, Week 8).
3. To evaluate the antihypertensive efficacy, by measuring dBP and sBP, using 24-hour ambulatory blood pressure monitoring (ABPM) (day-time, night-time and mean 24-hour BP) after 8 weeks (Visit 6, Week 16) compared with baseline (Visit 4, Week 8).
4. To evaluate the number and percentage (%) of patients in each treatment group achieving target BP (dBP <90 mmHg and sBP <140 mmHg for non-diabetics, and dBP <80 mmHg and sBP <130 mmHg for diabetics) after 4 weeks (Visit 5) and after 8 weeks (Visit 6) of double-blind treatment, assessed by conventional BP measurements.

5. To evaluate the risk-benefit ratio of OM/HCTZ 40/25 mg versus 20/25 mg.
6. To evaluate the safety and tolerability of OM/HCTZ 40/25 mg versus 20/25 mg combinations, after 8 weeks of double-blind treatment.

Trial Hypotheses:

After eight weeks of double-blind treatment (Period II), the combination therapy of OM/HCTZ 40/25 mg will be superior to OM/HCTZ 20/25 mg in lowering mean sitting trough dBP (mean change) from baseline (Visit 4, Week 8) assessed by conventional BP measurements.

Methodology:

This phase III trial was a randomised, double-blind, parallel-group, multi-national, multi-centre trial conducted in 92 investigational sites in Europe consisting of a 1- to 2-week taper-off phase (applicable to eligible patients being treated with antihypertensive medication other than OM 20 mg or OM 40 mg at the time of screening for the trial) and two treatment periods (Period I and Period II). Period I (Visit 2 to Visit 4; Day 1 to Week 8) was an 8-week open-label period during which patients received monotherapy with OM 40 mg. At the end of Period I (Visit 4/Week 8 [randomisation visit]), only non-responders were eligible to be randomised (see Diagnosis and Main Criteria for Inclusion) and to enter Period II. Patients whose BP was controlled on OM 40 mg at Week 8 were discontinued from the trial. Period II (Visit 4, Visit 5, and Visit 6; Week 8 to Week 16) was an 8-week double-blind period during which patients non-responsive to OM 40 mg treatment during Period I were assigned randomly in a 1:1 ratio to one of two treatment arms:

- OM/HCTZ 40/25 mg + OM/HCTZ 20/25 mg matching placebo
- OM/HCTZ 20/25 mg + OM/HCTZ 40/25 mg matching placebo

Patients recruited to participate in the trial had a history of moderate to severe hypertension or were patients with newly diagnosed moderate to severe hypertension. Patients with a history of hypertension were further classified by type of prior antihypertensive treatment (i.e., treated with OM therapy [20 mg or 40 mg] or treated with antihypertensive medications other than OM). See below for trial inclusion criteria regarding BP.

Sphygmomanometers were used for conventional BP measurements throughout the trial. After a 10-minute rest period, three separate sitting BP measurements were taken at least 1 minute apart. The three results were averaged and rounded to a whole integer. In addition, 24-hour ABPM was performed three times during the trial (1 day prior to Visits 2, 4, and 6).

Duration of Treatment:

16 weeks (8 weeks of open-label monotherapy and 8 weeks of double-blind treatment [only for patients not adequately controlled at the end of the open-label period]).

Number of Patients:

Planned: 1,054 patients

Screened: 2,661 patients

Entered Monotherapy (Period I): 1,404 patients

Randomised (Period II): 1,011 patients

Completed: 984

Discontinued after randomisation: 27 patients

Diagnosis and Main Criteria for Inclusion:

Patients enrolled in this trial included male or female patients ≥18 years of age, who gave written informed consent, and had moderate to severe hypertension, defined as follows using conventional BP measurement:

- For newly diagnosed patients (not currently on anytihypertensive medication), a mean trough sitting BP of ≥160/100 mmHg at Screening and a 24-hour mean dBP ≥85 mmHg and ≥30% of daytime dBP above 90 mmHg, as assessed by ABPM at Visit 2 (prior to start of Period I).
- For patients currently on antihypertensive medication other than OM, a mean trough sitting BP of ≥140/90 mmHg at Screening, a mean trough sitting BP of ≥160/100 mmHg at the end of the taper-off period and a 24-hour mean dBP ≥85 mmHg and ≥30% of daytime dBP above 90 mmHg at Visit 2 (prior to start of Period I).
- For patients on a stable dose of OM 20 mg or 40 mg for at least 4 weeks, a mean trough sitting BP of ≥140/90 mmHg prior to entering Period I, as well as a 24-hour mean dBP ≥80 mmHg and ≥30% of daytime dBP above 85 mmHg at Visit 2 (prior to start of Period I).

Patients were randomised to receive double-blind combination therapy (Period II) at Visit 4, Week 8, if they were non-responders in Period I, i.e., had mean trough sitting dBP and sBP of 90-115 mmHg and 140-180 mmHg, respectively, and a 24-hour mean dBP ≥80 mmHg, with ≥30% of daytime dBP above 85 mmHg. Following Protocol Amendment 1 implemented on 07 March 2008, patients who failed to meet the ABPM BP criteria at the end of Period I could be randomised to enter Period II if they met the conventional BP randomisation criteria.

In addition to BP requirements, patients had to meet all other entry qualifications based on medical history, physical examination, electrocardiogram (ECG) and laboratory tests.

Investigational Product and Comparator Information:

Dosage Form: OM 40 mg (Period I). OM/HCTZ 20/25 mg or OM/HCTZ 40/25 mg (Period II)

Route of Administration: Oral, once daily (o.d.)

Batch No.:

OM 40 mg (oblong film coated tablet):
OM/HCTZ 20/25 mg (round film coated tablet):
OM/HCTZ 40/25 mg: (oblong film coated tablet):

Placebo (round film coated tablet) to match OM/HCTZ 20/25 mg:
Placebo (oblong film coated tablet) to match OM/HCTZ 40/25 mg:

Packaging Information: medication was packaged into double aluminium blisters, which were packaged into double wallet cards. OM 40 mg dose or matching placebo (oblong tablets) were presented in white cards and OM 20 mg dose or matching placebo (round tablets) were presented in yellow cards.

Criteria for Evaluation:

Efficacy:
The primary efficacy parameter was the change from baseline (Visit 4, Week 8) to the end of the 8-week double-blind treatment period (Visit 6, Week 16) in mean trough sitting dBP, assessed by conventional BP measurement.

The secondary efficacy parameters were:

- Change from baseline (Visit 4, Week 8) to Week 12 in mean trough sitting dBP assessed by conventional BP measurements
- Change from baseline (Visit 4, Week 8) to Weeks 12 and 16 in mean trough sitting sBP assessed by conventional BP measurements
- Change from baseline (Visit 4, Week 8) to Week 16 in mean daytime, night-time and total dBP assessed by 24-hour ABPM
- Change from baseline (Visit 4, Week 8) to Week 16 in mean daytime, night-time and total sBP assessed by 24-hour ABPM
- Number and percentage of patients achieving target BP at Weeks 12 and 16
- Risk-benefit ratio of OM/HCTZ 40/25 mg versus OM/HCTZ 20/25 mg

Safety:
The primary safety parameter was the adverse event (AE) profile of OM/HCTZ 40/25 mg versus OM/HCTZ 20/25 mg. Vital signs, 12-lead ECGs, physical examination, clinical haematology, biochemistry and urinalysis were also evaluated during the trial.

Statistical Methods: Analysis of covariance (ANCOVA) techniques were used to compare the adjusted mean change from baseline (Visit 4, Week 8) to the end of Period II (after 8 weeks of double-blind treatment, Visit 6, Week 16) in mean trough sitting dBP, assessed by conventional BP measurements, between the OM/HCTZ treatments, 40/25 mg and 20/25 mg. The model included treatment as a main effect and baseline mean trough sitting dBP as a covariate. For a sensitivity analysis, this model for the primary analysis was extended to included pooled centre as an additional main effect. Analyses were performed on the Full Analysis Set (FAS) (primary) and on the Per Protocol Set (PPS) (per protocol approach; secondary). For the FAS approach, last observation carried forward (LOCF) methods were applied in case of prematurely terminating patients (withdrawals) and for missing values. The main analysis was performed on the FAS LOCF. Supportive efficacy analyses of the primary endpoint were performed on patients from the FAS, based on observed cases (OC) of available data. Pooling was applied for small centres.

Exploratory analyses were performed for the analysis of the secondary endpoints of change from baseline in mean trough sitting dBP (conventional measurements) after 4 weeks, the change from baseline in mean trough sitting sBP (conventional measurements) after 4 and 8 weeks and for the change from baseline in mean 24-hour dBP/sBP, mean daytime dBP/sBP and mean night-time dBP/sBP assessed by 24-hour ABPM after 8 weeks, using the same analytical methods as described above.

The number of patients and percentages (%) achieving target BP after 4 and after 8 weeks of double-blind treatment were compared between treatment groups using logistic regression.

The risk-benefit ratio of the OM/HCTZ 40/25 mg versus 20/25 mg combinations after 8 weeks of double-blind treatment was explored in a joint plot of safety and efficacy.

All statistical tests were two-sided tests with a 5% level of significance. Only the test on treatment differences with regard to the primary endpoint after 8 weeks of double-blind treatment was confirmatory. All tests on secondary endpoints were purely exploratory. Comprehensive data summaries were prepared

for AEs, vital signs, ECG and laboratory parameters to compare safety and tolerability across treatments.

Summary:

Analysis Sets:

Safety Set 1: 1,404

Safety Set 2: 1,010

Full Analysis Set: 1,010

Per-Protocol Set: 868

Efficacy Results: The table below presents the results for change in mean trough sitting dBP from baseline (Week 8) to Week 16 for FAS, using LOCF. Mean baseline dBP values were comparable between treatment groups: 97.0 mmHg in the OM/HCTZ 40/25 mg group and 96.8 mmHg in the OM/HCTZ 20/25 mg group. A reduction in mean trough sitting dBP was observed in both treatment groups. The mean change from baseline (Week 8) to Week 16 in LOCF was -11.16 mmHg for the OM/HCTZ 40/25 mg group and -10.45 mmHg for the OM/HCTZ 20/25 mg group. Based on the ANCOVA model, an estimated treatment difference of -0.5 mmHg in favour of OM/HCTZ 40/25 mg was found. No statistically significant difference between treatment groups was observed.

Analysis Variable	**OM/HCTZ 40/25 mg (N=502)**	**OM/HCTZ 20/25 mg (N=508)**	
N (Week 16)	502	508	
Baseline mean (SD) [1]	97.0 (5.62)	96.8 (5.55)	
Week 16 LOCF mean (SD)	85.9 (8.67)	86.3 (7.64)	
Mean change (SD)	-11.16 (8.851)	-10.45 (7.928)	
Pairwise comparisons at Week 16 FAS LOCF [2]:	**Treatment difference[3]**	**p-value**	**95% CI**
OM/HCTZ 40/12.5 mg - OM/HCTZ 20/25 mg	-0.5 = -11.1 – (-10.5)	0.2648	(-1.51, 0.42)

1. Baseline Period II is the last mean assessment prior to administration of double-blind trial medication, which is usually the data recorded at Week 8, but may be data recorded at an unscheduled visit.
2. Statistics are based on an ANCOVA model, including treatment as a main effect and baseline value as a covariate.
3. Treatment difference is based on the difference of LS means.

The treatment difference was calculated as difference in model base adjusted mean.
ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; HCTZ = hydrochlorothiazide; LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation.

The exploratory statistical analysis of the secondary efficacy parameter: change in mean trough sitting sBP after 8 weeks of double-blind treatment demonstrated no statistically significant difference between OM/HCTZ 40/25 mg versus OM/HCTZ 20/25 mg. However, an estimated treatment difference of -0.3 mmHg in favour of the 40/25 mg dose combination was observed. Results supported the conclusions of the confirmatory analysis on the primary efficacy parameter.

A similar proportion of patients achieved target BP (mean trough sitting BP decreased to <140/90 mmHg for non-diabetics or mean trough sitting BP decreased to <130/80 mmHg for diabetics) in the OM/HCTZ 40/25 mg and 20/25 mg groups (42.0% and 38.6%, respectively, at Week 12 and 51.8% and 50.2%, respectively, at Week 16). No significant treatment difference was found for the comparison of OM/HCTZ 40/25 mg with OM/HCTZ 20/25 mg.

The assessment of the antihypertensive efficacy using the changes in ABPM mean 24-hour, day-time and night-time dBP and sBP after 8 weeks of double-blind treatment as secondary efficacy parameters (FAS

OC) demonstrated clinically relevant and statistically significant treatment differences in favour of OM/HCTZ 40/25 mg. Based on an exploratory statistical analysis (ANCOVA), a clinically meaningful and statistically significant treatment difference of -1.6 mmHg in favour of the OM/HCTZ 40/25 mg group was found on reduction on mean 24-hour ABPM dBP, of -1.6 mmHg in favour of the OM/HCTZ 40/25 mg group on reduction on day-time ABPM dBP and of -1.5 mmHg in favour of the OM/HCTZ 40/25 mg group on reduction on night-time ABPM dBP. In the exploratory statistical analysis (ANCOVA), clinically relevant and statistically significant treatment differences for sBP lowering were found: -2.3 mmHg in favour of the higher dose combination were found on reduction on mean 24-hour ABPM sBP, -2.3 mmHg in favour of the higher dose combination on reduction on day-time ABPM sBP and -2.0 mmHg in favour of the higher dose combination on reduction on night-time ABPM sBP.

Safety Results: There was a low incidence of TEAEs during both Period I and Period II of the study, with most treatment-emergent SAEs considered by the Investigator to be unrelated to study medication. Those SAEs considered to be probably related to study medication were blood potassium decreased and blood sodium decreased, which are known adverse effects of HCTZ.

	OM/HCTZ 40/25 mg (N=502) n (%)	**OM/HCTZ 20/25 mg (N=508) n (%)**
Total number of AEs	354	366
Total number of patients with at least one:		
TEAE	108 (21.5)	112 (22.0)
Serious TEAE	6 (1.2)	4 (0.8)
Study medication related TEAE	30 (6.0)	26 (5.1)
Severe TEAE	5 (1.0)	6 (1.2)
Moderate TEAE	42 (8.4)	31 (6.1)
Mild TEAE	79 (15.7)	87 (17.1)
TEAE Leading to discontinuation	5 (1.0)	5 (1.0)
TEAE Leading to death	0	0

Percentage was calculated using the number of patients in the treatment group as denominator.
AE = adverse event; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil;
TEAE = treatment-emergent AE.

There was a low incidence of TEAEs during both Period I and Period II of the study, with most treatment-emergent SAEs considered by the Investigator to be unrelated to study medication. Those SAEs considered to be probably related to study medication were blood potassium decreased and blood sodium decreased, which are known adverse effects of HCTZ.

No safety concerns (i.e., versus the known safety profile and individual monotherapy components) were identified during the course of this study. There were no clinically meaningful TEAEs, drug-related TEAEs, SAEs, discontinuations due to TEAEs, or laboratory abnormalities that occurred with a higher incidence in the OM/HCTZ 40/25 mg group versus the OM/HCTZ 20/25 mg group. There were no particular differences in the safety issues across the different age groups, between males and females, by hypertension severity categories and by diabetic status.

No clinically meaningful trends were observed in the shifts in laboratory parameters from normal at baseline to low and clinically relevant or high and clinically relevant at the end of treatment in Period I or Period II of the trial. Shifts were noted in Period I and Period II only in a very limited number of patients. However, these shifts were in accordance with the known AE profile of these classes of drugs.

The safety profile in this study was consistent with the safety profile for an ARB and thiazide diuretic.

Considering only efficacy results related to conventional BP measurements, it can be concluded that OM/HCTZ 40/25 mg has at least a comparable risk-benefit ratio to OM/HCTZ 20/25 mg.

Taking all relevant efficacy and safety information into account, the risk-benefit was in favour of OM/HCTZ 40/25 mg as compared to OM/HCTZ 20/25 mg.

Conclusions: After 8 weeks of double-blind treatment, the results of the analysis for the primary endpoint mean trough sitting dBP as well as for the secondary endpoint sBP showed no statistically significant difference between OM/HCTZ 40/25 mg versus OM/HCTZ 20/25 mg.

The ABPM data showed clinically meaningful differences in favour of the OM/HCTZ 40/25 mg dose combination, which also reached statistical significance in the exploratory analysis. These results were consistent for 24-hour, day-time and night-time mean measurements.

It was shown that the risk-benefit assessment of the two treatment groups was at least comparable. However, taking also ABPM findings into account, it was in favour of OM/HCTZ 40/25 mg as compared to OM/HCTZ 20/25 mg.

All dosages tested in this study were safe and well tolerated.

Date of the Report: 03 October 2008