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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	(For National Authority Use only)
Name of Finished Product: CS-866CMB(E)		
Name of Active Ingredient: Olmestartan medoxomil + hydrochlorothiazide	Volume: Page:	

Title of Study: Efficacy and Safety of Hydrochlorothiazide Used as Add-on Therapy in Moderately to Severely Hypertensive Patients not Adequately Controlled by Olmesartan Medoxomil 40 mg Monotherapy (Protocol CS866CM-B-E301; EudraCT Number 2006-003876-37)

Investigators: [redacted]

Study Centres: 78 investigative sites screened patients in Europe (19 in Czech Republic, 11 in Germany, 8 in Bulgaria, 5 in Spain, 20 in Ukraine, 1 in France and 14 in Poland).

Publication (reference):None

Study Period:	**Phase of Development**:
First patient in: 17 January 2007 Last patient out: 30 March 2008	Phase III

Objectives:

The primary objective was to compare the efficacy in lowering mean trough sitting diastolic BP (dBP) between olmesartan medoxomil/hydrochlorothiazide (OM/HCTZ) 40/12.5 mg and OM/HCTZ 40/25 mg versus OM 40 mg monotherapy, and between OM/HCTZ 40/12.5 mg versus OM/HCTZ 20/12.5 mg, in those patients inadequately controlled on OM 40 mg monotherapy, assessed by conventional BP (BP) measurements, after 8 weeks of double-blind treatment (Visit 6, Week 16), as compared with baseline (Visit 4, Week 8).

The secondary objectives were:

1. To evaluate the additional antihypertensive efficacy of the combinations of OM/HCTZ 40/25 mg and OM/HCTZ 40/12.5 mg compared with OM 40 mg monotherapy, and between OM/HCTZ 40/12.5 mg versus OM/HCTZ 20/12.5 mg in lowering mean trough sitting dBP, assessed by conventional BP measurements, after 4 weeks of double-blind treatment (Visit 5, Week 12), compared with baseline (Visit 4, Week 8).

2. To evaluate the additional antihypertensive efficacy of the combinations of OM/HCTZ 40/25 mg and OM/HCTZ 40/12.5 mg compared with the OM 40 mg monotherapy, and between OM/HCTZ 40/12.5 mg versus OM/HCTZ 20/12.5 mg in lowering mean trough sitting systolic BP (sBP), assessed by conventional BP measurements, after 4 (Visit 5, Week 12) and 8 weeks of double-blind treatment (Visit 6, Week 16) compared with baseline (Visit 4, Week 8).

3. To evaluate the antihypertensive efficacy, by measuring dBP and sBP, using 24-hour ambulatory BP monitoring (ABPM) (day-time, night-time and mean 24-hour BP) after 8 weeks (Visit 6, Week 16) of double-blind treatment 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, Week 12) and after 8 weeks (Visit 6, Week 16) of double-blind treatment, assessed by conventional BP measurements.
5. To evaluate the risk-benefit ratio of the OM/HCTZ 40/12.5 mg versus OM/HCTZ 20/12.5 mg combination.
6. To evaluate the safety and tolerability of combinations of OM/HCTZ 40/25 mg and 40/12.5 mg versus OM 40 mg monotherapy, and OM/HCTZ 40/12.5 mg versus 20/12.5 mg, after 8 weeks of double-blind treatment.

Trial Hypotheses:

After 8 weeks of double-blind treatment (Period II), the combination therapies of OM/HCTZ 40/25 mg and OM/HCTZ 40/12.5 mg will be superior to OM 40 mg alone and the combination therapy of OM/HCTZ 40/12.5 mg will be superior to the combination therapy of OM/HCTZ 20/12.5 mg in lowering mean trough sitting 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 78 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 2 treatment periods (Period I and Period II). Period I (Visit 2 and Visit 3; 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 2 to Visit 4: Day 1 to Week 8), 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 study. 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 1:2:2:2 ratio (150 patients in the OM/HCTZ 40/25 mg group and 300 patients each in the OM/HCTZ 40/0 mg group, OM/HCTZ 40/12.5 mg group and OM/HCTZ 20/12.5 mg group) to 1 of 4 treatment arms:

- OM/HCTZ 40/25 mg + OM/HCTZ 20/12.5 mg matching placebo
- OM/HCTZ 40/0 mg + OM/HCTZ 20/12.5 mg matching placebo
- OM/HCTZ 40/12.5 mg + OM/HCTZ 20/12.5 mg matching placebo
- OM/HCTZ 20/12.5 mg + OM/HCTZ 40/0 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, 3 separate sitting BP measurements were taken at least 1 minute apart. The 3 results were averaged and rounded to a whole integer. In addition, 24-hour ABPM was performed 3 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).

Number of Patients:

Planned: 1,050 patients
Screened: 2,213 patients
Entered monotherapy (Period I): 1,226 patients
Randomised (Period II): 972 patients
Completed: 944 patients
Discontinued (dropped after randomisation): 28 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 antihypertensive medication), a mean trough sitting BP of ≥160/100 mmHg at Screening and a 24-hour mean dBP ≥85 mmHg and ≥30% of day-time 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 day-time 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 day-time 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 day-time dBP above 85 mmHg. Following Protocol Amendment 1 implemented from 20 December 2007, 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 or OM/HCTZ 40/12.5 mg or OM/HCTZ 40/25 mg or OM/HCTZ 20/12.5 mg

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

Batch No.:
OM 40 mg (oblong tablet):
OM/HCTZ 40/12.5 mg (oblong tablet):
OM/HCTZ 40/25 mg (oblong tablet):
OM/HCTZ 20/12.5 mg (round tablet): [redacted]

Placebo (oblong tablet) to match OM 40 mg, OM/HCTZ 40/12.5 mg, OM/HCTZ 40/25 mg: [redacted]
Placebo (round tablet) to match OM/HCTZ 20/12.5 mg: [redacted]

Packaging Information: medication was packaged into double aluminium blisters, which were packaged into double wallet cards. OM 40 mg dose or matching placebo (oblong shaped 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 day-time, night-time and 24-hour dBP assessed by 24-hour ABPM
- Change from baseline (Visit 4, Week 8) to Week 16 in mean day-time, 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 the OM/HCTZ 40/12.5 mg versus OM/HCTZ 20/12.5 mg combinations.

Safety:
The primary safety parameter was the adverse event (AE) profile of the different OM/HCTZ combinations versus the OM monotherapy. 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 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 40 mg treatment and the OM/HCTZ treatments, 40/25 mg and 40/12.5 mg and between the OM/HCTZ treatments 40/12.5 mg and 20/12.5 mg. The model included treatment as a main effect and baseline mean trough sitting sBP 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 day-time 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 40/12.5 mg versus 20/12.5 mg combinations after 8 weeks of double-blind treatment were explored in a joint plot of safety and efficacy.

All statistical tests were 2-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: 1,226

Safety Set 2: 971

Full Analysis Set: 970

Efficacy Results: The primary efficacy parameter was the change from Baseline (Week 8) to the end of the 8-week double-blind treatment period (Week 16) in mean trough sitting dBP, assessed by conventional BP measurement. Using the pre-specified closed test procedure for confirmatory statistical hypothesis testing of the primary efficacy parameter, it could be demonstrated:

1) that OM/HCTZ 40/25 mg showed statistically significant (p<0.0001) superiority over OM/HCTZ 40/0 mg with an estimated treatment difference of -5.3 mmHg in favour of OM/HCTZ 40/25 mg
2) that OM/HCTZ 40/12.5 mg showed statistically significant (p<0.0001) superiority over OM/HCTZ 40/0 mg with an estimated treatment difference of -3.4 mmHg in favour of OM/HCTZ 40/12.5 mg
3) the treatment comparison between OM/HCTZ 40/12.5 mg and OM/HCTZ 20/12.5 mg was not statistically significant (p=0.1788). However, an estimated treatment difference of -0.9 mmHg in favour of OM/HCTZ 40/12.5 mg was observed.

The table below presents the results for mean change and adjusted mean change in sitting dBP from baseline (Week 8) to Week 16 with last observation carried forward (LOCF) for the FAS.

Analysis Variable	**OM/HCTZ 40/25 mg (N=140)**	**OM/HCTZ 40/12.5 mg (N=277)**	**OM/HCTZ 20/12.5 mg (N=279)**	**OM/HCTZ 40/0 mg (N=274)**
N	140	277	279	274
Baseline mean (SD) [1]	98.0 (5.56)	97.5 (5.96)	97.2 (6.25)	97.3 (5.81)
Week 16 LOCF mean (SD)	86.9 (9.01)	88.3 (9.04)	89.1 (9.23)	91.6 (9.64)
Mean change (SD)	-11.16 (8.796)	-9.13 (8.622)	-8.10 (7.968)	-5.66 (8.546)
Pairwise comparisons at Week 16 [2]:	**Treatment difference**	**p-value**	**95% CI**	
1)OM/HCTZ 40/25 mg - OM/HCTZ 40/0 mg	-5.3 = -11.0 - (-5.7)	<0.0001	(-6.97, -3.60)	
2)OM/HCTZ 40/12.5 mg - OM/HCTZ 40/0 mg	-3.4 = -9.1 - (-5.7)	<0.0001	(-4.79, -2.03)	
3)OM/HCTZ 40/12.5 mg - OM/HCTZ 20/12.5 mg	-0.9 = -9.1 - (-8.2)	0.1788	(-2.32, 0.43)	

1. Baseline Period II is the last mean assessment prior to administration of double-blind study 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 is calculated at difference in model base adjusted mean.
Treatment difference is based on the difference of LS means which may differ from the difference in the estimate shown due to rounding of the results.
CI = confidence interval; 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 the following:

1) a statistically significant difference between OM/HCTZ 40/25 mg versus OM/HCTZ 40/0 mg with an estimated treatment difference of -7.4 mmHg in favour of the dose combination compared to monotherapy.
2) a statistically significant difference between OM/HCTZ 40/12.5 mg versus OM/HCTZ 40/0 mg with an estimated treatment difference of -5.2 mmHg in favour of the dose combination compared to monotherapy.
3) a statistically significant difference between OM/HCTZ 40/12.5 mg versus OM/HCTZ 20/12.5 mg. An estimated treatment difference of -2.6 mmHg in favour of the higher dose combination compared to the

lower dose combination was observed.

and supported the conclusions of the confirmatory analysis on the primary efficacy parameter.

The exploratory analysis of the secondary efficacy parameter: number of patients achieving target BP after 8 weeks of double-blind treatment demonstrated the following:

1) a statistically significant difference between OM/HCTZ 40/25 mg versus OM/HCTZ 40/0 mg regarding the response rates of 42.1% versus 24.8%. The odds of reaching target BP were 2.67 times higher among patients treated with OM/HCTZ 40/25 mg as compared to patients treated with OM/HCTZ 40/0 mg.
2) a statistically significant difference between OM/HCTZ 40/12.5 mg versus OM/HCTZ 40/0 mg regarding the response rates of 39.7% versus 24.8%. The odds of reaching target BP were 2.20 times higher among patients treated with OM/HCTZ 40/12.5 mg as compared to patients treated with OM/HCTZ 40/0 mg.
3) a statistically significant difference between OM/HCTZ 40/12.5 mg versus OM/HCTZ 20/12.5 mg regarding the response rates of 39.7% versus 31.5%. The odds of reaching target BP were 1.55 times higher among patients treated with OM/HCTZ 40/12.5 mg as compared to patients treated with OM/HCTZ 20/12.5 mg.

and supported the conclusions of the confirmatory analysis on the primary efficacy parameter.

The assessment of the antihypertensive efficacy using the changes on ABPM mean 24-hour, day-time and night-time dBP and sBP after 8 weeks of double-blind treatment as secondary efficacy parameters showed very similar results in the corresponding exploratory statistical analyses and supported the conclusions of the primary analysis.

In general, the results on the primary and secondary efficacy parameters after 4 weeks of double-blind therapy also supported the findings after 8 weeks. However, the effects were less pronounced due to the shorter treatment duration.

Overall, it can be concluded that both dose combinations, OM/HCTZ 40/25 mg and OM/HCTZ 40/12.5 mg, showed - independent from the parameter and the type of BP measurement - consistently greater reductions than the OM 40 mg monotherapy. These treatment differences in favour of the dose combinations were always clinically relevant and statistically significant. The dose combination OM/HCTZ 40/12.5 mg showed - independent from the parameter and the type of BP measurement - consistently greater lowering of BP compared to OM/HCTZ 20/12.5 mg group, which was considered clinically meaningful. However, the treatment comparison was only statistically significant on trough sitting sBP, but also showed a trend towards statistical significance on sBP as measured by ABPM. A dose response was observed. Compared with monotherapy, treatment with OM/HCTZ combinations resulted in a statistically significant higher proportion of patients who reached target BP at Week 16 and a statistically significant treatment difference was observed between OM/HCTZ 40/12.5 mg and OM/HCTZ 20/12.5 mg. Comparing all doses with each other, a dose response was observed with the highest reduction in BP achieved by the dose combination OM/HCTZ 40/25 mg followed by OM/HCTZ 40/12.5 mg, OM/HCTZ 20/12.5 mg and finally OM 40 mg monotherapy.

Safety Results: The table below provides an overview of AEs during Period I for Safety Set 1.

	OM 40 mg (N=1226) n (%)
Total number of AEs	572
Total number of patients with at least one:	
TEAE	206 (16.8)
Serious TEAE	11 (0.9)
Study medication related TEAE	33 (2.7)
Severe TEAE	11 (0.9)
Moderate TEAE	66 (5.4)
Mild TEAE	146 (11.9)
TEAE leading to discontinuation	27 (2.2)
TEAE leading to death	3 (0.2)

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

The table below provides an overview of AEs during Period II for Safety Set 2.

	OM/HCTZ 40/25 mg (N=140) n (%)	OM/HCTZ 40/12.5 mg (N=278) n (%)	OM/HCTZ 20/12.5 mg (N=279) n (%)	OM/HCTZ 40/0 mg (N=274) n (%)
Total number of AEs	78	124	105	122
Total number of patients with at least one:				
TEAE	20 (14.3)	42 (15.1)	33 (11.8)	42 (15.3)
Serious TEAE	1 (0.7)	5 (1.8)	3 (1.1)	3 (1.1)
Study medication related TEAE	5 (3.6)	7 (2.5)	8 (2.9)	9 (3.3)
Severe TEAE	2 (1.4)	2 (0.7)	1 (0.4)	2 (0.7)
Moderate TEAE	5 (3.6)	12 (4.3)	12 (4.3)	10 (3.6)
Mild TEAE	18 (12.9)	33 (11.9)	22 (7.9)	32 (11.7)
TEAE leading to discontinuation	2 (1.4)	3 (1.1)	5 (1.8)	3 (1.1)
TEAE leading to death	0	0	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.

In all treatment groups, the incidence of TEAEs was low during both Period I and Period II of the trial and no SAEs were considered by the Investigator to be drug-related.

No safety concerns (i.e., versus the individual monotherapy components) were identified during the course of this trial. There were no 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 or OM/HCTZ 40/12.5 mg groups versus OM/HCTZ 40/0 mg group or in the OM/HCTZ 40/12.5 mg group versus OM/HCTZ 20/12.5 mg group. Despite the involvement of elderly patients and those with severe hypertension, which have a higher risk and more vulnerable condition, the number of TEAEs did not differ from those in the general population. There were no particular differences in safety profile across the different age groups, between males and females, by hypertension severity categories or by diabetic status.

No trends were observed in the shifts in haematology 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 in biochemistry and urinalysis parameters were noted in Period I and Period II in a very limited number of patients. However, potassium decreases and uric acid increases are well-known side effects of HCTZ.

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

The risk-benefit assessment of OM/HCTZ 40/25 mg and OM/HCTZ 40/12.5 mg when compared with OM/HCTZ 40/0 mg was considered positive in favour of the combinations.

For the OM/HCTZ 40/12.5 mg versus the OM/HCTZ 20/12.5 mg comparison it can be concluded that OM/HCTZ 40/12.5 mg has at least a comparable risk-benefit ratio to OM/HCTZ 20/12.5 mg, considering the primary efficacy analysis only. Taking all efficacy and safety results, a positive risk-benefit ratio can be concluded in favour of OM/HCTZ 40/12.5 mg.

Conclusions: This trial showed clinically meaningful and statistically significant treatment differences on the primary and any secondary efficacy parameter in favour of both OM/HCTZ 40/25 mg and OM/HCTZ 40/12.5 mg combinations, as compared to OM 40 mg monotherapy. These results fully meet the requirements of the current guidelines.

In addition, it was shown that the risk-benefit assessment was in favour of OM/HCTZ 40/12.5 mg as compared to OM/HCTZ 20/12.5 mg, taking all relevant information on efficacy and safety into account.

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

Date of the Report: 03 October 2008