CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/Serial #:	22100
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INDICATION:	Antihypertensive
APPLICANT:	Daiichi Sankyo Inc.
DATE OF RECEIPT:	11/27/2006
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	Division of Biometrics I
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KEY WORDS: Olmesartan, Amlodipine, First Line Therapy.

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The main objective of study CS8663-A-U301 was to determine if co-administration of Olmesartan medoxomil (OM) and Amlodipine (AML) had a clinically significant benefit versus the respective monotherapy components in controlling blood pressure in patients with mild to severe hypertension. The results from the double-blind treatment period of study CS8663-A-U301 confirmed in the overall study population that Olmesartan medoxomil 10 mg, 20 mg, or 40 mg given together with Amlodipine 5 mg or 10 mg reduced both diastolic and systolic blood pressure to a greater extent than monotherapy with each of the component drugs that made up each combination. The combination of OM 40 mg + AML 10 mg resulted in the greatest mean reduction in SeDBP and SeSBP. The comparisons of the mean reductions in both SeDBP and SeSBP between the combination treatments and the individual monotherapy treatments were all highly statistically significant. Treatment goals were reached for a greater percentage of patients on the higher dose combinations. The combination treatments all reduced more blood pressure numerically than the individual monotherapy treatments in all of the subgroups analyzed.

1.2 Brief Overview of Clinical Studies

The submission of this NDA consisted of one randomized controlled phase III efficacy study CS8663-A-U301.

The main objective of study CS8663-A-U301 was to determine if co-administration of Olmesartan Medoxomil (OM) and Amlodipine (AML) had a clinically significant benefit versus the respective monotherapy components in controlling blood pressure in patients with mild to severe hypertension. Study CS8663-A-U301 was a 52-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group, factorial trial consisting of 3 periods: I) a washout period of approximately 2 weeks, II) an 8-week, double-blind treatment period, and III) a 44-week, open-label treatment period followed by a follow-up visit (Week 54) two weeks after discontinuing the study.

The primary objective of Period II was to demonstrate that OM and AML co-administration was more efficacious for seated diastolic blood pressure (SeDBP) lowering than each of the corresponding monotherapy components.

1.3 Statistical Issues and Findings

The primary variable, the change from baseline in SeDBP at the end of Period II, was been used to test the primary null hypothesis of no difference between the six combination therapies and their respective monotherapy components. The multiplicity issue was controlled by Hommel's procedure, which controlled the overall one-sided Type I error rate at 0.025. Hommel's procedure is based on the principle of closed test procedures and utilizes the larger p-value from each pair of p-values obtained from comparing each combination therapy with its respective

monotherapy components. The secondary null hypothesis of no difference between the 6 combination therapies and their respective monotherapy components in change from baseline in SeSBP at Week 8 with LOCF in the ITT population was evaluated similarly.

Tests of the primary and secondary null hypotheses indicated that each combination therapy had significantly greater reductions in SeDBP and SeSBP compared to both of its monotherapy components.

2 INTRODUCTION

2.1 Overview

This 505(b)(2) application for the fixed-dose combination of OM and AML is based on data from protocol number CS8663-A-U301, "A Randomized, Double-Blind, Placebo-Controlled Factorial Study Evaluating the Efficacy and Safety of Co-Administration of OM plus AML Compared to Monotherapy in Patients with Mild to Severe Hypertension."

The main objective of study CS8663-A-U301 was to determine if co-administration of OM and AML had a clinically significant benefit versus the respective monotherapy components in controlling blood pressure in patients with mild to severe hypertension. The primary objective of the double-blind treatment period of this study was to demonstrate that OM and AML co-administration was more efficacious for SeDBP lowering than each of the corresponding monotherapy components.

Study CS8663-A-U301 was a 52-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group, factorial trial consisting of 3 periods: 1) a washout period of approximately 2 weeks, 2) an 8-week, double-blind treatment period, and 3) a 44-week, open-label treatment period. Period 2 consisted of an 8-week treatment period. Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized equally to 12 treatment arms listed in Table 1.

Table 1 Randomized Treatment Groups

		AML		
		0 mg	5 mg	10 mg
OM	0 mg	A	E	F
	10 mg	B	G	H
	20 mg	C	I	J
	40 mg	D	K	L

A treatment effect of combination versus its individual component in SeDBP of 3 mmHg at the end of 8 weeks of treatment, a common standard deviation of 7.5 mmHg, 80% power, and each individual comparison tested at a one-sided level of 0.0083. Thus, 134 patients per treatment arm were required to complete the study. Assuming a dropout rate of 15%, 158 patients were to have been randomized to each treatment arm for a total of 1896 patients randomized into the study.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\CDSESUB1\evsprod\NDA022100\0000\m5\datasets\cs8663-a-u301\listings of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The study description in this section is based on the sponsor's study report, any discrepancy between the study report and the study protocol will be discussed in the section of statistical reviewer's findings and comments.

3.1.1 STUDY OBJECTIVES OF CS8663-A-U301

The primary objective of Period II was to demonstrate that OM and AML co-administration was more efficacious for seated diastolic blood pressure (SeDBP) lowering than each of the corresponding monotherapy components.

3.1.2 STUDY DESIGN

This was a 52-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group, factorial trial consisting of 3 periods:

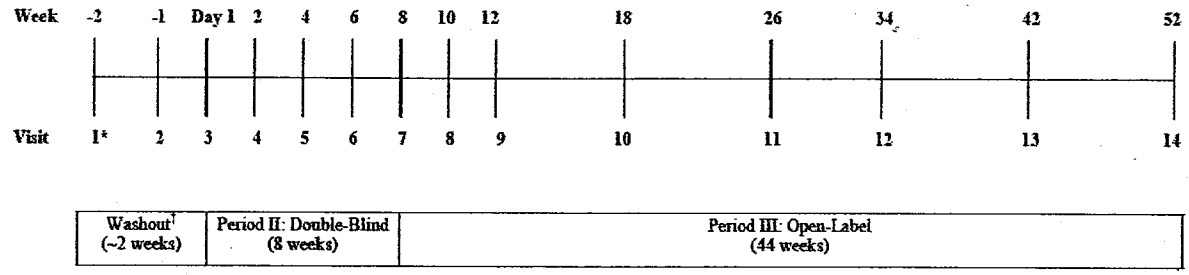
Period I – Washout (approximately 2 weeks): Period I consisted of a single screening visit for patients not on antihypertensive medications and a washout period with a minimum of 2 and a maximum of 3 visits for patients on antihypertensive medications.

Period II – Double-Blind Treatment (Day 1 to Week 8): Period II consisted of an 8-week treatment period. Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized equally to 1 of the 12 treatment arms listed in Table 1.

Period III – Open-Label Treatment (Week 8 through Week 52; follow-up after washout at Week 54): Period III consisted of a 44-week, open-label treatment period to assess long-term safety and efficacy of various treatment combinations. After completing Period II, all patients were switched to the combination of OM 40 mg + AML 5 mg.

The study design outline is shown in Figure 3.1.

Figure 3.1 Study Design



[Source: Sponsor's Study Report Figure 1.]

3.1.3 Efficacy Measures

The primary efficacy variable was the mean change in SeDBP from baseline to the end of the double-blind treatment period (Period II). If a patient withdrew from the study prior to Week 8, the last observed value during the randomized double-blind treatment period was carried forward (LOCF) for the primary efficacy analysis. Change from baseline in SeSBP at the end of Period II with LOCF was the secondary efficacy variable.

Other efficacy variables assessed for Period II included:

- Change from baseline in SeDBP and SeSBP at Weeks 2, 4, 6, and 8 without LOCF;
- Proportion of patients who reached blood pressure treatment goals (i.e., <140/90 mmHg or <130/80 mmHg for diabetic patients) at Weeks 2, 4, 6, and 8 (without LOCF), and Week 8 with LOCF; and
- Change from baseline to Week 8 (with LOCF) in inflammatory markers including hsCRP, metalloproteases 2 and 9, tPA, PAI-1, and microalbuminuria.

3.1.4 Statistical Analysis Plan

The primary null hypothesis of no difference between the 6 combination therapies and their respective monotherapy components in change from baseline in SeDBP at Week 8 with LOCF in the ITT population was evaluated using Hommel's procedure in order to control the overall one-sided Type I error rate at 0.025.

Hommel's procedure requires computing $m=\max \{i: P_{(n-i+k)} > k\alpha /i \text{ for } k=1,\ldots, i\}$, where $P_{(1)} \leq P_{(2)} \leq P_{(3)} \leq \ldots\ldots P_{(n)}$ are the n ordered p-values in ascending order, n is the number of comparisons and i=1, …, n. If the maximum does not exist, reject all H_i (i=1,…,n); otherwise reject all H_i with $P_i \leq \alpha / m$. In order to apply Hommel's procedure, the larger p-value of each pair of p-values obtained from comparing each combination with its components was used.

The resulting 6 p-values were arranged from the smallest, $P_{(1)}$, to the largest, $P_{(6)}$, each with its corresponding null hypothesis $H_{0(1)}$ to $H_{0(6)}$, and Hommel's procedure was applied. A combination was concluded as better than its 2 individual components if the corresponding null hypothesis was rejected. The secondary null hypothesis of no difference between the 6 combination therapies and their respective monotherapy components in change from baseline in SeSBP at

Week 8 with LOCF in the ITT population was evaluated similarly.

One-sided p-values for testing the primary and secondary null hypotheses were obtained from an Analysis of Covariance (ANCOVA) model that had fixed effects for treatment group, diabetic status (with or without diabetes) and age group (age ≥65 years or age <65 years), and study baseline blood pressure as a covariate.

The resulting p-values from Hommel's procedure were compared to a significance level of 0.025 to determine whether the given combination therapy could be declared statistically significantly better than both respective monotherapy components. The same analysis was applied to the secondary efficacy variable, change from baseline in SeSBP at Week 8 with LOCF in the ITT population and change from baseline for SeDBP and SeSBP at Weeks 2, 4, 6, and 8, all without LOCF imputation. For each of the above secondary endpoints, Hommel's procedure was used to control the Type I error rate of the treatment comparisons. Each secondary endpoint was evaluated only if statistically significant combinations were found for the preceding secondary endpoints.

The sample size was calculated based on the following assumptions: a treatment effect of co-administration versus its individual component in SeDBP of 3 mmHg at the end of 8 weeks of treatment, a common standard deviation of 7.5 mmHg, 80% power, and each individual comparison tested at a one-sided level of 0.0083. Thus, 134 patients per treatment arm were required to complete the study. Assuming a dropout rate of 15%, 158 patients were to have been randomized to each treatment arm for a total of 1896 patients randomized into the study.

3.1.5 Patient Disposition, Demographic and Baseline Characteristics

A total of 1940 patients were randomized to double-blind treatment; 251 (12.9% of 1940 randomized) of these patients discontinued during Period II. Figure 3.2 summarizes patient disposition information for the double-blind treatment period.

Of the 1940 patients in the All Randomized Patients population, 1054 (54.3%) were male, 1385 (71.4%) were Caucasian, 481 (24.8%) were Black, 36 (1.9%) were Asian, and 48 (2.5%) were all other races (including Other, American Indian/Alaskan Native, and Native Hawaiian/Pacific Islander). The mean age was 54.0 years. A total of 384 (19.8%) patients were ≥65 years of age. Weight, height, and BMI were also similar for the treatment groups, with no statistically significant differences among the treatment groups for these baseline characteristics. Mean weight was 95.1 kg, mean height was 170.1 cm, and mean BMI was 33.5 kg/m2. A total of 64.7% of patients were obese (BMI ≥30 kg/m2), and 13.5% of patients had diabetes.

Figure 3.2 Patient Disposition

Disposition	Pbo (N = 162) n (%)	OM10 (N = 161) n (%)	OM20 (N = 161) n (%)	OM40 (N = 162) n (%)	AML5 (N = 161) n (%)	AML10 (N = 163) n (%)	OM10/ AML5 (N = 163) n (%)	OM20/ AML5 (N = 161) n (%)	OM40/ AML5 (N = 162) n (%)	OM10/ AML10 (N = 162) n (%)	OM20/ AML10 (N = 160) n (%)	OM40/ AML10 (N = 162) n (%)
Randomized	162 (100)	161 (100)	161 (100)	162 (100)	161 (100)	163 (100)	163 (100)	161 (100)	162 (100)	162 (100)	160 (100)	162 (100)
Completed Period II	121 (74.7)	140 (87.0)	135 (83.9)	143 (88.3)	140 (87.0)	144 (88.3)	156 (95.7)	147 (91.3)	143 (88.3)	134 (82.7)	143 (89.4)	143 (88.3)
Discontinued During Period II	41 (25.3)	21 (13.0)	26 (16.1)	19 (11.7)	21 (13.0)	19 (11.7)	7 (4.3)	14 (8.7)	19 (11.7)	28 (17.3)	17 (10.6)	19 (11.7)
Adverse Event	21(13.0)	13 (8.1)	17 (10.6)	10 (6.2)	10 (6.2)	10 (6.1)	0 (0.0)	4 (2.5)	6 (3.7)	11 (6.8)	3 (1.9)	9 (5.6)
Due to Lack of Efficacy[1]	14 (8.6)	7 (4.3)	8 (5.0)	6 (3.7)	4 (2.5)	2 (1.2)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject Request	3 (1.9)	2 (1.2)	3 (1.9)	3 (1.9)	7 (4.3)	4 (2.5)	2 (1.2)	5 (3.1)	3 (1.9)	6 (3.7)	2 (1.3)	3 (1.9)
Required Restricted Medications	2 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
Lost to Follow-up	6 (3.7)	2 (1.2)	3 (1.9)	1 (0.6)	3 (1.9)	1 (0.6)	1 (0.6)	3 (1.9)	6 (3.7)	3 (1.9)	5 (3.1)	3 (1.9)
Investigator Judgment	4 (2.5)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Met Protocol Withdrawal Criteria	4 (2.5)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)
Other	1 (0.6)	3 (1.2)	1 (0.6)	4 (2.5)	0 (0.0)	4 (2.5)	3 (1.8)	2 (1.2)	4 (2.5)	8 (4.9)	6 (3.8)	1 (0.6)
Safety Population	162 (100)	161 (100)	161 (100)	162 (100)	161 (100)	163 (100)	163 (100)	161 (100)	162 (100)	162 (100)	160 (100)	162 (100)
Intent-to-Treat Population	160 (98.8)	160 (99.4)	159 (98.8)	160 (98.8)	161 (100)	163 (100)	163 (100)	160 (99.4)	157 (96.9)	161 (99.4)	158 (98.8)	161 (99.4)
Per-Protocol Population	130 (80.2)	136 (84.5)	135 (83.9)	144 (88.9)	141 (87.6)	146 (89.6)	151 (92.6)	147 (91.3)	136 (84.0)	129 (79.6)	144 (90.0)	140 (86.4)

[Source: Sponsor's Study Report Figure 3.]

Figure 3.3 provides mean baseline values of blood pressure and heart rate for the Safety population. The treatment groups were similar with respect to baseline values for blood pressure and heart rate, with no statistically significant differences among the treatment groups.

Figure 3.3 Baseline BP and HR

Treatment	n	SeDBP (mmHg) Mean ± SD	n	SeSBP (mmHg) Mean ± SD	n	Heart Rate (bpm) Mean ± SD
Placebo	162	102.3 ± 4.80	162	166.5 ± 17.64	162	76.8 ± 9.71
OM10	161	101.8 ± 5.92	161	162.9 ± 16.72	161	77.1 ± 10.66
OM20	161	101.5 ± 4.57	161	164.1 ± 16.52	161	77.7 ± 11.04
OM40	162	101.2 ± 5.06	162	162.8 ± 15.66	162	76.9 ± 8.91
AML5	161	101.5 ± 5.15	161	162.6 ± 17.20	161	76.3 ± 9.54
AML10	163	101.6 ± 4.84	163	163.5 ± 15.88	163	76.9 ± 10.13
OM10/AML5	163	102.1 ± 5.36	163	165.5 ± 15.60	163	76.9 ± 10.07
OM20/AML5[†]	160	101.7 ± 5.06	160	163.8 ± 14.93	160	77.6 ± 9.98
OM40/AML5	162	100.9 ± 4.76	162	161.7 ± 14.82	162	75.0 ± 9.99
OM10/AML10	162	101.4 ± 5.50	162	162.5 ± 15.56	162	77.4 ± 10.51
OM20/AML10	160	101.2 ± 4.67	160	164.1 ± 14.88	160	76.3 ± 9.31
OM40/AML10	162	102.4 ± 5.80	162	165.7 ± 16.73	162	76.7 ± 9.38
Total	1939	101.6 ± 5.15	1939	163.8 ± 16.05	1939	76.8 ± 9.95
p-value[1]	0.2216		0.2049		0.6089	

[Source: Sponsor's Study Report Table 5.]

Furthermore, the treatment groups were similar with respect to baseline hypertension class, with over 70% of patients in each treatment group having Stage 2 hypertension. Overall, a total of 1538 (79.3%) patients had Stage 2 hypertension, see Figure 3.4.

Figure 3.4 Baseline Hypertension Class

Treatment	N[3]	JNC7 Guidelines	
		Stage 1 (140-159/90-99 mmHg) n (%)	Stage 2 (≥160/≥100 mmHg) n (%)
Placebo	162	29 (17.9)	133 (82.1)
OM10	161	37 (23.0)	123 (76.4)
OM20	161	28 (17.4)	133 (82.6)
OM40	162	42 (25.9)	120 (74.1)
AML5	161	37 (23.0)	124 (77.0)
AML10	163	33 (20.2)	130 (79.8)
OM10/AML5	163	28 (17.2)	135 (82.8)
OM20/AML5	161	32 (19.9)	128 (79.5)
OM40/AML5	162	38 (23.5)	123 (75.9)
OM10/AML10	162	36 (22.2)	126 (77.8)
OM20/AML10	160	26 (16.3)	134 (83.8)
OM40/AML10	162	33 (20.4)	129 (79.6)
Total[1]	1940	399 (20.6)	1538 (79.3)
p-value[2]		0.5353	

[Source: Sponsor's Study Report Table 6.]

3.1.6 PRIMARY EFFICACY RESULTS

The primary efficacy variable was the mean change in SeDBP from baseline to the end of the double-blind treatment period (Period II). Table 2 presents the analysis results for mean change in SeDBP from baseline to Week 8 with LOCF for the ITT population.

Table 2 Mean change in SDBP from baseline to Week 8 With LOCF

Treatment	N	Mean Change ± SD
Placebo	160	-3.06 ± 10.67
OM10	160	-8.28 ± 9.28
OM20	159	-9.24 ± 9.73
OM40	160	-10.21 ± 10.69
AML5	161	-9.36 ± 8.25
AML10	163	-12.72 ± 8.25
OM10/AML5	163	-13.81 ± 7.48
OM20/AML5	160	-14.00 ± 9.07
OM40/AML5	157	-15.52 ± 8.15
OM10/AML10	161	-16.02 ± 8.62
OM20/AML10	158	-17.01 ± 8.04
OM40/AML10	161	-18.99 ± 8.90

[Source: Reviewer's results which confirmed Sponsor's Table 7.]

Table 3 presents the comparisons of combination therapy versus the monotherapy components of each combination with respect to mean change in SeDBP from baseline to Week 8 with LOCF for the ITT population. Each combination therapy had a significantly greater mean reduction in SeDBP compared to both of its monotherapy components ($p<0.001$ for all comparisons). According to the statistical analysis plan, the Hommel's procedure will reject all six null

hypotheses, and conclude that all combinations are more effective than their respective monotherapy components.

Table 3 Mean Change in SDBP from Baseline to Week 8 with LOCF – Combination Therapy vs. Monotherapy Comparisons

Treatment Comparison			N		Difference (Tmt 1 – Tmt 2)			
Tmt1	vs.	Tmt2	Tmt1	Tmt2	LS Mean	95% CI	p-value	Adjusted p-value
OM10 /AML5	vs.	OM10 AML5	163	160 161	-5.5 -4.3	(-7.4 , -3.5) (-6.3 , -2.4)	<0.0001 <0.0001	<0.0001
OM20 /AML5	vs.	OM20 AML5	160	159 161	-4.7 -4.6	(-6.6 , -2.7) (-6.5 , -2.6)	<0.0001 <0.0001	<0.0001
OM40 /AML5	vs.	OM40 AML5	157	160 161	-5.4 -6.3	(-7.3 , -3.4) (-8.2 , -4.3)	<0.0001 <0.0001	<0.0001
OM10 /AML10	vs.	OM10 AML10	161	160 163	-7.8 -3.3	(-9.8 , -5.9) (-5.3 , -1.4)	<0.0001 0.0004	0.0004
OM20 /AML10	vs.	OM20 AML10	158	159 163	-7.8 -4.4	(-9.8 , -5.9) (-6.3 , -2.4)	<0.0001 <0.0001	<0.0001
OM40 /AML10	vs.	OM40 AML10	161	160 163	-8.5 -6.1	(-10.5 , -6.6) (-8.0 , -4.2)	<0.0001 <0.0001	<0.0001

[Source: Reviewer's result confirms Sponsor's Table 9.]

Furthermore, the placebo-adjusted LS mean reduction in SeDBP from baseline to Week 8 with LOCF for each active treatment is listed in Table 4.

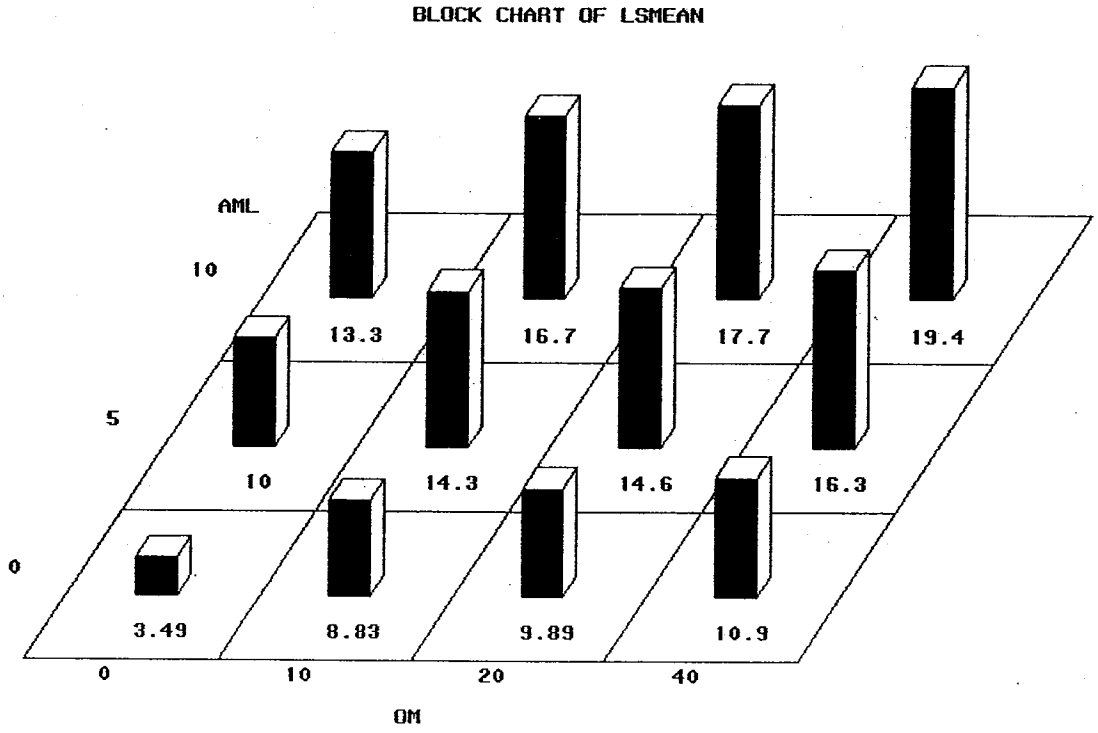
Table 4 Placebo-Adjusted LS Mean Reduction in SDBP

		OM			
		Placebo	10 mg	20 mg	40 mg
AML	Placebo	--	-5.3	-6.4	-7.4
	5 mg	-6.5	-10.8	-11.1	-12.8
	10 mg	-9.9	-13.2	-14.2	-15.9

[Source: Reviewer's result confirms Sponsor's Table 8.]

Sponsor also included a dose response chart displays the mean reduction in SeDBP from baseline to Week 8 with LOCF for each treatment group of ITT population, see Figure 3.5. The figure was able to paint a strong association between dosages and mean reduction in SeDBP for both the monotherapies and the combination therapies.

Figure 3.5 Mean Reduction in SeDBP from Baseline to Week 8 with LOCF



[Source: Reviewer's result]

3.1.7 Secondary Efficacy Results

The Change in SeSBP from baseline to Week 8 with LOCF has very similar results as the primary endpoint. Table 5 presents the analysis results for mean change in SeSBP from baseline to Week 8 with LOCF for the ITT population.

Table 5 Mean Change in SeSBP from Baseline to Week 8

Treatment	N	Mean Change ± SD
Placebo	160	-4.8 ± 18.70
OM10	160	-11.5 ± 15.23
OM20	159	-13.8 ± 15.90
OM40	160	-10.21 ± 10.69
AML5	161	-9.36 ± 8.25
AML10	163	-12.72 ± 8.25
OM10/AML5	163	-13.81 ± 7.48
OM20/AML5	160	-14.00 ± 9.07
OM40/AML5	157	-15.52 ± 8.15
OM10/AML10	161	-16.02 ± 8.62
OM20/AML10	158	-17.01 ± 8.04
OM40/AML10	161	-18.99 ± 8.90

[Source: Reviewer's result confirms Sponsor's Table 10.]

Table 6 resents the comparisons of combination therapy versus the monotherapy components of each combination with respect to mean change in SeSBP from baseline to Week 8 with LOCF for the ITT population. Each combination therapy had a significantly greater mean reduction in SeSBP compared with both of its monotherapy components ($p<0.001$ for all comparisons).

Table 6 Mean Change in SeSBP from baseline to Week 8 in LOCF- Combination Therapy vs. Monotherapy Comparisons

Treatment Comparison			Difference (Tmt 1 – Tmt 2)			
Tmt1	vs.	Tmt2	LS Mean	95% CI	p-value	Adjusted p-value
OM10 /AML5	vs.	OM10	-11.7	(-14.9, -8.5)	<0.0001	
		AML5	-8.2	(-11.4 , -5.0)	<0.0001	<0.0001
OM20 /AML5	vs.	OM20	-9.9	(-13.1, -6.7)	<0.0001	
		AML5	-8.3	(-11.5, -5.1)	<0.0001	<0.0001
OM40 /AML5	vs.	OM40	-9.7	(-12.9, -6.5)	<0.0001	<0.0001
		AML5	-10.8	(-14.0, -7.6)	<0.0001	
OM10 /AML10	vs.	OM10	-13.9	(-17.1, -10.7)	<0.0001	
		AML10	-5.9	(-9.1 , -2.7)	0.0002	0.0002
OM20 /AML10	vs.	OM20	-15.4	(-18.6, -12.1	<0.0001	
		AML10	-9.2	(-12.5, -6.0)	<0.0001	<0.0001
OM40 /AML10	vs.	OM40	-13.0	(-16.3 , -9.8)	<0.0001	
		AML10	-9.6	(-12.8, -6.4)	<0.0001	<0.0001

[Source: Reviewer's result confirms Sponsor's Table 12.]

The placebo-adjusted LS mean reduction in SeSBP from baseline to Week 8 with LOCF for each active treatment is listed in Table 4. We can easily conclude that there is a dose response based on this table.

Table 7 Placebo-Adjusted LS Mean Reduction in SDBP

		OM			
		Placebo	10 mg	20 mg	40 mg
AML	Placebo	--	-8.0	-9.9	-12.6
	5 mg	-11.5	-19.7	-19.8	-22.3
	10 mg	-16.1	-21.9	-25.3	-25.6

[Source: Reviewer's result confirms Sponsor's Table 11.]

3.1.8 Other Efficacy Results

The blood pressure treatment goals were defined as blood pressure <140/90 mmHg for patients without diabetes and <130/80 mmHg for patients with diabetes. Table 8 presents the comparisons of combination therapy versus monotherapy with respect to the number and percentage of patients who reached their blood pressure treatment goal from baseline to Week 8 with LOCF. Each combination therapy had a significantly greater percentage of patients who reached their blood pressure treatment goal compared with both of its monotherapy components.

Table 8 Proportion of Patients Reached BP Goal at Week 8 – Combination vs. Monotherapy

Treatment Comparison		BP Goal Achieved	
Tmt1 vs.	Tmt2	Tmt1 n(%)	Tmt2 n(%)
OM10 /AML5	vs. OM10 AML5	57 (35.0)	32 (20.0) 34 (21.1)
OM20 /AML5	vs. OM20 AML5	68 (42.5)	42 (26.4) 34 (21.1)
OM40 /AML5	vs. OM40 AML5	80 (51.0)	58 (36.3) 34 (21.1)
OM10 /AML10	vs. OM10 AML10	79 (49.1)	32 (20.0) 53 (32.5)
OM20 /AML10	vs. OM20 AML10	84 (53.2)	42 (26.4) 53 (32.5)
OM40 /AML10	vs. OM40 AML10	79 (49.1)	58 (36.3) 53 (32.5)

[Source: Sponsor's Table 14 confirmed by the reviewer.]

The proportions of patients who reached other blood pressure threshold, such as 120/80, 130/80 and 130/85 mmHg, at Week 8 with LOCF were listed in Table 9. The groups treated with a combination therapy had a greater percentage of patients who reached each blood pressure threshold compared with the respective monotherapy groups.

Table 9 # (%) of Patients reached BP Goals at Week 8

		Blood Pressure Goals		
Treatment	N	<120/80 n (%)	<130/80 n (%)	<130/85 n (%)
Placebo	160	1 (0.6)	4 (2.5)	6 (3.8)
OM10	160	2 (1.3)	6 (3.8)	15 (9.4)
OM20	159	5 (3.1)	10 (6.3)	22 (13.8)
OM40	160	8 (5.0)	22 (13.8)	32 (20.0)
AML5	161	1 (0.6)	3 (1.9)	10 (6.2)
AML10	163	2 (1.2)	12 (7.4)	25 (15.3)
OM10/AML5	163	7 (4.3)	19 (11.7)	31 (19.0)
OM20/AML5	160	11 (6.9)	19 (11.9)	28 (17.5)
OM40/AML5	157	14 (8.9)	32 (20.4)	49 (31.2)
OM10/AML10	161	14 (8.7)	31 (19.3)	49 (30.4)
OM20/AML10	158	22 (13.9)	42 (26.6)	56 (35.4)
OM40/AML10	161	22 (13.7)	37 (23.0)	49 (30.4)

[Source: Sponsor's Table 15 confirmed by reviewer.]

3.1.9 CONCLUSION

This study was able to confirm in the overall study population that Olmesartan medoxomil given together with Amlodipine reduced both diastolic and systolic blood pressure to a greater extent than monotherapy. The comparisons of the mean reductions in both SeDBP and SeSBP between the combination treatments and the individual monotherapy treatments were all statistically

significant. Treatment goals were reached for a greater percentage of patients on the higher dose combinations.

3.2 Evaluation of Safety

Please read Dr. Williams 's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Table 10 and Table 11 presented the numerical analysis results for mean change in SeDBP and SeSBP from baseline to Week 8 for the subgroup of patients <65 and ≥65 years of age.

Table 10 Mean Change in SeDBP from baseline to Week 8 by Age groups

	<65 Years of Age		≥65 Years of Age	
Treatment	N	Change Mean ± SD	N	Change Mean ± SD
Placebo	128	-2.2 ± 10.69	32	-6.4 ± 10.06
OM10	128	-7.8 ± 9.03	32	-10.1 ± 10.13
OM20	129	-8.3 ± 9.66	30	-13.2 ± 9.15
OM40	129	-10.6 ± 10.07	31	-8.8 ± 13.04
AML5	129	-8.3 ± 7.62	32	-13.7 ± 9.37
AML10	131	-11.9 ± 8.27	32	-16.1 ± 7.33
OM10/AML5	131	-13.8 ± 7.84	32	-13.9 ± 5.85
OM20/AML5	126	-13.9 ± 8.97	34	-14.6 ± 9.54
OM40/AML5	126	-15.5 ± 8.44	31	-15.8 ± 6.96
OM10/AML10	130	-15.8 ± 8.59	31	-16.8 ± 8.83
OM20/AML10	126	-17.3 ± 8.07	32	-15.9 ± 7.98
OM40/AML10	128	-18.5 ± 9.17	33	-20.9 ± 7.59

Table 11 Mean Change in SeSBP from baseline to Week 8 by Age groups

	<65 Years of Age		≥65 Years of Age	
Treatment	N	Change Mean ± SD	N	Change Mean ± SD
Placebo	128	-4.1 ± 18.54	32	-7.9 ± 19.33
OM10	128	-10.9 ± 15.30	32	-13.9 ± 14.92
OM20	129	-12.5 ± 15.07	30	-19.4 ± 18.29
OM40	129	-16.2 ± 15.63	31	-15.7 ± 20.33
AML5	129	-13.3 ± 13.44	32	-21.1 ± 18.94
AML10	131	-18.8 ± 16.39	32	-23.4 ± 16.82
OM10/AML5	131	-23.3 ± 14.38	32	-27.5 ± 11.70
OM20/AML5	126	-23.5 ± 15.38	34	-24.0 ± 12.95
OM40/AML5	126	-25.1 ± 13.62	31	-26.8 ± 18.66
OM10/AML10	130	-25.1 ± 14.79	31	-26.3 ± 15.45
OM20/AML10	126	-28.9 ± 15.86	32	-30.4 ± 19.98
OM40/AML10	128	-29.1 ± 16.30	33	-33.9 ± 13.88

For both SeDBP and SeSBP, the magnitude of reductions in the combination treatment was similar between the two age groups. Furthermore, both age groups identified that increases in doses were generally associated with greater mean reductions in BP across the treatment groups compared with the monotherapy groups.

Table 12 and Table 13 presented the analysis results for mean change in SeDBP and SeSBP from baseline to Week 8 with LOCF for the gender subgroups. There were associations between increases in dose and greater mean reductions in SeDBP and SeSBP across the treatment groups for both males and females. For both genders, mean reductions in SeDBP and SeSBP were numerically greater in the combination therapy groups compared with the monotherapy groups.

Table 12 Mean change in SeDBP based on Gender

	Male		Female	
Treatment	N	Change Mean ± SD	N	Change Mean ± SD
Placebo	91	-2.7 ± 10.77	69	-3.5 ± 10.60
OM10	86	-7.7 ± 8.83	74	-9.0 ± 9.78
OM20	90	-9.5 ± 9.45	69	-8.9 ± 10.15
OM40	81	-9.3 ± 10.32	79	-11.1 ± 11.05
AML5	87	-9.2 ± 8.11	74	-9.5 ± 8.48
AML10	98	-12.2 ± 7.49	65	-13.5 ± 9.28
OM10/AML5	84	-13.4 ± 7.20	79	-14.3 ± 7.77
OM20/AML5	82	-14.0 ± 9.17	78	-14.0 ± 9.03
OM40/AML5	94	-15.5 ± 8.01	63	-15.5 ± 8.43
OM10/AML10	93	-16.3 ± 7.97	68	-15.7 ± 9.49
OM20/AML10	71	-15.3 ± 7.60	87	-18.4 ± 8.18

Table 13 Mean change in SeSBP based on Gender

	Male		Female	
Treatment	N	Change Mean ± SD	N	Change Mean ± SD
Placebo	91	-2.9 ± 15.93	69	-7.4 ± 21.70
OM10	86	-10.3 ± 15.45	74	-12.9 ± 14.96
OM20	90	-13.8 ± 15.90	69	-13.9 ± 16.01
OM40	81	-16.7 ± 15.81	79	-15.4 ± 17.41
AML5	87	-13.6 ± 12.87	74	-16.3 ± 17.06
AML10	98	-16.6 ± 14.56	65	-24.5 ± 18.22
OM10/AML5	84	-22.7 ± 12.27	79	-25.7 ± 15.50
OM20/AML5	82	-20.8 ± 14.33	78	-26.5 ± 14.94
OM40/AML5	94	-23.7 ± 13.53	63	-28.0 ± 16.07
OM10/AML10	93	-24.9 ± 14.60	68	-25.9 ± 15.33
OM20/AML10	71	-23.8 ± 15.40	87	-33.7 ± 16.51
OM40/AML10	88	-26.5 ± 14.82	73	-34.5 ± 16.16

Table 14 and Table 15 presented the numerical results for mean change in SeDBP and SeSBP from baseline to Week 8 with LOCF for the race subgroups, Black vs. Non-Black. There were, again, general associations between increases in dose and greater mean reductions in SeDBP and SeSBP across the treatment groups for both the Black and non-Black subgroups. For both race

subgroups, mean reductions in SeDBP and SeSBP were numerically greater in the combination therapy groups compared with the monotherapy groups. Across the range of combination therapies, the non-Black subgroup had numerically greater mean reductions in SeDBP and SeSBP compared with the Black subgroup.

Table 14 Mean Change in SeDBP Based on Race

	Black		Non-Black	
Treatment	N	Change Mean ± SD	N	Change Mean ± SD
Placebo	45	-1.3 ± 9.55	115	-3.8 ± 11.04
OM10	32	-5.3 ± 8.44	128	-9.0 ± 9.35
OM20	34	-4.5 ± 9.98	125	-10.5 ± 9.30
OM40	44	-5.5 ± 9.51	116	-12.0 ± 10.61
AML5	42	-8.3 ± 8.66	119	-9.7 ± 8.11
AML10	39	-13.4 ± 8.40	124	-12.5 ± 8.22
OM10/AML5	34	-9.4 ± 6.94	129	-15.0 ± 7.20
OM20/AML5	43	-12.4 ± 9.17	117	-14.6 ± 9.00
OM40/AML5	38	-13.9 ± 8.35	119	-16.0 ± 8.06
OM10/AML10	43	-15.5 ± 8.45	118	-16.2 ± 8.71
OM20/AML10	46	-15.2 ± 7.92	112	-17.8 ± 8.01
OM40/AML10	34	-15.7 ± 9.05	127	-19.9 ± 8.68

Table 15 Mean change in SeSBP based on Race

	Black		Non-Black	
Treatment	N	Change Mean ± SD	N	Change Mean ± SD
Placebo	45	-4.3 ± 21.29	115	-5.0 ± 17.69
OM10	32	-6.0 ± 12.30	128	-12.9 ± 15.62
OM20	34	-5.5 ± 17.06	125	-16.1 ± 14.84
OM40	44	-8.2 ± 16.07	116	-19.1 ± 15.83
AML5	42	-11.9 ± 13.40	119	-15.9 ± 15.39
AML10	39	-22.1 ± 15.12	124	-19.0 ± 16.93
OM10/AML5	34	-18.8 ± 12.53	129	-25.6 ± 14.02
OM20/AML5	43	-23.7 ± 12.57	117	-23.5 ± 15.66
OM40/AML5	38	-24.7 ± 13.84	119	-25.7 ± 15.01
OM10/AML10	43	-24.1 ± 16.10	118	-25.8 ± 14.45
OM20/AML10	46	-25.3 ± 13.76	112	-30.9 ± 17.59
OM40/AML10	34	-28.7 ± 14.85	127	-30.5 ± 16.22

4.2 Other Subgroup Populations

One of the covariate in the ANOCA is the patients' diabetic status. Table 16 and Table 17 presented the analysis results for mean change in SeDBP and SeSBP from baseline to Week 8 with LOCF for the subgroups of patients with and without diabetes. Based on the following results, we came to the conclusion that the mean reductions in SeDBP and SeSBP were numerically greater in the combination therapy groups compared with the monotherapy groups.

Table 16 Mean Change in SeDBP based on Diabetes Status Subgroups

	Without Diabetes		With Diabetes	
Treatment	N	Change Mean ± SD	N	Change Mean ± SD
Placebo	137	-2.2 ± 9.63	23	-8.2 ± 14.77
OM10	140	-8.0 ± 9.50	20	-9.9 ± 7.50
OM20	137	-9.2 ± 9.38	22	-9.4 ± 11.96
OM40	139	-10.5 ± 10.33	21	-8.3 ± 12.94
AML5	139	-9.0 ± 7.86	22	-11.6 ± 10.36
AML10	140	-12.9 ± 8.35	23	-11.7 ± 7.69
OM10/AML5	140	-13.6 ± 7.65	23	-15.1 ± 6.34
OM20/AML5	138	-14.9 ± 9.02	22	-8.3 ± 7.23
OM40/AML5	140	-15.6 ± 8.16	17	-14.6 ± 8.26
OM10/AML10	141	-16.0 ± 8.49	20	-16.0 ± 9.75
OM20/AML10	137	-17.3 ± 8.26	21	-15.0 ± 6.20
OM40/AML10	137	-19.1 ± 9.08	24	-18.4 ± 7.95

Table 17 Mean Change in SeSBP based on Diabetes Status Subgroups

	Without Diabetes		With Diabetes	
Treatment	N	Change Mean ± SD	N	Change Mean ± SD
Placebo	137	-3.1 ± 15.50	23	-15.3 ± 30.18
OM10	140	-11.1 ± 15.58	20	-14.4 ± 12.49
OM20	137	-14.2 ± 15.70	22	-11.6 ± 17.28
OM40	139	-16.9 ± 15.88	21	-10.5 ± 20.17
AML5	139	-14.0 ± 14.29	22	-20.3 ± 18.04
AML10	140	-20.1 ± 16.72	23	-17.7 ± 15.48
OM10/AML5	140	-23.9 ± 13.87	23	-25.6 ± 14.79
OM20/AML5	138	-25.1 ± 14.67	22	-14.2 ± 12.67
OM40/AML5	140	-25.5 ± 14.23	17	-25.0 ± 18.65
OM10/AML10	141	-25.0 ± 14.33	20	-27.9 ± 18.49
OM20/AML10	137	-29.7 ± 16.92	21	-26.3 ± 15.44
OM40/AML10	137	-30.1 ± 16.40	24	-30.3 ± 13.08

The study CS8663-A-U301 recruited patients from Stage 1 and Stage 2 hypertension. Table 18 and Table 19 presented the analysis results for mean change in SeDBP and SeSBP from baseline to Week 8 with LOCF for the hypertension class subgroups. The conclusions are similar to all other subgroups' conclusions, i.e. for both subgroups; mean reductions in SeDBP and SeSBP were numerically greater in the combination therapy groups compared with the monotherapy groups. However, the mean change in SeDBP among OM 40mg, OM 40mg + AML 5mg, and OM 40mg +AML 10mg are really small in Stage 1 hypertension patients. The contributions of higher doses of AML in terms of reducing DBP is almost negligible when Stage 1 hypertensive patients already taking the OM 40 mg.

Table 18 Mean Change in SeDBP based on Hypertension Class Subgroups

	Stage 1		Stage 2	
Treatment	N	Change Mean ± SD	N	Change Mean ± SD
Placebo	27	-3.6 ± 7.92	133	-3.0 ± 11.17
OM10	37	-8.0 ± 7.38	122	-8.4 ± 9.84
OM20	28	-8.0 ± 11.27	131	-9.5 ± 9.40
OM40	42	-13.4 ± 8.63	118	-9.1 ± 11.16
AML5	37	-6.9 ± 8.24	124	-10.1 ± 8.15
AML10	33	-9.3 ± 7.17	130	-13.6 ± 8.30
OM10/AML5	28	-14.8 ± 6.07	135	-13.6 ± 7.74
OM20/AML5	32	-14.8 ± 7.30	128	-13.8 ± 9.48
OM40/AML5	36	-15.8 ± 9.04	120	-15.3 ± 7.88
OM10/AML10	35	-15.3 ± 7.66	126	-16.2 ± 8.89
OM20/AML10	26	-15.8 ± 8.42	132	-17.3 ± 7.98
OM40/AML10	33	-15.7 ± 8.10	128	-19.8 ± 8.93

Table 19 Mean Change in SeSBP based on Hypertension Class Subgroups

	Stage 1		Stage 2	
Treatment	N	Change Mean ± SD	N	Change Mean ± SD
Placebo	27	-2.2 ± 13.38	133	-5.4 ± 19.61
OM10	37	-10.0 ± 11.11	122	-12.0 ± 16.34
OM20	28	-10.5 ± 13.69	131	-14.5 ± 16.29
OM40	42	-14.9 ± 11.31	118	-16.5 ± 18.11
AML5	37	-8.1 ± 13.59	124	-16.9 ± 14.79
AML10	33	-10.3 ± 13.02	130	-22.1 ± 16.50
OM10/AML5	28	-19.1 ± 10.78	135	-25.2 ± 14.34
OM20/AML5	32	-17.7 ± 8.83	128	-25.1 ± 15.70
OM40/AML5	36	-21.1 ± 13.01	120	-26.7 ± 15.03
OM10/AML10	35	-19.5 ± 9.74	126	-26.9 ± 15.67
OM20/AML10	26	-23.7 ± 11.81	132	-30.3 ± 17.36
OM40/AML10	33	-20.1 ± 13.77	128	-32.7 ± 15.44

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary variable, the change from baseline in SeDBP at the end of Period II, was been used to test the primary null hypothesis of no difference between the six combination therapies and their respective monotherapy components. The multiplicity issue was controlled by Hommel's procedure, which controlled the overall one-sided Type I error rate at 0.025. Hommel's procedure is based on the principle of closed test procedures and utilizes the larger p-value from each pair of p-values obtained from comparing each combination therapy with its respective monotherapy components. The secondary null hypothesis of no difference between the 6 combination therapies and their respective monotherapy components in change from baseline in SeSBP at Week 8 with LOCF in the ITT population was evaluated similarly.

Tests of the primary and secondary null hypotheses indicated that each combination therapy had significantly greater reductions in SeDBP and SeSBP compared to both of its monotherapy components. See the Table 3 and Table 6.

5.2 Conclusions and Recommendations

The results from the double-blind treatment period of study CS8663-A-U301 confirmed in the overall study population that Olmesartan medoxomil 10 mg, 20 mg, or 40 mg given together with Amlodipine 5 mg or 10 mg reduced both diastolic and systolic blood pressure to a greater extent than monotherapy with each of the component drugs that made up each combination. The combination of OM 40 mg + AML 10 mg resulted in the greatest mean reduction in SeDBP and SeSBP. The comparisons of the mean reductions in both SeDBP and SeSBP between the combination treatments and the individual monotherapy treatments were all highly statistically significant. Treatment goals were reached for a greater percentage of patients on the higher dose combinations. The combination treatments all reduced more blood pressure numerically than the individual monotherapy treatments in all of the subgroups analyzed.

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