

## INTEGRATED REVIEW OF SAFETY

### METHODS AND FINDINGS

The duration of exposure is presented in Tables 107 and 108; and tables 119 -121

**Table 109: Duration of Exposure during Period II \_NDA 22100**

Treatment	N <sup>2</sup>	Extent of Exposure (Days) <sup>1</sup>			
		Mean ± SD	Median	Minimum	Maximum
Placebo	163	49.2 ± 16.80	56.0	1	74
OM10	161	52.3 ± 13.05	56.0	2	65
OM20	161	51.5 ± 14.41	56.0	1	78
OM40	162	53.3 ± 12.65	56.0	1	77
AML5	161	52.8 ± 12.12	56.0	1	70
AML10	163	53.4 ± 12.07	56.0	1	67
OM10/AML5	163	55.9 ± 7.64	56.0	5	79
OM20/AML5	161	54.8 ± 10.19	57.0	2	77
OM40/AML5	162	53.5 ± 14.60	56.0	1	89
OM10/AML10	162	51.9 ± 14.27	56.0	1	101
OM20/AML10	160	54.3 ± 10.88	56.0	1	67
OM40/AML10	162	54.3 ± 10.57	56.0	7	71
Total	1940	53.0 ± 12.73	56.0	1	101

<sup>1</sup> Extent of Exposure to Study Medication (Days) = Last Dose Date of double-blind study medication - First Dose Date of double-blind study medication + 1.  
<sup>2</sup> N is the number of patients whose extent of exposure to study medication could be calculated.  
 SD = standard deviation.  
 Source: Post-test Table 14.1.13

**Table 110: Duration of exposure during Period III**

**Table 5: Exposure to Study Medication During the CS8663-A-U301 Open-Label Period – All Patients Entering Period III**

	OM40/ AML5	OM40/ AML10	OM40/ AML10/ HCTZ12.5	OM40/ AML10/ HCTZ25	Total <sup>3</sup>
Extent of Exposure (Days) <sup>1</sup>					
N	1679	1124	736	440	1684
Mean ± SD	107.5 ± 122.09	101.4 ± 100.60	113.6 ± 83.90	181.1 ± 69.20	278.6 ± 76.73
Number (%) <sup>2</sup> in Specified Exposure Ranges					
1 Day to ≤2 Weeks	571 (34.0)	331 (29.4)	22 (3.0)	7 (1.6)	23 (1.4)
>2 Weeks to ≤4 Weeks	310 (18.5)	99 (8.8)	28 (3.8)	2 (0.5)	25 (1.5)
>4 Weeks to ≤10 Weeks	163 (9.7)	221 (19.7)	298 (40.5)	45 (10.2)	43 (2.6)
>10 Weeks to ≤18 Weeks	105 (6.3)	118 (10.5)	144 (19.6)	61 (13.9)	55 (3.3)
>18 Weeks to ≤26 Weeks	73 (4.3)	100 (8.9)	78 (10.6)	82 (18.6)	46 (2.7)
>26 Weeks to ≤34 Weeks	41 (2.4)	75 (6.7)	69 (9.4)	147 (33.4)	46 (2.7)
>34 Weeks to ≤44 Weeks	268 (16.0)	175 (15.6)	95 (12.9)	95 (21.6)	922 (54.8)
>44 Weeks	148 (8.8)	5 (0.4)	2 (0.3)	1 (0.2)	524 (31.1)

<sup>1</sup> Extent of Exposure to Study Medications (Days) = Start Date of New Dose - Start Date of Current Dose. For the final dosing regimen, Extent of Exposure is calculated as Last Dose Date of Open-label study medication - Start Date of Final Dosing Regimen + 1. In cases of back-titration, Extent of Exposure is calculated by summing all time intervals for the given study medication.  
<sup>2</sup> Percentage is calculated using the number of patients exposed to each dosing regimen as the denominator.  
<sup>3</sup> Other regimens not included except in Total column. Total column represents mean number of days of exposure to study treatment, independent of dose regimens.  
 AML = amlodipine, HCTZ = hydrochlorothiazide, OM = olmesartan medoxomil.  
 Source: CSR 8663-A-U301 Post-text Table 14.1.8

### **Analysis of Adverse Events**

All adverse events:

Tables 111 to 114 summarize the most common TEAEs and TEAEs ( $\geq 3\%$  in any treatment group) TEAEs by system organ class and preferred term.

The system organ classes with the greatest number and percentage of TEAEs were general disorders and administration site conditions (455 [23.5%] patients) followed by nervous system disorders (239 [12.3%] patients), infections and infestations (181 [9.3%] patients), musculoskeletal and connective tissue disorders (167 [8.6%] patients), and gastrointestinal disorders (152 [7.8%] patients) (Table 111a).

There were a number of differences among the treatment groups with regard to the frequency of TEAEs reported by system organ class.

The frequency of edema (including the preferred terms of edema, edema peripheral, pitting edema, generalized edema, and localized edema) was markedly greater in the AML 10 mg group (36.8%) compared to the OM monotherapy groups (9.9% to 18.5%) and the groups that used AML 10 mg as one of their treatment components (23.5% to 26.5%). There appeared to be a progressive decrease in the incidence of edema when the amlodipine 10 mg was combined with olmesartan medoxomil 10 mg, 20 mg, and 40 mg.

For this study, investigators reported hypertension as an adverse event using 1 of the following preferred terms: 'hypertension,' 'systolic hypertension,' 'diastolic hypertension,' 'accelerated hypertension,' 'blood pressure increased,' 'blood pressure diastolic increased,' or 'blood pressure inadequately controlled.' The frequency of hypertension (with all preferred terms combined) was greatest in the placebo group (8.0%) and ranged from 0.0% to 5.0% among the active treatment groups, with the lowest incidence rates in the combination dose groups.

The placebo group also had a greater incidence of headache compared with the active treatment groups. The frequency of headache was 14.2% in the placebo group and ranged from 2.5% to 8.7% among the active treatment groups without clear dose-response. Across all treatment groups there was no apparent trend with regard to the frequency of dizziness, which ranged from 1.8% to 6.2%. Vertigo was reported in 8 cases: 1 mild case in each of the groups of OM 10 mg, OM 40 mg, OM 10 mg + AML 10 mg, and OM 20 mg + AML 5 mg. Vertigo reported in 3 cases within the OM 40 mg + AML 5 mg group was more severe (1 case of moderate severity, and 2 cases of severe severity). In addition, 1 patient in the placebo group had vertigo of moderate severity (see Post-text Table 14.3.1.5). Syncope occurred in one case each in the OM 10 mg arm and the OM 20 mg + AML 10 mg arm.

A total of 9 (0.5%) patients experienced hypotension (including the preferred terms of hypotension and orthostatic hypotension). Of these 9 patients, 1 (0.6%) was in the OM 10 mg group, 1 (0.6%) was in the AML 10 mg group, 1 (0.6%) was in the OM 40 mg + AML 5 mg group, 2 (1.2%) were in the OM 10 mg + AML 10 mg group, 2 (1.3%) were in the OM 20 mg + AML 10 mg group, and 2 (1.2%) were in the OM 40 mg + AML 10

mg group. In addition, there was a low overall frequency of cough (1.4%). Across the treatment groups, the frequency of cough ranged from 0.6% to 2.5%. There were no apparent differences in the frequency of other TEAEs among the treatment groups.

Table 111: Overview of frequency of adverse events by drug and severity - Safety population

Table 75: Overview of Adverse Events - Safety Population

Treatment	N	TEAEs <sup>1</sup>		TEAE by Maximum Severity (All AE <sub>s</sub> )			Deaths	SAEs <sup>1</sup>			Discontinuations due to AE <sup>3</sup>	
		All AE <sub>s</sub>	Drug-Related <sup>2</sup> AE <sub>s</sub>	Mild	Moderate	Severe		All SAE <sub>s</sub>	TE SAE <sub>s</sub> <sup>1</sup>	Drug-Related <sup>2</sup> SAE <sub>s</sub>	All AE <sub>s</sub>	Drug-Related <sup>2</sup> AE <sub>s</sub>
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Placebo	162	91 (56.2)	48 (29.6)	53 (32.7)	33 (20.4)	5 (3.1)	1 (0.6)	3 (1.9)	3 (1.9)	0 (0.0)	21 (13.0)	11 (6.8)
OM10	161	88 (54.7)	43 (26.7)	54 (33.5)	32 (19.9)	2 (1.2)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	13 (8.1)	10 (6.2)
OM20	161	83 (51.6)	36 (22.4)	48 (29.8)	32 (19.9)	3 (1.9)	0 (0.0)	4 (2.5)	4 (2.5)	1 (0.6)	17 (10.6)	11 (6.8)
OM40	162	78 (48.1)	40 (24.7)	45 (27.8)	30 (18.5)	3 (1.9)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	10 (6.2)	7 (4.3)
AML5	161	73 (45.3)	32 (19.9)	41 (25.5)	28 (17.4)	4 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (6.2)	4 (2.5)
AML10	163	96 (58.9)	54 (33.1)	54 (33.1)	34 (20.9)	8 (4.9)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	10 (6.1)	6 (3.7)
OM10/AML5	163	74 (45.4)	32 (19.6)	45 (27.6)	26 (16.0)	3 (1.8)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
OM20/AML5	161	90 (55.9)	44 (27.3)	49 (30.4)	36 (22.4)	5 (3.1)	0 (0.0)	2 (1.2)	2 (1.2)	0 (0.0)	4 (2.5)	3 (1.9)
OM40/AML5	162	83 (51.2)	46 (28.4)	47 (29.0)	31 (19.1)	5 (3.1)	0 (0.0)	2 (1.2)	2 (1.2)	0 (0.0)	6 (3.7)	4 (2.5)
OM10/AML10	162	92 (56.8)	51 (31.5)	53 (32.7)	35 (21.6)	4 (2.5)	0 (0.0)	3 (1.9)	3 (1.9)	0 (0.0)	11 (6.8)	9 (5.6)
OM20/AML10	160	85 (53.1)	48 (30.0)	54 (33.8)	25 (15.6)	6 (3.8)	0 (0.0)	3 (1.9)	3 (1.9)	0 (0.0)	3 (1.9)	1 (0.6)
OM40/AML10	162	87 (53.7)	47 (29.0)	47 (29.0)	33 (20.4)	7 (4.3)	0 (0.0)	5 (3.1)	5 (3.1)	0 (0.0)	9 (5.6)	8 (4.9)
Total	1940	1020 (52.6)	521 (26.9)	590 (30.4)	375 (19.3)	55 (2.8)	1 (0.1)	26 (1.3)	25 (1.3)	1 (0.1)	114 (5.9)	74 (3.8)

Percentage was calculated using the number of patients in the "N" column as denominator.  
<sup>1</sup> TEAEs: adverse events that had a start date on or after the first dose of randomized study medication, or occurred prior to the first dose and worsened in severity during the randomized treatment period.  
<sup>2</sup> Drug-related was defined as definitely, possibly, or probably related to randomized study medication.  
<sup>3</sup> Occurred during the double-blind treatment period.  
 AE = adverse event, AML = amlodipine, OM = olmesartan medoxomil, SAE = serious adverse event, TE = treatment emergent, TEAE = treatment-emergent adverse event.  
 Source: Post-test Table 143.1.1

Table 112: Overview of adverse events double blind period II - ITT

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Table 14.1.1.1  
 Overview of Adverse Events - Number (%) of Patients  
 Safety Population  
 Period II - Day 1 to Week 8

Adverse Event Category	Placebo (N=162)	OM10 (N=161)	OM20 (N=161)	OM40 (N=162)	AM25 (N=161)	AML10 (N=163)
<b>Treatment-Emergent Adverse Events (TEAE) [1]</b>						
All AEs	91 (56.2)	88 (54.7)	83 (51.5)	78 (48.1)	73 (45.3)	96 (58.9)
Drug-Related [2] AEs	48 (29.6)	43 (26.7)	36 (22.4)	40 (24.7)	32 (19.9)	54 (33.1)
<b>TEAE by Maximum Severity</b>						
All AEs						
Mild	32 (32.7)	54 (33.5)	48 (29.8)	45 (27.4)	41 (25.5)	54 (33.1)
Moderate	33 (20.4)	32 (19.9)	32 (19.9)	30 (18.5)	28 (17.4)	34 (20.9)
Severe	5 (3.1)	2 (1.2)	3 (1.9)	3 (1.9)	4 (2.5)	8 (4.9)
<b>Drug-Related AEs</b>						
Mild	31 (19.1)	30 (18.6)	25 (15.5)	21 (13.0)	19 (11.8)	38 (23.3)
Moderate	15 (9.3)	12 (7.5)	10 (6.2)	17 (10.5)	11 (6.8)	17 (10.5)
Severe	2 (1.2)	1 (0.6)	1 (0.6)	2 (1.2)	2 (1.2)	3 (1.8)
Deaths	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Serious AEs During Randomized Treatment Period</b>						
All SAEs	3 (1.9)	1 (0.6)	4 (2.5)	1 (0.6)	0 (0.0)	1 (0.6)
TE SAEs	3 (1.9)	1 (0.6)	4 (2.5)	1 (0.6)	0 (0.0)	1 (0.6)
Drug-Related SAEs	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Discontinuation Due to AEs During Randomized Treatment Period</b>						
All AEs	21 (13.0)	13 (8.1)	17 (10.6)	10 (6.2)	10 (6.2)	10 (6.1)
Drug-Related AEs	11 (6.8)	10 (6.2)	11 (6.8)	7 (4.3)	6 (3.7)	6 (3.7)

Percentage is calculated using number of patients in the column heading as denominator.  
 [1] TEAE: adverse event that has a start date on or after the first dose of randomized study medication, or occurred prior to first dose and worsens in severity during the randomized treatment period.  
 [2] Drug-related is defined as definitely, possibly, or probably related to randomized study medication.

Table 113: Overview of adverse events double blind period II - ITT

Overview of Adverse Events - Number (%) of Patients  
 Safety Population  
 Period II - Day 1 to Week 8

Adverse Event Category	OM10/AM25 (N=163)	OM10/AML10 (N=162)	OM20/AM25 (N=161)	OM20/AML10 (N=160)	OM40/AM25 (N=162)	OM40/AML10 (N=162)	Total (N=1340)
<b>Treatment-Emergent Adverse Events (TEAE) [1]</b>							
All AEs	74 (45.4)	92 (56.8)	90 (55.9)	83 (53.1)	83 (51.2)	87 (53.7)	1020 (52.6)
Drug-Related [2] AEs	32 (19.6)	51 (31.5)	44 (27.3)	48 (30.0)	46 (28.4)	47 (29.0)	521 (36.9)
<b>TEAE by Maximum Severity</b>							
All AEs							
Mild	45 (27.6)	53 (32.7)	49 (30.4)	54 (33.8)	47 (29.0)	47 (29.0)	590 (36.4)
Moderate	26 (16.0)	35 (21.6)	35 (22.0)	29 (18.6)	31 (19.1)	23 (14.2)	378 (23.2)
Severe	3 (1.8)	4 (2.5)	3 (1.9)	6 (3.8)	5 (3.1)	7 (4.3)	55 (3.2)
<b>Drug-Related AEs</b>							
Mild	24 (14.7)	32 (19.8)	29 (18.0)	36 (22.5)	31 (19.1)	30 (18.5)	365 (23.2)
Moderate	8 (4.9)	18 (11.1)	13 (8.1)	11 (6.9)	13 (8.0)	15 (9.3)	158 (10.0)
Severe	0 (0.0)	1 (0.6)	2 (1.2)	1 (0.6)	2 (1.2)	2 (1.2)	19 (1.4)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
<b>Serious AEs During Randomized Treatment Period</b>							
All SAEs	1 (0.6)	3 (1.9)	2 (1.2)	3 (1.9)	2 (1.2)	5 (3.1)	26 (1.3)
TE SAEs	0 (0.0)	3 (1.9)	2 (1.2)	3 (1.9)	2 (1.2)	5 (3.1)	25 (1.3)
Drug-Related SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
<b>Discontinuation Due to AEs During Randomized Treatment Period</b>							
All AEs	0 (0.0)	11 (6.8)	4 (2.5)	3 (1.9)	6 (3.7)	9 (5.6)	114 (8.5)
Drug-Related AEs	0 (0.0)	9 (5.6)	3 (1.9)	1 (0.6)	4 (2.5)	8 (4.9)	74 (5.5)

Percentage is calculated using number of patients in the column heading as denominator.  
 [1] TEAE: adverse event that has a start date on or after the first dose of randomized study medication, or occurred prior to first dose and worsens in severity during the randomized treatment period.  
 [2] Drug-related is defined as definitely, possibly, or probably related to randomized study medication.

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**Table 114: Most frequent TEAE by system organ class (Incidence >3% in any treatment group Period II**

**Table 13: Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Incidence ≥3% in Any Treatment Group) – Pivotal Study (Double-Blind Treatment Period) – Safety Population**

System Organ Class Preferred Term	Flu (N=182)	OM10 (N=161)	OM10 (N=161)	OM10 (N=161)	AME5 (N=161)	AME10 (N=165)	OM10/ AME5 (N=165)	OM10/ AME5 (N=161)	OM10/ AME5 (N=162)	OM10/ AME10 (N=162)	OM10/ AME10 (N=166)	OM10/ AME10 (N=162)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<b>General disorders and administration site conditions</b>												
Edema combined terms <sup>1</sup>	29 (17.9)	30 (18.6)	25 (15.5)	30 (18.5)	30 (18.6)	61 (37.4)	38 (23.3)	34 (21.1)	39 (24.1)	48 (29.6)	51 (31.9)	40 (24.7)
Edema combined terms <sup>1</sup>	20 (12.3)	23 (14.3)	16 (9.9)	30 (18.5)	21 (13.0)	60 (36.8)	34 (20.9)	29 (18.0)	30 (18.5)	43 (26.3)	41 (25.6)	38 (23.5)
Edema peripheral	12 (7.4)	15 (9.3)	13 (8.1)	24 (14.8)	14 (8.7)	38 (23.5)	21 (12.9)	16 (9.9)	15 (9.3)	30 (18.5)	32 (20.0)	29 (17.9)
Edema	3 (1.9)	4 (2.5)	2 (1.2)	5 (3.1)	5 (3.1)	18 (11.0)	8 (4.9)	10 (6.2)	12 (7.4)	12 (7.4)	7 (4.4)	9 (5.6)
Pitting edema	5 (3.1)	4 (2.5)	1 (0.6)	4 (2.5)	3 (1.9)	6 (3.7)	6 (3.7)	5 (3.1)	5 (3.1)	4 (2.5)	5 (3.1)	2 (1.2)
Fatigue	6 (3.7)	7 (4.3)	3 (1.9)	3 (1.9)	3 (1.9)	3 (1.9)	3 (1.9)	5 (3.1)	8 (4.9)	2 (1.2)	14 (8.8)	3 (1.9)
<b>Nervous system disorders</b>	29 (17.9)	19 (11.8)	27 (16.8)	23 (14.3)	19 (11.8)	12 (7.4)	10 (6.1)	15 (11.2)	16 (9.9)	17 (10.5)	24 (15.0)	23 (14.4)
Headache	23 (14.2)	9 (5.6)	14 (8.7)	14 (8.6)	13 (8.1)	8 (4.9)	4 (2.5)	9 (5.6)	6 (3.7)	10 (6.2)	11 (6.9)	9 (5.6)
Dizziness	9 (5.6)	5 (3.1)	10 (6.2)	8 (4.9)	5 (3.1)	4 (2.5)	3 (1.9)	8 (4.9)	7 (4.3)	6 (3.7)	5 (3.1)	8 (4.9)
<b>Infections and infestations</b>	13 (8.0)	15 (9.3)	16 (9.9)	11 (6.8)	11 (6.8)	18 (11.2)	16 (9.9)	14 (8.7)	17 (10.5)	18 (11.1)	12 (7.5)	12 (7.4)
Upper respiratory tract infection	3 (1.9)	2 (1.2)	2 (1.2)	1 (0.6)	4 (2.5)	5 (3.1)	5 (3.1)	1 (0.6)	4 (2.5)	1 (0.6)	1 (0.6)	0 (0.0)
Urinary tract infection	1 (0.6)	3 (1.9)	0 (0.0)	1 (0.6)	2 (1.2)	4 (2.5)	1 (0.6)	7 (4.3)	2 (1.2)	4 (2.5)	3 (1.9)	1 (0.6)
<b>Musculoskeletal and connective tissue disorders</b>	15 (9.3)	16 (9.9)	12 (7.5)	14 (8.6)	15 (9.3)	14 (8.6)	12 (7.4)	17 (10.5)	13 (8.0)	6 (3.7)	17 (10.6)	18 (9.9)
Back pain	5 (3.1)	4 (2.5)	1 (0.6)	5 (3.1)	3 (1.9)	3 (1.9)	1 (0.6)	2 (1.2)	1 (0.6)	3 (1.9)	3 (1.9)	4 (2.5)
Pain in extremity	0 (0.0)	2 (1.2)	0 (0.0)	1 (0.6)	1 (0.6)	3 (1.9)	0 (0.0)	5 (3.1)	5 (3.1)	1 (0.6)	3 (1.9)	2 (1.2)
Muscle spasms	3 (1.9)	3 (1.9)	3 (1.9)	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)
<b>Gastrointestinal disorders</b>	11 (6.8)	12 (7.5)	9 (5.6)	10 (6.2)	13 (8.1)	13 (8.1)	10 (6.1)	14 (8.7)	13 (8.0)	11 (6.8)	15 (9.3)	16 (9.9)
Nausea	5 (3.1)	2 (1.2)	3 (1.9)	2 (1.2)	2 (1.2)	3 (1.9)	1 (0.6)	5 (3.1)	3 (1.9)	2 (1.2)	2 (1.2)	5 (3.1)
<b>Skin and subcutaneous tissue disorders</b>	10 (6.2)	7 (4.3)	6 (3.7)	5 (3.1)	4 (2.5)	8 (4.9)	3 (1.9)	9 (5.6)	9 (5.6)	4 (2.5)	6 (3.8)	6 (3.7)
Rash	2 (1.2)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	5 (3.1)	3 (1.9)	1 (0.6)	3 (1.9)	1 (0.6)	2 (1.2)	1 (0.6)
<b>Vascular disorders</b>	12 (7.4)	8 (5.0)	9 (5.6)	4 (2.5)	2 (1.2)	3 (1.9)	1 (0.6)	6 (3.7)	3 (1.9)	5 (3.1)	4 (2.5)	5 (3.1)
Hypertension combined terms <sup>2</sup>	13 (8.0)	7 (4.3)	8 (5.0)	6 (3.7)	4 (2.5)	2 (1.2)	1 (0.6)	3 (1.9)	2 (1.2)	1 (0.6)	1 (0.6)	0 (0.0)

<sup>1</sup> Included preferred terms of edema, edema peripheral, pitting edema, generalized edema, and localized edema. Patients were counted once for any instance of these preferred terms relating to edema.  
<sup>2</sup> Included preferred terms of hypertension, systemic hypertension, diastolic hypertension, accelerated hypertension, blood pressure increased, blood pressure diastolic increased, or blood pressure inadequately controlled. Patients were counted once for any instance of these preferred terms relating to hypertension. While the preferred term 'hypertension' was assigned to the system organ class of Vascular disorders, the 'hypertension combined terms' encompasses preferred terms that were assigned to several other system organ classes (i.e., other than Vascular disorders).  
 Treatment-emergent adverse events: adverse events that had a start date after the first dose of randomized study medication, or occurred prior to the first dose and worsened in severity during the randomized treatment period.  
 Percentage was calculated using the number of patients in the column heading as denominator.  
 Although a patient may have had two or more treatment-emergent adverse events, the patient was counted only once within a category. The same patient may have appeared in different categories.  
 AME = amlodipine, OM = olmesartan medoxomil, Flu = placebo.  
 Sources: Post-test Tables 6 and 6.1 and CS8663-4-E301 Final Report (Period III), Post-test Tables 14.3.1.28 and 14.3.1.29

This 120-day safety update for CS-8663 covers the period of 14 July 2006 to 12 January 2007 for all studies with CS-8663. Additionally, adverse events occurring prior to 14 July 2006 that were not included in the original submission are also presented. This includes all adverse events from studies conducted in Europe as well as newly reported adverse events from studies in the US. This document contains narratives and listings of serious adverse events (SAEs) and listings of those events which led to the discontinuation of a patient that were reported during the specified time period.

During this period one study was completed (no final study report), and one is ongoing. Both studies are not in the US IND. The studies are:

- Study CS8663-A-U301, "Results of the Open-Label Period – Week 8 to Week 52, A Randomized, Double-Blind, Placebo-Controlled Factorial Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil plus Amlodipine Compared to Monotherapy in Patients with Mild to Severe Hypertension," was completed and will be included in this submission (the interim report for this study was included in the New Drug Application, NDA 22-100, submitted 27 November 2006); •

Study CS8663-A-E302, "Efficacy and Safety of Amlodipine Used as Add-On Therapy in Moderately to Severely Hypertensive Patients Not Adequately Controlled by Olmesartan Medoxomil 20 mg Monotherapy," has been concluded (no final study

report). It was conducted in Europe and not under the US Investigational New Drug Application (IND); and •

Study CS8663-A-E303, “Add-on Study of Olmesartan Medoxomil in Patients with Moderate to Severe Hypertension not Achieving Target Blood Pressure on Amlodipine 5 mg Alone,” is ongoing. It is being conducted in Europe, not under the US IND.

During this time period, no preclinical study reports became available. Furthermore, there are no publications that contain preclinical data.

Overall, the adverse event profile as reported in the NDA submission does not fundamentally differ from the adverse event profile in this 120-day safety update.

#### 7.1.1 Deaths

There were 2 deaths. One patient from the placebo group died during Period II and the other died prior to randomization. None of the 2 deaths was related to the drug. No deaths were reported for study CS8663-A-U301 during the reporting period.

#### Serious Adverse Events from CS8663-A-E302

Deaths : No deaths were reported for study CS8663-A-E302 during the reporting period.

#### Other Serious Adverse Events

During the reporting time period, SAEs were reported for 10 patients on OM 40 mg + AML 5 mg, 6 patients on OM 40 mg + AML 10 mg, 3 patients on OM 40 mg + AML 10 mg + HCTZ 12.5 mg, and 11 patients on OM 40 mg + AML 10 mg + HCTZ 25 mg, and 1 patient on the non-standard dosing regimen of OM 20 mg + AML 5 mg. A total of 40 events were experienced by 31 patients, 23 events were severe in severity, 14 were moderate in severity, and 3 were mild in severity. None of the events was considered by the investigator to be related to study drug.

#### 7.1.2 Other Serious Adverse Events

In the analysis of SAEs, there did not appear to be any event or trends in events that signified a safety issue within any of the treatment groups. All of the reported events were consistent with what would be expected in a hypertensive population of the age recruited for this study. There were 2 deaths in the study, 1 prior to randomization and 1 during the active treatment period (placebo group). Neither of these deaths was considered drug-related. (See Appendix)

During the study, SAEs were experienced by 2 patients on OM 20 mg monotherapy (1 patient was non-randomized and 1 patient was later randomized into the OM 20 mg + AML 10 mg treatment group) and 1 patient on OM 20 mg + AML 5 mg. A total of 4 events were experienced by the 3 patients, all events were moderate in severity. None of the events was considered by the investigator to be related to study medication.

A review of the frequency of SAEs during the double blind and the open label treatment periods, the specific types of events as well as assessment of potential relationships between the events and study medication confirmed that there was no greater incidence of SAEs associated with AZOR compared to the monotherapies. Three patients died during the study and all deaths were considered unrelated to the drug.

### 120 day safety update

Double blind and 120 day safety update: From the 120 day safety update report, overall, the adverse event profile as reported in the NDA submission does not fundamentally differ from the adverse event profile in this 120-day safety update.

During the reporting time period, 11 patients were reported as discontinued due to adverse events. Adverse event discontinuations were experienced by 3 patients on OM 40 mg + AML 5 mg, 2 patients on OM 40 mg + AML 10 mg, 4 patients on OM 40 mg + AML 10 mg + HCTZ 12.5 mg, and 2 patients on OM 40 mg + AML 10 mg + HCTZ 25 mg. For a patient on the OM 40 mg + AML 10 mg treatment regimen (056-033), the events of fatigue and rash on arms, legs, and ankles that led to discontinuation were considered probably related to study medication. For a patient on the OM 40 mg + AML 10 mg + HCTZ 12.5 mg treatment regimen (059-024), the event of worsening edema was considered possibly related to study medication. No other events were considered by the investigator to be related to study medication. Section 12.4 includes listings of adverse events that led to discontinuation for study CS8663-A-U301.

### Serious Adverse Events from CS8663-A-E303

#### Deaths

One patient (505-28) died during the study from a probable acute cerebral hemorrhage; the investigator considered this event unlikely related to study medication. Section 12.3.1 includes listings of deaths for study CS8663-A-E303. Narrative of the death during the study is below.

**b(6)**

Study-Center-Patient Number (Initials): 505-28

Narrative: Patient: 49-year-old Caucasian male Treatment Regimen at Onset of Event: OM 40 mg/AML 5 mg. 49-year-old Caucasian male, was screened for study CS8663-A-E303 on 11-JAN-2006. At the onset of the event, the patient was in Period III of the study receiving olmesartan 40 mg and amlodipine 5 mg. On Study Day

the patient developed a probable acute cerebral hemorrhage and died while walking in the woods. Blood pressure values were 171/102 mmHg prior to the study, 164/96 mmHg during the study, 138/92 at the last visit, and 126/75 mmHg during exercise at the last visit. The diagnosis of probable acute cerebral hemorrhage was based on the patient's wife's report of the acute clinical symptoms. At the request of the patient's wife, an autopsy was not performed. Medical history included essential hypertension and sterilization. No concomitant medications were taken during the event. The outcome was recorded as death. The last dose of study drug was taken on Study Day

**b(6)**

The investigator assessed the event as severe in severity and unlikely related to study drug.

**b(6)**

### Other Serious Adverse Events

During the study, SAEs were experienced by 4 patients on AML 5 mg monotherapy, 2 patients on AML 5 mg + Placebo, 2 patients on OM 10 mg + AML 5 mg, 2 patients on OM 20 mg + AML 5 mg, 8 patients on OM 40 mg + AML 5 mg, 1 patient on OM 40 mg + AML 10 mg, 2 patients in the taper-off phase, and 2 patients reported after the Week 34 Visit. A total of 30 events were experienced by the 23 patients, 12 events were severe in severity, 14 were moderate in severity, and 4 were mild in severity. None of the events was considered by the investigator to be related to study medication. Section 12.3.2 includes listings of SAEs for study CS8663-A-E303. Section 11.3.2 includes narratives of SAEs during the time period.

#### 7.1.3 Dropouts and other significant adverse events

- Study CS8663-A-U301,(Period II) Double blind Period week 1 -8 “A Randomized, Double-Blind, Placebo-Controlled Factorial Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil plus Amlodipine Compared to Monotherapy in Patients with Mild to Severe Hypertension.”
- Study CS8663-A-U301, “Results of the Open-Label Period – Week 8 to Week 52, A Randomized, Double-Blind, Placebo-Controlled Factorial Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil plus Amlodipine Compared to Monotherapy in Patients with Mild to Severe Hypertension,” was completed and will be included in this submission (the interim report for this study was included in the New Drug Application, NDA 22-100, submitted 27 November 2006);
- Study CS8663-A-E302, “Efficacy and Safety of Amlodipine Used as Add-On Therapy in Moderately to Severely Hypertensive Patients Not Adequately Controlled by Olmesartan Medoxomil 20 mg Monotherapy,” has been concluded (no final study report). It was conducted in Europe and not under the US Investigational New Drug Application (IND);
- Study CS8663-A-E303, “Add-on Study of Olmesartan Medoxomil in Patients with Moderate to Severe Hypertension not Achieving Target Blood Pressure on Amlodipine 5 mg Alone,” is ongoing. It is being conducted in Europe, not under the US IND.

#### Discontinuations during Double blind period-U301- Week 1 to 8

Prior to breaking the blind, lack of efficacy was defined as an adverse event of “continued, increased, or inadequately controlled hypertension/blood pressure” or “lack of efficacy” and this was the specific reason for discontinuation in 43 of the 114 cases of

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withdrawal due to an adverse event. A total of 74 (3.8%) patients were discontinued due to drug-related adverse events, mainly hypertension (lack of efficacy) and edema.

A total of 114 (5.9%) patients were discontinued from the study due to an adverse event; 74 (3.8%) of these patients were discontinued due to drug related adverse events. The placebo group had the greatest percentage of patients who were discontinued due to an adverse event (13%). Most of the discontinued patients from the placebo group were due to lack of efficacy to study drug treatment (Table 115).

**Table 115: Patient disposition**

**Table 3: Patient Disposition – All Randomized Patients Population**

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 <sup>1</sup>	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)	2 (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)

<sup>1</sup> Adverse event discontinuations due to lack of efficacy were determined following a review of the specific reason for termination on the Subject Status at End of Double-Blind Period/Early Termination Case Report Form prior to breaking the blind.  
 Percentage was calculated using the number of patients in the column heading as denominator.  
 AML = amlodipine, OM = olmesartan medoxomil, Pbo = placebo.  
 Source: Post-text Table 14.1.2

**Safety during open label extension period of Double blind treatment-U301 Week 8 - 52**

Adverse events were experienced by 622 (37%) patients on OM40/AML5mg, 455 (40.5%) patients on OM40/AML10; 312( 42.4%) patients on OM40/AML10/HCTZ12.5 and 248 (56.4%) patients on OM40/AML10/HCTZ25. Drug related adverse events were experienced by 221 (13.2%) patients on OM40/AML5mg, 195 (17.3%) patients on OM40/AML10; 124(16.8%) patients on OM40/AML10/HCTZ12.5 and 89 (20.2%) patients on OM40/AML10/HCTZ25.

One patient on OM40/AML10 died of a gunshot wound to the head. This was not thought to be related to the drug. Serious adverse events were experienced by 31 (1.8%) patients on OM40/AML5mg, 23 (2.0%) patients on OM40/AML10; 15 (2.0%) patients on OM40/AML10/HCTZ12.5 and 18 (4.1%) patients on OM40/AML10/HCTZ25.

**Discontinuation during open label period**

A total of 77 (4.6%) patients were discontinued during the open label treatment period due to an adverse event. Seventy (4.2%) patients were discontinued from the study for adverse events. Adverse event discontinuations were experienced by 28 (1.7%) patients on OM40/AML5mg, 17 (1.5%) patients on OM40/AML10; 11(1.5%) patients on

OM40/AML10/HCTZ12.5 and 11 (2.5%) patients on OM40/AML10/HCTZ25. Thirty five (2.1%) patients were discontinued due to drug related adverse events. Edema was the most common drug-related adverse event and was experienced by a total of 318 (18.9%) patients. Across the 4 standard treatment regimens, the frequency of drug related edema ranged from 7% to 11.1%. This was followed by dizziness ranging from 1.4% to 2% as the next most common drug – related treatment emergent adverse event. Shifts in peripheral edema severity were also evaluated. Throughout the open label period there was an approximate doubling in the frequency of patients with shift towards worsening peripheral edema grade with OM40/AML/10 treatment (12.2%) compared to Om40/AML5 (7.2%). The worsening was associated with increasing dose of amlodipine from 5mg to 10 mg. This was attenuated by HCTZ when added to the dosing regimen.

Hypotension was experienced by 0.8% to 1.6% of patients on the 3 lowest doses of treatment regimen and (0.7% ) on OM40/AML10/HCTZ 25.

The mean baseline pressure was 163.6/101.5mmHg. BP reductions were observed across all combination treatments to week 52 with 66.7% of the study cohort achieving treatment goals. The mean blood pressure for the total cohort at week 52 was 131.1/81.9mmHg. The greatest percentage of patients reaching BP goal was the cohort on OM40/AM5 that had no need for increase of amlodipine to 10mg and no need for additional HCTZ. The cohorts requiring uptitration of amlodipine and addition of HCTZ were more severe hypertensive and or more resistant to the antihypertensive effects of treatment. This observation supports the reviewer's recommendation that the combination should be reserved for those with severe hypertension not responsive to other anti-hypertensive agents.

#### **Double blind and 120 day safety update**

During the reporting time period, 11 patients were reported as discontinued due to adverse events. Adverse event discontinuations were experienced by 3 patients on OM 40 mg + AML 5 mg, 2 patients on OM 40 mg + AML 10 mg, 4 patients on OM 40 mg + AML 10 mg + HCTZ 12.5 mg, and 2 patients on OM 40 mg + AML 10 mg + HCTZ 25 mg. For a patient on the OM 40 mg + AML 10 mg treatment regimen (056-033), the events of fatigue and rash on arms, legs, and ankles that led to discontinuation were considered probably related to study medication. For a patient on the OM 40 mg + AML 10 mg + HCTZ 12.5 mg treatment regimen (059-024), the event of worsening edema was considered possibly related to study medication. No other events were considered by the investigator to be related to study medication.

#### **Discontinuations Due to Adverse Events from CS8663-A-E302**

A total of 11 patients were discontinued due to adverse events during the study. Adverse event discontinuations were experienced by 6 patients on OM 20 mg monotherapy, 2 patients on OM 20 mg + Placebo, 1 patient on OM 20 mg + AML 5 mg, and 2 patients on OM 20 mg + AML 10 mg. For 3 patients on OM 20 mg monotherapy (717-08, 901-29, and 909-25) and 1 patient on OM 20 mg + AML 10 mg (202-22), the adverse events that led to discontinuation were considered possibly related to study medication. For 1 patient on OM 20 mg + AML 5 mg (717-05), the event that led to discontinuation was

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considered probably related to study medication. For 1 patient on OM 20 mg monotherapy (615-20 [hypotension]) and 1 patient on OM 20 mg + AML 10 mg (902-06 [edema peripheral]) the adverse events that led to discontinuation were considered definitely related to study medication. Section 12.5 includes listings of adverse events that led to discontinuation for study CS8663-A-E302.

### **Discontinuations Due to Adverse Events from CS8663-A-E303**

A total of 50 patients were discontinued due to adverse events during the study. Adverse event discontinuations were experienced by 20 patients on AML 5 mg monotherapy, 3 patients on AML 5 mg + Placebo, 6 patient on OM 10 mg + AML 5 mg, 4 patients on OM 20 mg + AML 5 mg, 13 patients on OM 40 mg + AML 5 mg, 1 patient on OM 40 mg + AML 10 mg, and 3 patients without a dose. For 4 patients on AML 5 mg (203-19 [headache], 507-01 [flushing], 507-04 [flushing], and 912-52 [blood pressure diastolic increased]), 1 patient on OM 10 mg + AML 5 mg (205-05 [dizziness and headache]), 4 patients on OM 40 mg + AML 5 mg (202-06 [dizziness], 205-07 [vertigo], 603-08 [hypotension], and 705-19 [cold sweat, asthenia, and dizziness]) and 1 patient without a dose (407-38 [hypotension]), the adverse events that led to discontinuation were considered definitely related to study medication. Section 12.6 includes listings of adverse events that led to discontinuation for study CS8663-A-E303.

The relative frequencies of drug-related TEAEs due to edema, hypertension, dizziness, and cough were similar to the frequencies of reported TEAEs described above. The numbers of patients experiencing hypotension were very small but slightly greater in the combination treatment groups. A total of 7 patients experienced drug-related hypotension (1 patient in the OM 10 mg group, 2 patients in the OM 10 mg + AML 10 mg group, 1 patient in the OM 20 mg + AML 10 mg group, 1 patient in the OM 40 mg + AML 5 mg group, and 2 patients in the OM 40 mg + AML 10 mg treatment group).

#### 7.1.4 Other search strategies

For this submission, a comprehensive search of electronic medical literature databases was conducted. Search terms included olmesartan medoxomil in combination with hypertension, cardiovascular risk reduction, stroke, and myocardial infarction and amlodipine besylate in combination with hypertension, cardiovascular risk reduction, myocardial infarction, and stroke. The search period extended from 14 July 2006 (the cutoff date for the NDA) through the final safety updated cutoff date of 12 January 2007.

Two publications were found that contained clinical data involving amlodipine. No publications found contained information on olmesartan medoxomil.

### **RISK BENEFIT**

Based on the additional safety information in the 120-day safety update, there is no change in the risk benefit assessment of AZOR.

Some of the other more common adverse events leading to discontinuation included:

- Headache (12 patients): 3 patients on placebo, 1 patient on OM 10 mg, 1 patient on OM 20 mg, 2 patients on OM 40 mg, 1 patient on AML 5 mg, 2 patients on OM 10 mg + AML 10 mg, 1 patient on OM 20 mg + AML 5 mg, and 1 patient on OM 40 mg + AML 5 mg.
- Dizziness (7 patients): 1 patient on placebo, 1 patient on OM 10 mg, 2 patients on OM 20 mg, 1 patient on OM 10 mg + AML 10 mg, 1 patient on OM 40 mg + AML 5 mg, and 1 patient on OM 40 mg + AML 10 mg.
- Fatigue (5 patients): 1 patient on placebo, 1 patient on OM 10 mg, 1 patient on OM 40 mg, 1 patient on AML 5 mg, and 1 patient on AML 10 mg.

The most common adverse event leading to patient discontinuation was hypertension (including preferred terms of hypertension, systolic hypertension, accelerated hypertension, blood pressure increased, blood pressure diastolic increased, drug ineffective, or blood pressure inadequately controlled). A total of 45 patients were discontinued from the study due to hypertension. Thirty-nine of these patients were discontinued from the study due exclusively to hypertension, including 14 patients in the placebo group, 6 patients in the OM 10 mg group, 7 patients in the OM 20 mg group, 5 patients in the OM 40 mg group, 4 patients in the AML 5 mg group, 1 patient in the AML 10 mg group, and 2 patients in the OM 20 mg + AML 5 mg group. The remaining 6 patients were discontinued from the study due to hypertension in conjunction with other adverse events, including 1 patient in each of the following groups: placebo, OM 10 mg, OM 20 mg, OM 40 mg, AML 10 mg, and OM 40 mg + AML 5 mg.

The second most common adverse event leading to patient discontinuation was edema (including preferred terms of edema, peripheral edema, pitting edema, generalized edema, and localized edema). A total of 18 patients were discontinued from the study due to edema. Twelve of these patients were discontinued from the study due exclusively to edema, including 3 patients in the AML 10 mg group, 4 patients in the OM 10 mg + AML 10 mg group, 1 patient in the OM 20 mg + AML 10 mg group, and 4 patients in the OM 40 mg + AML 10 mg group. The remaining 6 patients were discontinued from the study due to edema in conjunction with other adverse events, including 1 patient in the OM 40 mg group, 2 patients in the AML 10 mg group, 2 patients in the OM 10 mg + AML 10 mg group, and 1 patient in the OM 40 mg + AML 10 mg group.

#### 7.1.6 Less common adverse events

No new safety concerns were identified during the course of this study. The frequencies of adverse events reported in this study were consistent with the expected frequencies of adverse events for an ARB and a dihydropyridine CCB. Outside of an interaction that modified the frequency of peripheral edema (discussed below) there did not appear to be any safety issues that were caused by the concomitant use of olmesartan medoxomil with amlodipine.

None except that the frequency of headache, dizziness, and cough did not differ across the different active treatment groups.

7.1.7 Laboratory findings

The following tables 116 – 118 show comparisons between high dose combination tablet and monotherapy for 3 laboratory parameters, namely: ALT, AST and Platelets. They show no statistically significant differences except for platelets. The reviewer considered these findings in the overall assessment and in recommending approval of the combination tablet even though there is an increase in the mean change from baseline to week 8 in all 3 parameters- Platelets, ALT and AST. These have been discussed in Section 1.3.3.

**Table 116: ALT High doses vs. Monotherapy**

Label	Estimate	Standard Error	Pr >  t	Lower	Upper
20/10 vs. 20	-1.8081	2.9642	0.5425	-7.6470	4.0308
20/10 vs. 10	1.9646	2.9642	0.5081	-3.8742	7.8035
40/10 vs. 40	-0.2000	2.7980	0.9431	-5.7115	5.3115
40/10 vs. 10	3.2091	2.7265	0.2403	-2.1614	8.5796

**Table 117: AST High Doses vs. Monotherapy**

Label	Estimate	Standard Error	Pr >  t	Lower	Upper
20/10 vs. 20	0.1717	1.8280	0.9252	-3.4290	3.7725
20/10 vs. 10	1.3081	1.8280	0.4749	-2.2927	4.9088
40/10 vs. 40	-0.9600	1.7255	0.5785	-4.3588	2.4388
40/10 vs. 10	0.9036	1.6814	0.5915	-2.4083	4.2155

**Table 118: Platelets High doses vs. Monotherapy**

Label	Estimate	Standard Error	Pr >  t	Lower	Upper
20/10 vs. 20	43.9444	20.4266	0.0324	3.7087	84.1801
20/10 vs. 10	36.8611	20.0399	0.0671	-2.6130	76.3352
40/10 vs. 40	-8.4589	19.5611	0.6658	-46.9898	30.0719
40/10 vs. 10	-1.9633	18.3669	0.9150	-38.1419	34.2153

There are minor significant statistically significant differences in the heart rates of patients taking olmesartan 20 mg and amlodipine 5 mg from baseline to week 8 or early termination. There are no changes in the heart rates of patients exposed to the combination tablet (Table 119).

**Table 119: Heart rates from baseline to week 8 - Period II - ITT**

Table 14.5.4.1E  
 Change in 12-lead Electrocardiogram Parameters From Baseline to Week 8/Early Termination (ITT)  
 Safety Population  
 Period II - Day 1 to Week 8

Parameter (unit)/ Treatment	N [1]	-Baseline [2]-		--Week 8/ET--		-----Change-----		
		Mean	SD	Mean	SD	Mean	SD	p-value [3]
Heart Rate (bpm)								
Placebo	152	76.6	9.56	75.7	12.24	-0.9	10.12	0.2740
OM10	157	77.1	10.70	76.8	11.50	-0.4	8.81	0.6095
OM20	154	77.8	11.06	76.2	10.44	-1.6	9.06	0.0329
OM40	158	76.8	8.88	76.2	9.50	-0.6	8.78	0.4342
AML5	156	76.2	9.38	74.7	10.10	-1.5	9.42	0.0482
AML10	160	77.0	10.07	76.9	11.60	-0.1	8.24	0.9465
OM10/AML5	160	76.9	10.10	76.0	9.77	-1.0	9.44	0.2006
OM10/AML10	155	77.2	10.23	76.2	10.21	-1.0	8.43	0.3432
OM20/AML5	152	77.6	10.13	76.9	10.20	-0.7	10.47	0.3346
OM20/AML10	153	76.4	9.38	77.4	10.29	1.0	7.90	0.1194
OM40/AML5	154	75.0	9.84	76.1	10.39	1.1	8.33	0.1117
OM40/AML10	155	76.6	9.17	76.4	9.42	-0.2	9.23	0.7977

[1] N is the number of patients with both baseline and Week 8/ET measurements.  
 [2] Baseline is defined as the mean of the two measurements taken at Day 1 and the one measurement taken at screening.  
 [3] Two-sided p-value is obtained from t-test testing whether change is equal to 0 within the treatment group.

## Best Possible Copy

### 7.1.9 Electrocardiograms

There were no changes in physical examination or in the electrocardiographic findings that were unexpected across the different treatment groups.

Table presents mean changes in 12 lead ECG parameters from baseline to week 8/ET. There were no clinically relevant mean changes in any 12-lead ECG parameter for any treatment group. Throughout the study, there were no differences among the treatment groups based on individual 12-lead ECG results (Table 120).

**Table 120: Mean changes in ECG from baseline to week8/early termination**

Parameter (unit)/ Treatment	N [1]	-Baseline [2]-		--Week 8/ET--		-----Change-----		
		Mean	SD	Mean	SD	Mean	SD	p-value [3]
PR Interval (msec)								
Placebo	147	166.0	21.09	165.1	21.34	-0.9	11.88	0.3694
OM10	151	165.2	25.29	164.0	25.65	-1.2	13.31	0.2705
OM20	149	161.7	22.39	160.8	22.35	-0.9	11.64	0.3216
OM40	151	167.9	25.52	165.7	26.67	-2.2	11.23	0.0158
AML5	153	163.6	21.27	163.1	21.21	-0.5	11.73	0.6028
AML10	155	162.6	19.15	162.1	20.36	-0.5	12.28	0.6068
OM10/AML5	155	163.6	23.15	162.6	21.55	-1.0	10.67	0.2676
OM10/AML10	147	163.0	20.18	163.9	22.37	0.9	12.01	0.3908
OM20/AML5	148	161.3	19.89	160.7	19.46	-0.5	12.41	0.5946
OM20/AML10	148	164.1	20.91	164.2	21.94	0.0	13.26	0.9671
OM40/AML5	149	166.0	24.46	164.2	25.35	-1.7	10.10	0.0372
OM40/AML10	150	166.2	23.86	167.2	23.60	1.0	13.22	0.3510

<sup>2</sup> Baseline is defined as the mean of the two measurements taken at day 1 and at the one measurement taken at the screening

<sup>3</sup> Two sided p-value is obtained from t test testing whether change is equal to 0 within the treatment group.

7.1.10 Immunogenicity

Not relevant

7.1.11 Carcinogenicity

Both components are approved drugs and there is no evidence of carcinogenicity.

7.1.12 Special safety studies

Comparisons between patients receiving high dose combination tablets versus monotherapy were carried out. Despite the increase in mean change from baseline to week 8 of the liver enzymes, there was no statistically significant difference between the high dose and monotherapy (Tables 116-117).

One recent article relating to amlodipine is cited below. It is similar to what has been reported with phenytoin sodium.

Lafzi A, Farahani RM, Shoja MA. Amlodipine-induced gingival hyperplasia. Med Oral Patol Oral Cir Bucal 2006;11:E480-E482.

7.1.13 Withdrawal phenomena and/or Abuse potential

No information available.

7.1.14 Human Reproduction and Pregnancy data

See Section 9

7.1.15 Assessments of effect on growth

No information available.

7.1.16 Overdose experience

There is no information on overdosage with AZOR in humans as it has not been marketed.

Amlodipine: Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium

gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Recently two cases of fatal amlodipine overdose have been reported in the literature: Sklerov JH, Levine B, Ingwersen KM, Aronica-Pollack PA, Fowler D. Two cases of fatal amlodipine overdose. J Anal Toxicol 2006;30:346-51.

**Olmesartan Overdosage:**

Limited data are available relating to olmesartan overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If symptomatic hypotension should occur, supportive treatment should be initiated. The dialyzability of olmesartan is unknown.

**7.1.17 Post marketing experience**

There is none as this is a new product.

**7.2 Adequacy of patient exposure and safety assessments**

For this class of drugs the duration of exposure is considered adequate for safety assessments (Section 7) and tables showing adequate exposure to drug during other clinical studies including those not in the US IND (Tables 121 – 124).

**Table 121: Duration of Exposure during open label extension period**

**Table 5: Exposure to Study Medication During the CS8663-A-U301 Open-Label Period – All Patients Entering Period III**

	OM40/ AML5	OM40/ AML10	OM40/ AML10/ HCTZ12.5	OM40/ AML10/ HCTZ25	Total <sup>3</sup>
<b>Extent of Exposure (Days)<sup>1</sup></b>					
N	1679	1124	736	440	1684
Mean ± SD	107.5 ± 122.09	101.4 ± 100.60	113.6 ± 83.90	181.1 ± 69.20	278.6 ± 76.73
<b>Number (%)<sup>2</sup> in Specified Exposure Ranges</b>					
1 Day to ≤2 Weeks	571 (34.0)	331 (29.4)	22 (3.0)	7 (1.6)	23 (1.4)
>2 Weeks to ≤4 Weeks	310 (18.5)	99 (8.8)	28 (3.8)	2 (0.5)	25 (1.5)
>4 Weeks to ≤10 Weeks	163 (9.7)	221 (19.7)	298 (40.5)	45 (10.2)	43 (2.6)
>10 Weeks to ≤18 Weeks	105 (6.3)	118 (10.5)	144 (19.6)	61 (13.9)	55 (3.3)
>18 Weeks to ≤26 Weeks	73 (4.3)	100 (8.9)	78 (10.6)	82 (18.6)	46 (2.7)
>26 Weeks to ≤34 Weeks	41 (2.4)	75 (6.7)	69 (9.4)	147 (33.4)	46 (2.7)
>34 Weeks to ≤44 Weeks	268 (16.0)	175 (15.6)	95 (12.9)	95 (21.6)	922 (54.8)
>44 Weeks	148 (8.8)	5 (0.4)	2 (0.3)	1 (0.2)	524 (31.1)
<sup>1</sup> Extent of Exposure to Study Medications (Days) = Start Date of New Dose - Start Date of Current Dose. For the final dosing regimen, Extent of Exposure is calculated as Last Dose Date of Open-label study medication - Start Date of Final Dosing Regimen + 1. In cases of back-titration, Extent of Exposure is calculated by summing all time intervals for the given study medication. <sup>2</sup> Percentage is calculated using the number of patients exposed to each dosing regimen as the denominator. <sup>3</sup> Other regimens not included except in Total column. Total column represents mean number of days of exposure to study treatment, independent of dose regimens. AML = amlodipine, HCTZ = hydrochlorothiazide, OM = olmesartan medoxomil. Source: CSR 8663-A-U301 Post-text Table 14.1.8					

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**Table 122: Duration of Exposure during open label period- Protocol CS8663 – A-E302**

**Table 6: Exposure to Study Medication in Period I (Monotherapy) and Period II (Double-Blind Treatment) – Safety Set 1 and Safety Set 2**

Extent of Exposure (Days) [1]	OM20	OM20/ Placebo	OM20/ AML5	OM20/ AML10	Overall
<b>Period I (Monotherapy) – Safety Set 1</b>					
N [2]	722				
Mean (SD)	56.5 (8.91)				
<b>Period II (Double-Blind Treatment) – Safety Set 2</b>					
N [2]		179	182	177	538
Mean (SD)		56.8 (5.44)	56.3 (5.86)	55.8 (7.23)	56.3 (6.22)
1. For Period I: extent of exposure to study medication = (date of last monotherapy dose – date of first monotherapy dose) + 1. For Period II: extent of exposure to study medication = (date of last double-blind dose – date of first double-blind dose) + 1. 2. N is the number of patients whose extent of exposure to study medication could be calculated. AML = amlodipine; OM = olmesartan medoxomil; SD = standard deviation. Sources: CS8663-A-E302 Study Database Tables D22.1 and D22.2					

**Table 123: Protocol CS8663 – A-E303**

**Table 7: Duration of Treatment –Period I (Monotherapy) and Period II (Double-Blind Treatment) – Safety Set 1 and Safety Set 2**

Extent of Exposure (Days) [1]	AML5	AML5/ Placebo	OM10/ AML5	OM20/ AML10	OM40/ AML5
<b>Period I (Monotherapy) – Safety Set 1</b>					
N [2]	1012				
Mean (SD)	56.0 (10.40)				
<b>Period II (Double-Blind Treatment) – Safety Set 2</b>					
N [2]		188	191	188	186
Mean (SD)		55.2 (10.08)	54.5 (10.27)	56.0 (7.70)	56.2 (8.15)
1 For Period I: Duration of Treatment (Days) = Date of Last Monotherapy Dose – Date of First Monotherapy Dose + 1. For Period II: Extent of Exposure to Study Medication (Days) = Last Dose Date of double-blind study medication – First Dose Date of double-blind study medication + 1. 2 N is the number of patients whose extent of exposure to study medication could be calculated. AML = amlodipine; OM = olmesartan medoxomil; SD = standard deviation. Sources: CS8663-A-E303 Study Database Tables D39.1 and D39.2					

**Table 124: Duration of exposure Period III Double blind up titration-Protocol CS8663 – A-E303**

**Table 8: Duration of Treatment – Period III (Double-Blind Up-Titration)**

Extent of Exposure (Days) [1]	AML5/Placebo	AML5/Placebo to OM10/AML5	OM10/AML5	OM10/AML5 to OM20/AML5	OM20/AML5	OM20/AML5 to OM40/AML5	OM40/AML5	OM40/AML5 to OM40/AML10
<b>Period III (Double-blind Up-titration)</b>								
N [2]	68	107	97	82	118	58	119	57
Mean (SD)	57.4 (4.81)	56.4 (5.12)	56.9 (5.03)	57.2 (6.13)	56.4 (6.00)	58.2 (4.57)	56.3 (8.65)	55.4 (4.77)
1 For Period III: Duration of Treatment (Days) = Last Dose Date of double-blind study medication – First Dose Date of double-blind study medication + 1. 2 N is the number of patients whose extent of exposure to study medication could be calculated. AML = amlodipine; OM = olmesartan medoxomil; SD = standard deviation. Sources: CS8663-A-E303 Study Database Table D39.3								

### 7.3 Summary of selected Drug-related adverse events

Possible drug-related adverse reactions during the double-blind period occurring in the patients treated with AZOR at about the same or greater incidence than patients receiving

Amlodipine besylate and Olmesartan Medoxomil NDA22-100

placebo included hypotension, orthostatic hypotension, rash, pruritus, palpitation, urinary frequency, and nocturia. (Table 125)

Table 125: Drug related adverse events by system organ class > 1%.

Table 77: Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Incidence ≥1% in Any Treatment Group) – Safety Population

	Pbo (N = 162)	OM10 (N = 161)	OM20 (N = 161)	OM40 (N = 162)	AML5 (N = 161)	AML10 (N = 163)	OM10/ AML5 (N = 163)	OM20/ AML5 (N = 161)	OM40/ AML5 (N = 162)	OM10/ AML10 (N = 162)	OM20/ AML10 (N = 160)	OM40/ AML10 (N = 162)
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
General disorders and administration site conditions	18 (11.1)	24 (14.9)	12 (7.5)	23 (14.2)	19 (11.8)	45 (27.6)	27 (16.6)	24 (14.9)	30 (18.5)	35 (21.6)	38 (23.8)	28 (17.3)
Edema combined terms <sup>1</sup>	13 (8.0)	18 (11.2)	9 (5.6)	20 (12.3)	13 (8.1)	45 (27.6)	25 (15.3)	22 (13.7)	23 (14.2)	33 (20.4)	29 (18.1)	27 (16.7)
Fatigue	5 (3.1)	7 (4.3)	3 (1.9)	3 (1.9)	3 (1.9)	2 (1.2)	1 (0.6)	3 (1.9)	7 (4.3)	2 (1.2)	8 (5.0)	2 (1.2)
Asthenia	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)	0 (0.0)	2 (1.3)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	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 (1.3)	0 (0.0)
Nervous system disorders	15 (9.3)	11 (6.8)	14 (8.7)	15 (9.3)	10 (6.2)	4 (2.5)	4 (2.5)	8 (5.0)	10 (6.2)	8 (4.9)	10 (6.3)	11 (6.8)
Headache	11 (6.8)	7 (4.3)	6 (3.7)	9 (5.6)	6 (3.7)	2 (1.2)	2 (1.2)	4 (2.5)	4 (2.5)	5 (3.1)	6 (3.8)	4 (2.5)
Dizziness	6 (3.7)	3 (1.9)	7 (4.3)	6 (3.7)	4 (2.5)	2 (1.2)	1 (0.6)	5 (3.1)	6 (3.7)	3 (1.9)	2 (1.3)	5 (3.1)
Hypoesthesia	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
Vascular disorders	9 (5.6)	5 (3.1)	5 (3.1)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)	2 (1.3)	2 (1.2)
Hypertension combined terms <sup>2</sup>	9 (5.6)	5 (3.1)	5 (3.1)	3 (1.9)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	0 (0.0)
Hypotension combined terms <sup>3</sup>	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.2)	1 (0.6)	2 (1.2)
Gastrointestinal disorders	7 (4.3)	4 (2.5)	3 (1.9)	2 (1.2)	4 (2.5)	3 (1.8)	2 (1.2)	8 (5.0)	2 (1.2)	5 (3.1)	6 (3.8)	4 (2.5)
Nausea	3 (1.9)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	3 (1.9)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
Diarrhea	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.3)	2 (1.2)
Constipation	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	2 (1.2)	2 (1.3)	0 (0.0)
Dyspepsia	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.2)	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)
Dry mouth	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (1.2)	0 (0.0)	3 (1.9)	3 (1.9)	3 (1.9)	1 (0.6)	1 (0.6)	1 (0.6)	5 (3.1)	0 (0.0)	3 (1.9)	3 (1.9)
Muscle spasms	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.2)	0 (0.0)	0 (0.0)	1 (0.6)
Pain in extremity	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)	0 (0.0)	0 (0.0)	1 (0.6)
Skin and subcutaneous tissue disorders	2 (1.2)	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.6)	3 (1.8)	1 (0.6)	3 (1.9)	1 (0.6)	3 (1.9)	1 (0.6)	1 (0.6)
Pruritus	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (0.6)	6 (3.7)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.2)	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
Palpitations	0 (0.0)	1 (0.6)	2 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.2)	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
Psychiatric disorders	1 (0.6)	3 (1.9)	1 (0.6)	0 (0.0)	2 (1.2)	1 (0.6)	1 (0.6)	2 (1.2)	2 (1.2)	1 (0.6)	0 (0.0)	1 (0.6)
Anxiety	0 (0.0)	3 (1.9)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (1.2)	0 (0.0)	2 (1.2)	0 (0.0)	1 (0.6)	3 (1.8)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.2)	0 (0.0)	1 (0.6)
Dyspnea	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)

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Table 77: Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Incidence ≥1% in Any Treatment Group) – Safety Population (Continued)

	Pbo (N = 162)	OM10 (N = 161)	OM20 (N = 161)	OM40 (N = 162)	AML5 (N = 161)	AML10 (N = 163)	OM10/ AML5 (N = 163)	OM20/ AML5 (N = 161)	OM40/ AML5 (N = 162)	OM10/ AML10 (N = 162)	OM20/ AML10 (N = 160)	OM40/ AML10 (N = 162)
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Renal and urinary disorders	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	5 (3.1)	0 (0.0)	2 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
Pollakiuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Nocturia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)	3 (1.9)	0 (0.0)	0 (0.0)
Influenza	0 (0.0)	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)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	2 (1.2)	0 (0.0)	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)
Erectile dysfunction	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

<sup>1</sup> Included preferred terms of edema, edema peripheral, pitting edema, generalized edema, and localized edema. Patients were counted once for any instance of these preferred terms relating to edema.

<sup>2</sup> Included preferred terms of hypertension, systolic hypertension, diastolic hypertension, accelerated hypertension, blood pressure increased, blood pressure diastolic increased, or blood pressure inadequately controlled. Patients were counted once for any instance of these preferred terms relating to hypertension.

<sup>3</sup> Included preferred terms of hypotension, orthostatic hypotension, blood pressure decreased, blood pressure diastolic decreased, and blood pressure systolic decreased. Patients were counted once for any instance of these preferred terms relating to hypotension. While the preferred terms "hypertension" and "hypotension" were assigned to the system organ class of Vascular disorders, the "hypertension combined term" and "hypotension combined term" encompass preferred terms that were assigned to several other system organ classes (i.e., other than Vascular disorders).

Treatment-emergent adverse events: adverse events that had a start date after the first dose of randomized study medication, or occurred prior to the first dose and worsened in severity during the randomized treatment period. Drug-related was defined as definitely, probably, or possibly related to randomized study medication. Percentage was calculated using the number of patients in the column heading as denominator. Although a patient may have had two or more treatment-emergent adverse events, the patient was counted only once within a category. The same patient may have appeared in different categories.

AML = amlodipine, OM = olmesartan medoxomil, Pbo = placebo.

Sources: Post-text Table 14.3.1.6 and Post-text Data Listing 16.2.7.1

Adverse events by severity

The number and percentage of patients with clinical TEAEs by maximum severity are summarized in Post-text Table 14.3.1.5. Throughout the study, 590 (30.4%) patients

Amlodipine besylate and Olmesartan Medoxomil NDA22-100

experienced mild TEAEs, 375 (19.3%) patients experienced moderate TEAEs, and 55 (2.8%) patients experienced severe TEAEs. The distribution of patients with mild, moderate, and severe TEAEs was similar in all treatment groups. There was a slightly lower incidence of severe TEAEs within the olmesartan medoxomil monotherapy groups, each of which had a frequency of severe TEAEs <2%. None of the treatment groups had an incidence of severe TEAEs >5%.

For all treatment groups, the majority of edema (including the preferred terms of edema, edema peripheral, pitting edema, generalized edema, and localized edema) was of mild severity. The frequency of moderate edema was 9.2% in the AML 10 mg group compared with 9.3% in the OM 10 mg + AML 10 mg group, 3.8% in the OM 20 mg + AML 10 mg group, and 6.2% in the OM 40 mg + AML 10 mg group. For the remaining treatment groups, the frequency of moderate edema ranged from 1.2% to 6.8%. Severe edema was experienced by a total of 5 (0.3%) patients: 1 (0.6%) patient in the AML 5 mg group, 2 (1.2%) patients in the AML 10 mg group, 1 (0.6%) patient in the OM 10 mg + AML 10 mg group, and 1 (0.6%) patient in the OM 40 mg + AML 10 mg group. See Tables in Section 9.3.1 under Risk management activity.

Hypertension (including the preferred terms of hypertension, systolic hypertension, diastolic hypertension, accelerated hypertension, blood pressure increased, blood pressure diastolic increased, or blood pressure inadequately controlled) was mild in 16 (0.8%) patients, moderate in 25 (1.3%) patients, and severe in 7 (0.4%) patients. The frequency of moderate hypertension was 4.9% in the placebo group and ranged from 0.0% to 3.1% in the remaining treatment groups. Severe hypertension was experienced by 1 (0.6%) patient in the placebo group, 1 (0.6%) patient in the OM 20 mg group, 2 (1.2%) patients in the OM 40 mg group, 1 (0.6%) patient in the AML 5 mg group, and 2 (1.2%) patients in the OM 40 mg + AML 5 mg group (see Post-text Data Listing 16.2.7.1).

There were no other treatment-related trends with respect to the frequency of specific TEAEs by maximum severity.

The number and percentage of patients with clinical drug-related TEAEs by maximum severity is summarized in Post-text Table 14.3.1.7.

Overall, most of the clinical drug-related TEAEs experienced by patients were considered to be mild in severity.

#### Edema

Edema is an important impediment to compliance with CCBs, and since a potential benefit of the combination product is attenuation of CCB-related edema, Sankyo decided to better profile the edema response during the conduct of the factorial design trial. On the basis of known experience with the combination of benazepril and amlodipine, it was anticipated that co-administration of olmesartan medoxomil would potentially reduce or eliminate the incidence of amlodipine-induced edema.

Specifically, the results demonstrate the benefits of CS-8663, while at the same time the relatively aggressive harvesting of edema reveals a considerably higher incidence of edema in all groups, especially in placebo-treated patients (Table 126).

Table 126: Patients with peripheral edema

Table 78: Number (%) of Patients with Categorical Shifts Up in Peripheral Edema – Safety Population

Treatment	N	Number of Categories Shifted Up During Randomized Treatment Period Based on Severity of Worst Grade					
		Exactly One n (%)	At Least One n (%)	Exactly Two n (%)	At Least Two n (%)	Exactly Three n (%)	At Least Three n (%)
Placebo	162	12 (7.4)	13 (8.0)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)
OM10	161	18 (11.2)	22 (13.7)	4 (2.5)	4 (2.5)	0 (0.0)	0 (0.0)
OM20	161	7 (4.3)	8 (5.0)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)
OM40	162	14 (8.6)	20 (12.3)	6 (3.7)	6 (3.7)	0 (0.0)	0 (0.0)
AML5	161	14 (8.7)	16 (9.9)	2 (1.2)	2 (1.2)	0 (0.0)	0 (0.0)
AML10	163	35 (21.5)	50 (30.7)	9 (5.5)	15 (9.2)	4 (2.5)	6 (3.7)
OM10/AML5	163	37 (16.6)	38 (17.2)	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.6)
OM20/AML5	161	19 (11.8)	22 (13.7)	2 (1.2)	3 (1.9)	1 (0.6)	1 (0.6)
OM40/AML5	162	21 (13.0)	25 (15.4)	4 (2.5)	4 (2.5)	0 (0.0)	0 (0.0)
OM10/AML10	162	26 (16.0)	40 (24.7)	8 (4.9)	14 (8.6)	6 (3.7)	6 (3.7)
OM20/AML10	160	23 (14.4)	34 (21.3)	9 (5.6)	11 (6.9)	1 (0.6)	2 (1.3)
OM40/AML10	162	24 (14.8)	33 (20.4)	8 (4.9)	9 (5.6)	0 (0.0)	1 (0.6)

Severity of worst grade was defined as the worst case of edema experienced by the patient during the randomized treatment period.  
 Categories were: no edema, mild pitting edema, moderate pitting edema, deep pitting edema (with minor leg swelling), and deep pitting edema (with major leg swelling).  
 Percentages were calculated using the number of patients in the "N" column as denominator.  
 Cochran-Armitage trend test p-value = 0.0275 for testing trend in reduced proportions among AML10, OM10/AML10, OM20/AML10, and OM40/AML10 with increased duration metoprolol dose within the "At Least One" category shifted up.  
 AML = amlodipine, OM = olmesartan medoxomil.  
 Source: Post-text Table 14.3.1.17

Table 127: Mean change in Platelet count from baseline to week 8/Early termination

Table 82: Mean Change in Platelet Count (K/cu mm) from Baseline to Week 8/Early Termination – Safety Population

Treatment	N <sup>1</sup>	Baseline <sup>2</sup> Mean ± SD	Week 8/ET Mean ± SD	Change
				Mean ± SD
Placebo	146	257.27 ± 63.115	257.33 ± 70.340	0.03 ± 37.790
OM10	152	264.08 ± 52.950	267.14 ± 53.397	3.06 ± 30.864
OM20	148	253.66 ± 63.334	256.99 ± 62.736	3.33 ± 35.302
OM40	154	262.99 ± 65.239	269.18 ± 67.821	6.19 ± 34.991
AML5	151	234.39 ± 63.187	264.57 ± 67.088	10.18 ± 39.341
AML10	155	252.53 ± 64.119	274.61 ± 64.289	22.08 ± 31.614
OM10/AML5	152	262.69 ± 68.780	274.71 ± 67.667	12.02 ± 30.666
OM20/AML5	151	266.09 ± 67.736	278.76 ± 73.261	12.68 ± 30.797
OM40/AML5	149	254.77 ± 60.237	267.43 ± 64.864	12.66 ± 37.498
OM10/AML10	151	259.00 ± 67.051	276.17 ± 65.576	17.17 ± 39.180
OM20/AML10	145	258.59 ± 57.736	279.42 ± 63.776	20.83 ± 36.820
OM40/AML10	150	256.48 ± 51.725	275.51 ± 60.241	19.03 ± 33.514

<sup>1</sup>N was the number of patients with both baseline and Week 8/ET measurements.  
<sup>2</sup>Baseline was defined as the last available measurement prior to randomization.  
 AML = amlodipine, ET = early termination, OM = olmesartan medoxomil, SD = standard deviation.  
 Source: Post-text Table 14.3.4.2

7.4 General methodology

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Described in Sections 1, 6, and 7.

Regulatory

Several changes were made to Version 1 of the final study protocol (7 January 2005) including additional accepted methods of antihypertensive medication withdrawal,

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changes in visit dates for the pharmacokinetic substudy evaluations, adjustments to the description of blood pressure measurements during the pharmacokinetic substudy, additional safety assessments of peripheral edema and body weight, and changes to the requirements for removal of patients from the study. These changes were incorporated into Version 2 of the study protocol (30 June 2005). In addition, a response letter from the FDA (23 February 2005 noted below), specified changes to the statistical analysis plan in Version 1 of the protocol. The statistical methods were revised within Version 2 of the protocol to reflect these FDA-specified changes.

## 8 ADDITIONAL CLINICAL ISSUES

### **Additional clinical study: E-302:**

**(CS 8663 – A-E302) Protocol Title : Efficacy and Safety of amlodipine used as Add-on therapy in moderately severely hypertensive patients not adequately controlled by Olmesartan Medoxomil 20 mg monotherapy. Not under the US IND.**

A review of this study is not essential for the approval for this NDA. Although it is not under the US IND, the data from the completed study contributed to the safety data on the monotherapy components of the combination tablet.

The study demonstrated the significant add on effect of Amlodipine on 20 mg olmesartan medoxomil (Table 126).

**Efficacy:** The primary efficacy endpoint was the mean change from baseline (Week 8) to Week 16 (end of double-blind treatment period) using last observation carried forward (LOCF) in trough sitting DBP.

**Methodology:** This was a multi-centre, multi-national, randomized, double-blind, parallel-group trial 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 all patients received monotherapy with OM 20 mg. At the end of Period I (Visit 4/Week 8 [randomization visit]), only non-responders were eligible to be randomized (see Diagnosis and Main Criteria for Inclusion) and enter Period II. Patients whose BP was controlled on OM 20 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 20 mg treatment during Period I were assigned randomly in a 1:1:1 ratio to 1 of 3 treatment groups:

- OM 20 mg + placebo, • OM 20 mg + AML 5 mg, or • OM 20 mg + AML 10 mg.

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).

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 study (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)

Planned: 429 randomized patients Screened: 1519 patients Entered Monotherapy (Period I): 722 patients Randomized: 538 patients Discontinued: 13 patients Completed: 525 patients

**Summary:**

Efficacy Results: The primary efficacy analysis demonstrated that 8 weeks of double-blind treatment with the combination of OM + AML (OM 20 mg + AML 5 mg and OM 20 mg + AML 10 mg) reduced mean sitting DBP to a significantly greater extent than treatment with OM 20 mg + placebo. The table below presents the results for mean change and adjusted mean change in sitting DBP from baseline (Week 8) to Week 16 with LOCF for the Full Analysis Set. Treatment with OM + AML combination therapy resulted in statistically significant reductions in adjusted mean sitting DBP when compared with OM 20 mg + placebo therapy: -2.7 mmHg for OM 20 mg + AML 5 mg (p=0.0006) and -3.2 mmHg for OM 20 mg + AML 10 mg (P<0.0001) (Table 128).

Safety in Section 7.

**Table 128: Add-on effect of amlodipine- Monotherapy versus placebo with baseline at 8 weeks from Period II (P<0.0001).**

Week 16 LOCF Analysis Variable	OM20/Placebo (N = 179)	OM20/AML5 (N = 182)	OM20/AML10 (N = 177)
N [1]	179	182	177
Baseline mean (SD) [2]	97.2 (4.89)	97.5 (4.34)	97.1 (4.22)
Week 16 LOCF mean (SD) [3]	89.4 (8.54)	86.9 (7.39)	86.0 (7.59)
Mean change (SD)	-7.8 (7.86)	-10.6 (7.20)	-11.1 (8.01)
Adjusted mean change (SE) [4]	-7.6 (0.55)	-10.4 (0.55)	-10.9 (0.56)
Treatment comparison with OM20/Placebo			
Adjusted mean change (SE) [4]		-2.7 (0.75)	-3.2 (0.76)
95% confidence interval [4]		-4.4, -1.1	-4.9, -1.5
P-value [4]		0.0006	<0.0001

1. N = the number of patients with values at both time points.  
 2. Baseline = Week 8.  
 3. Week 16 LOCF was defined as the last available measurement during the double-blind treatment period.  
 4. Statistics were based on an Analysis of Covariance model, including treatment, pooled centre, and baseline value as a covariate. All comparisons are with OM20/Placebo using Dunnett's test to adjust for multiple testing.  
 AML = amlodipine; LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation; SE = standard error.  
 Sources: Post-text Tables 14.2.3, 14.2.4, and 14.2.5

### 8.1 Dosing Regimen and Administration

The recommended starting dose of AZOR is 5/20 mg once daily. Dosage should be guided by clinical response. The dose of AZOR may be increased after 2 weeks in patients requiring further reduction in blood pressure to goal, to a maximum dose of 10/40 mg once daily.”

In principle, the starting dose of AZOR should be selected based on the dose of the component already in use. The dose of AZOR may be increased after 2 weeks in patients requiring further reduction in blood pressure to goal, to a maximum dose of 10/40 mg once daily orally. There are three formulated strengths 5/20, 5/40, and 10/20. The 10 mg olmesartan has not been approved in the US although it has been approved in Europe and the sponsor carried out studies with 10 mg Olmesartan. The reason for including the 10mg olmesartan dose in this study is to allow the sponsor obtain approval for this combination outside of the United States.

### DOSAGE FORMS AND STRENGTHS

AZOR tablets are formulated for oral administration in the following strength combinations:

	5/20	5/40	10/20	1
amlodipine equivalent (mg)	5	5	10	
olmesartan medoxomil (mg)	20	40	20	

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This reviewer does not agree with the above proposal because there are no safety data or risk-benefit analysis to support use of AZOR as initial therapy in patients that physicians **consider unlikely to reach their blood pressure goal with one agent.**

In the amlodipine 5 mg and 10 mg combination treatment groups, increasing the dose of olmesartan medoxomil from 10 mg to 20 mg and then to 40 mg resulted in approximately 1 to 2 mmHg greater lowering of mean SeDBP for each doubling of the dose. The risk of doubling the dose for the clinical benefit will have to be further evaluated particularly with the relatively higher frequency of thrombocytosis, hypotension and edema in patients receiving the higher dose.

## 8.2 Drug-Drug Interactions

See Section 1.3.5 and Section 5

## 8.3 Special populations

See Section 6

## 8.4 Pediatrics

No studies have been carried out on children.

## 8.5 Advisory Committee Meeting

Not recommended unless the sponsor wishes to contest the claim that the combined should be approved for initial therapy.

## 8.6 Literature review

### **Advantages and Disadvantages of Monotherapy**

Monotherapy with antihypertensive agents achieves target blood pressure in only a proportion of patients treated. In a trial conducted by the Department of Veterans Affairs Cooperative Study Groups on Antihypertensive Agents, monotherapy with any of 6 different study drugs was found to reduce blood pressure to target levels (diastolic blood pressure <90 mmHg and systolic blood pressure <140 mmHg) in only about 50% of unselected patients with mild to moderate hypertension.<sup>2</sup> Similar results were found in the Hydrochlorothiazide, Atenolol, Nitrendipine, Enalapril (HANE) study and the Treatment of Mild Hypertension Study (TOMHS).<sup>3,4</sup> The results of clinical trials with olmesartan medoxomil monotherapy reflect this general experience. In placebo-controlled studies with olmesartan medoxomil monotherapy, the proportion of patients achieving target diastolic blood pressure (<90 mmHg) over the dosage range of 10 mg-80 mg was found to be about 50%-60%.<sup>6, 7</sup> Responder rate (defined as the percentage of patients with a decrease in diastolic blood pressure to =90 mmHg or a decrease from baseline of =10 mmHg) was higher at about 70%-80%. Similar results have been reported for other angiotensin II antagonists. Control of systolic blood pressure with monotherapy is even more difficult than control of diastolic blood pressure.

The inability of any single agent to reduce blood pressure to target levels in all patients treated is not surprising, given the polygenic and multifactorial nature of the pathogenesis

of hypertension.<sup>11</sup> Even with modern potent antihypertensive agents, combination therapy is likely to be required to achieve target blood pressure in many patients. The need for combination therapy has been demonstrated in recent large-scale clinical studies. In the Hypertension Optimal Treatment (HOT) trial, 77% of the patients allocated to a target diastolic blood pressure of  $\geq 90$  mmHg remained on calcium channel blocker (CCB) baseline therapy at the end of the study, but usually together with an angiotensin-converting enzyme (ACE) inhibitor (35%) or a beta-blocker (25%).<sup>12</sup> Similarly, in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, 78% of patients randomized to Losartan received add-on therapy with a CCB.<sup>13</sup> In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, only 11% of patients randomized to Losartan remained on monotherapy at the end of the study.<sup>14</sup> In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the mean number of antihypertensive medications taken was 1.4 to 1.5 after the first year and 1.8 to 2.0 by year 5.<sup>15</sup>

The different mechanisms of action of the different antihypertensive agents can augment the overall blood pressure-lowering effects of the combination regimen. Furthermore, the actions of one agent can ameliorate the adverse effects of another agent being used concomitantly. For instance, dihydropyridine CCBs activate the sympathetic nervous system and renin-angiotensin-aldosterone axis to varying extents. These effects may be minimized by the co-administration of an ACE inhibitor or an angiotensin receptor blocker (ARB). In addition, CCBs are intrinsically natriuretic and induce a state of negative sodium balance, which further reinforces the antihypertensive effects of drugs acting on the renin-angiotensin system. Peripheral edema is one of the most common adverse effects of dihydropyridine CCBs and probably results from vasodilatation and reduction in pre-capillary resistance. This effect can be ameliorated during concomitant use with ACE inhibitors or ARBs, which lower post-capillary resistance and hence tend to normalize intracapillary pressure and reduce fluid exudation.<sup>16,17</sup>

These efficacy and safety data illustrate the importance of combination therapy when monotherapy fails to achieve blood pressure targets. In addition, fixed combination formulations can contribute significantly to improved compliance with antihypertensive therapy. Without adequate compliance, blood pressure targets are logically less likely to be met, and hence, the reduction in cardiovascular risk may be less than could be achieved with regular medication intake.

The European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines on the clinical management of hypertension published in 2003 recognize ARB/CCB combination treatment as an effective and well-tolerated therapeutic

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option.<sup>18</sup> As described above, the JNC7 guidelines also recommend the use of  
combination therapy in appropriate circumstances.

Based on these internationally recognized guidelines and the need to facilitate  
enhanced compliance and blood pressure control, a tablet containing a combination of  
olmesartan medoxomil and amlodipine is being developed for the treatment of mild to  
severe hypertension. Data on the clinical development of both olmesartan medoxomil  
and amlodipine can be found highlighted in the Investigator's Brochure<sup>19</sup> and in the  
respective package inserts.<sup>20,21</sup>

Olmesartan medoxomil (the prodrug form of active olmesartan) is an orally active  
angiotensin II antagonist intended for use in treating hypertension. The drug was  
granted marketing approval by the Food and Drug Administration (FDA) on 25 April  
2002, and is available in the US as 5, 20, and 40 mg Benicar<sup>®</sup> tablets. The experience  
derived from the clinical trials conducted with olmesartan medoxomil is accounted  
for by the most recent version of the US package insert (July 2005).<sup>20</sup> In addition,  
olmesartan medoxomil is approved in Japan, Europe, and some Latin American  
countries.

The antihypertensive effect of olmesartan medoxomil was demonstrated in 7 placebo-  
controlled studies at doses ranging from 2.5 mg to 80 mg for 6 to 12 weeks. The  
response in terms of reductions in peak and trough blood pressure was dose related;  
however, olmesartan medoxomil doses greater than 40 mg had little additional effect.  
The onset of the antihypertensive effect occurred within 1 week and was largely  
manifest after 2 weeks, with effects on blood pressure maintained throughout a  
24-hour period.

The antihypertensive effect of olmesartan medoxomil is similar in men and women,  
and in patients older and younger than 65 years. The effect is smaller in Black  
patients, who are usually a low-renin population, as has been seen with other ACE  
inhibitors and ARBs.

## 8.7 Post Marketing Risk Management Plan

See Section 1.2.1

## 8.8 Other relevant materials

## 9 OVERALL ASSESSMENTS

The combination of olmesartan medoxomil and amlodipine reduced both mean SeDBP  
and mean SeSBP to a significantly greater extent compared to the component  
monotherapies that made up each combination. The combination of OM 40 mg + AML  
10 mg resulted in the greatest mean reductions in both SeDBP and SeSBP. Although  
there were minor differences in some of the subgroups, similar reductions in blood  
pressure were observed in all of the subgroups analyzed.

For approval, the primary efficacy endpoint has to demonstrate that co-administration of olmesartan medoxomil (OM) and amlodipine (AML) is more efficacious for lowering seated diastolic blood pressure (SeDBP) compared to each of the corresponding monotherapy components. This regulatory requirement was satisfied by the data from the pivotal study.

The double blind treatment period of study which randomized 1940 patients out of 4234 patients screened, referred to as Period II, demonstrated that Olmesartan medoxomil 10 mg, 20mg and 40 mg given together with Amlodipine 5mg and 10 mg reduced significantly both diastolic and systolic blood pressure to a greater degree than its constituent components. The combination of 40 mg Olmesartan and 10 mg Amlodipine produced the greatest mean reduction in SeDBP and SeSBP.

This reviewer is unable to recommend this for initial therapy based on the fact that there are 1) no studies to show a "stepped care" approach as advocated by the Advisory committee on Avalide (See minutes of AC on April 18 2007).

- 2) There is no evidence to show that the improved response rate on the combination is improved with corresponding reduction of adverse event ;
- 3) That the arbitrariness of BP reduction in the indication sought has not been validated for cardiovascular risks and other clinical outcomes
- 4) There is a temporal factor of 8 weeks (Period II) that militates against optimal safety evaluation
- 5) there is a need for enrichment of patient subsets including age (>70 or 75 years) (N=384 for > 65) and race for adequate safety evaluation; the numbers of randomized patients with co-morbid conditions such as kidney disease, congestive heart failure, coronary artery disease and diabetes mellitus are inadequate for safety evaluation. For example, of the total number of subjects in the double-blind clinical study of AZOR, 20% (384/1940) were 65 years of age or older and 3% (62/1940) were 75 years or older. With these shortcomings, there is a lack of data for a quantitative and qualitative risk-benefit assessment for initial therapy.

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## 9.1 CONCLUSIONS

AZOR tablets are formulated in four strengths for oral administration with a combination of amlodipine besylate, equivalent to 5mg and 10 mg of amlodipine free-base, with 20 mg, or 40 mg of olmesartan providing for the following available combinations: 5/20, 10/20, 5/40, and 10/40 mg.

- The combination of olmesartan medoxomil and amlodipine reduced both mean SeDBP and mean SeSBP to a significantly greater extent compared to the component monotherapies that made up each combination.
- The drug effect for combination therapy was defined on the basis of exposures to both compounds, and it was greater than either of the monotherapy components alone.

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- The magnitude of the placebo-subtracted reduction of both the diastolic and systolic blood pressure by the combined tablet in all sub groups analyzed is relatively great; thus making it a potentially effective antihypertensive for patients who are not responding adequately to monotherapy. It is however noteworthy that 2 patients on the combination tablet withdrew from the study for lack of efficacy.
- The combination of OM 40 mg + AML 10 mg resulted in the greatest mean reductions in both SeDBP and SeSBP.
- Although there were minor differences in some of the subgroups, similar reductions in blood pressure were observed in all of the subgroups analyzed.
- The combination treatments, particularly the higher dose combination treatments, did result in abnormal laboratory parameters compared to their component monotherapies.
- Edema, which is commonly associated with amlodipine 10 mg therapy, reduced in frequency when it was given in combination with increasing dose of olmesartan medoxomil.
- A positive benefit-risk assessment was confirmed for patients with blood pressure  $\geq 160/100$  mmHg who received the combination tablet compared to the lower doses of monotherapy, particularly, Olmesartan 10 and 20 mg and Amlodipine 5 mg. The magnitude of such risk-benefit by all the combination doses however was not that great compared to amlodipine 10 mg monotherapy.
- A review of the safety profile based on frequency and specific types of events, as well as an assessment of potential relationships between the events and study medication, suggest that there was no greater incidence of SAEs or adverse event discontinuations due to the combination of olmesartan medoxomil and amlodipine than with the monotherapies.
- However the reviewer notes that the safety evaluation of the combination tablet at high doses reveals adverse events that include elevated liver enzymes, abnormal laboratory parameters, hypotension and edema, albeit modulated by increasing doses of olmesartan medoxomil. This is perhaps not surprising as one of the components has dose related adverse events.
- Generally, the response to all therapy groups, monotherapy and combination, was found to be greater in the non-Black population, except for the AML 10 mg monotherapy. There was no age or gender differences.
- There was a higher frequency of edema in patients given the combined tablet compared to those given Olmesartan alone.

The review of the efficacy results and safety profile of the combination tablet supports the recommendation for approval for treatment of hypertension subject to the usual post-marketing surveillance for all new drugs.

## 9.2 RECOMMENDATIONS ON REGULATORY ACTION

AZOR is an immediate release, fixed-dose combination film-coated drug product for oral use. Daiichi-Sankyo submitted this 505(b)(2) application electronically for AZOR (amlodipine besylate and olmesartan medoxomil) Tablets for the following proposed indications:

- AZOR is indicated either alone or in combination with other antihypertensive agents for the treatment of hypertension
- AZOR is indicated for initial therapy in selected patients with hypertension requiring a blood pressure reduction of greater than or equal to 20/10 mmHg.

This reviewer recommends that the combination tablet of amlodipine and olmesartan be approved for the treatment of mild to severe essential hypertension having demonstrated statistically significant lowering of seated diastolic and systolic blood pressure compared to the corresponding monotherapy components, hence in compliance with regulatory criteria.

This reviewer however does not recommend that AZOR can be used for initial therapy in selected patients with hypertension requiring a blood pressure reduction of greater than or equal to 20/10 mmHg (See Section 9.1).

## 9.3 RECOMMENDATIONS ON POSTMARKETING ACTIONS

### 9.3.1 Risk management Activity

The laboratory abnormalities that appeared to be changed as a result of treatment will need to be monitored as part of the post marketing surveillance particularly the elevated liver enzymes and the increased platelets. The mean platelet counts did increase in all active treatment groups with the least change observed in the olmesartan medoxomil monotherapy treatment groups. The greatest increases occurred with amlodipine 10 mg and in the combination treatment groups that contained amlodipine 10 mg. None of these laboratory abnormalities are considered to be clinically meaningful by the sponsor but this reviewer recommends that these abnormalities be monitored during the post marketing period.

There are no other specific risk management activities recommended other than those in place for the individual component drugs particularly peripheral edema. The following two tables illustrate the importance of edema in the patients exposed to the combination tablet

**Table 129: Frequency of Edema in the safety population during the double blind period**

Table 14.3.1.28  
 Summary of Edema Combined Terms - Number (%) of Patients  
 Safety Population  
 Period II - Day 1 to Week 8

Group/Subgroup	Placebo (N=162)	OM10 (N=161)	OM20 (N=161)	OM40 (N=162)	OM5 (N=161)	AML10 (N=163)
Safety Population	20 (12.3)	23 (14.3)	16 (9.9)	30 (18.5)	21 (13.0)	60 (36.8)
Patients < 65 Years of Age	13 (11.5)	20 (15.5)	14 (10.7)	23 (17.7)	16 (14.0)	53 (40.5)
Patients ≥ 65 Years of Age	5 (15.6)	3 (9.4)	2 (6.7)	7 (21.9)	3 (9.4)	7 (21.9)
Diabetic Patients	4 (17.4)	1 (5.0)	2 (9.3)	4 (18.2)	2 (9.1)	5 (21.7)
Non-Diabetic Patients	16 (11.5)	22 (15.6)	14 (10.1)	26 (18.6)	19 (13.7)	55 (39.3)
Male Patients	8 (8.5)	6 (6.9)	7 (7.8)	15 (18.3)	5 (5.7)	33 (33.7)
Female Patients	12 (17.4)	17 (23.0)	9 (12.7)	15 (18.8)	16 (21.6)	27 (41.5)
Black Patients	6 (13.3)	7 (21.9)	2 (5.6)	7 (15.9)	3 (7.1)	10 (25.9)
Non-Black Patients	14 (12.0)	16 (12.4)	14 (11.2)	23 (19.5)	18 (15.1)	50 (40.3)
Naive Patients	7 (13.5)	10 (16.7)	7 (13.2)	7 (13.2)	8 (14.5)	23 (37.7)
Non-Naive Patients	13 (11.9)	13 (12.9)	9 (8.3)	23 (21.1)	13 (12.3)	37 (36.3)
Patients With Stage 1 HTN	4 (13.0)	6 (16.2)	4 (14.3)	8 (14.3)	2 (5.4)	13 (39.4)
Patients With Stage 2 HTN	16 (12.0)	17 (13.8)	12 (9.0)	24 (20.0)	19 (15.3)	47 (36.2)
Naive Stage 2 HTN Patients	6 (14.0)	8 (16.7)	4 (10.3)	7 (16.7)	8 (18.6)	18 (36.0)
Non-Naive Stage 2 HTN Patients	10 (11.1)	9 (12.0)	8 (8.5)	17 (21.8)	11 (13.6)	29 (36.3)

Percentage is calculated using number of patients in each group within the subgroup.  
 Edema includes MedDRA Preferred Terms of Edema peripheral, Edema, Pitting edema, Generalized edema, and Localized edema.  
 Cochran-Armitage trend test p-value = 0.0095 for testing trend in reduced proportions among AML10, OM10/AML10, OM20/AML10,  
 and OM40/AML10 in the Safety Population.

**Table 130: Frequency of Edema in the safety population during the double blind period**

Summary of Edema Combined Terms - Number (%) of Patients  
 Safety Population  
 Period II - Day 1 to Week 8

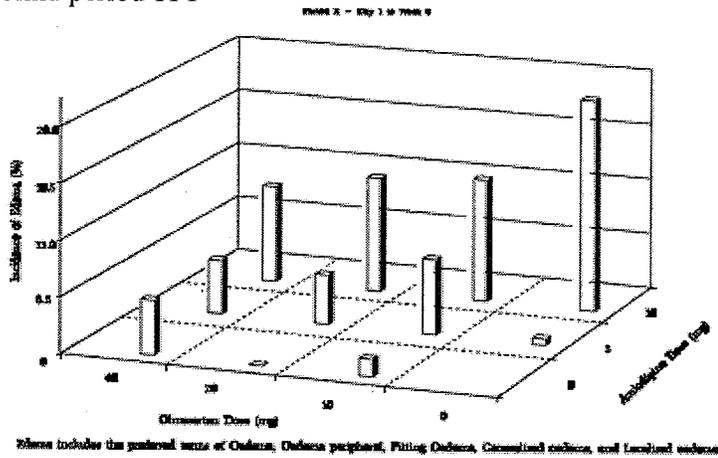
Group/Subgroup	OM10/AML5 (N=163)	OM10/AML10 (N=162)	OM20/AML5 (N=161)	OM20/AML10 (N=160)	OM40/AML5 (N=162)	OM40/AML10 (N=162)	Total (N=1940)
Safety Population	34 (20.9)	43 (26.5)	29 (18.0)	41 (25.6)	30 (18.5)	38 (23.5)	305 (19.6)
Patients < 65 Years of Age	27 (20.4)	35 (26.7)	25 (19.7)	29 (22.7)	27 (20.8)	28 (21.7)	314 (20.2)
Patients ≥ 65 Years of Age	7 (21.9)	8 (25.8)	4 (11.8)	12 (37.5)	3 (9.4)	10 (30.3)	71 (18.5)
Diabetic Patients	6 (25.1)	5 (25.0)	3 (11.6)	2 (9.1)	5 (27.8)	4 (16.7)	43 (16.5)
Non-Diabetic Patients	28 (20.0)	38 (26.8)	26 (18.7)	39 (28.3)	25 (17.4)	34 (24.6)	342 (20.4)
Male Patients	12 (14.3)	19 (20.2)	13 (15.7)	18 (24.4)	19 (19.6)	18 (20.5)	173 (16.4)
Female Patients	22 (27.8)	24 (35.3)	16 (19.5)	23 (26.9)	11 (16.9)	20 (27.9)	232 (23.9)
Black Patients	9 (26.5)	9 (28.5)	9 (28.9)	10 (21.3)	8 (20.0)	6 (17.1)	86 (17.9)
Non-Black Patients	25 (19.4)	34 (26.8)	20 (16.9)	31 (27.4)	22 (18.0)	32 (25.2)	239 (20.5)
Naive Patients	3 (8.3)	9 (16.7)	13 (22.0)	14 (25.0)	14 (22.6)	7 (13.2)	123 (18.5)
Non-Naive Patients	30 (26.1)	34 (31.5)	16 (15.7)	27 (26.0)	16 (16.0)	31 (28.4)	262 (20.6)
Patients With Stage 1 HTN	4 (14.7)	7 (19.4)	3 (9.4)	7 (26.9)	8 (21.1)	8 (24.2)	70 (18.0)
Patients With Stage 2 HTN	30 (22.2)	36 (26.9)	26 (20.3)	34 (25.4)	22 (17.9)	30 (23.3)	313 (20.4)
Naive Stage 2 HTN Patients	4 (10.3)	7 (15.9)	12 (26.5)	12 (26.8)	11 (23.4)	4 (10.3)	101 (19.1)
Non-Naive Stage 2 HTN Patients	26 (27.1)	29 (35.4)	14 (17.3)	22 (25.4)	11 (14.5)	26 (28.9)	212 (21.6)

Percentage is calculated using number of patients in each group within the subgroup.  
 Edema includes MedDRA Preferred Terms of Edema peripheral, Edema, Pitting edema, Generalized edema, and Localized edema.  
 Cochran-Armitage trend test p-value = 0.0093 for testing trend in reduced proportions among AML10, OM10/AML10, OM20/AML10,  
 and OM40/AML10 in the Safety Population.

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Figure 13: Placebo-subtracted incidence of Edema in safety population during the double blind period-ITT



### 9.3.2 Required Phase 4 Commitments

None recommended. However, the sponsor may consider carrying out a larger study in the future if the need for an indication for initial therapy is pursued. The sponsor may benefit from the guidelines to be suggested by the Cardiorenal Advisory Committee on Avalide (Irbesartan/HCTZ).

### 9.3.2 Required phase 4 commitments

There are no phase 4 requirements recommended

### 9.3.3 Other Phase 4 requests

There are no other phase 4 requirements recommended

## 9.4 LABELING REVIEW

This will be done with the other division reviewers. The clinical areas of the label that will probably need some fine tuning include the paragraphs reproduced below and underlined/boldened and the areas of indication sought and safety. The comments of the reviewer on the proposed label will be discussed during the Division's meeting.

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       Trade Secret / Confidential (b4)

  8   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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A.Olufemi Williams M.D.

Medical Reviewer (AZOR)

Amlodipine besylate and Olmesartan Medoxomil NDA22-100

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Amlodipine besylate and Olmesartan Medoxomil NDA22-100

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\_\_\_\_\_ Draft Labeling (b5)

\_\_\_\_\_ Deliberative Process (b5)

A.Olufemi Williams M.D.  
 Medical Reviewer (AZOR)  
 Amlodipine besylate and Olmesartan Medoxomil NDA22-100

Randomized Treatment Patient ID	A/G/R	VT: Adverse Event (Verbatim) PT: MedDRA Preferred Term SOC: System Organ Class	Start/Study Day Stop/Duration	TEAE? Severity	Relat. to Study Med.	Action Taken	Treat-ment [2]	Outcome
ON10/AM10								
082-010	61/M/B	VT: SLEEP APNEA PT: Sleep apnea syndrome SOC: Respiratory, thoracic and mediastinal disorders	01SEP2005/ 53 09SEP2005/ 2	Yes moderate	unrelated	interrupted	1	recovered
096-052	65/F/W	VT: MALIGNANT NEOPLASM OF SPECIFIED PARTS OF PERITONEUM PT: Malignant peritoneal neoplasm SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13NOV2005/ 54 Continuing [1]	Yes severe	unrelated	discontinued	1,3	AE still present
128-018	45/M/M	VT: WORSENING OF BIPOLAR DISORDER PT: Bipolar disorder SOC: Psychiatric disorders	26SEP2005/ 14 26SEP2005/ 2	Yes moderate	unrelated	discontinued	2	recovered with sequelae

A/G/R: Age is in years; Gender: M = Male, F = Female; Race: W = White, B = Black, A = Asian, AI = American Indian/Alaskan Native, NH = Native Hawaiian/Pacific Islander, O = Other; Note: Patients are permitted to select more than one race.  
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 Duration is calculated as Stop Date of Adverse Event - Start Date of Adverse Event + 1.  
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 [1] Adverse event is continuing at the end of the double-blind active treatment period - Period II.  
 [2] None = No treatment is required, 1 = Hospitalization, 2 = Medication, 3 = Other non-medical treatment.

Randomized Treatment Patient ID	A/G/R	VT: Adverse Event (Verbatim) PT: MedDRA Preferred Term SOC: System Organ Class	Start/Study Day Stop/Duration	TEAE? Severity	Relat. to Study Med.	Action Taken	Treat-ment [2]	Outcome
ON20/AM5								
030-007	65/F/W	VT: CHOLEDOCHOLITHIASIS PT: Bile duct stone SOC: Hepatobiliary disorders	18SEP2005/ 54 21SEP2005/ 4	Yes severe	unlikely	interrupted	1,2	recovered
175-012	60/M/M	VT: ADENOCARCINOMA OF PROSTATE PT: Prostate cancer SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	26SEP2005/ 4 Continuing [1]	Yes severe	unrelated	none	1	AE still present
		VT: ELEVATED PSA PT: Prostatic specific antigen increased SOC: Investigations	07NOV2005/ 46 Continuing [1]	Yes mild	unrelated	none	2	unknown
		VT: ADENOCARCINOMA OF PROSTATE PT: Prostate cancer SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	07NOV2005/ 46 Continuing [1]	Yes mild	unrelated	none	2	AE still present

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Randomized Treatment Patient ID	A/G/R	VT: Adverse Event (Verbatim) PT: MedDRA Preferred Term SOC: System Organ Class	Start/Study Day Stop/Duration	TEAEY	Severity	Relat. to Study Med.	Action Taken	Treat-ment [2]	Outcome
<b>0826/2013</b>									
038-003	65/F/W	VT: CHOLELITHIASIS PT: Bile duct stone SOC: Hepatobiliary disorders	18SEP2005/ 54 31SEP2005/ 4	Yes	severe	unlikely	interrupted	1,2	recovered
175-032	66/M/W	VT: ADENOCARCINOMA OF PROSTATE PT: Prostate cancer SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	26SEP2005/ 4 Continuing [1]	Yes	severe	unrelated	none	1	AE still present
		VT: ELEVATED PSA PT: Prostatic specific antigen increased SOC: Investigations	07NOV2005/ 46 Continuing [1]	Yes	mild	unrelated	none	2	unknown
		VT: ADENOCARCINOMA OF PROSTATE PT: Prostate cancer SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	07NOV2005/ 46 Continuing [1]	Yes	mild	unrelated	none	2	AE still present

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Randomized Treatment Patient ID	A/G/R	VT: Adverse Event (Verbatim) PT: MedDRA Preferred Term SOC: System Organ Class	Start/Study Day Stop/Duration	TEAEY	Severity	Relat. to Study Med.	Action Taken	Treat-ment [2]	Outcome
<b>0820/2010</b>									
075-010	43/M/O	VT: ACUTE PANCREATITIS PT: Pancreatitis acute SOC: Gastrointestinal disorders	31JUL2005/ 34 02AUG2005/ 3	Yes	moderate	unrelated	none	1,2	recovered
114-022	42/M/AI	VT: RECURRENT DISC HERNIATION PT: Intervertebral disc protrusion SOC: Musculoskeletal and connective tissue disorders	05AUG2005/ 49 01SEP2005/ 26	Yes	severe	unrelated	none	1,2	recovered
		VT: BILATERAL FORAMINAL STENOSIS PT: Acquired foramen magnum stenosis SOC: Musculoskeletal and connective tissue disorders	05AUG2005/ 49 01SEP2005/ 26	Yes	severe	unrelated	none	1,2	recovered
121-001	65/M/W	VT: MELANOMA IN SITU (CHEST LESION-INTERLOR) PT: Malignant melanoma in situ SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)	06JUL2005/ 10 18JUL2005/ 11	Yes	mild	unrelated	none	3	recovered

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Randomized Treatment Patient ID	A/G/R	VT: Adverse Event (Verbatim) PT: MedDRA Preferred Term SOC: System Organ Class	Start/Study Day Stop/Duration	TEAE?	Severity	Relat. to Study Med.	Action Taken	Treat-ment [2]	Outcome
<b>0M43/AM15</b>									
100-013	16/F/W	VT: RIGHT UPPER QUADRANT PAIN PT: Abdominal pain upper SOC: Gastrointestinal disorders	06OCT2005/ 60 17OCT2005/ 12	Yes	severe	unrelated	discontinued	1	recovered
		VT: UNCONTROLLED HYPERTENSION PT: Hypertension SOC: Vascular disorders	11OCT2005/ 67 17OCT2005/ 5	Yes	severe	unrelated	discontinued	1,2	recovered
158-020	48/M/W	VT: ACUTE CHOLECYSTITIS PT: Cholecystitis acute SOC: Hepatobiliary disorders	31AUG2005/ 3 15SEP2005/ 16	Yes	moderate	unrelated	discontinued	1	recovered
<b>0M45/AM18</b>									
002-009	68/F/B	VT: ATRIAL FIBRILLATION PT: Atrial fibrillation SOC: Cardiac disorders	16AUG2005/ 26 23AUG2005/ 8	Yes	moderate	unrelated	none	1	recovered

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Randomized Treatment Patient ID	A/G/R	VT: Adverse Event (Verbatim) PT: MedDRA Preferred Term SOC: System Organ Class	Start/Study Day Stop/Duration	TEAE?	Severity	Relat. to Study Med.	Action Taken	Treat-ment [2]	Outcome
<b>0M43/AM18</b>									
002-009	56/F/B	VT: NECROTIC GALLBLADDER PT: Gallbladder necrosis SOC: Hepatobiliary disorders	16MAY2005/ 25 23MAY2005/ 8	Yes	severe	unrelated	none	1	recovered
002-017	66/M/W	VT: BOWEL OBSTRUCTION PT: Intestinal obstruction SOC: Gastrointestinal disorders	22SEP2005/ 20 26SEP2005/ 5	Yes	severe	unrelated	none	1	recovered
		VT: POST-OPERATION ILEUS PT: Postoperative ileus SOC: Injury, poisoning and procedural complications	22SEP2005/ 28 26SEP2005/ 5	Yes	severe	unrelated	none	1	recovered
087-072	76/M/W	VT: ISCHEMIC COLITIS PT: Colitis ischemic SOC: Gastrointestinal disorders	02NOV2005/ 35 05NOV2005/ 4	Yes	severe	unlikely	none	1,2	recovered

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Randomized Treatment Patient ID	A/G/R	VF: Adverse Event (Verbatim) PT: MedDRA Preferred Term SOC: System Organ Class	Start/Study Day Stop/Duration	TEAE? Severity	Relat.to Study Med.	Action Taken	Treat-ment [2]	Outcome
OM40/AM110								
667-023	74/M/W	VF: ISCHEMIC COLITIS PT: Colitis ischaemic SOC: Gastrointestinal disorders	06OCT2005/ 10 19OCT2005/ 12	Yes severe	unlikely	none	1,2	recovered
150-042	70/F/B	VF: ROTATOR CUFF TEAR, RIGHT SHOULDER PT: Rotator cuff syndrome SOC: Musculoskeletal and connective tissue disorders	14OCT2005/ 39 16FEB2006/120	Yes moderate	unrelated	none	1,2	recovered
154-008	29/M/W	VF: RIGHT ANKLE FRACTURE PT: Ankle fracture SOC: Injury, poisoning and procedural complications	19JUL2005/ 35 10MAY2005/115	Yes severe	unrelated	none	1,2	recovered

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Randomized Treatment Patient ID	A/G/R	VF: Adverse Event (Verbatim) PT: MedDRA Preferred Term SOC: System Organ Class	Start/Study Day Stop/Duration	TEAE? Severity	Relat.to Study Med.	Serious?	Treat-ment [2]	Outcome
Placebo								
616-027	58/M/O	VF: WORSENING HYPERTENSION PT: Hypertension SOC: Vascular disorders	31AUG2005/ 17 Continuing [1]	Yes moderate	probable	no	2	AE still present
020-029	53/M/W	VF: INCREASED SEVERITY/FREQUENCY OF HEADACHES PT: Headache SOC: Nervous system disorders	04SEP2005/ 4 03OCT2005/ 30	Yes moderate	possible	no	2	recovered
		VF: DIZZINESS PT: Dizziness SOC: Nervous system disorders	02OCT2005/ 34 04OCT2005/ 3	Yes mild	possible	no	none	recovered
038-007	51/M/R	VF: VOMITING PT: Vomiting SOC: Gastrointestinal disorders	01OCT2005/ 01 03OCT2005/ 3	Yes moderate	unlikely	no	none	recovered

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Randomized Treatment Patient ID	A/G/R	VT: Adverse Event (Verbatim) PT: MedDRA Preferred Term SOC: System Organ Class	Start/Study Day Stop/Duration	TRAE? Severity	Relat. to Study Med.	Serious?	Treat -ment [2]	Outcome
Placebo								
039-005	49/M/H	VT: MURDER PT: Murder SOC: Social circumstances		Yes severe	unrelated	yes	none	death
041-010	63/M/W	VT: EXACERBATION OF HYPERTENSION PT: Hypertension SOC: Vascular disorders	26JUN2005/ 15 Continuing [1]	Yes moderate	possible	no	2	AE still present
044-018	56/F/W	VT: EXACERBATION OF HYPERTENSION PT: Hypertension SOC: Vascular disorders	10JUL2005/ 17 15JUL2005/ 4	Yes moderate	possible	no	2	Recovered
046-028	70/F/W	VT: ELEVATED BLOOD PRESSURE-LACK OF EFFICACY PT: Hypertension SOC: Vascular disorders	31NOV2005/ 28 Continuing [1]	Yes moderate	unrelated	no	2	AE still present

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A/G/R: Age is in years; Gender: M = Male, F = Female; Race: W = White, B = Black, A = Asian, AI = American Indian/Alaskan Native, NH = Native Hawaiian/Pacific Islander, O = Other; Note: Patients are permitted to select more than one race.  
 Study Day is calculated as Start Date of Adverse Event - Date of First Dose + 1.  
 Duration is calculated as Stop Date of Adverse Event - Start Date of Adverse Event + 1.  
 TRAE: adverse event that has a start date on or after the first dose of randomized study medication, or occurred prior to first dose and worsens in severity during the randomized treatment period.  
 [1] Adverse event is continuing at the end of the double-blind active treatment period - Period II.  
 [2] None = No treatment is required, 1 = Hospitalization, 2 = Medication, 3 = Other non-medical treatment;

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Randomized Treatment Patient ID	A/G/R	VT: Adverse Event (Verbatim) PT: MedDRA Preferred Term SOC: System Organ Class	Start/Study Day Stop/Duration	TRAE? Severity	Relat. to Study Med.	Serious?	Treat -ment [2]	Outcome
Placebo								
079-004	59/M/W	VT: GENERAL WORSENING OF HYPERTENSION PT: Hypertension SOC: Vascular disorders	30JUN2005/ 15 Continuing [1]	Yes mild	probable	no	none	AE still present
083-038	62/F/W	VT: HEADACHE PT: Headache SOC: Nervous system disorders	28AUG2005/ 16 22AUG2005/ 3	Yes severe	possible	no	2	Recovered
087-004	78/F/W	VT: ELEVATED BP PT: Blood pressure increased SOC: Investigations	13JUN2005/ 13 Continuing [1]	No moderate	unlikely	no	2	AE still present
104-003	62/M/W	VT: WORSENING HYPERTENSION PT: Hypertension SOC: Vascular disorders	22JUL2005/ 16 22JUL2005/ 1	Yes severe	definite	no	2	Recovered

A/G/R: Age is in years; Gender: M = Male, F = Female; Race: W = White, B = Black, A = Asian, AI = American Indian/Alaskan Native, NH = Native Hawaiian/Pacific Islander, O = Other; Note: Patients are permitted to select more than one race.  
 Study Day is calculated as Start Date of Adverse Event - Date of First Dose + 1.  
 Duration is calculated as Stop Date of Adverse Event - Start Date of Adverse Event + 1.  
 TRAE: adverse event that has a start date on or after the first dose of randomized study medication, or occurred prior to first dose and worsens in severity during the randomized treatment period.  
 [1] Adverse event is continuing at the end of the double-blind active treatment period - Period II.  
 [2] None = No treatment is required, 1 = Hospitalization, 2 = Medication, 3 = Other non-medical treatment;

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**OPEN LABEL-E 302 Not on US IND**

<b>Title of Trial:</b> Efficacy and Safety of Amlodipine Used as Add-On Therapy in Moderately to Severely Hypertensive Patients Not Adequately Controlled by Olmesartan Medoxomil 20 mg Monotherapy (CS8663-A-E302)
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<b>Investigators:</b> Peter Brommer, MD, PhD, et al.	
<b>Trial Centres:</b> 47 investigative sites in Europe	
<b>Publication (reference):</b> none	
<b>Trial Period:</b> 60 weeks	<b>Phase of Development:</b> III
<b>Initiation date:</b> 28 October 2005	
<b>Completion date:</b> 22 December 2006	

**Initiation date: 28 October 2005 Completion date: 22 December 2006**

**Trial Objectives:**

**Primary Objective:** The primary objective was to demonstrate the additional antihypertensive efficacy in lowering trough sitting diastolic blood pressure (DBP) gained by adding amlodipine (AML) 5 mg or 10 mg to the treatment regimen in patients with hypertension not adequately controlled on olmesartan medoxomil (OM) 20 mg alone as assessed by conventional blood pressure (BP) measurements after 8 weeks of double-blind treatment.

**Secondary Objectives:** Secondary objectives were:

- To evaluate after 4 weeks and 8 weeks of double-blind treatment, the additional antihypertensive efficacy in trough sitting systolic blood pressure (SBP) lowering of the combinations of OM and AML compared to monotherapy with OM 20 mg using conventional BP measurements;
- To evaluate after 4 weeks of double-blind treatment, the additional antihypertensive efficacy in trough sitting DBP lowering of the combinations of OM and AML compared to monotherapy with OM 20 mg using conventional BP measurements;
- To evaluate the additional antihypertensive efficacy in DBP and SBP lowering using 24-hour ambulatory blood pressure monitoring (ABPM) after 8 weeks of double-blind treatment;
- To evaluate the number and percentage of patients in each treatment group achieving BP goal (defined as BP <140/90 mmHg, <130/80 mmHg for diabetic patients) as assessed by conventional BP measurements after 4 weeks and after 8 weeks of double-blind treatment; and

- To evaluate the safety and tolerability of the co-administration of OM and AML versus monotherapy with OM 20 mg after 8 weeks of double-blind treatment.

**Methodology:** This was a multi-centre, multi-national, randomized, double-blind, parallel-group trial 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 all patients received monotherapy with OM 20 mg. At the end of Period I (Visit 4/Week 8 [randomization visit]), only non-responders were eligible to be randomized (see Diagnosis and Main Criteria for Inclusion) and enter Period II. Patients whose BP was controlled on OM 20 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 20 mg treatment during Period I were assigned randomly in a 1:1:1 ratio to 1 of 3 treatment groups:

- OM 20 mg + placebo, • OM 20 mg + AML 5 mg, or • OM 20 mg + AML 10 mg.

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 study (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: 429 randomized patients Screened: 1519 patients Entered Monotherapy (Period I): 722 patients Randomized: 538 patients Discontinued: 13 patients Completed: 525 patients

**Sample Size:** The sample size was calculated based on the following assumptions for Period II: a treatment effect of OM + AML combination therapy versus OM monotherapy in DBP of  $\geq 3$  mmHg at the end of 8 weeks of double-blind treatment, a common standard deviation of 7.5 mmHg, 80% power, and an overall Type I error of 0.05. Thus, 121 patients per treatment group were required to complete the study. Assuming a dropout rate of 15%, at least 143 patients were to have been randomized to each treatment group, for a total of 429 patients randomized into the study.

Diagnosis and Main Criteria for Inclusion: Patients enrolled in this study included males and females  $\geq 18$  years of age, with a history of moderate to severe hypertension (SBP  $\geq 160$  mmHg and DBP  $\geq 100$  mmHg). At the screening visit, newly diagnosed hypertensive patients were required to have a mean sitting BP of  $\geq 160/100$  mmHg. There were no specific BP requirements at this visit for patients who were required to taper-off their antihypertensive medication (other than OM 20 or 40 mg). Patients being treated with either OM 20 mg or OM 40 mg had to have a previous diagnosis of moderate to severe hypertension and were required to have a mean sitting BP of  $\geq 140/90$  mmHg.

The BP requirements for entering the open-label monotherapy treatment period at Visit 2 included a mean sitting BP of  $\geq 160/100$  mmHg, a mean 24-hour DBP of  $\geq 84$  mmHg, and at least 30% of daytime DBP readings  $>90$  mmHg. Patients treated with either OM 20 mg or OM 40 mg at the beginning of the trial had to have a mean sitting BP of  $\geq 140/90$  mmHg, a mean 24-hour DBP of  $\geq 80$  mmHg, and at least 30% of daytime DBP readings  $>85$  mmHg.

To enter the double-blind treatment period at Visit 4, patients needed to be non-responders to OM 20 mg. A non-responder was defined as mean trough sitting DBP  $\geq 90$  mmHg; mean trough sitting SBP  $\geq 140$  mmHg; and mean 24-hour DBP  $\geq 80$  mmHg with at least 30% of daytime DBP readings  $>85$  mmHg. In addition to the BP requirements, patients should have met all other entry qualifications based on medical history, physical examination, electrocardiogram (ECG), and laboratory tests.

At any time during the course of the trial, a patient was withdrawn immediately for any of the following reasons:

- Major protocol violations (e.g., pregnancy) if there was a safety risk associated with continuation of the trial;
- Any change in the patient's condition which in the Investigator's opinion, for reasons of safety or ethics, precluded further participation in the trial;
- Mean sitting DBP  $>115$  mmHg;
- Mean sitting SBP  $>200$  mmHg;
- Mean 24-hour DBP as assessed by 24-hour ABPM  $>104$  mmHg; or
- Bradycardia ( $<50$  beats/min at rest).

Investigational Product and Comparator Information: Investigational Product: OM 20 mg tablets (Daiichi Sankyo Batch No. 2004 337572 01) AML 5 mg tablets (Daiichi Sankyo Batch No. 3998V04011; Pfizer Lot No. 410 203 830) AML 10 mg tablets (Daiichi Sankyo Batch No. 3998V04014; Pfizer Lot No. 410 241530) Comparator: AML 5 mg placebo tablets (Daiichi Sankyo Batch No. 3998V05002) AML 10 mg placebo tablets (Daiichi Sankyo Batch No. 3998V05003)

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the mean change from baseline (Week 8) to Week 16 (end of double-blind treatment period) using last observation carried forward (LOCF) in trough sitting DBP.

- Mean change from baseline (Week 8) to Week 12 and Week 16 (end of double-blind treatment period) without LOCF in trough sitting DBP;
- Mean change from baseline (Week 8) to Week 12 and Week 16 (end of double-blind treatment period) without LOCF and Week 16 with LOCF in trough sitting SBP;
- Mean change from baseline (Week 8) to Week 16 (end of double-blind treatment period) in daytime, nighttime, and 24-hour DBP and SBP as assessed by 24-hour ABPM; and
- Comparison of the number and percentage of patients who achieved BP goal (DBP <90 mmHg and SBP <140 mmHg for non-diabetic patients; DBP <80 mmHg and SBP <130 mmHg for diabetic patients) after 4 weeks (Week 12) and 8 weeks (Week 16) of double-blind treatment.

Safety: Safety assessments included adverse events, clinical laboratory measurements (hematology, biochemistry, and urinalysis), vital signs, physical examinations, and 12-lead ECG assessments. The primary safety variable was the adverse event profile of the combinations of OM and AML versus OM 20 mg + placebo.

Statistical Methods: The statistical analysis of the primary efficacy parameter was performed on the Full Analysis Set (Intent-to-Treat approach) using the LOCF approach for missing data. The primary analysis was repeated for the Full Analysis Set using the observed case (OC) approach and for the Per-Protocol Set (using OC). Analysis of the primary efficacy parameter was performed using an Analysis of Covariance (ANCOVA) model with treatment and pooled centre as effects and baseline DBP as a covariate. Comparisons of the combination therapies (OM 20 mg + AML 5 mg and OM 20 mg + AML 10 mg) versus monotherapy (OM 20 mg + placebo) were made using Dunnett's test to ensure an overall Type I error of 5%.

Analyses for the secondary efficacy parameters were conducted using the statistical model as described above on the Full Analysis Set (LOCF), with supportive analyses utilizing the Full Analysis Set (OC) and the Per-Protocol Set. The secondary efficacy parameters concerning the 24-hour ABPM and the conventional BP measurements were analyzed using the same ANCOVA model as used for the confirmatory analysis. Analysis of the number and percentage of patients reaching BP goal after 4 and 8 weeks of double-blind treatment was accomplished by means of the Cochran-Mantel-Haenszel test stratified by trial centre. Pooling was applied to small centers randomizing a small number of patients (i.e., <10 patients).

The incidence of treatment-emergent adverse events (TEAEs) is provided for both the monotherapy treatment period (Period I) and the double-blind treatment period (Period II). For both treatment periods, TEAEs are summarized by system organ class (SOC) and preferred term. Further, for the double-blind treatment period, summaries are provided by treatment group and in total. Adverse event summaries are similarly provided for

treatment-related TEAEs, TEAEs by maximum severity, treatment-emergent serious adverse events (SAEs), and adverse events leading to discontinuation from the trial.

**Summary:**

**Efficacy Results:**

The primary efficacy analysis demonstrated that 8 weeks of double-blind treatment with the combination of OM + AML (OM 20 mg + AML 5 mg and OM 20 mg + AML 10 mg) reduced mean sitting DBP to a significantly greater extent than treatment with OM 20 mg + placebo. The table below presents the results for mean change and adjusted mean change in sitting DBP from baseline (Week 8) to Week 16 with LOCF for the Full Analysis Set. Treatment with OM + AML combination therapy resulted in statistically significant reductions in adjusted mean sitting DBP when compared with OM 20 mg + placebo therapy: -2.7 mmHg for OM 20 mg + AML 5 mg ( $p=0.0006$ ) and -3.2 mmHg for OM 20 mg + AML 10 mg ( $P<0.0001$ )

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