CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-100

MEDICAL REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 22-100 (olmesartan medoxomil plus amlodipine; Azor)

Sponsor: Daiichi-Sankyo

Review date: 22 September 2007

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-100
DCaRP/Hinton/Karkowsky/Williams/Jagadeesh
OB/Bai
OCP/Velazquez/Madabushi

AZOR is a new fixed-dose combination product containing olmesartan medoxomil 20 or 40 mg and amlodipine besylate 5 or 10 mg, for the treatment of hypertension.

The description here is based upon the secondary review by Dr. Karkowsky (29 August 2007), and primary reviews of CMC by Dr. Shiromani (9 August 2007), pharmacology/toxicology by Dr. Jagadeesh (30 July 2007), clinical pharmacology and pharmacometrics by Dr. Velazquez and Madabushi (25 July 2007), clinical by Dr. Williams (1 August 2007), and statistics by Dr. Bai (2 July 2007).

DDMAC (Ms, Hubbard) and DMETS (Dr. Parks) raise no issues with respect to the proprietary name AZOR, and I agree. There are no outstanding issues with respect to CMC. Pediatric studies under PREA were waived, as is commonly done with combination products. Financial disclosure was adequate.

A 13-week toxicology study in rats uncovered no new safety concerns.

Pharmacokinetic properties of olmesartan medoxomil and amlodipine were unaffected by co-administration. Although the factorial study described below was performed using individual drugs, the to-be-marketed formulation was bioequivalent with respect to both components.

All combinations of olmesartan medoxomil 0, 20, and 40 mg with amlodipine besylate 0, 5, and 10 mg were compared in an 8-week, randomized, parallel study of patients with mild to moderate essential hypertension. Rates of discontinuation ran from 4% to 25%, with the highest rate on placebo and a middling 12% on the high-dose combination. Both systolic and diastolic pressure assessed at the interdosing interval decreased monotonically with the dose of either component, up to 26/16 mmHg (placebo-subtracted) at the high-dose combination. Superiority of the high-dose combination to the high doses of the components was statistically persuasive.

As shown in Dr. Karkowsky's table 5, effects of olmesartan medoxomil around the time of peak plasma levels were often less than effects at the inter-dosing interval, despite its relatively short (7 h) half-life, an effect that, perhaps, is attributable to different kinetics of the active metabolite, olmesartan. Plasma levels of amlodipine peak later, and, at all dose combinations, the blood pressure effects at the inter-dosing interval are well over half of the effects at peak plasma levels. Once-daily dosing seems entirely appropriate.

The only dose-related adverse event in evidence was edema, and the reviewers pooled various edema terms to show that edema seems more common with olmesartan medoxomil plus amlodipine 5 mg than with amlodipine 5 mg alone, but somewhat less common with olmesartan medoxomil plus amlodipine 10 mg than with amlodipine

10 mg alone. An analysis of edema as a contribution to discontinuation retains some of the same features.

I concur with the reviewers that the combination product AZOR should be approved for use in the treatment of hypertension. I concur with Dr. Karkowsky that labeling should include cautionary language regarding initiation of amlodipine in the elderly or hepatically impaired, recommending a starting dose of 2.5 in such patients, a dose that is not available in the AZOR line. (No clinical data would be necessary to get such a combination approved, however.)

Although not a factor for this action, Dr. Karkowsky raises a question about whether these data should suffice to garner AZOR a first-line indication similar to the one under imminent consideration for AVALIDE, since a severely hypertensive population and a particularly vulnerable population (e.g., those with renal impairment or the very elderly) have not been studied with AZOR. Whether this should lead to disclosure of the limitations in labeling or to denial of a first-line claim will need discussion at some point.

8/29/07

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 29, 2007

FROM: Abraham Karkowsky, M.D., Ph.D., Acting Deputy Director, Division of Cardiovascular and Renal Products HFD-110

TO: Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products HFD-110

SUBJECT: Approvable recommendation for Azor® (olmesartan medoxomil-amlodipine besylate combination product, NDA 22-100, Daichii Sankyo Pharm)

This memo supports the approvability of Azor (amlodipine besylate **[AML]** and olmesartan medoxomil **[OM]**) for the treatment of hypertension. The combination at dose of OM from 10-40 mg and AML at doses of 5 or 10 mg is clearly superior to the individual components in decreasing both systolic and diastolic blood pressure. Full approval of Azor is dependent on the resolution of several chemistry and biopharmaceutic issues. The chemistry issues are likely to be addressed within the week (a telecom is pending between the review chemists and Daichii Sankyo Pharm). The receipt of the establishment evaluation report is also still outstanding, full approval would be dependent on an acceptable inspection report.

In addition, the biopharmaceutic reviewer notes that there is insufficient information to grant waivers of the intermediate dose strengths of the combination. Consequently, full approval of all the proposed to-be-marketed dosing strengths, is dependent on receiving the necessary dissolution and other information to allow granting the bio-waiver.

Other issues that remain are labeling in nature. These issues are:

- The use of Azor as initial therapy.
- Recommendations for use of Azor for those who develop peripheral edema while on amlodipine.

Although I am in agreement that Azor® should be approved and may be used first line therapy for selected populations, the specifics in labeling and the specifics as to how to represent the currently available data in the labeling would delay approval. The

INDICATION for Azor® as initial therapy should be addressed after approval for other INDICATIONS. As the Division gains some experience with the most appropriate way to represent the blood pressure effect of combination products in labeling, the issue of initial therapy for Azor® should be revisited.

The data in support of the use of Azor® for those who develop edema on amlodipine monotherapy is far from convincing. Consequently, I am recommending that the label allow a claim for equivalent or better blood pressure control on the combination product that would allow a lower dose of amlodipine and consequently diminish the risk of edema. There is no information that adding OM to patients treated with AML who have already developed edema would speedily resolve this adverse event.

The following reviews and memos were consulted in the composition of this document.

- Medical Review by A. O. Williams, M.D., dated August 1, 2007.
- Statistical Review by Steve Bai, Ph.D., dated July 2, 2007.
- Clinical Pharmacology and Biopharmaceutics Review by Lydia Velazquez, Pharm.D., dated July 25, 2007.
- Pharmacometric review by Rajanikanth Madabushi, Ph.D., dated July 25, 2007.
- Pharmacology Review by G. Jagadeesh, Ph.D., dated July 30, 2007.
- Chemistry review by Prafull Shiromani, Ph.D., dated August 9, 2007.
- DDMAC review by Lisa Hubbard, R. Ph., DDMAC, dated April 25, 2007.
- DMETS review of trade name by Judy Park, Pharm.D, dated May 16, 2007.

The body of this memo, in general, agrees with the above reviews.

Housekeeping issues:

- There were no requests for inspection of clinical sites and none were performed.
- Dr. Williams reviewed the financial disclosure information and there did not appear to be any conflicts.
- A pediatric waiver for Azor® is appropriate, since we in general do not require pediatric studies in fixed dose combination products.
- In an initial review DMETS considered the name Azor® as acceptable. A repeat review is currently pending.

Chemistry:

The application is currently approvable, still pending are the establishment evaluation report and resolution of issues dealing with stability and labeling. Approval would be for the following dosing strengths:

- amlodipine besylate 5/olmesartan medoxomil 20,
- amlodipine besylate 10/ olmesartan medoxomil 20,
- amlodipine besylate 5/ olmesartan medoxomil 40,

- amlodipine besylate 10/ olmesartan medoxomil 40.

The combination products do not include the 2.5 mg AML dose strength in any combination with OM. In the approved current labeling for amlodipine, the 2.5 mg AML dose is recommended as the initial dose for the elderly and for patients with hepatic dysfunction. The amlodipine label also notes a decrease in clearance among those with severe heart failure. Consequently, Azor® as initial therapy should specifically exclude these more vulnerable populations.

Biopharmaceutics:

The sponsor performed 4 biopharmaceutic studies in support of this NDA. In conjunction with the one large clinical study, these five studies were the basis for PK-PD modeling.

- Study U112 was a pharmacokinetic study and described the modest deviations from linearity of pharmacokinetics (AUC) of OLM (less than linear) and AML (greater than linear) when used in combination.

- Study U111 was a bridging study demonstrating bioequivalence of the clinical trial formulations to the final market formulation.

- Study U101 described no interaction in the pharmacokinetics of AML and OM at the highest doses.

- Study E102 demonstrated the bioequivalence of three amlodipine besylate formulations from the UK (Istin®), Italy (Antacal®) and USA (Norvasc®).

- Study U110- determined that there was no food effect with the fixed dose Azor combination.

The results from the above studies adequately link the clinical trial results with the to-be-marketed formulation. The study also details the lack of a food effect.

Pharmacokinetic –Pharmacodynamic modeling.

The key findings from the pharmacokinetic and pharmacodynamic modeling are:

- Pharmacokinetic:

The pharmacokinetic properties of amlodipine were characterized by a one-compartmental model with first order absorption and time lag. The following parameters were predictors for oral clearance: gender (female gender has decrease in clearance), weight (increased clearance), age (decreased clearance), serum creatinine (small decrease in clearance) and baseline ALT (small decrease in clearance).

Olmesartan's pharmacokinetics properties were characterized by a two-compartment model with first order absorption and time lag. The following were predictors of apparent oral clearance: gender (small decrease in females), weight

(increase in clearance), serum creatinine (slight decrease) and hypertensive status (small decrease in clearance in volunteers relative to hypertensive patients).

Neither drug had a significant effect on the kinetic properties of the other.

- Pharmacodynamics:

Exposure-response relationships were derived for both drugs. For AML the models of exposure (AUC) versus sitting diastolic blood pressure were best fit by a linear model. For OM, the exposure effect on sitting diastolic blood pressure was fit to an E_{max} model. Black race was the most important covariate, decreasing the possible maximal effect of OM on diastolic blood pressure. Black race, however, increased the effect of AML on the seated diastolic blood pressure.

Pharmacology:

The effect of combination therapy compared to the individual components in a 13 week toxicity study in F344 rats with a dose ratio of 1: 10 AML: OM (maximum dose was 300 OM and 30 AML) the results showed treatment was associated with pathologic findings in the stomach, intestine, adrenal cortex and kidneys. The effects that were observed could be attributed to either the effects of AML alone or OM alone. No new or amplified toxicities were observed.

Clinical:

The approval of Azor is based on the results of a single eight week, placebo-controlled, factorial-designed study in patients with stage 1 or 2 hypertension (CS8663-A-U301). Subjects were randomized to combination doses of OM (0, 10, 20 and 40 mg/day) or AML (0, 5 or 10 mg/day). The doses were initiated at the time of enrollment without titration.

Following the 8 week randomized study the same subjects were included in an open-label continuation study for an additional 44 weeks. During the open label phase patients were started on a dose of OM 40 mg/AML 5 mg and titrated as necessary to OM 40/AML10 mg. Further blood pressure control, if necessary, was achieved with the addition of hydrochlorothiazide 12.5 and 25 mg followed by other treatments.

The primary null hypothesis for the randomized, controlled portion of the study was that there were no differences between the 6 combination therapies and the corresponding monotherapy components in the change from baseline seated diastolic blood pressure at the end of the eight week placebo-controlled period. Rejection of this hypothesis defines efficacy of the combination product. Missing values of blood pressure were imputed by a LOCF method. In order to control the overall type one error, Hommel's procedure was applied. This procedure orders all p-values and rejects the null hypothesis for each p-value where the observed p-value is less than the overall alpha divided by its rank order. In this case the rank order ranges from 1 to 6. Since the combination product compared to the monotherapy components generates two p-values per dose, only the larger p-value was used in this procedure.

The study enrolled 1960 patients into the double-blind portion of the study, approximately 162 per treatment group. Of those enrolled, 54% were male; 71% Caucasian, 25% Black. The mean age was 54 years; 20% were older than 65 years and 3% were older 75 years.

The disposition of the study subjects by treatment dose is shown below.

Table 1: Disposition of patients in study CS8663-A-U301

			Olmesartan medoxomil dose (mg)			
			0	10	20	40
Amlodipine besylate dose (mg)	0	Randomized	162 (100%)	161 (100%)	161 (100%)	162 (100%)
		Completed	121 (75%)	140 (87%)	135 (84%)	143 (88%)
		Discontinued	41 (25%)	21 (13%)	26 (16%)	19 (12%)
		Adverse event	21 (13%)	13 (8%)	17 (11%)	10 (6%)
		(lack of efficacy]	(14 (9%))	(7 (4%))	(8 (5%))	(6 (4%))
		[AE minus lack of efficacy]	[7 (4%)]	[6 (4%)]	[11 (6%)]	[4(2%)]
		Subject request	3 (2%)	2 (1%)	3 (2%)	3 (2%)
		Needed new meds	2 (1%)	0 (0%)	1 (1%)	0 (0%)
		Lost to follow up	6 (4%)	2 (1%)	3 (1%)	1 (1%)
		Investigator judgment	4 (3%)	1 (1%)	0 (0%)	1 (1%)
		Met protocol withdrawal criteria	4 (3%)	1 (1%)	1 (1%)	0 (0%)
		Other	1 (1%)	2 (1%)	1 (1%)	4 (3%)
	5	Randomized	161 (100%)	163 (100%)	161 (100%)	162 (100%)
		Completed	140 (87%)	156 (96%)	147 (92%)	143 (88%)
		Discontinued	21 (13%)	7 (4%)	14 (9%)	19 (12%)
		Adverse event	10 (6%)	0 (0%)	6 (4%)	6 (4%)
		(lack of efficacy]	(4 (3%))	(0 (0%))	(4 (3%))	(0 (0%))
		[AE minus lack of efficacy]	[6 (3%)]	[0 (0%)]	[2 (1%)]	[6(4%)]
		Subject request	7 (4%)	2 (1%)	2 (1%)	3 (2%)
		Needed new meds	1 (1%)	1 (1%)	0 (0%)	0 (0%)
		Lost to follow up	3 (2%)	1 (1%)	3 (2%)	6 (4%)
		Investigator judgment	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Met protocol withdrawal criteria	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Other	0 (0%)	3 (2%)	2 (1%)	4 (3%)
	10	Randomized	163 (100%)	162 (100%)	160 (100%)	162 (100%)
		Completed	144 (88%)	134 (83%)	143 (89%)	143 (88%)
		Discontinued	19 (12%)	28 (17%)	17 (11%)	19 (12%)
		Adverse event	10 (6%)	11 (7%)	3 (2%)	9 (6%)
		(lack of efficacy]	(2 (1%))	(0 (0%))	(0 (0%))	(0 (0%))
		[AE minus lack of efficacy]	[8 (5%)]	[11 (7%)]	[3(2%)]	[9 (6%)]
		Subject request	4 (3%)	6 (4%)	2 (1%)	3 (2%)
		Needed new meds	0 (0%)	0 (0%)	1 (1%)	1 (1%)
		Lost to follow up	1 (1%)	3 (2%)	5 (3%)	3 (2%)
		Investigator judgment	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Met protocol withdrawal criteria	0 (0%)	0 (0%)	0 (0%)	2 (1%)
		Other	4 (3%)	8 (5%)	6 (4%)	1 (1%)

Completion rate in the combined therapy was comparable to its individual components. Excluding lack of efficacy (mostly in the placebo group) there were no differences in the adverse event profile, suggesting that over the 8 week period there was no strong safety signal (in this modest data base).

The effect of treatment on systolic and diastolic blood pressure at the end of the study is shown below. The effects on blood pressure were largely present by the first measurement (2 weeks, data not shown here). Consequently, it seems reasonable to recommend dose increments at 2 week intervals.

Table 2: Placebo-subtracted mean change in sitting DBP and sitting SBP after 8 weeks of therapy

		Seated diastolic blood pressure					Seated systolic blood pressure			
		Olmesartan medoxomil dose (mg)					Olmesartan medoxomil dose (mg)			
		0	10	20	40		0	10	20	40
Amlodipine besylate dose (mg)	0	---	-5.3	-6.4	-7.4		----	-8.0	-9.9	-12.6
	5	-6.5	-10.8	-11.1	-12.8		-11.5	-19.7	-19.8	-22.3
	10	-9.9	-13.2	-14.2	-15.9		-16.1	-21.9	-25.3	-25.6

All comparisons of the combination product to the individual components were statistically significant at a p-value of < 0.0005. The combination products are, therefore, superior to the individual components.

The most appropriate representation of the data for describing the risk and benefits of the use as Azor® as initial therapy is still being refined. The sponsor, however, submitted a categorical assessment based on treatment blood pressure goals as currently described in JNC7. The response rates for the combination therapy were numerically higher than those for the component monotherapies.

Table 3: Number who achieve goal divided by number vulnerable (%)

		Olmesartan medoxomil dose (mg)			
		0	10	20	40
Amlodipine besylate dose (mg)	0	14/160 (9%)	32/160 (20%)	42/159 (26%)	38/160 (36%)
	5	34/161(21%)	57/163 (35%)	68/160 (43%)	80/157 (51%)
	10	53/163 (33%)	79/161 (49%)	84/158 (53%)	79/161 (49%)

Blood pressure treatment goals are defined as a BP of < 140/90 or < 130/80 for diabetics.

The comparison between the combination product and the individual monotherapies for the achievement of goal blood pressure is shown below. As with absolute blood pressure change there was a contribution of each of the monotherapies to the effect of the combination therapy.

Table 4: Comparison of percent achieving goal of combination therapy versus monotherapies

Comparisons		N		Achieved goal		p-value	Adj. p-value
		Treat #1	Treat #2	Treat #1	Treat #2		
OM 10/AML5	versus OM 10	163	160	57 (35%)	32 (20%)	0.0009	
	AML 5		161		34 (21%)	0.0023	0.0045
OM 20/AML5	versus OM 20	160	159	68 (43%)	42 (26%)	0.0009	0.0035
	AML 5		161		34 (21%)	<0.0001	
OM 40/AML5	versus OM 40	157	160	80 (51%)	58 (36%)	0.0045	0.0045
	AML 5		161		34 (21%)	<0.0001	
OM 10/AML10	versus OM 10	161	160	79 (49%)	32 (20%)	<0.0001	
	AML 10		163		53 (33%)	0.0012	0.0044
OM 20/AML10	versus OM 20	158	159	84 (53%)	42 (26%)	<0.0001	
	AML 10		163		53 (33%)	<0.0001	0.0002
OM 40/AML10	versus OM 40	161	160	79 (49%)	58 (36%)	0.0033	0.0045
	AML 10		163		53 (33%)	0.0004	

Blood pressure treatment goals are defined as a BP of < 140/90 or < 130/80 for diabetics.
Derived from the individual one-sided p-value using a Cochran-Mantel Haenszel test stratified by age group and diabetic status comparing the combination product to the individual monotherapies.
Adjusted p-value via Hommel's procedure against the larger of the two p-values.

Peak effects:

In a cohort of patients (N=617), two peak measurements corresponding to olmesartan medoxomil's peak (0.5 to 2 hours post dose) and amlodipine besylate's peak (4-10 hours post dose). The trough and peak effects are shown below. The excursion of effects over the dosing interval is acceptable.

Table 5: Peak and trough measurements of combination therapy and monotherapies (mm Hg)

			Olmesartan medoxomil dose (mg)			
			0	10	20	40
Amlodipine besylate dose (mg)	0	Trough	-----	-7.2	-8.6	-8.9
		Pk_1 (0.5-2 hours	-----	-4.8	-8.5	-9.2
		$Peak_2$ (4-10 hours)	------	-6.3	-8.8	-12.3
	5	Trough	-8.1	-15.6	-12.9	-14.1
		Pk_1 (0.5-2 hours	-14.6	-14.6	-11.5	-14.0
		$Peak_2$ (4-10 hours)	-18.0	-18.0	-15.4	-16.4
	10	Trough	-12.8	-16.0	-16.3	-17.9
		Pk_1 (0.5-2 hours	-9.6	-14.6	-15.6	-16.9
		$Peak_2$ (4-10 hours))	-11.8	-18.0	-17.8	-20.9

No information is available as to orthostatic effects at either peak or trough.

Safety double-blind phase:

- Edema-

During each study visit the subject was queried as to the presence and severity of peripheral edema and the severity of edema.

Edema was graded as follows

- Mild pitting, slight indentation
- Moderate pitting, slight indentation
- Deep pitting, indentation remains for a short time, leg looks swollen
- Deep pitting, leg very swollen.

Edema included the preferred terms of "edema", "edema peripheral", "pitting edema", "generalized edema" and "localized edema". The reported incidence of edema is shown below.

Table 6; Crude rates of reporting of edema number (%)

		Olmesartan medoxomil dose (mg)			
		0	10	20	40
Amlodipine besylate dose (mg)	0	20 (12%)	23 (14%)	16 (10%)	30 (18.5%)
	5	21 (13%)	34 (21%)	29 (18%)	30 (19%)
	10	60 (37%)	43 (27%)	41 (26%)	38 (24%)

Although there was an apparent decrease in edema rate with olmesartan in conjunction with the amlodipine 10 mg. There was an apparent increase in edema when olmesartan was used in conjunction with the 5 mg dose. Consequently, it is difficult to conclude that the addition of OM to AML alters the risk of edema.

Edema shift table.

A shift table for increasing edema is shown below. The shift table is consistent with the overall event rates of edema. The co-administration of olmesartan with 10 mg amlodipine seems to somewhat decrease the incidence of edema. The administration of olmesartan with 5 mg amlodipine seems to increase the rate of edema.

Table 7: Shift table for edema increase

			Olmesartan medoxomil dose (mg)			
			0	10	20	40
Amlodipine besylate dose (mg)	0	Shift up 1	12 (7%)	18 (11%)	7 (4.3%)	14 (9%)
		Shift up 2	1 (<1%)	4 (2.5%)	1 (< 1%)	6 (4%)
		Shift up 3	0	0	0	0
		Shift up > 3	0	0	0	0
	5	Shift up 1	14 (9%)	27 (17%)	19 (12%)	21 (13%)
		Shift up 2	2 (1%)	0	2 (1%)	4 (3%)
		Shift up 3	0	1 (< 1%)	1 (<1%)	0
		Shift up > 3	0	1 (< 1%)	1 (<1%)	0
	10	Shift up 1	32 (22%)	26 (16%)	23 (14%)	24 (15%)
		Shift up 2	9 (6%)	8 (5%)	9 (6%)	8 (5%)
		Shift up 3	4 (3%)	6 (4%)	1 (< 1%)	0
		Shift up > 3	6 (4%)	6 (4%)	2 (1%)	1 (<1%)

Edema leading to discontinuation:

The numbers of subjects who discontinued with edema as part of the reason for this discontinuation is shown below.

Table 8: Number of subjects with edema as contributory to discontinuation:

		Olmesartan medoxomil dose (mg)			
		0	10	20	40
Amlodipine besylate dose (mg)	0	0	2	1	2
	5	1	3	5	3
	10	11	12	3	6

In summary, there is unconvincing evidence that olmesartan diminishes the risk of edema among patients who are taking amlodipine. There are numerically fewer edema events with the high dose monotherapy amlodipine dose when OM is added than with monotherapy AML alone There are however more edema events with the lower dose AML when OM is added as combination therapy.

Laboratory

There was a greater decrease in hemoglobin (shown) and hematocrit (not shown) in the combination product compared to either component. The other changes in the combination therapy labs can usually be attributed to either monotherapy components.

Table 9: Lab values of interest comparing combination therapy to monotherapies (mean ± SD) N~160 patients/group:

			Olmesartan medoxomil dose (mg)			
			0	10	20	40
Amlodipine besylate dose (mg)	0	Hgb	0.17 ± 0.7	0.03 ± 0.7	0.02 ± 0.7	-0.07 ± 0.8
		Platelets	0.05 ±38	3.1± 31	3.3 ± 36	6.2 ± 39
		ALT	0.6 ± 4.9	0.8 ± 8.9	2.54 ± 16.4	1.3 ± 6.3
		AST	0.5 ± 4.0	0.5 ± 12.0	1.0 ± 9.7	0.5 ± 5.5
	5	Hgb	0.1 ± 0.7	-0.14 ± 0.6	-0.14 ± 0.7	-0.21± 0.7
		Platelets	10.2 ± 30	12 ± 31	12.7 ± 31	12.7 ± 37
		ALT	1.1 ± 5.6	0.8 ± 6.3	3.0 ± 31	0.6 ± 9.4
		AST	0.9 ± 5.1	-0.1 ± 4.8	2.1 ± 22.9	0.6 ± 6.7
	10	Hgb	0.07 ± 0.8	-0.21 ± 0.8	-0.21 ± 0.7	-0.37 ± 0.7*
		Platelets	22.1 ± 32	17.2 ± 39	20.8 ± 37	19 ±34
		ALT	0.7 ± 7.0	2.1 ± 15.8	0.8 ± 9.1	1.4 ± 8.4
		AST	0.6 ± 5.6	0.9 ± 11.5	0.9 ± 8.5	0.6 5.1

Long-term safety

Following the 8 week, double-blind study subjects were enrolled in an open label study. Subjects were initiated on therapy at a dose of olmesartan 40 mg/amlodipine 5 mg. They were sequentially advanced in dose to olmesartan 40/amlodipine 10, followed by the addition of 12.5 and then 25 mg daily of hydrochlorothiazide then followed by the addition of other medications based on the need to achieve goal blood pressure.

The cut-off date for the study was defined so that all subjects who continued had received treatment for at least 26 weeks. The mean duration of exposure during the open-label portion was 215 days. Of the 1684 subjects entering the open-label portion of the study 228 prematurely discontinued. The reason per sponsor for discontinuation is shown below.

Table 10: Disposition of subjects during open-label treatment

Enrolled	1684	
Discontinued	228	
Adverse events		67
Subject request		70
Requirement for restricted meds		6
Lost to follow-up		40
Investigator's judgment		13
Treatment terminated by protocol		0
Met withdrawal criteria by protocol		1
Other		31
Lack of efficacy		19

Adverse events:

With respect to the adverse events reported during the open-label portion of the study edema was reported in 20% of those enrolled, dizziness in 6%, headache in 4% and hypotension in 2% of those enrolled.

Discussion-labeling issues:
Initial therapy:

The sponsor requests initial therapy for use of Azor® at a dose of olmesartan 20/amlodipine 5 mg for subjects who require a blood pressure effect b(4)
The set of information that supports the use of Azor® as initial therapy, however, differs from the algorithm suggested by a recent advisory committee meeting (April 18, 2007) that considered use of Avalide® as initial therapy.

The deliberations of that advisory committee concluded that Avalide® (Irbesartan with hydrochlorothiazide) be approved as initial therapy, with the label mute as to the degree of hypertension that would trigger the recommended combination product as initial therapy. Graphical representations of the likelihood to achieve certain cut-off blood pressures (e.g. systolic blood pressure of < 140, < 130 and < 120 mm Hg; diastolic blood pressures of < 90 or < 80) were to be included in the label to allow the prescribing physician the latitude as to when to initiate treatment with combination therapy. This guidance would allow the physician to alter decisions as the ever-changing goals for blood pressure evolve.

The advisory committee was concerned regarding the potential safety consequences of the initial use of combination therapy in selected populations. In particular, they expressed some concern for combination product use as initial therapy in patients with renal dysfunction and in the extremes of the elderly. The database for Avalide®, however, was reasonable rich in these populations. In addition, Avalide® was studied in severely hypertensive population (DBP > 120 mm Hg) as initial therapy (with a single dose titration step) and there were no excessive adverse events due to aggressive therapy. Consequently the Avalide® program as a whole was sufficiently comforting that aggressive use as initial therapy in a wide population base would not result in harm.

The case to be made for Azor® as initial therapy is substantially weaker than for Avalide®. There is no doubt that a lower dose of amlodipine plus olmesartan that was studied was superior to the highest approved doses of each of the combinations (see table 2) in a generally healthy population. As such, the initiation of therapy for a selected relatively healthy population is a reasonable option. There is some inherent additional risk in aggressively using more than one medication. Neither the benefit on outcomes nor the risk on unanticipated adverse events can be accurately established with the short term studies as generally performed for combination products.

What is missing from the Azor® database is the safety in populations that might be particularly vulnerable for excessive hypotensive effects than for the healthy population that was studied in the factorial study.

In contradistinction to Avalide® there is no information on the safety or efficacy of Azor® in a severely hypertensive population. The only factorial designed study did not include patients with BP $\geq$ 120 mm Hg. The lack of an empirical database in the extremes

of doses of OM. The proper role for the use of Azor® appears to allow a decrease in dose of amlodipine while still maintaining the blood pressure effects.

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Abraham Karkowsky
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MEDICAL OFFICER
Secondary review

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CLINICAL REVIEW

Application Type	NDA
Submission Number	22-100
Submission Code	000
Letter Date	December 21, 2005
Stamp Date	December 23, 2005
PDUFA Goal Date	October 21, 2006
Reviewer's Name	A.O.Williams, M.D.
Review Completion Date	August 1, 2007

Established Names	Amlodipine besylate and Olmesartan Medoxomil
Trade Name	AZOR
Therapeutic Class	CCB and ARB
Applicant	Daichii Sankyo Pharma
Priority Designation	S
Formulation	Combination Tablet
Dosing Regimen	5/20, 10/20, 5/40, and 10/40 mg
Indications	Treatment of Hypertension
Intended Population	Patients with Essential Hypertension not controlled/reaching "goals" after antihypertensive monotherapy

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1 EXECUTIVE SUMMARY

Blood pressure control to goal should be the guide to the treatment of hypertension and should be achieved with a drug combination when monotherapy is ineffective. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7), issued under the auspices of the National Heart, Lung and Blood Institute (NHLBI), recommends the addition of a second drug when the use of a single drug is inadequate and fails to achieve the blood pressure goal. Specifically, the JNC7 guidelines recommend that when blood pressure is 20/10 mmHg above goal, consideration should be given to initiating therapy with 2 drugs. The JNC7 guidelines also recommend the use of drug combinations as initial therapy for Stage 2 hypertension (systolic blood pressure $\geq$60 mmHg or diastolic blood pressure $\geq$100 mmHg) to avoid drug titration and multiple patient visits. The FDA has not approved these specific guidelines that are suggestions from the NHLBI of the NIH.

However, based on these internationally recognized guidelines and the need to facilitate enhanced compliance and blood pressure control, one tablet containing a combination of olmesartan medoxomil and amlodipine has been developed by the sponsor for the treatment of mild to severe hypertension. The data from the clinical development of combined olmesartan medoxomil and amlodipine form the basis of this clinical review.

Concomitant use of ARBs and CCBs is a rational choice for combination antihypertensive therapy. These two classes of agents have different modes of action and should provide at least an additive blood pressure-lowering effect, with the combination being more effective than either monotherapy component. Studies are ongoing in Europe

to demonstrate these additive blood pressure lowering effects (E 301 and E 303). The use of a single tablet in a fixed-dose combination of olmesartan medoxomil and amlodipine is expected to help patients reach their target blood pressure goals in a more convenient and consistent manner and increase patient compliance.

The co-administered doses selected for olmesartan medoxomil and amlodipine were based on the approved dose ranges specified within the respective package inserts. The 10 mg dose of olmesartan medoxomil was however used in this study because it has been approved for use in European countries. The doses selected represent the combined recommended dosage range internationally (Table 2 and Section 2.1). This NDA application refers to reports of investigations contained in Pfizer's NDA 19-787 (Norvasc/amlodipine besylate) and the findings for safety and efficacy for information in Daiichi-Sankyo's application for NDA 21-286 (Benicar/olmesartan medoxomil). AZOR (amlodipine and olmesartan) is a fixed combination of amlodipine and valsartan.

The data presented in this NDA reflect exposure to AZOR in more than 1600 patients including more than 1000 exposed for at least 6 months and more than 700 exposed for 1 year. AZOR was studied in one placebo-controlled factorial trial. The population had a mean age of 54 years and included approximately 55% males. Seventy-one percent were Caucasian and 25% were Black. Patients received doses ranging from 5/20 mg to 10/40 mg orally once daily. Both components of AZOR have been approved by the FDA under NDA 19-787 for amlodipine besylate and NDA 21-286 for Olmesartan medoxomil.

Data from one completed study, Protocols E 302 and an ongoing protocol E 303, both not in the US IND, were also referred to in this submission. Where applicable these data were used for safety evaluation. Both studies evaluated the efficacy add on effects of the component monotherapies on one another and safety (Section 1.3). In addition, data from 13 clinical pharmacology studies are also submitted (Section 4.2 in this review).

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 two indications:

1) -AZOR is indicated either alone or in combination with other antihypertensive agents for the treatment of hypertension

2) -AZOR is indicated for initial therapy in patients with hypertension requiring a blood pressure reduction

The first indication is recommended for approval but not the second indication.

This reviewer recommends that the combination tablet (AZOR) of amlodipine besylate and olmesartan medoxomil be approved for the treatment of mild to severe essential hypertension. The pivotal study demonstrated statistically significant lowering of seated diastolic and systolic blood pressure compared to the corresponding monotherapy components. This is in compliance with regulatory criteria for approval of combination tablet.

include elevated liver enzymes and platelets. For initial therapy the risk benefit regarding safety concerns having been evaluated and compared to monotherapy cannot be justified.

Furthermore, to institute AZOR as initial therapy for reduction of blood pressure by , there should be compelling evidence that the patients" will not reach their goals on monotherapy. The use of goals for efficacy and for dose selection has not been approved by the Agency. Assuming that a population can be defined, the patients may be a subset of hypertensive patients that may fall into the category of "refractory hypertension". If that is the case this reviewer is of the opinion that this subset will need to be studied. So far, there are no studies of AZOR in patients with renal or hepatic impairment. b(4)

While it could be argued that drug combinations could be used for initial therapy to avoid drug titration and multiple patient visits, adequate safety data should be a pre-requisite for exposing a drug to the population at risk. Therefore studies that will include enriched populations at risk is strongly recommended. For example, of the total number of elderly or black subjects in the current double-blind study of AZOR are considered inadequate. Of the total subjects randomized, 20% (384/1940) were 65 years of age or older and 3% (62/1940) were 75 years or older; 25% (481/1940) were black patients and the other ethnic populations constituted 4%. Even though the percentages of blacks are relatively high, numerically a total of less than 500 black patients and less than 90 patients from other ethnic groups is considered inadequate by this reviewer.

RECOMMENDATIONS ON POSTMARKETING ACTIONS

1.2.1 Risk Management Activity

The specific risk management activities recommended here is management of edema and hypotension particularly in those patients exposed to high doses of the combination tablet particularly 40/10 (Olmesartan/Amlodipine) and in other combination that has amlodipine 10 mg. These will be in the warnings section of

the label and are already in the package inserts for the individual component drugs.

For this study, the investigator was required to ascertain from the patient whether any edema was present and to specifically examine the patient looking for the presence of edema at each visit. It is evident from the relative frequencies of edema found in this study that this approach resulted in a much higher frequency of edema reported both on the specific CRF and as a TEAE compared to previous studies using the same therapies. In this study, the frequency of edema reported as a treatment emerging adverse event (TEAE) for placebo, amlodipine besylate, and olmesartan medoxomil was considerably higher compared to the frequencies reported in their respective package inserts. Edema is a well recognized adverse event in patients exposed to amlodipine. The relatively increased frequency of edema observed in this study is noteworthy for both drugs. This may either be the real frequency of edema in patients exposed to both drugs or the methodology for reporting it has harvested more cases. In any event, the question which has to be addressed is whether previous data on edema for both drugs reflect underreporting due to criteria adopted for ascertainment and recording on CRF or whether this is the true frequency s documented for this study. It is recommended that this proactive approach and methodology should be adopted prospectively in a defined post-marketing surveillance study of the combined tablet and the individual component.

This reviewer also suggests that a systematic re-evaluation of CRFs of some previously approved selected anti-hypertensive drugs may resolve this issue. This may lead to amendment of label regarding frequency of edema in this class of drugs. The reviewer recommends that subsequent studies and protocols on anti-hypertensive drugs should

adopt this proactive approach to ascertain the true relative frequencies of edema, particularly CCBs and ARBs. Regardless of the credible frequency data, addition of olmesartan to increasing dose of amlodipine in the combined tablet reduced the frequency of edema (Section 7; Tables 129 – 130 and Figure 14).

According to the sponsor, the two major laboratory abnormalities that appeared to have changed as a result of treatment include elevation in liver transaminases at high dose and platelet count at all doses of the combination tablet. Other laboratory abnormalities that are statistically significant are summarized in Table 30 of this review. The mean platelet counts significantly increased in nearly 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. Although these observed increases in platelet counts were not associated with any identifiable clinical feature or syndrome it is recommended that post marketing vigilance should be instituted for both hepatotoxicity and thrombocytosis. It is also recommended that post marketing vigilance of the other abnormal laboratory parameters be encouraged.

1.2.2 Required phase 4 commitments

There are no phase 4 requirements recommended.

1.2.3 Other phase 4 requests

There are no other phase 4 requirements recommended.

1.3 Summary of Clinical findings

1.3.1 Brief Overview of Clinical Program

The submitted NDA application is for an immediate release tablet formulation that is to be taken once daily orally designed to deliver 5/20, 10/20, 5/40, and 10/40 mg of amlodipine besylate and Olmesartan medoxomil, respectively. Both components have been previously approved by the Agency under two separate NDAs.

For this application, there was only one double-blind, placebo controlled, factorial, pivotal study with Periods I and II being the wash out and double blind study periods and Period III being the open label extension of period II. In addition data from two other clinical protocols (E302 and E303) that are not in the US IND were also submitted. They were not reviewed in depth as they did not contribute to the overall evaluation of this NDA except for safety data.

The clinical pharmacology submission includes 13 studies of which 7 studies had been used for previous formulations and are considered not relevant to the current application. The remaining 6 studies deal with dose-proportionality (study U112), bioequivalence (study U111), drug interaction between amlodipine and olmesartan (study U101), bioavailability of 3 amlodipine formulations (study E102) used in their phase III trial (study 301), pharmacometrics report from the phase III study U301, and food effect (study U110) study conducted in healthy volunteers (See Clinical pharmacology review by Dr. Velaquez). (Section 4.2).

The titles of the two additional clinical studies that are not in the US INDs are as follows:

(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. Completed but Not under the US IND.

(CS 8663 – A-E303) Protocol Title: 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. Ongoing study in Europe, and not under the US IND.

The Protocol and Overall Trial Design and Plan of Pivotal study CS 8663-A-U301

The pivotal study was based on Sankyo protocol CS8663-A-U301,(Period II) titled **"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."**

This was a 52-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group, factorial trial, consisting of 3 treatment periods (Section 6.1.3). The rationale for the study design for each period attempted to elucidate issues concerning combination therapy that may occur in clinical practice. Table 1 presents the disposition of the subjects.

While Period I was the washout period, the 8-week duration for blinded Period II was sufficient to maximize the therapeutic potential of each dosing arm of the study. Period II assessed the efficacy gained in hypertension management by comparing the respective monotherapy components with the same dose equivalent as co-administered components. Period II assessed the respective monotherapy component with placebo and comparisons were carried out between combination therapy and monotherapy (Tables 2-5).

Period I Week -2 to Day 1	Period II Day 1 to Week 8	Period III Week 8 to Week 52
Washout	**Treatment arms:** Placebo OM 10 mg OM 20 mg OM 40 mg AML 5 mg AML 10 mg OM 10 mg + AML 5 mg OM 20 mg +AML 5 mg OM 40 mg + AML 5 mg OM 10 mg + AML 10 mg OM 20 mg + AML 10 mg OM 40 mg + AML 10 mg	**Starting dose:** OM 40 mg + AML 5 mg Treat-to-goal sequence: OM 40 mg + AML 10 mg **Then:** OM 40 mg + AML 10 mg + HCTZ 12.5 mg **Then:** OM 40 mg + AML 10 mg + HCTZ 25 mg Back-titration available
~2 weeks	Double-Blind 8 weeks	Open-Label 44 weeks

Of the 1940 patients in the All Randomized Patient population, 1054 (54.3%) were male, 1385 (71.4%) were Caucasian, 481 (24.8%) were Black, 36 (1.9%) were Asian, and 48

(2.5%) were all other races (including Other, American Indian/Alaskan Native, and Native Hawaiian/Pacific Islander). The mean age was 54.0 years. A total of 384 (19.8%) patients were ≥65 years of age.

Weight, height, and BMI were also similar for the treatment groups, with no statistically significant differences among the treatment groups for these baseline characteristics. Mean weight was 95.1 kg, mean height was 170.1 cm, and mean BMI was 33.5 kg/m^2. A total of 64.7% of patients were obese (BMI =30 kg/m^2), and 13.5% of patients had diabetes.

Approximately one-third of patients were not taking an antihypertensive medication at the time of screening [666 (34.3%)].

Evidence of some peripheral edema was present at baseline in 264 (13.6%) patients. Of those patients with peripheral edema, 215 (11.1%) had mild pitting edema, 38 (2.0%) had moderate pitting edema, and 11 (0.6%) had deep pitting-minor edema. No patients had deep pitting-major edema at baseline. In addition, 37 of the 264 patients with peripheral edema at baseline washed out of amlodipine prior to randomization.

A total of 4234 patients were screened of which 2294 were not enrolled for randomization. The study was planned for 1896 randomized patients but 1940 patients were randomized. The treatment groups were comparable with respect to demographics, with no statistically significant differences among the treatment groups..
The major reasons for discontinuation prior to randomization was that 42.5% did not meet inclusion/exclusion criteria. Of the 251 patients who discontinued during the double blind period, about 45% withdrew due to adverse events. One hundred and fourteen (5.9% of the 1940 randomized) patients withdrew due to adverse events, 43 (2.2%) patients requested to be removed from the study, 37 (1.9%) patients were lost to follow up, 8 (0.4%) patients met the study withdrawal criteria , 7 (0.4%) patients were removed from the study for taking restricted medications, 6 (0.3%) patients were removed from the study by the investigator and 36 (1.9%) patients were removed from the study for other reasons. Of the 114 patients discontinued due to an adverse event, 43 showed lack of efficacy which should not have been categorized as adverse event. However the placebo group had the greatest percentage of patients with lack of efficacy that was categorized as adverse events. Only two patients from the combination group were withdrawn due to lack of efficacy and both were receiving OM20/AML 5. There were no significant differences among the 12 treatment groups (Table 1) regarding specific reasons for discontinuation. The disposition of patients is presented in Table 2.

Table 1: Showing 12 treatment arms and number of patients per cell in factorial study. NDA 22-100

		Amlodipine		
		0mg	5mg	10mg
Olmesartan	0mg	1N=162	5 N=161	9 N=163
	10mg	2 N=161	6 N=163	10 N=162
	20mg	3 N=161	7 N=161	11 N=160
	40mg	4 N=162	8 N=162	12 N=162

In the analysis of both SeDBP and SeSBP over time, the greatest mean reductions (70% to 80% of the maximum effect) in blood pressure occurred between baseline and Week 2. At Week 4, continued slight reductions were observed and plateaued in most of the treatment groups (Figures 3 and 4). The peak to trough ratio was between 70% and 75%.

Period III was the open label extension of Period II that had all patients initially assigned to OM 40 mg + AML 5 mg. Patients were titrated to goal as proposed by JNC7 by maximizing the therapeutic potential of the combination OM + AML (i.e., OM 40 mg + AML 10 mg). Patients not reaching goal were offered HCTZ (i.e., 12.5 mg then 25 mg) for additional therapeutic benefit. The treatment scheme was developed to assess long-term efficacy and safety.

Table 2: Patient disposition -NDA 22100-Period II- Double blind

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[1]	14 (8.6)	7 (4.3)	8 (5.0)	6 (3.7)	4 (2.5)	2 (1.2)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject Request	3 (1.9)	2 (1.2)	3 (1.9)	3 (1.9)	7 (4.3)	4 (2.5)	2 (1.2)	5 (3.1)	3 (1.9)	6 (3.7)	2 (1.3)	3 (1.9)
Required Restricted Medications	2 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
Lost to Follow-up	6 (3.7)	2 (1.2)	3 (1.9)	1 (0.6)	3 (1.9)	1 (0.6)	1 (0.6)	3 (1.9)	6 (3.7)	3 (1.9)	5 (3.1)	3 (1.9)
Investigator Judgment	4 (2.5)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Met Protocol Withdrawal Criteria	4 (2.5)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)
Other	1 (0.6)	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)

[1] 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

Table 2a: Summary of patients Period II (D-B) and Period III- Open Label

Number of Patients Receiving Study Treatment
All Patients

Treatment	Cohort: Double-blind Treatment Period	Cohort: Open-label Treatment Period	Phase I Studies
Placebo	162	0	0
OM10	161	0	0
OM20	161	0	0
OM40	162	0	28
AML5	161	0	0
AML10	163	0	41
OM10/AML5	163	0	60
OM10/AML10	162	0	29
OM20/AML5	161	0	29
OM20/AML10	160	0	29
OM40/AML5	162	1678	60
OM40/AML10	162	1100	280
OM40/AML10/HCTZ12.5	0	732	0
OM40/AML10/HCTZ25	0	434	0
Total	1940	1684	358

1.3.2 Efficacy

The primary objective of this NDA was to determine if co-administration of olmesartan medoxomil (OM) and amlodipine (AML) had a clinically significant benefit versus the respective monotherapy components in controlling blood pressure in patients with mild to severe hypertension.

Primary efficacy

The primary efficacy variable was the mean change in SeDBP from baseline to the end of the double blind treatment period (Period II). If a patient withdrew from the factorial study prior to week 8, the LOCF during the randomized double blind treatment period was used for the primary efficacy analysis. Table 2 shows the 12 treatment arms.

Efficacy evaluations were based on the ITT population. Since less than 90% of the ITT population met the per-protocol definition (determined prior to database lock and unblinding), a per-protocol analysis was also performed on the following primary and secondary efficacy variables:

- Change from baseline in SeDBP and SeSBP at Weeks 2, 4, 6, and 8 (with and without LOCF). (Figures 3 and 4)
- Change from baseline in SeSBP at the end of Period II with LOCF was one of the other secondary efficacy variables.
  Other secondary efficacy variables in Period II included the following:
- Change from baseline in SeDBP and SeSBP at weeks 2,4,6, and 8 without LOCF(Figures 3 and 4)
- Proportion of patients who reached BP goals at weeks 2, 4, 6, and 8 without LOCF and week 8 with LOCF.
- **Change from baseline to week 8 (with LOCF) in inflammatory markers including hsCRP, metallopreteases 2 and 9, tPA, PAI-1 and Microalbuminuria.**

The intention of the last objective (boldened) was really to perform exploratory evaluation of various doses of OM + AML on surrogate markers of cardiovascular risk (high-sensitivity C-reactive protein [hsCRP], metalloproteases, tissue plasminogen activator [tPA], plasminogen activator inhibitor-1 [PAI-1], and microalbuminuria).

Efficacy Results (Tables 3-5)

The primary efficacy analysis demonstrated that after 8 weeks of double-blind treatment, the groups treated with any combination of olmesartan medoxomil and amlodipine had greater mean reductions in SeDBP compared to the groups treated with the corresponding monotherapy components. Across the 6 combination therapies evaluated, the treatment differences in mean SeDBP between the combination treatment groups and their respective monotherapy components were all highly statistically significant ($p=0.0004$ for OM 10 mg + AML 10 mg vs. AML 10 mg, and $p<0.0001$ for the rest of the comparisons). With combination treatment, mean SeDBP was reduced by an additional 3.3 to 8.5 mmHg compared to the respective monotherapy components (Tables 3 - 5).

Across all treatment groups, increases in dose were associated with progressively greater mean reductions in SeDBP from baseline to Week 8 with LOCF. All of the combination treatments achieved numerically greater mean reductions in SeDBP than the highest doses of any of the monotherapy treatments. 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 greatest within-treatment mean reductions in SeDBP were observed with the highest combination doses (-19.0 mmHg for the OM 40 mg + AML 10 mg group and -17.0 mmHg for the OM 20 mg + AML 10 mg group)(Table 3 and Figure 1). (Table 5)
The placebo-subtracted adjusted mean reduction in SeDBP is presented in Table 2.

Table 3: Placebo-adjusted LS mean reduction in SeDBP from baseline to wk 8 with LOCF – ITT-

		Olmesartan			
		Placebo	10 mg	20 mg	40 mg
Amlodipine					
	0	---	-5.3	-6.4	-7.4
	5mg	-6.5	-10.8	-11.1	-12.8
	10mg	-9.9	-13.2	-14.2	-15.9

Table 4: Mean Change in seated Diastolic BP from baseline to wk 8 with LOCF- ITT- Combination versus Monotherapy comparisons- Pivotal Study

Table 3: Mean Change in Seated Diastolic Blood Pressure (mmHg) from Baseline to Week 8 with LOCF – Combination Therapy Versus Monotherapy Comparisons – Pivotal Study (Double-Blind Treatment Period) – Intent-to-Treat Population

Treatment Comparison			N		LS Mean (SE)		Difference (Tmt 1 – Tmt 2)			
Tmt 1	vs.	Tmt 2	Tmt 1	Tmt 2	Tmt 1	Tmt 2	LS Mean (SE)	95% CI	p-value	Adjusted p-value
OM10/AML5	vs.	OM10	163	160	-14.3 (0.74)	-8.8 (0.75)	-5.5 (0.99)	(-7.4 , -3.5)	<0.0001	
	vs.	AML5		161		-10.0 (0.75)	-4.3 (0.99)	(-6.3 , -2.4)	<0.0001	<0.0001
OM20/AML5	vs.	OM20	160	159	-14.6 (0.75)	-9.9 (0.75)	-4.7 (1.00)	(-6.6 , -2.7)	<0.0001	
	vs.	AML5		161		-10.0 (0.75)	-4.6 (0.99)	(-6.5 , -2.6)	<0.0001	<0.0001
OM40/AML5	vs.	OM40	157	160	-16.3 (0.76)	-10.9 (0.75)	-5.4 (1.00)	(-7.3 , -3.4)	<0.0001	<0.0001
	vs.	AML5		161		-10.0 (0.75)	-6.3 (1.00)	(-8.2 , -4.3)	<0.0001	
OM10/AML10	vs.	OM10	161	160	-16.7 (0.75)	-8.8 (0.75)	-7.8 (0.99)	(-9.8 , -5.9)	<0.0001	
	vs.	AML10		163		-13.3 (0.74)	-3.3 (0.99)	(-5.3 , -1.4)	0.0004	0.0004
OM20/AML10	vs.	OM20	158	159	-17.7 (0.75)	-9.9 (0.75)	-7.8 (1.00)	(-9.8 , -5.9)	<0.0001	
	vs.	AML10		163		-13.3 (0.74)	-4.4 (0.99)	(-6.3 , -2.4)	<0.0001	<0.0001
OM40/AML10	vs.	OM40	161	160	-19.4 (0.74)	-10.9 (0.75)	-8.5 (0.99)	(-10.5 , -6.6)	<0.0001	
	vs.	AML10		163		-13.3 (0.74)	-6.1 (0.99)	(-8.0 , -4.2)	<0.0001	<0.0001

Baseline was defined as the average of the visit values from the randomization visit (Visit 3) and the visit prior to the randomization visit.
Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
LS Mean, SE, 95% CI, and one-sided p-values were obtained from an Analysis of Covariance model with fixed effects for treatment, age group, and diabetic status, and baseline as a covariate.
Adjusted p-value was obtained from applying Hommel's multiple comparison procedure to the larger of the two p-values from the treatment comparisons of the combination therapy with each of its components.
AML = amlodipine, CI = confidence interval, LS = least squares, OM = olmesartan medoxomil, SE = standard error, Tmt = treatment, vs. = versus.
Source: CSR663-A-U301 Final Report (Period II), Post-text Table 14.2.2

Similar results to SeDBP were observed in the analysis of mean SeSBP. Across the 6 combination therapies evaluated, the treatment differences in mean SeSBP between combination therapy and their respective monotherapy components were all highly statistically significant (p=0.0002 for OM 10 mg + AML 10 mg vs AML 10, (Section 6.1.4)

Table 5: Mean change in SeSBP from baseline to week 8 Combination vs Monotherapy-

Treatment Comparison			N		LS Mean (SE)		Difference (Tmt 1 – Tmt 2)			
Tmt 1	vs.	Tmt 2	Tmt 1	Tmt 2	Tmt 1	Tmt 2	LS Mean (SE)	95% CI	p-value	Adjusted p-value
OM10/AML5	vs.	OM10	163	160	-22.6 (1.23)	-10.9 (1.24)	-11.7 (1.64)	(-14.9 , -8.5)	<0.0001	
	vs.	AML5		161		-14.3 (1.24)	-8.2 (1.63)	(-11.4 , -5.0)	<0.0001	<0.0001
OM20/AML5	vs.	OM20	160	159	-22.6 (1.24)	-12.8 (1.25)	-9.9 (1.65)	(-13.1 , -6.7)	<0.0001	
	vs.	AML5		161		-14.3 (1.24)	-8.3 (1.64)	(-11.5 , -5.1)	<0.0001	<0.0001
OM40/AML5	vs.	OM40	157	160	-25.1 (1.26)	-15.4 (1.24)	-9.7 (1.65)	(-12.9 , -6.5)	<0.0001	<0.0001
	vs.	AML5		161		-14.3 (1.24)	-10.8 (1.65)	(-14.0 , -7.6)	<0.0001	
OM10/AML10	vs.	OM10	161	160	-24.8 (1.24)	-10.9 (1.24)	-13.9 (1.64)	(-17.1 , -10.7)	<0.0001	
	vs.	AML10		163		-18.9 (1.23)	-5.9 (1.63)	(-9.1 , -2.7)	0.0002	0.0002
OM20/AML10	vs.	OM20	158	159	-28.1 (1.25)	-12.8 (1.25)	-15.4 (1.65)	(-18.6 , -12.1)	<0.0001	
	vs.	AML10		163		-18.9 (1.23)	-9.2 (1.64)	(-12.5 , -6.0)	<0.0001	<0.0001
OM40/AML10	vs.	OM40	161	160	-28.5 (1.24)	-15.4 (1.24)	-13.0 (1.64)	(-16.3 , -9.8)	<0.0001	
	vs.	AML10		163		-18.9 (1.23)	-9.6 (1.63)	(-12.8 , -6.4)	<0.0001	<0.0001

Baseline was defined as the average of the visit values from the randomization visit (Visit 3) and the visit prior to the randomization visit.
Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
LS Mean, SE, 95% CI, and one-sided p-values were obtained from an Analysis of Covariance model with fixed effects for treatment, age group, and diabetic status, and baseline as a covariate.
Adjusted p-value was obtained from applying Hommel's multiple comparison procedure to the larger of the two p-values from the treatment comparisons of the combination therapy with each of its components.
AML = amlodipine, CI = confidence interval, LS = least squares, OM = olmesartan medoxomil, SE = standard error, Tmt = treatment, vs. = versus.
Source: CSR663-A-U301 Final Report (Period II), Post-text Table 14.2.6

Generally, the response to all the monotherapy and combination groups, was found to be greater in the non-Black population, except for the AML 10 mg monotherapy where the blacks seem to have responded better than the non-black population (Section 5.3 - Exposure response relationship; Tables 62-63; section 6)

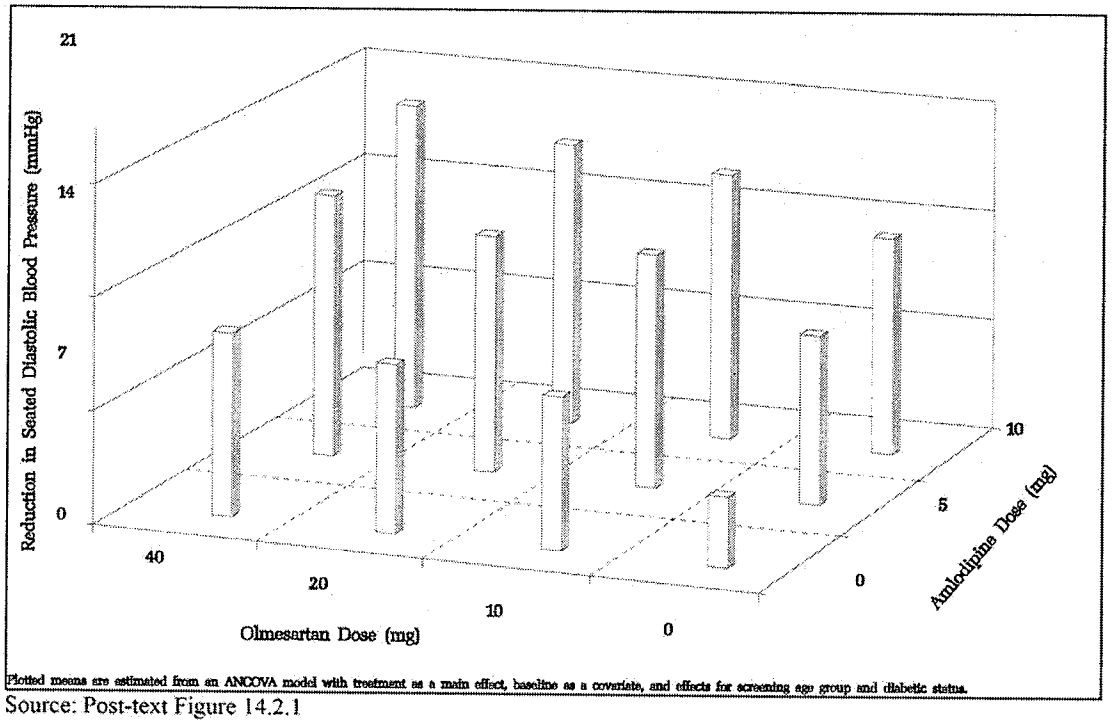
Table 6: Mean change of SeDBP from Baseline to week 8 with LOCF - ITT- NDA 22-100

Treatment	N[1]	Baseline[2] Mean ± SD	Week 8 with LOCF[3] Mean ± SD	Change	
				Mean ± SD	p-value[4]
Placebo	160	102.4 ± 4.79	99.3 ± 11.18	-3.1 ± 10.67	<0.0001
OM10	160	101.8 ± 5.93	93.5 ± 10.45	-8.3 ± 9.28	<0.0001
OM20	159	101.5 ± 4.59	92.3 ± 10.77	-9.2 ± 9.73	<0.0001
OM40	160	101.2 ± 5.09	91.0 ± 12.23	-10.2 ± 10.69	<0.0001
AML5	161	101.5 ± 5.15	92.1 ± 8.94	-9.4 ± 8.25	<0.0001
AML10	163	101.6 ± 4.84	88.8 ± 7.80	-12.7 ± 8.25	<0.0001
OM10/AML5	163	102.1 ± 5.36	88.3 ± 9.06	-13.8 ± 7.48	<0.0001
OM20/AML5	160	101.7 ± 5.06	87.7 ± 9.51	-14.0 ± 9.07	<0.0001
OM40/AML5	157	100.9 ± 4.74	85.4 ± 9.69	-15.5 ± 8.15	<0.0001
OM10/AML10	161	101.4 ± 5.50	85.4 ± 9.56	-16.0 ± 8.62	<0.0001
OM20/AML10	158	101.1 ± 4.67	84.1 ± 8.41	-17.0 ± 8.04	<0.0001
OM40/AML10	161	103.3 ± 5.80	83.3 ± 9.77	-19.0 ± 8.90	<0.0001

[1]N was the number of patients with values at both time points.
[2]Baseline for vital sign parameters was defined as the average of the values from the randomization visit (Visit 3) and the visit prior to the randomization visit.
[3]Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
[4]P-values were obtained from an Analysis of Covariance model with fixed effects for treatment, age group, and diabetic status, and baseline as a covariate.
AML = amlodipine, LOCF = last observation carried forward, OM = olmesartan medoxomil, SD = standard deviation.
Source: CS8663-A-U301 Final Report (Period II), Post-text Table 14.2.1

Figure 1: Mean reduction in SeDBP (mmHg) from baseline to week 8 with LOCF

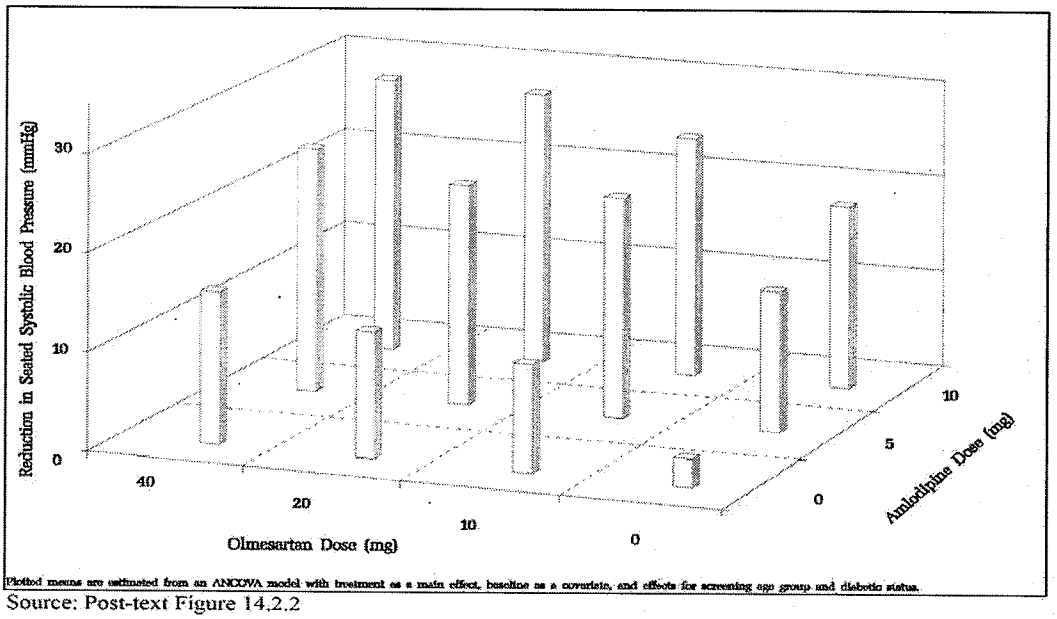
Figure 3: Mean Reduction in SeDBP (mmHg) from Baseline to Week 8 with LOCF – Intent-to-Treat Population



Source: Post-text Figure 14.2.1

Figure 2: Mean reduction in SeSBP (mmHg) from baseline to week 8 with LOCF - ITT

Figure 4: Mean Reduction in SeSBP (mmHg) from Baseline to Week 8 with LOCF – Intent-to-Treat Population



Source: Post-text Figure 14.2.2

Primary Efficacy - for monotherapies versus placebo

All of the monotherapy treatments (OM 10 mg, OM 20 mg, OM 40 mg, AML 5 mg, and AML 10 mg) reduced mean SeDBP compared to placebo in a statistically significant manner, which provides validation of the primary analysis that compared the combination treatments to the individual monotherapy components (Section 6.1.4).

Secondary Efficacy variables

- Change from baseline in SeDBP and SeSBP at Weeks 2, 4, 6, and 8 (with and without LOCF).
- Change from baseline in SeDBP and SeSBP at weeks 2, 4, 6, and 8 without LOCF
- Change from baseline in SeSBP at the end of Period II with LOCF was one of the other secondary efficacy variables.
- Proportion of patients who reached BP goals at weeks 2, 4, 6, and 8 without LOCF and week 8 with LOCF.
- Change from baseline to week 8 (with LOCF) in inflammatory markers including hsCRP, metallopreteases 2 and 9, tPA, PAI-1 and microalbuminuria.

Secondary Efficacy Variables (Tables 6 -24)

- **Change from baseline in SeSBP at the end of Period II with LOCF (Tables5 and 8).**

With combination treatment, mean SeSBP was reduced by a further 5.9 to 15.4 mmHg compared to the monotherapy component treatments. All the combination treatment groups lowered mean SeSBP to a greater extent than their respective monotherapy treatments. In the amlodipine 5 mg combination groups, the dose effect of olmesartan medoxomil was less consistent. However, in the amlodipine 10 mg combination groups, increased doses of olmesartan medoxomil from 10 mg to 20 mg and then to 40 mg resulted in a further 4 to 5 mmHg mean reduction in SeSBP. The greatest within-treatment mean reductions in SeSBP were observed in the highest combination doses (-30.1 mmHg for the OM 40 mg + AML 10 mg group and -29.2 mmHg for the OM 20 mg + AML10 mg group). (Table 8 and Section 6.1.4). The placebo-subtracted adjusted mean reduction in SeSBP is presented in Table 7 below.

Table 7: Placebo-adjusted LS mean reduction in SeSBP from baseline to wk 8 with LOCF – ITT-

		Olmesartan			
		Placebo	10 mg	20 mg	40 mg
Amlodipine					
	Plcbo	---	-8.0	-9.9	-12.6
	5mg	-11.5	-19.7	-19.8	-22.3
	10mg	-16.1	-21.9	-25.3	-25.6

Table 8: LS mean change in SeSBP from baseline to wk 8 with LOCF – ITT- NDA 22100

Treatment	N[1]	Baseline[2] Mean ± SD	Week 8 with LOCF[3] Mean ± SD	Change	
				Mean ± SD	p-value[4]
Placebo	160	166.7 ± 17.65	161.8 ± 20.97	-4.8 ± 18.70	0.0235
OM10	160	162.8 ± 16.73	151.3 ± 21.45	-11.5 ± 15.23	<0.0001
OM20	159	164.1 ± 16.54	150.2 ± 21.90	-13.8 ± 15.90	<0.0001
OM40	160	162.8 ± 15.73	146.8 ± 21.43	-16.1 ± 16.58	<0.0001
AML5	161	162.6 ± 17.20	147.7 ± 16.39	-14.9 ± 14.95	<0.0001
AML10	163	163.5 ± 15.88	143.7 ± 15.92	-19.7 ± 16.52	<0.0001
OM10/AML5	163	165.5 ± 15.60	141.4 ± 16.21	-24.2 ± 13.96	<0.0001
OM20/AML5	160	163.8 ± 14.93	140.2 ± 16.99	-23.6 ± 14.86	<0.0001
OM40/AML5	157	161.8 ± 14.95	136.4 ± 15.19	-25.4 ± 14.70	<0.0001
OM10/AML10	161	162.6 ± 15.56	137.3 ± 15.65	-25.3 ± 14.88	<0.0001
OM20/AML10	158	164.1 ± 14.95	134.9 ± 14.76	-29.2 ± 16.72	<0.0001
OM40/AML10	161	165.7 ± 16.79	135.6 ± 16.49	-30.1 ± 15.91	<0.0001

[1]N was the number of patients with values at both time points.
[2]Baseline for vital sign parameters was defined as the average of the values from the randomization visit (Visit 3) and the visit prior to the randomization visit.
[3]Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
[4]P-values were obtained from an Analysis of Covariance model with fixed effects for treatment, age group, and diabetic status, and baseline as a covariate.
AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.
Source: Post-text Table 14.2.5

Change from baseline in SeDBP and SeSBP at Weeks 2, 4, 6, and 8 (with and without LOCF). Time course:

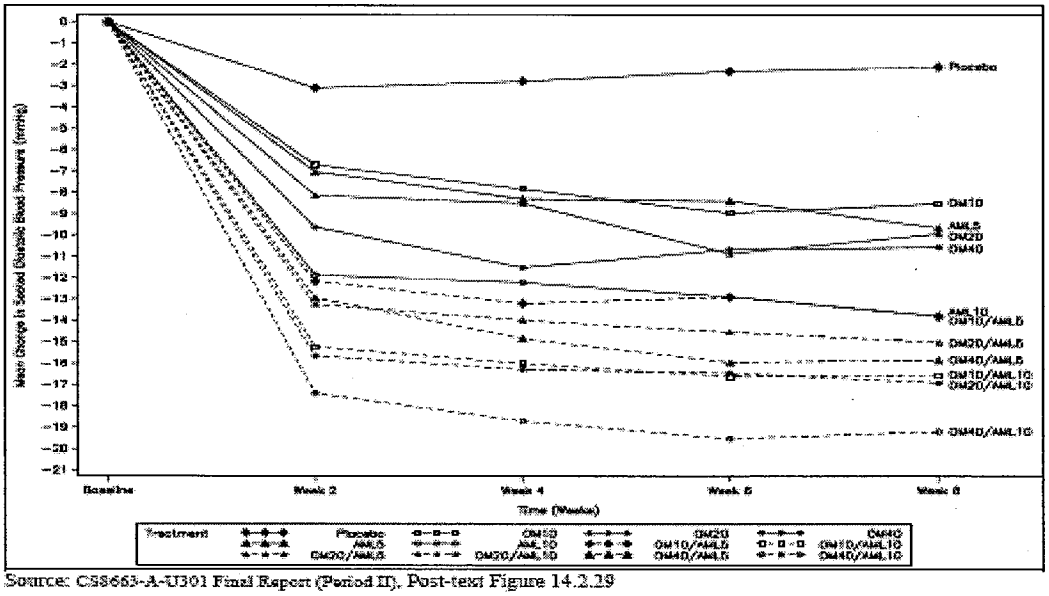
In the analysis of both SeDBP and SeSBP over time, the greatest mean reductions (70% to 80% of the maximum effect) in blood pressure occurred between baseline and Week 2. At Week 4, continued slight reductions were observed and plateaued in most of the treatment groups (Figures 3 and 4).

In all of the combination treatment groups, further mean reductions in blood pressure, albeit at a reduced rate, occurred from Week 2 to Week 8. From the figure of mean change in SeDBP over time (Figure 5), it is apparent that the greatest differences in mean SeDBP between any of the active treatment groups was observed between the OM 40 mg + AML 10 mg and the OM 20 mg + AML 10 mg treatment groups. From Week 2 there was a consistent 2 mmHg to 3 mmHg difference in mean SeDBP between these 2 treatment arms. Although the OM 40 mg + AML 10 mg treatment group achieved the greatest mean SeDBP and mean SeSBP reductions, a higher percentage of patients in the OM 20 mg + AML 10 mg (53.2%) and OM 40 mg + AML 5 mg (51.0%) treatment groups achieved goal blood pressures. In the OM 40 mg + AML 10 mg treatment group, 49.1% of the patients achieved goal blood pressures.

Baseline mean blood pressures were slightly lower in the OM 20 mg + AML 10 mg (164.1/101.2 mmHg) and OM 40 mg + AML 5 mg (161.7/100.9 mmHg) treatment groups compared to the OM 40 mg + AML 10 mg treatment group (165.7/102.4 mmHg). Also, with threshold analysis it is feasible for a treatment group with overall greater mean reductions in blood pressure to have fewer patients who reach the established blood pressure target.

Figure 3: Mean reduction from baseline in SeDBP (mmHg) over time-ITT

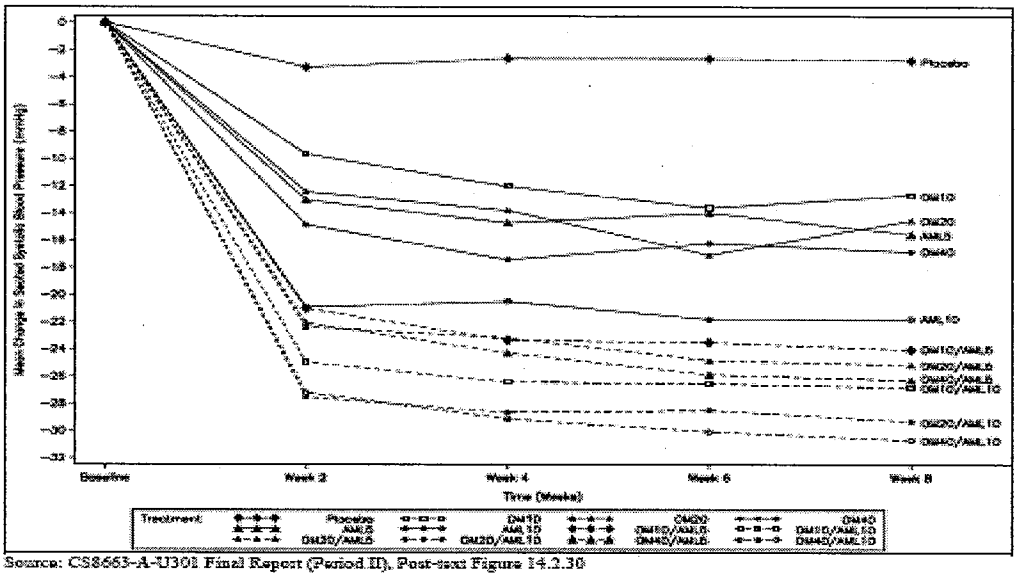
Figure 1: Mean Reduction from Baseline in SeDBP (mmHg) Over Time – All Treatment Groups – Pivotal Study (Double-Blind Treatment Period) – Intent-to-Treat Population



Source: CS8663-A-U301 Final Report (Period II), Post-text Figure 14.2.2.9

Figure 4: Mean reduction from baseline in SeSBP (mmHg) over time-ITT

Figure 2: Mean Reduction from Baseline in SeSBP (mmHg) Over Time – All Treatment Groups – Pivotal Study (Double-Blind Treatment Period) – Intent-to-Treat Population



Source: CS8663-A-U302 Final Report (Period II), Post-text Figure 14.2.30

Patients on prior Antihypertensive Medication Use

The reductions in both mean SeDBP and mean SeSBP were all statistically significant in both patients who had their blood pressure medications discontinued prior to entry into the study and those patients who were initiating therapy for their blood pressure as part of the study. There did not appear to be any difference in the mean reductions in SeDBP and SeSBP between these 2 subgroups. There also did not appear to be any difference between these subgroups in the comparisons between the combination treatments and the monotherapy component treatment groups or in the percentage of patients achieving blood pressure goals.

Among the groups treated with one of the combination therapies, the percentage of patients achieving blood pressure goals at Week 8 with LOCF ranged from 36.2% to 55.0% for the subgroup of patients who were naïve compared with 31.3% to 52.9% for the subgroup of patients who were not naïve to antihypertensive medications.

These results confirm that from an efficacy standpoint an equivalent blood pressure response could be achieved whether the combinations used in this study are given as part of an ongoing antihypertensive regimen or whether they are used as initial treatment for the hypertensive patient. Be that as it may, this cannot justify a claim for initial therapy in the absence of adequate safety data in a population that may be at risk.

Proportions reaching Target Blood Pressure Goals

The proportions of patients reaching their blood pressure targets are in Tables 8-10.

Table 9: Proportion of patients who reached BP goals at weeks 2,4,6, and 8 without LOCF and week 8 with LOCF

Timepoint Category		Placebo (N=160)	OM10 (N=160)	OM20 (N=159)	OM40 (N=160)	AML5 (N=161)	AML10 (N=163)
Week 8 With LOCF							
Number Exposed (N)		160	160	159	160	161	163
Number Achieving Goal (n)		14	32	42	58	34	53
Percent Achieving Goal (n/N)		8.8	20.0	26.4	36.3	21.1	32.5
Treatment p-value	<0.0001						
Week 8							
Number Exposed (N)		121	140	135	143	140	144
Number Achieving Goal (n)		9	28	37	55	30	52
Percent Achieving Goal (n/N)		7.4	20.0	27.4	38.5	21.4	36.1
Treatment p-value	<0.0001						
Week 6							
Number Exposed (N)		128	139	137	146	144	148
Number Achieving Goal (n)		8	31	43	51	22	42
Percent Achieving Goal (n/N)		6.3	22.3	31.4	34.9	15.3	28.4
Treatment p-value	<0.0001						
Week 4							
Number Exposed (N)		134	145	141	148	148	151
Number Achieving Goal (n)		8	31	30	56	30	42
Percent Achieving Goal (n/N)		6.0	21.4	21.3	37.8	20.3	27.8
Treatment p-value	<0.0001						
Week 2							
Number Exposed (N)		148	153	153	154	154	154
Number Achieving Goal (n)		5	19	34	48	22	44
Percent Achieving Goal (n/N)		3.4	12.4	22.2	31.2	14.3	28.6
Treatment p-value	<0.0001						

Blood pressure treatment goal is defined as blood pressure < 140/90 mmHg (130/80 mmHg for diabetics).
Treatment p-value is obtained from Chi-Square test for comparing the proportion of patients reaching goal among the treatment groups.

Table 10: Proportion of patients who reached BP goals at weeks 2,4,6, and 8 without LOCF and week 8 with LOCF

Timepoint Category	OM10/AML5 (N=163)	OM10/AML10 (N=161)	OM20/AML5 (N=160)	OM20/AML10 (N=158)	OM40/AML5 (N=157)	OM40/AML10 (N=161)
Week 8 With LOCF						
Number Exposed (N)	163	161	160	158	157	161
Number Achieving Goal (n)	57	79	68	84	80	79
Percent Achieving Goal (n/N)	35.0	49.1	42.5	53.2	51.0	49.1
Week 8						
Number Exposed (N)	154	134	146	143	143	143
Number Achieving Goal (n)	56	70	68	75	75	70
Percent Achieving Goal (n/N)	36.4	52.2	46.6	52.4	52.4	49.0
Week 6						
Number Exposed (N)	157	139	150	147	145	148
Number Achieving Goal (n)	59	74	64	75	79	76
Percent Achieving Goal (n/N)	37.6	53.2	42.7	51.0	54.5	51.4
Week 4						
Number Exposed (N)	159	142	152	151	146	152
Number Achieving Goal (n)	58	74	56	77	67	72
Percent Achieving Goal (n/N)	36.5	52.1	36.8	51.0	45.9	47.4
Week 2						
Number Exposed (N)	160	153	157	154	152	158
Number Achieving Goal (n)	44	70	50	75	58	79
Percent Achieving Goal (n/N)	27.5	45.8	31.8	48.7	38.2	50.0

Blood pressure treatment goal is defined as blood pressure < 140/90 mmHg (130/80 mmHg for diabetics).
Treatment p-value is obtained from Chi-Square test for comparing the proportion of patients reaching goal among the treatment groups.

Table 11: Proportion of patients reaching BP goals at week 8 with LOCF Combination therapy versus Monotherapy Period II - ITT

Table 8: Number (%) of Patients Reaching Blood Pressure Treatment Goal at Week 8 with LOCF – Combination Therapy Versus Monotherapy Comparisons – Pivotal Study (Double-Blind Treatment Period) – Intent-to-Treat Population

Treatment Comparison			N		BP Goal Achieved			
Tmt 1	vs.	Tmt 2	Tmt 1	Tmt 2	Tmt 1 n (%)	Tmt 2 n (%)	p-value	Adjusted p-value
OM10/AML5	vs.	OM10	163	160	57 (35.0)	32 (20.0)	0.0009	
	vs.	AML5		161		34 (21.1)	0.0023	0.0045
OM20/AML5	vs.	OM20	160	159	68 (42.5)	42 (26.4)	0.0009	0.0035
	vs.	AML5		161		34 (21.1)	<0.0001	
OM40/AML5	vs.	OM40	157	160	80 (51.0)	58 (36.3)	0.0045	0.0045
	vs.	AML5		161		34 (21.1)	<0.0001	
OM10/AML10	vs.	OM10	161	160	79 (49.1)	32 (20.0)	<0.0001	
	vs.	AML10		163		53 (32.5)	0.0012	0.0044
OM20/AML10	vs.	OM20	158	159	84 (53.2)	42 (26.4)	<0.0001	
	vs.	AML10		163		53 (32.5)	<0.0001	0.0002
OM40/AML10	vs.	OM40	161	160	79 (49.1)	58 (36.3)	0.0053	0.0045
	vs.	AML10		163		53 (32.5)	0.0004	

Blood pressure treatment goal was defined as blood pressure <140/90 mmHg (130/80 mmHg for diabetic patients).
Each one-sided p-value was obtained from an individual Cochran-Mantel-Haenszel test stratified by age group and diabetic status comparing combination therapy in Tmt 1 column to the respective monotherapy in Tmt 2 column.
Adjusted p-value was obtained from applying Hommel's multiple comparison procedure to the larger of the two p-values from the treatment comparisons of the combination therapy with each of its components.
AML = amlodipine, BP = blood pressure, OM = olmesartan medoxomil, Tmt = treatment, vs. = versus.
Source: CS8668-A-U301 Final Report (Period II), Post-text Table 14.2.74

Table 12: Proportion of patients reaching BP goals at wk 8 with LOCF by race

Race Subgroup Category	Pbo	OM10	OM20	OM40	AML5	AML10	OM10/ AML5	OM20/ AML5	OM40/ AML5	OM10/ AML10	OM20/ AML10	OM40/ AML10
Black												
Number Exposed (N)	45	32	34	44	42	39	34	43	38	43	46	34
Number Achieving Goal (n)	2	3	4	7	7	17	6	12	15	22	21	13
Percent Achieving Goal (n/N)	(4.4)	(9.4)	(11.8)	(15.9)	(16.7)	(43.6)	(17.6)	(27.9)	(39.5)	(51.2)	(45.7)	(38.2)
Treatment p-value	<0.0001											
Non-Black												
Number Exposed (N)	115	128	125	116	119	124	129	117	119	118	112	127
Number Achieving Goal (n)	12	29	38	51	27	36	51	56	65	57	63	66
Percent Achieving Goal (n/N)	(10.4)	(22.7)	(30.4)	(44.0)	(22.7)	(29.0)	(39.5)	(47.9)	(54.6)	(48.3)	(56.3)	(52.0)
Treatment p-value	<0.0001											

Blood pressure treatment goal was defined as blood pressure <140/90 mmHg (<130/80 mmHg for diabetic patients).
Treatment p-values were obtained from Chi-square test for comparing the proportion of patients reaching goal among the treatment groups. This tested the hypothesis that there was no difference among treatment groups in the proportion of patients achieving blood pressure goal.
AML = amlodipine, OM = olmesartan medoxomil, Pbo = placebo.
Sources: Post-text Tables 14.2.182 and 14.2.184

Analysis of data to evaluate initial therapy indication
Proportion of patients with BP > 160/100 who had reduction or 20/10 from baseline at week 8

This reviewer sets out to identify a subset of population that may require a reduction of BP. In an attempt to identify this population of patients, stage 2 hypertension hitherto defined strictly on blood pressure criterion of > 160/100, was adopted. A small study was carried out to find out the percentage of these patients who had achieved a reduction of 20/10 in BP. The data generated differ from those of the sponsor because the sponsor did not adhere to a prespecified cut off point in BP. When a patient was classified at one level on systolic and a different level on diastolic, the higher classification was used for secondary hypertension by the sponsor. However, the sponsor is seeking approval for initial therapy for those patients requiring a reduction b(4)
and not in patients with secondary hypertension as reflected in their table.

Our findings reveal that out of the total 1924 subjects randomized in the pivotal trial CS8663-A-U301, 695 patients (36.12%) had baseline of ≥160/100 mm Hg. In general a higher percentage of patients reached a reduction of 20/10 (BP140/90) with the combination tablet compared to any of its component monotherapies particularly at the OM40/10AML dose level. There is however no significant difference between the percent of patients on Amlodipine 10 mg (31.7%) versus combination of 40/5 (32.1%). Percent of patients with 20/10 reduction on combination tablet of 20/5 and 10/5 was smaller (28.3% and 25.8%) compared to percent of patients on Amoldipine 10 mg (31.7%). With these data, b(4)
, it will be difficult to recommend approval of certain dose levels of combination tablet for initial therapy in preference to monotherapy with amlodipine.

Table 13: Threshold Rates of all randomized patients with BP> 160/100 Source:Dr Raj Madabushi & AOWilliams

Randomized treatment group	Number of patients with baseline ≥160/100	% Threshold (140/90)	% Threshold (130/80)	% Threshold (120/80)
Placebo	70	7.1	2.9	1.4
OM10	50	12.0	0.0	0.0
OM20	55	12.7	0.0	0.0
OM40	56	12.5	1.8	1.8
AML5	56	14.3	1.8	0.0
AML10	60	31.7	8.3	1.7
OM10/AML5	66	25.8	4.5	3.0
OM10/AML10	54	33.3	9.3	3.7
OM20/AML5	53	28.3	9.4	3.8
OM20/AML10	53	52.8	22.6	7.5

Randomized treatment group	Number of patients with baseline ≥160/100	% Threshold (140/90)	% Threshold (130/80)	% Threshold (120/80)
OM40/AML5	53	32.1	11.3	3.8
OM40/AML10	69	40.6	14.5	5.8

For the sponsor's analysis, when a patient was classified at one level on systolic and a different level on diastolic, the higher classification was used. We decided to evaluate only patients with BP > 160/100 for reduction of 20/10.

In contrast, the numbers of patients in the sponsors analysis was much higher as shown in Table 14 below. In our studies about 41% achieved reduction of 20/10 compared to 49% by the sponsor in patients exposed to OM40/AML10.

Table 14: Threshold rates in stage 2 hypertensive patients Source : Sponsor

Table 68: Number (%) of Patients with Stage 2 Hypertension Reaching Blood Pressure Thresholds at Week 8 with LOCF – Pivotal Study (Double-Blind Treatment Period) – Intent-to-Treat Population

Treatment	N	<120/80 mmHg n (%)	<130/80 mmHg n (%)	<130/85 mmHg n (%)	<140/90 mmHg n (%)
Placebo	133	1 (0.8)	3 (2.3)	4 (3.0)	9 (6.8)
OM10	122	1 (0.8)	4 (3.3)	9 (7.4)	17 (13.9)
OM20	131	2 (1.5)	7 (5.3)	15 (11.5)	29 (22.1)
OM40	118	6 (5.1)	14 (11.9)	20 (16.9)	31 (26.3)
AML5	124	0 (0.0)	1 (0.8)	5 (4.0)	23 (18.5)
AML10	130	2 (1.5)	8 (6.2)	17 (13.1)	40 (30.8)
OM10/AML5	135	3 (2.2)	11 (8.1)	18 (13.3)	42 (31.1)
OM20/AML5	128	7 (5.5)	12 (9.4)	19 (14.8)	50 (39.1)
OM40/AML5	120	5 (4.2)	16 (13.3)	28 (23.3)	56 (46.7)
OM10/AML10	126	8 (6.3)	17 (13.5)	29 (23.0)	57 (45.2)
OM20/AML10	132	14 (10.6)	32 (24.2)	44 (33.3)	69 (52.3)
OM40/AML10	128	13 (10.2)	24 (18.8)	33 (25.8)	63 (49.2)

Percentage was calculated by dividing the number reaching the given threshold, n, by the number exposed to the given regimen, N.
AML = amlodipine, OM = olmesartan medoxomil.
Source: CS8663-A-U301 Final Report (Period II), Post-text Table 14.2.260

Table 13 shows comparisons between percentage of patients given monotherapy compared to those given combination tablets reaching a target reduction of 20/10. Table 14 is from the sponsor but the patients included those classified at one level on systolic and a different level on diastolic, and the higher classification was used for secondary hypertension. Since the indication sought is purely on the basis of BP reduction this reviewer considers that patients in the sponsor's table were not all above 160/90 requiring a reduction ‹

b(4)

We also compared percentage of patients reaching threshold BP between monotherapy components on one hand versus combination tablet on the other hand using a cut off BP of >160/100. Our findings are summarized in Table 15.

Table 15: Mean % of patients reaching threshold of reduction of 20/10 mmHg – Comparisons between monotherapy and combination Source : Madabushi and Williams

Treatment group	Number of patients with baseline ≥160/100	% Threshold (140/90)	% Threshold (130/80)	% Threshold (120/80)
Placebo	70	7.1	2.9	1.4
Olmesartan Monotherapy	161	12.4	0.6	0.6
Amlodipine Monotherapy	116	23.3	5.2	0.9
Olmesartan + Amlodipine	348	35.3	11.8	4.6

From the reviewer's analyses we make the following observations based on Tables13 -15:

From the sponsor's table 14, about 30.8 % of patients exposed to 10 mg AML monotherapy reached their threshold compared to 49.2 % on combined OM40/10 at week 8 of pivotal study.

From the sponsor's table about 26.3% of patients exposed to 40 mg OM monotherapy reached their threshold compared to 49.2 % on combined OM40/10

Based on all the population randomized, Stages 1 and 2 , the sponsor showed that about 31.7 % of patients exposed to 10 mg AML monotherapy reached their threshold compared to 40.6 % on combined OM40/10 and

About 12.5 % of patients exposed to 40 mg OM monotherapy reached their threshold compared to 40.6 % on combined OM40/10 (Table 13).

b(4)

It is evident that goals were reached by more patients on combination tablets than on monotherapy. Assuming these differences are significant an outcome study needs to be carried out to evaluate whether these differences are clinically meaningful in the selected population of stage 2 hypertension patients.

From our own study:

The mean percent of patients with BP> 160/100 that was reduced by 20/10 after OM monotherapy was 12.4% and after AML monotherapy was 23.3% and for all patients on combined tablet the percent was 35.3% while placebo was 7% (Table 15). This

confirms the sponsor's data that more patients reached their goals on combined tablet compared to either of the monotherapy components.

When the mean percent of patients reaching their goals on maximum dose of monotherapy for OM was 12.5% and for AML 31.7% the number of patients reaching goal on combined tablet on minimum dose was 25.8% and on maximum dose was 40.6%. All these point to the relative superiority of the combined tablet compared to monotherapy using threshold levels.

From tables 13 and 15 it is evident that olmesartan may not facilitate reaching the BP threshold as quickly if at all as amlodipine. However, the overall difference between the combined tablet (all doses) and amlodipine (all doses) in reaching threshold is about 50% more in favor of the combined tablet: 23.3% versus 35.3% (Table 15). This provides some evidence that more patients with BP of ≥160/100 given AZOR are more likely to reach a threshold of BP reduction by 20/10 compared to monotherapy (Tables 13 and 15) but the caveat is that this should only be recommended if and when it has been shown that Amlodipine 10 mg has failed in this group of patients. Reaching certain blood pressure thresholds/goals was however not a pre-specified primary or secondary endpoint in the protocol (Table 16).

Proportion of patients who reached BP goals at week 8 -

Table 16: Proportion of patients reaching treatment goal by week 8 comparison between combined and monotherapy-ITT

Table 14.2.7a
Number (%) of Patients Reaching Blood Pressure Treatment Goal by Week
Combination Therapy Versus Monotherapy Comparisons
Intent-to-Treat Population
Period II - Day 1 to Week 8

Timepoint	Treatment Comparison Trt 1	vs. Trt 2	Number Exposed Trt 1	Number Exposed Trt 2	BP Goal Achieved Trt 1 n	Trt 1 (%)	Trt 2 n	Trt 2 (%)	P-value	Adjusted P-value
Week 8 With LOCF	OM10/AML5	vs. OM10	162	160	57	(35.0)	32	(20.0)	0.0009	
		vs. AML5		161			34	(21.1)	0.0023	0.0045
	OM10/AML10	vs. OM10	161	160	79	(49.1)	32	(20.0)	<0.0001	
		vs. AML10		163			53	(32.5)	0.0012	0.0044
	OM20/AML5	vs. OM20	160	159	68	(42.5)	42	(26.4)	0.0009	0.0035
		vs. AML5		161			34	(21.1)	<0.0001	
	OM20/AML10	vs. OM20	158	159	84	(53.2)	42	(26.4)	<0.0001	
		vs. AML10		163			53	(32.5)	<0.0001	0.0003
	OM40/AML5	vs. OM40	157	160	80	(51.0)	58	(36.3)	0.0045	0.0045
		vs. AML5		161			34	(21.1)	<0.0001	
	OM40/AML10	vs. OM40	161	160	79	(49.1)	58	(36.3)	0.0033	0.0045
		vs. AML10		163			53	(32.5)	0.0004	

Change from baseline to week 8 (with LOCF) in inflammatory markers including hsCRP, metallopreteases 2 and 9, tPA, PAI-1 and microalbuminuria.

The following studies were carried out in order to evaluate various doses of OM + AML on surrogate markers of cardiovascular risk (high-sensitivity C-reactive protein [hsCRP], metalloproteases 2 and 9, tissue plasminogen activator [tPA], plasminogen activator inhibitor-1 [PAI-1], and microalbuminuria).

Analysis of the mean changes and mean percent changes in all the inflammatory markers selected as surrogate markers of cardiovascular risk showed no consistent pattern that would indicate a treatment effect. This was an exploratory study on inflammatory markers for CV risk. The data presented in Tables 17-26 below do not demonstrate any significant reductions in any of the inflammatory markers selected as surrogate markers for cardiovascular risk in patients with hypertension.

Table 17: Change in hsCRP (mg/L) from baseline to week 8 with LOCF - ITT Period II Day 1 – week 8

Change in hsCRP (mg/L) From Baseline to Week 8 With LOCF
Intent-to-Treat Population
Period II - Day 1 to Week 8

Timepoint Statistic	Placebo (N=160)	OM40 (N=160)	AML10 (N=163)	OM20/AML5 (N=160)	OM40/AML10 (N=161)
N [1]	116	136	137	140	138
Baseline [2]					
Mean	4.086	4.878	4.895	4.684	4.182
Standard Deviation	4.2779	5.2730	5.7902	5.2445	4.4884
Median	2.800	3.500	3.500	2.850	2.900
Minimum - Maximum	0.200 - 20.900	0.121 - 36.700	0.183 - 53.000	0.078 - 29.100	0.154 - 25.000
Week 8 With LOCF [3]					
Mean	5.026	4.878	5.238	5.459	4.316
Standard Deviation	5.7176	5.1213	6.1994	6.8516	5.5041
Median	3.600	2.900	3.500	3.200	2.300
Minimum - Maximum	0.155 - 39.500	0.200 - 29.100	0.117 - 46.100	0.075 - 45.300	0.200 - 37.700
Change					
Mean	0.940	0.008	0.343	0.775	0.123
Standard Deviation	3.8906	3.2208	5.9163	5.8349	4.3279
Median	0.200	0.015	0.000	0.200	0.000
Minimum - Maximum	-8.200 - 21.100	-21.200 - 12.500	-46.100 - 26.600	-24.700 - 43.100	-13.100 - 26.600
LS Mean (SE)	0.8 (0.43)	0.1 (0.40)	0.4 (0.39)	0.8 (0.39)	0.0 (0.39)
95% CI	(-0.0, 1.7)	(-0.7, 0.9)	(-0.3, 1.2)	(0.0, 1.6)	(-0.7, 0.8)
P-value	0.0582	0.8179	0.2728	0.0387	0.9500
Percent Change					
Mean	60.3	21.2	26.3	55.0	23.4
Standard Deviation	244.84	75.85	108.24	291.31	106.28
Median	9.8	4.6	0.0	9.2	0.0
Minimum - Maximum	-78 - 2222	-94 - 300	-87 - 624	-85 - 3315	-92 - 599
LS Mean (SE)	58.8 (16.83)	22.7 (15.58)	27.9 (15.52)	55.6 (15.35)	21.6 (15.47)
95% CI	(24.9, 91.1)	(-7.9, 53.2)	(-2.5, 58.4)	(25.5, 85.8)	(-8.7, 52.0)
P-value	0.0026	0.1462	0.0723	0.0003	0.1624

Baseline is defined as the last available measurement prior to randomization
Week 0 with LOCF is defined as the last available measurement during the double blind active treatment period
LS Mean, SE, 95% CI, and one sided p-value are obtained from an ANCOVA model with treatment as a fixed effect and baseline as a covariate.

Table 18: Change in hsCRP (mg/L) from baseline to week 8 with LOCF paired comparisons among treatment groups ITT Period II Day 1 – week 8

Table 14.2.79
Change in hsCRP (mg/L) From Baseline to Week 8 With LOCF
Paired Comparisons Among Treatment Groups
Intent-to-Treat Population
Period II - Day 1 to Week 8

Treatment Comparison		N		LS Mean (SE)		Difference (Tmt 1 - Tmt 2)		
Tmt 1	vs. Tmt 2	Tmt 1	Tmt 2	Tmt 1	Tmt 2	LS Mean (SE)	95% CI	p-value
Mean Change								
OM40	vs. Placebo	136	116	0.1 (0.40)	0.8 (0.43)	-0.7 (0.58)	(-1.9, 0.4)	0.1082
AML10	vs.	137		0.1 (0.39)		-0.6 (0.58)	(-1.5, 0.3)	0.1578
OM20/AML5	vs.	140		0.8 (0.39)		-0.0 (0.58)	(-1.1, 1.1)	0.4961
OM40/AML10	vs.	136		0.8 (0.39)		-0.6 (0.58)	(-1.8, 0.4)	0.0976
OM40/AML10	vs. OM40	136	136	0.0 (0.39)	0.1 (0.40)	-0.1 (0.56)	(-1.2, 1.0)	0.4526
	vs. AML10		137		0.4 (0.39)	-0.4 (0.56)	(-1.5, 0.7)	0.2329
OM20/AML5	vs. OM40	140	136	0.8 (0.39)	0.1 (0.40)	0.7 (0.56)	(-0.4, 1.8)	0.0989
	vs. AML10		137		0.4 (0.39)	0.4 (0.55)	(-0.7, 1.5)	0.2496
Percent Change								
OM40	vs. Placebo	136	116	22.7 (15.58)	58.8 (16.86)	-36.3 (22.98)	(-80.4, 9.8)	0.8624
AML10	vs.	137		27.9 (15.52)		-30.9 (22.94)	(-75.8, 15.0)	0.6954
OM20/AML5	vs.	140		55.6 (15.35)		-3.4 (22.82)	(-47.2, 42.4)	0.4588
OM40/AML10	vs.	136		21.6 (15.47)		-36.4 (22.88)	(-81.3, 8.6)	0.0563
OM40/AML10	vs. OM40	136	136	21.6 (15.47)	22.7 (15.58)	-1.0 (21.96)	(-44.2, 42.1)	0.4813
	vs. AML10		137		27.9 (15.52)	-6.3 (21.93)	(-49.4, 36.7)	0.3868
OM20/AML5	vs. OM40	140	136	55.6 (15.35)	22.7 (15.58)	33.0 (21.87)	(-10.0, 75.9)	0.0661
	vs. AML10		137		27.9 (15.52)	27.7 (21.83)	(-15.2, 70.5)	0.1026

Baseline is defined as the last available measurement prior to randomization
Week 0 with LOCF is defined as the last available measurement during the double blind active treatment period
LS Mean, SE, 95% CI, and one sided p-value are obtained from an ANCOVA model with treatment as a fixed effect and baseline as a covariate.

Table 19: Change in metalloproteases from baseline to week 8 with LOCF - ITT Period II Day 1 – week 8

Change in Metalloproteases 2 (ng/mL) From Baseline to Week 8 With LOCF
Intent-to-Treat Population
Period II - Day 1 to Week 8

Timepoint Statistic	Placebo (N=160)	OM40 (N=166)	AML10 (N=163)	OM20/AML5 (N=160)	OM40/AML10 (N=161)
N [1]	117	136	137	140	136
Baseline [2]					
Mean	297.6	296.1	287.5	294.7	297.1
Standard Deviation	68.41	58.88	58.02	70.99	67.70
Median	292.0	288.0	284.0	291.0	289.0
Minimum - Maximum	128 - 565	96 - 493	114 - 443	125 - 618	144 - 488
Week 8 With LOCF [3]					
Mean	291.9	289.2	285.2	279.9	290.9
Standard Deviation	87.67	58.24	53.68	63.88	62.40
Median	284.0	291.0	289.0	271.5	281.5
Minimum - Maximum	132 - 552	93 - 448	120 - 444	131 - 640	144 - 524
Change					
Mean	-5.0	-6.9	-2.3	-14.8	-6.2
Standard Deviation	30.55	37.56	40.75	42.02	42.56
Median	-6.0	-3.0	0.0	-9.0	-6.0
Minimum - Maximum	-89 - 85	-113 - 91	-144 - 111	-192 - 75	-167 - 132
LS Mean (SE)	-4.4 (3.33)	-6.5 (3.09)	-3.9 (3.08)	-14.7 (3.05)	-5.6 (3.07)
95% CI	(-11.0, 2.1)	(-12.5, -0.4)	(-10.0, 2.1)	(-20.7, -8.8)	(-11.6, 0.5)
P-value	0.1847	0.0366	0.2049	<0.0001	0.0722
Percent Change					
Mean	-1.1	-1.5	0.5	-3.8	-0.7
Standard Deviation	10.92	13.10	14.54	13.12	14.55
Median	-2.1	-1.9	0.0	-3.5	-2.2
Minimum - Maximum	-26 - 35	-38 - 39	-44 - 62	-37 - 42	-42 - 68
LS Mean (SE)	-0.9 (1.15)	-1.4 (1.07)	-0.9 (1.07)	-3.8 (1.05)	-0.5 (1.06)
95% CI	(-3.1, 1.4)	(-3.5, 0.7)	(-2.1, 2.1)	(-5.8, -1.7)	(-2.6, 1.6)
P-value	0.4476	0.1815	0.9886	0.0004	0.6163

Table 20: Change in metalloproteases from baseline to week 8 with LOCF paired comparisons among treatment groups ITT Period II Day 1 – week 8

Change in Metalloproteases 2 (ng/mL) From Baseline to Week 8 With LOCF
Paired Comparisons Among Treatment Groups
Intent-to-Treat Population
Period II - Day 1 to Week 8

Treatment Comparison		N		LS Mean (SE)		Difference (Trt 1 - Trt 2)		
Trt 1	vs. Trt 2	Trt 1	Trt 2	Trt 1	Trt 2	LS Mean (SE)	95% CI	p-value
Mean Change								
OM40	vs. Placebo	136	117	-6.5 (3.09)	-4.4 (3.33)	-2.0 (4.54)	(-11.0, 6.9)	0.3261
AML10	vs.	137		-3.9 (3.08)		0.5 (4.54)	(-8.4, 9.4)	0.4551
OM20/AML5	vs.	140		-14.7 (3.05)		-10.3 (4.51)	(-19.2, -1.4)	0.0113
OM40/AML10	vs.	138		-5.5 (3.07)		-1.1 (4.53)	(-10.0, 7.8)	0.4040
OM40/AML10	vs. OM40	138	136	-6.5 (3.07)	-6.5 (3.09)	0.9 (4.35)	(-7.6, 9.5)	0.4139
	vs. AML10		137		-3.9 (3.08)	-1.6 (4.35)	(-10.2, 6.9)	0.3584
OM20/AML5	vs. OM40	140	136	-14.7 (3.05)	-6.5 (3.09)	-8.3 (4.34)	(-16.9, 0.3)	0.0286
	vs. AML10		137		-3.9 (3.08)	-10.8 (4.33)	(-19.3, -2.3)	0.0064
Percent Change								
OM40	vs. Placebo	136	117	-1.4 (1.07)	-0.9 (1.15)	-0.6 (1.57)	(-3.6, 2.5)	0.3623
AML10	vs.	137		-0.0 (1.07)		0.9 (1.57)	(-2.2, 3.9)	0.2929
OM20/AML5	vs.	140		-3.8 (1.05)		-2.8 (1.56)	(-6.0, 0.2)	0.0323
OM40/AML10	vs.	138		-0.5 (1.06)		0.3 (1.57)	(-2.7, 3.4)	0.4132
OM40/AML10	vs. OM40	138	136	-0.5 (1.06)	-1.4 (1.07)	0.9 (1.51)	(-2.1, 3.9)	0.2757
	vs. AML10		137		-0.0 (1.07)	-0.5 (1.51)	(-3.5, 2.4)	0.3687
OM20/AML5	vs. OM40	140	136	-3.8 (1.05)	-1.4 (1.07)	-2.3 (1.50)	(-5.3, 0.6)	0.0600
	vs. AML10		137		-0.0 (1.07)	-3.8 (1.50)	(-6.7, -0.8)	0.0063

Table 21: Change in tPA from baseline to week 8 with LOCF - ITT Period II Day 1 – week 8

Table 14.2.84
Change in tPA (ng/mL) From Baseline to Week 8 With LOCF
Intent-to-Treat Population
Period II - Day 1 to Week 8

Timepoint Statistic	Placebo (N=160)	OM40 (N=160)	AML10 (N=165)	OM20/AML5 (N=160)	OM40/AML10 (N=161)
N [1]	95	108	108	117	112
Baseline [2]					
Mean	13.98	12.21	12.84	11.21	13.83
Standard Deviation	15.796	8.336	7.450	6.287	22.624
Median	10.60	10.95	11.35	10.20	10.80
Minimum - Maximum	3.3 - 144.0	2.8 - 80.8	3.3 - 60.8	3.9 - 49.8	3.7 - 245.8
Week 8 With LOCF [3]					
Mean	13.24	12.72	12.70	12.46	14.02
Standard Deviation	9.802	8.232	8.522	9.723	24.370
Median	11.30	11.15	11.05	11.10	11.00
Minimum - Maximum	3.3 - 74.0	3.1 - 84.4	3.1 - 45.6	2.7 - 91.6	4.8 - 265.0
Change					
Mean	-0.75	0.51	-0.13	1.25	0.19
Standard Deviation	8.529	2.857	2.943	8.823	3.628
Median	0.20	0.05	-0.20	0.40	-0.20
Minimum - Maximum	-70.0 - 15.2	-6.2 - 9.6	-15.2 - 7.5	-20.6 - 51.5	-18.0 - 20.0
LS Mean (SE)	-0.6 (0.83)	0.5 (0.56)	-0.2 (0.56)	1.1 (0.54)	0.3 (0.55)
95% CI	(-1.8, 0.5)	(-0.6, 1.6)	(-1.2, 1.0)	(0.0, 2.2)	(-0.8, 1.4)
P-value	0.2825	0.4126	0.8250	0.0403	0.5762
Percent Change					
Mean	6.7	8.5	8.3	16.5	4.2
Standard Deviation	33.74	25.03	26.89	79.54	29.71
Median	2.9	0.6	-2.1	4.5	-2.8
Minimum - Maximum	-49 - 176	-38 - 107	-56 - 164	-49 - 789	-39 - 190
LS Mean (SE)	7.1 (4.60)	8.3 (4.331)	8.3 (4.33)	16.9 (4.14)	4.6 (4.21)
95% CI	(-1.9, 16.1)	(-3.1, 13.8)	(-5.2, 11.7)	(7.8, 26.1)	(-3.7, 12.8)
P-value	0.1226	0.2162	0.4431	0.0001	0.2788

Table 22: Change in tPA from baseline to week 8 with LOCF paired comparisons among treatment groups ITT Period II Day 1 – week 8

Change in tPA (ng/mL) From Baseline to Week 8 With LOCF
Paired Comparisons Among Treatment Groups
Intent-to-Treat Population
Period II - Day 1 to Week 8

Treatment Comparison Trt 1	vs. Trt 2	N Trt 1	N Trt 2	LS Mean (SE) Trt 1	Trt 2	Difference (Trt 1 - Trt 2) LS Mean (SE)	95% CI	p-value
Mean Change								
OM40	vs. Placebo	108	95	0.5 (0.56)	-0.6 (0.60)	1.1 (0.82)	(-0.5, 2.7)	0.0913
AML10	vs.	108		-0.1 (0.56)		0.5 (0.82)	(-1.1, 2.1)	0.2674
OM20/AML5	vs.	117		1.3 (0.54)		1.9 (0.81)	(0.2, 3.3)	0.0155
OM40/AML10	vs.	113		0.3 (0.55)		0.9 (0.81)	(-0.7, 2.5)	0.1279
OM40/AML10	vs. OM40	113	108	0.3 (0.55)	0.5 (0.56)	-0.2 (0.78)	(-1.7, 1.4)	0.4146
	vs. AML10		108		-0.1 (0.56)	0.4 (0.78)	(-1.1, 2.0)	0.2976
OM20/AML5	vs. OM40	117	108	1.3 (0.54)	0.5 (0.56)	0.8 (0.78)	(-0.9, 2.3)	0.2021
	vs. AML10		108		-0.1 (0.56)	1.2 (0.78)	(-0.3, 2.8)	0.0965
Percent Change								
OM40	vs. Placebo	108	95	5.3 (4.31)	7.1 (4.60)	-1.8 (6.36)	(-14.2, 10.6)	0.3892
AML10	vs.	108		3.3 (4.31)		-3.8 (6.36)	(-16.2, 8.5)	0.2717
OM20/AML5	vs.	117		16.0 (4.14)		8.9 (6.19)	(-3.3, 21.0)	0.0761
OM40/AML10	vs.	113		4.8 (4.31)		-2.5 (6.23)	(-14.8, 9.7)	0.9419
OM40/AML10	vs. OM40	113	108	4.8 (4.31)	5.3 (4.31)	-0.8 (6.03)	(-12.6, 11.1)	0.4495
	vs. AML10		108		3.3 (4.31)	1.3 (6.03)	(-10.5, 13.1)	0.4152
OM20/AML5	vs. OM40	117	108	16.0 (4.14)	5.3 (4.31)	10.3 (5.97)	(-1.1, 22.4)	0.0375
	vs. AML10		108		3.3 (4.31)	12.7 (5.98)	(1.0, 24.5)	0.0169

Table 23: Change in microalbuminuria from baseline to week 8 with LOCF - ITT Period II Day 1 – week 8

Table 14.2.8B
Change in Microalbuminuria (mg/dL) From Baseline to Week 8 With LOCF
Intent-to-Treat Population
Period II - Day 1 to Week 8

Timepoint Statistic	Placebo (N=160)	OM40 (N=160)	AML10 (N=163)	OM20/AML5 (N=160)	OM40/AML10 (N=161)
N [1]	66	63	76	53	58
Baseline [2]					
Mean	13.79	14.30	13.67	12.99	14.99
Standard Deviation	55.184	48.173	35.808	32.329	41.688
Median	3.00	2.90	3.05	3.30	4.15
Minimum - Maximum	1.0 - 379.0	1.0 - 267.3	1.0 - 243.5	1.0 - 211.1	0.5 - 264.8
Week 8 With LOCF [3]					
Mean	13.09	7.64	14.02	17.68	9.46
Standard Deviation	37.859	15.564	38.480	60.330	23.256
Median	4.20	2.70	2.80	2.50	2.30
Minimum - Maximum	0.9 - 250.8	1.0 - 76.4	1.0 - 238.4	1.0 - 398.7	0.2 - 147.9
Change					
Mean	-0.70	-6.66	0.35	4.69	-5.54
Standard Deviation	19.982	38.339	31.331	59.451	35.406
Median	0.65	0.60	-0.05	-0.50	-0.70
Minimum - Maximum	-118.2 - 49.6	-365.6 - 43.3	-74.3 - 223.1	-118.4 - 395.8	-196.2 - 124.5
LS Mean (SE)	-0.8 (3.81)	-6.5 (3.96)	0.2 (3.63)	4.2 (4.32)	-5.0 (4.21)
95% CI	(-8.4, 6.8)	(-14.3, 1.3)	(-6.9, 7.3)	(-4.3, 12.7)	(-13.3, 3.3)
P-value	0.8406	0.1033	0.9527	0.3306	0.2348
Percent Change					
Mean	99.3	28.7	352.6	263.6	8.6
Standard Deviation	317.32	115.72	862.71	1876.26	106.38
Median	28.4	8.0	-5.1	-13.3	-20.3
Minimum - Maximum	-84 - 3471	-93 - 558	-93 - 5984	-93 - 13648	-93 - 532
LS Mean (SE)	99.2 (102.73)	21.0 (105.13)	102.4 (95.72)	262.8 (114.62)	6.5 (111.51)
95% CI	(-102.9, 301.3)	(-185.8, 227.9)	(-86.0, 290.7)	(37.3, 488.4)	(-212.3, 225.3)
P-value	0.3349	0.8415	0.2856	0.0225	0.9537

Table 24: Change in microalbuminuria from baseline to week 8 with LOCF paired comparisons among treatment groups ITT Period II Day 1 – week 8

Table 14.2.89
Change in Microalbuminuria (mg/dL) From Baseline to Week 8 With LOCF
Paired Comparisons Among Treatment Groups
Intent-to-Treat Population
Period II - Day 1 to Week 8

Treatment Comparison		N		LS Mean (SE)		Differences (Trt 1 - Trt 2)		
Trt 1	vs. Trt 2	Trt 1	Trt 2	Trt 1	Trt 2	LS Mean (SE)	95% CI	p-value
Mean Change								
OM40	vs. Placebo	63	66	-6.5 (3.96)	-0.8 (3.87)	-5.7 (5.54)	(-16.6, 5.2)	0.1524
AML10	vs.	76		0.2 (3.61)		1.0 (5.29)	(-9.4, 11.4)	0.4256
OM20/AML5	vs.	53		4.2 (4.32)		5.0 (5.80)	(-6.4, 16.4)	0.1952
OM40/AML10	vs.	56		-5.0 (4.21)		-4.2 (5.72)	(-15.5, 7.0)	0.2301
OM40/AML10	vs. OM40	56	63	-5.0 (4.21)	-6.5 (3.96)	1.5 (5.78)	(-9.9, 12.8)	0.3996
	vs. AML10		76		0.2 (3.61)	-5.2 (5.54)	(-16.1, 5.7)	0.1735
OM20/AML5	vs. OM40	53	63	4.3 (4.32)	-6.5 (3.96)	10.7 (5.87)	(-0.9, 22.2)	0.0367
	vs. AML10		76		0.2 (3.61)	4.0 (5.63)	(-7.1, 15.1)	0.2391
Percent Change								
OM40	vs. Placebo	63	66	21.0 (106.13)	99.2 (102.71)	-78.2 (146.98)	(-367.4, 211.0)	0.2976
AML10	vs.	76		102.4 (96.72)		3.2 (140.40)	(-273.1, 279.4)	0.4910
OM20/AML5	vs.	53		283.8 (114.62)		183.6 (153.93)	(-119.2, 486.5)	0.1443
OM40/AML10	vs.	56		8.5 (111.51)		-92.7 (151.63)	(-391.0, 205.6)	0.2706
OM40/AML10	vs. OM40	56	63	8.5 (111.51)	21.0 (105.13)	-14.6 (153.25)	(-316.1, 287.0)	0.4622
	vs. AML10		76		102.4 (95.72)	-98.9 (146.96)	(-388.1, 193.3)	0.2573
OM20/AML5	vs. OM40	53	63	283.8 (114.62)	21.0 (105.13)	241.8 (155.56)	(-64.3, 547.8)	0.0605
	vs. AML10		76		102.4 (95.72)	160.4 (149.33)	(-133.4, 454.3)	0.1417

Table 25: Change in PA-I from baseline to week 8 with LOCF - ITT Period II Day 1 – week 8

Table 14.2.86
Change in PAI-1 (ng/mL) From Baseline to Week 8 With LOCF
Intent-to-Treat Population
Period II - Day 1 to Week 8

Timepoint Statistic	Placebo (N=160)	OM40 (N=160)	AML10 (N=163)	OM20/AML5 (N=160)	OM40/AML10 (N=161)
N [1]	94	108	108	117	112
Baseline [2]					
Mean	47.12	39.85	45.28	37.50	33.60
Standard Deviation	89.138	54.666	74.651	62.344	33.991
Median	22.80	21.80	26.40	22.00	23.80
Minimum - Maximum	4.2 - 662.0	4.0 - 480.0	5.2 - 652.0	4.0 - 524.0	3.0 - 194.0
Week 8 With LOCF [3]					
Mean	43.58	34.82	39.76	36.93	35.15
Standard Deviation	62.451	32.447	43.834	38.167	31.922
Median	27.40	26.20	27.40	26.80	28.40
Minimum - Maximum	6.1 - 520.0	3.4 - 208.0	4.8 - 344.0	6.4 - 278.0	5.2 - 262.0
Change					
Mean	-3.59	-5.07	-5.52	-0.57	2.49
Standard Deviation	94.880	61.554	72.285	68.846	32.944
Median	2.80	-2.10	-3.60	2.80	4.40
Minimum - Maximum	-630 - 506.8	-439 - 179.6	-648 - 155.0	-513 - 240.8	-187 - 150.2
LS Mean (SE)	2.1 (4.25)	-5.5 (3.96)	-1.4 (3.98)	-3.0 (3.81)	-3.2 (3.88)
95% CI	(-6.2, 10.4)	(-13.3, 2.3)	(-9.2, 6.3)	(-10.5, 4.5)	(-10.8, 4.4)
P-value	0.6270	0.1644	0.7153	0.4294	0.4145
Percent Change					
Mean	86.1	55.5	45.5	52.0	56.4
Standard Deviation	497.99	192.65	358.41	135.60	258.52
Median	13.2	13.8	-4.6	21.2	28.5
Minimum - Maximum	-95 - 3539	-84 - 1212	-95 - 1155	-98 - 736	-89 - 1880
LS Mean (SE)	90.3 (23.31)	55.2 (21.73)	45.6 (21.74)	50.9 (20.88)	52.2 (21.27)
95% CI	(44.5, 136.1)	(12.5, 97.8)	(3.0, 88.3)	(9.9, 91.9)	(10.4, 93.9)
P-value	0.0001	0.0116	0.0358	0.0151	0.0146

Table 26: Change in PA-I from baseline to week 8 with LOCF paired comparisons among treatment groups ITT Period II Day 1 – week 8

Table 14.2.87
Change in PAI-I (ng/mL) From Baseline to Week 8 With LOCF
Paired Comparisons Among Treatment Groups
Intent-to-Treat Population
Period II - Day 1 to Week 8

Treatment Comparison Tmt 1	vs. Tmt 2	N Tmt 1	N Tmt 2	LS Mean (SE) Tmt 1	LS Mean (SE) Tmt 2	Difference (Tmt 1 - Tmt 2) LS Mean (SE)	95% CI	p-value
Mean Change								
OM40	vs. Placebo	108	96	-5.5 (3.96)	2.1 (4.25)	-7.6 (5.81)	(-19.0, 3.8)	0.0962
AML10	vs.	108		-3.4 (3.96)		-5.5 (5.81)	(-16.9, 7.0)	0.3737
OM20/AML5	vs.	117		-3.0 (3.81)		-5.1 (5.71)	(-16.3, 6.1)	0.1971
OM40/AML10	vs.	113		-3.2 (3.88)		-5.3 (5.76)	(-16.5, 6.1)	0.1829
OM40/AML10	vs. OM40	113	108	-3.2 (3.88)	-5.5 (3.96)	2.3 (5.54)	(-8.5, 13.2)	0.2359
	vs. AML10		108		-3.4 (3.96)	-1.7 (5.55)	(-12.6, 9.2)	0.3784
OM20/AML5	vs. OM40	117	108	-3.0 (3.81)	-5.5 (3.96)	2.5 (5.49)	(-8.3, 13.3)	0.5242
	vs. AML10		108		-3.4 (3.96)	-1.6 (5.50)	(-12.4, 9.2)	0.3881
Percent Change								
OM40	vs. Placebo	108	96	55.3 (21.93)	90.3 (23.31)	-35.3 (31.87)	(-97.8, 27.4)	0.1351
AML10	vs.	108		48.6 (21.93)		-41.7 (31.86)	(-104.1, 20.9)	0.0954
OM20/AML5	vs.	117		50.9 (20.88)		-39.4 (31.31)	(-100.9, 22.1)	0.1043
OM40/AML10	vs.	113		52.3 (21.23)		-38.0 (31.59)	(-100.1, 23.8)	0.1135
OM40/AML10	vs. OM40	113	108	52.3 (21.23)	55.2 (21.72)	-3.0 (30.40)	(-62.8, 56.7)	0.4604
	vs. AML10		108		48.6 (21.74)	3.5 (30.44)	(-56.3, 63.3)	0.4561
OM20/AML5	vs. OM40	117	108	50.9 (20.88)	55.2 (21.72)	-4.2 (30.16)	(-63.4, 55.0)	0.4441
	vs. AML10		108		48.6 (21.74)	2.3 (30.16)	(-56.9, 61.5)	0.4697

1.3.3 Safety Evaluation

For the safety population, total overall mean compliance to study medication was 97.4% and ranged from 96.9% for placebo group to 98.4% for the OM10mg/AMK5mg group. Concomitant Medications was similar among the treatment groups. A total of 79.3% of the safety population used concomitant medication during the double blind period. The most commonly used medications were HMG Co A reductase inhibitors (19.7%) propionic acid derivatives (19.3%); platelet aggregation inhibitors (17.8%); and plain multivitamins (14.6%). There were no significant differences among the treatment groups with regard to the use of specific concomitant medications.

Possible drug-related adverse reactions during the double-blind period occurring in patients treated with AZOR at about the same or greater incidence than patients receiving placebo include edema, hypotension, orthostatic hypotension, rash, pruritus, palpitation, urinary frequency, and nocturia.

The adverse event profile obtained from 44 weeks of open-label combination therapy with amlodipine plus olmesartan was however similar to that observed during the 8-week, double-blind, placebo-controlled period.

The overall safety evaluation was carried out on the pivotal study with a double blind period of 8 weeks followed by an open label period of 44 weeks. The reports on 120 day safety update will also be reviewed as well as safety data from one completed add-on study - CS8663-A-E302. E- 303 is an ongoing study in Europe. Table 27 shows comparisons of exposure to AZOR during the development program. The duration of exposure in the double blind and open label study is presented in Tables 27 – 29 below.

Table 27: Comparisons of Duration of exposure between double blind, open label and monotherapy

Study	No of Patients	Average number of days ± SD
U301 double blind – 8wks	1940	Median : 56±
U301 -open label - 44 weeks	1684	Mean: 278 ±76.73
E302 –monotherapy-add-on	722	*56.5 ± 8.91
E303-monotherapy – ongoing	1012	*56.2 ± 10.08

*Not in US IND. Note similarity in duration of exposure with double blind period in

Table 27 reflects exposure to AZOR in more than 1600 patients including more than 1000 exposed for at least 6 months and more than 700 exposed for 1 year.
AZOR was studied in one placebo-controlled factorial trial. The population had a mean age of 54 years and included approximately 55% males. Seventy-one percent were Caucasian and 25% were Black. Patients received doses ranging from 5/20 mg to 10/40 mg orally once daily. The duration of exposure is in Tables 27-29 and in Section 7.

Table 28: Duration of exposure during the double blind period – Period II

Treatment	N[2]	Extent of Exposure (Days)[1]			
		Mean ± SD	Median	Minimum	Maximum
Placebo	162	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	163	52.5 ± 14.60	56.0	1	89
OM10/AML10	163	51.9 ± 14.27	56.0	1	101
OM20/AML10	160	54.3 ± 10.88	56.0	1	67
OM40/AML10	163	54.3 ± 10.57	56.0	7	71
Total	1940	53.0 ± 12.73	56.0	1	101

[1] 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.
SD = standard deviation.
Source: Post-text Table 14.1.13

Table 29:Mean Duration of exposure during the open label period (wk 8 – wk 52) -

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[3]
Extent of Exposure (Days)[1]					
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 (%)[2] 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)

[1] 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.
[2] Percentage is calculated using the number of patients exposed to each dosing regimen as the denominator.
[3] 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

Duration of exposure during the open label extension period is presented in Section 7.
Adverse events- Study CS8663-A-U301- Pivotal factorial study.
A total of 1020 (52.6% of 1940) patients experienced a treatment-emergent adverse event (TEAE) during the study. Across the 12 treatment groups the percentage experiencing a TEAE ranged from 45.3% to 58.9%, with no apparent trend in the distribution of TEAEs among the treatment groups (placebo incidence: 56.2%). Drug-related TEAEs were experienced by a total of 521 (26.9%) patients, ranging from 19.6% to 33.1% with the incidence in the placebo group being 29.6%. Again, there was no trend observed among the treatment groups with regard to differences in the percentage of patients experiencing drug-related TEAEs. Across all treatment groups, most TEAEs and drug-related TEAEs were considered mild in intensity.

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 (Section 7). However, there were three major adverse events that were noteworthy. These include: Edema, Hypotension, and laboratory abnormalities (chemistry and hematology).
An overview of the frequencies and severity of adverse events during the double blind period is presented in tables 5a 5b and 5c below.

Table 5a: Overview of Adverse events-Period II

Table 5
Overview of Adverse Events - Number (%) of Patients
Double-blind Treatment Period

Adverse Event Category	Placebo (N=162)	OM10 (N=161)	OM20 (N=161)	OM40 (N=162)	AML5 (N=161)	AML10 (N=163)
Treatment-Emergent Adverse Events (TEAE) [1]						
All AEs	91 (56.2)	88 (54.7)	83 (51.6)	78 (48.1)	73 (45.3)	90 (55.2)
Drug-Related [2] AEs	48 (29.6)	43 (26.7)	36 (22.4)	40 (24.7)	32 (19.9)	54 (33.1)
TEAE by Maximum Severity						
All AEs						
Mild	53 (32.7)	54 (33.5)	48 (29.8)	45 (27.8)	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)
Drug-Related AEs						
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)	15 (9.2)
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)
Serious AEs During Randomized Treatment Period						
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)
Discontinuation Due to AEs During Randomized Treatment Period						
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)	4 (2.5)	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 5b: Overview of Adverse events- Period II

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Table 5
Overview of Adverse Events - Number (%) of Patients
Double-blind Treatment Period

Adverse Event Category	OM10/AML5 (N=159)	OM10/AML10 (N=162)	OM20/AML5 (N=161)	OM20/AML10 (N=160)	OM40/AML5 (N=162)	OM40/AML10 (N=162)	Total (N=1940)
Treatment-Emergent Adverse Events (TEAE) [1]							
All AEs	74 (45.4)	92 (56.8)	90 (55.9)	85 (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)	48 (29.6)	521 (26.9)
TEAE by Maximum Severity							
All AEs							
Mild	45 (27.6)	53 (32.7)	49 (30.4)	54 (33.8)	47 (29.0)	47 (29.0)	590 (30.4)
Moderate	26 (16.0)	35 (21.6)	36 (22.4)	25 (15.6)	31 (19.1)	33 (20.4)	375 (19.3)
Severe	3 (1.8)	4 (2.5)	5 (3.1)	6 (3.8)	5 (3.1)	7 (4.3)	55 (2.8)
Drug-Related AEs							
Mild	24 (14.7)	32 (19.8)	29 (18.0)	36 (22.5)	31 (19.1)	30 (18.5)	346 (17.8)
Moderate	8 (4.9)	18 (11.1)	13 (8.1)	11 (6.9)	13 (8.0)	15 (9.3)	156 (8.0)
Severe	0 (0.0)	1 (0.6)	2 (1.2)	1 (0.6)	2 (1.2)	2 (1.2)	19 (1.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Serious AEs During Randomized Treatment Period							
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)
Discontinuation Due to AEs During Randomized Treatment Period							
All AEs	0 (0.0)	11 (6.8)	4 (2.5)	3 (1.9)	6 (3.7)	9 (5.6)	113 (5.8)
Drug-Related AEs	0 (0.0)	9 (5.6)	3 (1.9)	1 (0.6)	4 (2.5)	8 (4.9)	74 (3.8)

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.

During the open label extension period, adverse events were experienced by 573 (34.1%) patients on OM40/AML5, 394 (35.8%) patients on OM40/AML10, 263 (35.9%) patients on OM40/AML10/HCTZ12.5 and 172 (39.6%) patients on OM40/AML10/HCTZ25mg. Across the 4 treatment regimens the frequency of edema ranged from 8.3% to 11.2%, the frequency of dizziness ranged from 2.3% to 3.7% and headache ranged from 1.6% to 1.9%. The frequency of drug related edema ranged from 6.7% to 8.9%. Hypotension was experienced by 0.6% to 1.1% of patients on the 3 lowest doses and 0.5% on OM40/AML10/HCTZ25.

Table 5c: Frequencies of adverse events at onset dosing regimen Period III with HCTZ

Table 15
Overview of Adverse Events
Number (%) of Patients by Onset Dosing Regimen
Open-Label Treatment Period

Adverse Event Category	OM40/AML5 (N=1678) n (%)	OM40/AML10 (N=1100) n (%)	OM40/AML10/HCTZ12.5 (N= 782) n (%)	OM40/AML10/HCTZ25 (N= 424) n (%)	Total (N=1684) n (%)
All AEs	573 (34.1)	394 (35.8)	268 (35.9)	172 (39.6)	1056 (62.7)
Drug-Related [1] AEs	212 (12.6)	156 (14.2)	108 (14.9)	62 (14.6)	458 (27.2)
All AEs by Maximum Severity					
Mild	310 (18.5)	202 (18.5)	144 (19.7)	104 (24.0)	483 (28.7)
Moderate	226 (13.5)	161 (14.6)	102 (13.9)	57 (13.1)	480 (28.5)
Severe	37 (2.2)	30 (2.7)	17 (2.3)	11 (2.5)	93 (5.5)
Drug-Related AEs by Maximum Severity					
Mild	139 (8.3)	98 (8.9)	70 (9.6)	46 (10.6)	280 (16.6)
Moderate	68 (4.1)	54 (4.9)	35 (4.8)	16 (3.7)	166 (9.9)
Severe	5 (0.3)	4 (0.4)	3 (0.4)	0 (0.0)	12 (0.8)
Death	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Serious AEs During Open-label Treatment Period					
All SAEs	25 (1.5)	20 (1.8)	12 (1.6)	6 (1.8)	66 (3.9)
Drug-Related SAEs	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Discontinuation Due to AEs During Open-label Treatment Period					
All AEs	26 (1.5)	14 (1.3)	8 (1.1)	9 (2.1)	60 (3.6)
Drug-Related AEs	17 (1.0)	9 (0.8)	2 (0.2)	4 (0.9)	33 (2.0)

Adverse events

A total of 1020 (52.6% of 1940) patients experienced a treatment-emergent adverse event (TEAE) during the study. Across the 12 treatment groups the percentage experiencing a TEAE ranged from 45.3% to 58.9%, with no apparent trend in the distribution of TEAEs among the treatment groups (placebo incidence: 56.2%). Drug-related TEAEs were experienced by a total of 521 (26.9%) patients, ranging from 19.6% to 33.1% with the incidence in the placebo group being 29.6%. Again, there was no trend observed among the treatment groups with regard to differences in the percentage of patients experiencing drug-related TEAEs. Across all treatment groups, most TEAEs and drug-related TEAEs were considered mild in intensity.

This overview of the adverse events during the double blind period gives a reasonable assessment of adverse events.

1) Edema: Edema is a known, dose-dependent adverse effect of amlodipine but not of olmesartan. In the randomized trial of AZOR, the reporting of edema was actively solicited, using a protocol-specified ascertainment method. As a consequence, the rates observed in the placebo, amlodipine, and olmesartan groups were all higher than those described in the labeling for amlodipine or olmesartan.

The proactive approach used for this study revealed a relatively higher rate of peripheral edema. The sponsor made a post-hoc modification to the edema shift analysis to normalize the relative overestimation in the frequency of peripheral edema. In this modified shift analysis, the "no edema" category was combined with the "mild edema" category.

The modified shift analysis, carried out by the sponsor, included no edema (combining the original "no edema" and "mild edema" categories), edema (combining the original "moderate pitting," "deep pitting-minor leg swelling," and "deep pitting-major leg swelling" categories), and the original edema categories of

"moderate pitting," "deep pitting-minor leg swelling," and "deep pitting-major leg swelling" edema presented separately .

Placebo-Subtracted Incidence of Edema during the Double-Blind Treatment Period (See Figure 14)

		Olmesartan Medoxomil			
		Placebo	10 mg	20 mg	40 mg
Amlodipine	Placebo	0%*	2.0%	(-2.4%)	6.2%
	5 mg	0.7%	8.6%	5.7%	6.2%
	10 mg	24.5%	14.2%	13.3%	11.2%

*12.3%=actual placebo incidence

This reviewer does not agree with the proposed modification by the sponsor because this approach was not prespecified in the approved protocol, knowing that the combined tablet was amlodipine, a dose-dependent component, and olmesartan a non dose-dependent component; the latter was to reduce the edema effects of amlodipine.

If combination tablet was to be used as initial therapy or in preference to olmesartan, or other anti-hypertensive drugs that are not edema dose-dependent, then patients receiving the combination will be at a higher risk of peripheral edema.

In this study, 16 (9.8%) patients in the AML 10 mg group shifted from no edema at baseline to edema during the randomized treatment period. In contrast, 1.9% of the patients treated with placebo, 1.2% to 7.4% of patients treated with olmesartan medoxomil monotherapy, and 2.5% of patients treated with amlodipine 5 mg monotherapy had a shift from no edema to edema.

Across the combination therapy groups, the frequency of shift in this direction ranged from 2.5% to 9.3%. With the increasing of olmesartan medoxomil dose in combination with amlodipine 10 mg, the frequency of the shift from no edema to edema became progressively less.

Across all treatment groups, the frequency of edema was generally higher in women than men.

Outside of an interaction that modified the frequency of peripheral edema (discussed above) there appears to be no major safety issues that were caused by the concomitant use of olmesartan medoxomil with amlodipine compared to olmesartan alone.

Clinical Studies Experience

Only 18 (0.9%) patients in Period II discontinued due to edema and only 5(0.3%) patients who completed Period II did not enter into Period III suggesting that the frequency of edema is less with continued treatment. The frequency of edema during Period III was 8.3% with OM40/AML5, 11.2% with OM40.AML10, 11.2% with OM40/AML10/HCTZ12.5 and 8.5% with OM40/AML10/HCTZ25.

2) Laboratory abnormalities

There are statistically significant differences in laboratory values in mean change from baseline to end of week 8 in patients exposed to the combined tablet. These include Hemoglobin, hematocrit, red blood count, platelet count, alkaline phosphatase, ALT, Sodium, urea nitrogen and uric acid (Table 30). In addition there appears to be increased elevation of liver enzymes (ALT and AST) that appeared to increase with time (Figures

Laboratory Parameter	Dose Monotherapy	Dose of Combined Tablet	Change from baseline to week 8 p-value
		OM40/AML5	<.0001
		OM40/AML10	<.0001
Alk. Phosphatase	AML5 p=0.0006	OM10/AML5	
	AML10p=0.0001	OML10/AML10	0.0575
		OM20/AML5	
		OM20/AML10	
		OM40/AML5	
		OM40/AML10	0.0643
ALT	OM40 p=0.0115	OM10/AML5	
	AML5 p=0.0139	OML10/AML10	
		OM20/AML5	
		OM20/AML10	
		OM40/AML5	
		OM40/AML10	P=0.0370
Sodium		OM10/AML5	<.0001
		OML10/AML10	0.0020
		OM20/AML5	0.0700
		OM20/AML10	0.0007
		OM40/AML5	0.0970
		OM40/AML10	<0.0001
Urea Nitrogen		OM10/AML5	0.0006
		OML10/AML10	0.0901
		OM20/AML5	0.1501
		OM20/AML10	0.0015
		OM40/AML5	0.0126
		OM40/AML10	0.0016
Uric Acid	OM40 p=0.001	OM10/AML5	0.0095
	AML5 p=<.0001	OML10/AML10	0.0024
	AML10 p<.0001	OM20/AML5	NS
		OM20/AML10	<.0001
		OM40/AML5	NS
		OM40/AML10	NS

Of the clinically significant laboratory abnormalities reported, elevations in liver transaminases and platelet counts are noteworthy.
A total of 71 (3.7%) patients had marked elevations of GGT with an incidence that ranged from 1.3 to 8.1% across the treatment groups during the study including the open label period.
Table 31 summarizes the list of patients with clinically significant laboratory abnormalities

Table 31: Patients with clinically significant Lab abnormalities-Safety population

Table 85: Patients with Clinically Significant Laboratory Abnormalities – Safety Population

Treatment Patient Number	Adverse Event (Preferred Term)	Parameter (Normal Range)	Highest Value
Placebo			
134-014	Blood ALP increased	ALP (32 – 72 mU/mL)	81 mU/mL
136-038	GGT increased	GGT 5 – 29 mU/mL)	128 mU/mL
162-003	Hepatic enzyme increased	ALT (5 – 25 mU/mL) AST (8 – 22 mU/mL) GGT (5 – 29 mU/mL)	39 mU/mL 31 mU/mL 104 mU/mL
OM40			
174-001	GGT increased	GGT (5 – 29 mU/mL)	560 mU/mL
AML10			
174-005	Blood ALP increased GGT increased	ALP (32 – 72 mU/mL) GGT (5 – 29 mU/mL)	324 mU/mL 345 mU/mL
OM10/AML5			
114-038	Hepatic enzyme increased	ALP (32 – 72 mU/mL) ALT (5 – 25 mU/mL) AST (8 – 22 mU/mL) GGT (5 – 29 mU/mL)	76 mU/mL 92 mU/mL 41 mU/mL 37 mU/mL
OM20/AML5			
162-016	GGT increased	GGT (5 – 29 mU/mL)	54 mU/mL
OM20/AML10			
105-019	ALT increased AST increased	ALT (5 – 25 mU/mL) AST (8 – 22 mU/mL)	71 mU/mL 36 mU/mL
OM40/AML10			
003-024	Hepatic enzyme increased	ALT (5 – 25 mU/mL) AST (8 – 22 mU/mL) GGT (5 – 29 mU/mL)	112 mU/mL 54 mU/mL 62 mU/mL
147-008	Hepatic enzyme increased	ALP (32 – 72 mU/mL) AST (8 – 22 mU/mL) GGT (5 – 29 mU/mL)	80 mU/mL 37 mU/mL 76 mU/mL

Clinically significant laboratory abnormalities were identified as adverse events reported by the investigator due to significant changes in the given parameter relative to the patient's measurement history.
ALP = alkaline phosphatase, ALT = alanine transaminase, AML = amlodipine, AST = aspartate transaminase, GGT = gamma-glutamyl-transferase, OM = olmesartan medoxomil.
Source: Post-text Table 14.3.4.15

Table 32 shows statistically significant increase of mean platelet count from baseline to end of week 8 with all doses of the combined tablet. The mean platelet counts in patients administered AZOR 20/10 versus 20 mg olmesartan monotherapy and shows a statistically significant increase ($p<0.0324$) and similarly patients given AZOR 20/10 versus 10 mg amlodipine shows a statistically significant increase ($p<0.0671$). The clinical significance of this is not known. Suffice it to say that there is an association between polycythemia vera (PV) with increased platelets as a component (in the so-called "Hypertrophic" form of hypertension-) in Gaisbock's syndrome. While the enrolled patients did not have PV, the statistically significant increase in platelets which may be thrombocytosis or result from thrombocytopoeisis appears drug related. There are no data on megakaryocytes in this study that might distinguish between the two pathogenetic mechanisms for the drug related changes.

Table 33 shows statistically significant increase of mean platelet count from baseline to end of week 8 with all doses of the combined tablet and also amlodipine monotherapy.

Table 32:Comparison of platelet counts between high dose and monotherapy at week 8

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

Source: Dr S. Bai

Table 33: Change in Platelet count from baseline to wk 8- Period II

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Table 14.3.4.2
Change in Hematology Parameters From Baseline to
Week 8/Early Termination (ET)
Safety Population
Period II - Day 1 to Week 8

Parameter (unit)/ Treatment	N [1]	-Baseline [2]- Mean	SD	--Week 8/ET-- Mean	SD	Change Mean	SD	p-value [3]
Platelet Count (E/cu mm)								
Placebo	148	257.27	63.115	257.33	70.340	0.05	37.790	0.9868
CM10	152	264.08	62.350	267.14	62.397	3.06	30.854	0.2236
CM20	148	253.66	60.334	256.99	62.726	3.32	35.302	0.2538
CM40	154	262.93	65.239	269.12	67.821	6.19	34.991	0.0227
AML5	151	254.39	63.187	264.57	67.088	10.18	39.341	0.0018
AML10	156	253.62	64.119	274.61	64.269	22.98	31.614	<.0001
CM10/AML5	152	262.69	68.788	274.71	67.667	12.02	30.868	<.0001
CM10/AML10	151	258.86	67.051	276.17	65.576	17.19	39.280	<.0001
CM20/AML5	152	268.69	67.736	278.76	73.261	12.68	30.797	<.0001
CM20/AML10	145	255.69	57.736	279.42	63.776	28.83	36.830	<.0001
CM40/AML5	149	254.77	68.237	267.45	64.864	12.68	37.458	<.0001
CM40/AML10	150	256.48	61.725	275.51	69.241	19.03	33.514	<.0001

Other abnormal laboratory values in hematology and chemistry are presented below but they have been abstracted by this reviewer and summarized in Tables 30 and also in 44.

Table 34: Change in hemoglobin from baseline to wk 8- Period II

Table 14.3.4.2
Change in Hematology Parameters From Baseline to
Week 8/Early Termination (ET)
Safety Population
Period II - Day 1 to Week 8

Parameter (unit)/ Treatment	N [1]	-Baseline [2]- Mean	SD	--Week 8/ET-- Mean	SD	Change Mean	SD	p-value [3]
Hemoglobin (gm/dl)								
Placebo	148	14.36	1.245	14.53	1.328	0.17	0.703	0.0038
CM10	152	14.31	1.335	14.35	1.338	0.03	0.702	0.6402
CM20	148	14.53	1.350	14.55	1.327	0.02	0.667	0.7585
CM40	154	14.12	1.356	14.05	1.457	-0.07	0.837	0.2798
AML5	151	14.37	1.387	14.46	1.417	0.10	0.684	0.0712
AML10	156	14.30	1.402	14.37	1.239	0.07	0.770	0.2984
CM10/AML5	152	14.32	1.327	14.18	1.381	-0.14	0.635	0.0068
CM10/AML10	151	14.16	1.579	13.95	1.435	-0.21	0.813	0.0021
CM20/AML5	152	14.32	1.486	14.15	1.534	-0.16	0.589	0.0167
CM20/AML10	145	14.29	1.445	14.09	1.294	-0.21	0.681	0.0003
CM40/AML5	149	14.24	1.365	14.11	1.282	-0.13	0.930	0.0869
CM40/AML10	150	14.40	1.410	14.02	1.334	-0.37	0.795	<.0001

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Table 35: Change in Hematocrit from baseline to wk 8- Period II

Table 14.3.4.2
Change in Hematology Parameters From Baseline to
Week 8/Early Termination (ET)
Safety Population
Period II - Day 1 to Week 8

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Parameter (unit)/ Treatment	N [1]	-Baseline [2]- Mean	SD	--Week 8/ET-- Mean	SD	----------Change---------- Mean	SD	p-value [3]
Hematocrit (%)								
Placebo	146	43.0	3.67	43.4	3.83	0.5	2.48	0.0296
OM10	152	42.7	3.81	42.7	3.96	0.1	2.34	0.6283
OM20	148	43.4	3.66	43.3	3.82	-0.1	2.25	0.5966
OM40	154	42.3	3.91	41.9	4.25	-0.4	2.54	0.0880
AML5	151	42.9	3.91	43.0	4.02	0.2	2.16	0.3243
AML10	156	42.7	4.17	42.7	3.81	-0.0	2.53	0.9799
OM10/AML5	152	42.7	3.80	42.3	3.76	-0.5	2.20	0.0961
OM10/AML10	151	42.3	4.57	41.5	4.28	-0.7	2.70	0.0009
OM20/AML5	151	42.9	4.23	42.2	4.49	-0.5	2.31	0.0083
OM20/AML10	145	42.8	4.16	41.9	3.69	-0.9	2.23	<.0001
OM40/AML5	149	42.8	3.93	42.1	3.56	-0.8	2.95	0.0018
OM40/AML10	150	43.6	4.11	41.6	3.80	-1.9	2.39	<.0001

Table 36: Change in RBC from baseline to wk 8- Period II

Table 14.3.4.2
Change in Hematology Parameters From Baseline to
Week 8/Early Termination (ET)
Safety Population
Period II - Day 1 to Week 8

Parameter (unit)/ Treatment	N [1]	-Baseline [2]- Mean	SD	--Week 8/ET-- Mean	SD	----------Change---------- Mean	SD	p-value [3]
Red Blood Cell (10**6/cu mm)								
Placebo	146	4.730	0.4866	4.793	0.4182	0.063	0.2599	0.0040
OM10	152	4.701	0.4378	4.718	0.4433	0.017	0.2351	0.3639
OM20	148	4.788	0.4337	4.804	0.4467	0.006	0.2425	0.7736
OM40	154	4.718	0.4868	4.699	0.5131	-0.019	0.2795	0.4874
AML5	151	4.738	0.3973	4.781	0.4131	0.043	0.2267	0.0274
AML10	156	4.725	0.4711	4.763	0.4315	0.038	0.2356	0.0875
OM10/AML5	152	4.803	0.4746	4.764	0.4595	-0.040	0.2474	0.0502
OM10/AML10	151	4.698	0.5009	4.631	0.4684	-0.067	0.2771	0.0037
OM20/AML5	151	4.722	0.4582	4.678	0.5060	-0.044	0.2455	0.0295
OM20/AML10	145	4.745	0.4687	4.671	0.4527	-0.074	0.2235	0.0001
OM40/AML5	149	4.768	0.3810	4.703	0.3938	-0.065	0.3128	0.0125
OM40/AML10	150	4.765	0.4674	4.638	0.4394	-0.127	0.2511	<.0001

Table 37: Change in Alkaline phosphate from baseline to wk 8- Period II

Table 14.3.4.1
Change in Chemistry Parameters From Baseline to Week 8/Early Termination (ET)
Safety Population
Period II - Day 1 to Week 8

Parameter (unit)/ Treatment	N [1]	-Baseline [2]- Mean	SD	--Week 8/ET-- Mean	SD	----------Change---------- Mean	SD	p-value [3]
Alkaline Phosphatase (mu/mL)								
Placebo	141	62.4	23.54	61.8	26.86	-0.6	6.34	0.2397
OM10	154	58.7	15.73	58.0	15.31	-0.7	6.03	0.1669
OM20	148	60.1	15.62	59.6	18.50	-0.5	11.48	0.5677
OM40	156	61.7	18.83	60.4	19.58	-1.3	7.96	0.0448
AML5	154	56.5	15.06	58.8	15.69	2.3	8.12	0.0006
AML10	155	61.3	21.29	64.5	26.89	3.2	10.11	0.0001
OM10/AML5	154	59.1	14.41	58.7	14.44	-0.4	5.88	0.5288
OM10/AML10	152	59.7	18.22	61.0	18.82	1.2	8.80	0.0575
OM20/AML5	152	59.4	15.87	60.7	22.97	1.3	11.49	0.1687
OM20/AML10	148	57.6	13.39	57.3	13.13	-0.3	8.01	0.6401
OM40/AML5	152	57.3	16.41	57.2	17.08	-0.1	9.12	0.8878
OM40/AML10	153	58.2	16.96	57.1	16.34	-1.1	7.55	0.0643

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Table 38: Change in ALT from baseline to wk 8- Period II

Table 14.3.4.1
Change in Chemistry Parameters From Baseline to Week 8/Early Termination (ET)
Safety Population
Period II - Day 1 to Week 8

Parameter (unit)/ Treatment	N [1]	-Baseline [2]- Mean	SD	--Week 8/ET-- Mean	SD	Change Mean	SD	p-value [3]
ALT (su/mL)								
Placebo	148	18.5	11.75	19.1	11.38	0.6	4.87	0.1150
OM10	154	18.8	11.45	19.6	12.58	0.8	5.51	0.2486
OM20	148	19.3	8.68	21.8	17.12	2.4	16.35	0.0723
OM40	157	17.1	8.59	18.4	9.49	1.3	6.31	0.0115
AML5	154	18.8	9.66	19.1	10.98	1.1	5.64	0.0130
AML10	155	18.1	9.45	18.8	8.21	0.7	7.02	0.2141
OM10/AML5	154	19.0	8.27	19.8	11.00	0.8	5.33	0.1138
OM10/AML10	152	18.3	9.87	20.4	16.66	2.1	15.78	0.1031
OM20/AML5	152	18.8	10.81	21.6	31.09	3.8	30.79	0.2325
OM20/AML10	148	19.1	11.30	19.9	13.86	0.8	9.05	0.2959
OM40/AML5	152	18.9	11.63	19.4	10.50	0.6	9.38	0.3979
OM40/AML10	153	18.2	10.95	19.6	13.07	1.4	5.42	0.0370

There were a few other laboratory measurement changes that signify a safety concern (Figures 5 – 7 and Section 7). There were no significant mean changes or shifts in potassium levels, or any of the renal parameters in any of the treatment groups. There were 3 patients with TEAEs of increased potassium and 3 patients with TEAEs of decreased potassium. These changes were observed across the combination and monotherapy dose groups (Section 7).
There were no shifts with the chloride but there are significant differences between the treatment groups in sodium (Tables 30 and 39). There are also statistically significant differences in alkaline phosphatase with shifts.

Table 39: Change in Sodium from baseline to wk 8- Period II

Table 14.3.4.1
Change in Chemistry Parameters From Baseline to Week 8/Early Termination (ET)
Safety Population
Period II - Day 1 to Week 8

Parameter (unit)/ Treatment	N [1]	-Baseline [2]- Mean	SD	--Week 8/ET-- Mean	SD	Change Mean	SD	p-value [3]
Sodium (meq/L)								
Placebo	148	141.0	2.63	140.4	2.50	-0.6	2.75	0.0030
OM10	154	141.2	2.39	140.4	2.48	-0.9	2.76	0.0002
OM20	148	141.1	2.02	140.3	2.57	-0.8	2.89	0.0009
OM40	157	140.9	2.61	140.2	2.35	-0.8	2.76	0.0007
AML5	154	140.8	2.60	140.5	2.54	-0.3	3.20	0.2806
AML10	155	141.0	2.49	140.6	2.78	-0.5	2.83	0.0488
OM10/AML5	154	141.2	2.36	140.3	2.58	-0.9	2.74	<.0001
OM10/AML10	152	141.1	2.31	140.3	2.67	-0.8	2.84	0.0020
OM20/AML5	152	140.9	2.46	140.4	2.58	-0.4	2.98	0.0706
OM20/AML10	148	141.3	2.66	140.4	2.28	-0.9	3.00	0.0007
OM40/AML5	152	141.0	2.79	140.5	2.71	-0.5	3.35	0.0970
OM40/AML10	153	141.0	2.44	140.1	2.74	-0.9	2.90	<.0001

Table 40: Change in Blood Urea Nitrogen from baseline to wk 8- Period II

Table 14.3.4.1
Change in Chemistry Parameters From Baseline to Week 8/Early Termination (ET)
Safety Population
Period II - Day 1 to Week 8

Parameter (unit)/ Treatment	N [1]	-Baseline [2]- Mean	SD	--Week 8/ET-- Mean	SD	----------Change---------- Mean	SD	p-value [3]
Blood Urea Nitrogen (mg/dL)								
Placebo	148	14.1	4.08	14.8	4.44	0.6	4.01	0.0533
OM10	154	15.1	4.78	15.3	4.88	0.2	3.22	0.4533
OM20	148	14.1	3.97	14.9	4.55	0.8	3.56	0.0077
OM40	157	14.6	4.10	15.4	4.54	0.7	3.23	0.0049
AML5	154	14.3	4.01	13.8	3.88	-0.5	3.39	0.0935
AML10	155	14.3	4.65	14.6	4.74	-0.8	3.47	0.8715
OM10/AML5	154	13.7	3.76	14.6	4.09	0.9	3.32	0.0006
OM10/AML10	152	14.9	4.31	15.4	4.98	0.5	3.61	0.0301
OM20/AML5	152	15.2	4.33	15.7	4.23	0.5	4.15	0.1501
OM20/AML10	148	14.1	3.83	15.0	4.25	0.9	3.52	0.0015
OM40/AML5	152	14.8	4.77	15.5	5.38	0.7	3.41	0.0126
OM40/AML10	153	14.1	4.01	15.0	3.78	0.9	3.45	0.0016

Table 41: Change in Uric acid from baseline to wk 8- Period II

Table 14.3.4.1
Change in Chemistry Parameters From Baseline to Week 8/Early Termination (ET)
Safety Population
Period II - Day 1 to Week 8

Parameter (unit)/ Treatment	N [1]	-Baseline [2]- Mean	SD	--Week 8/ET-- Mean	SD	----------Change---------- Mean	SD	p-value [3]
Uric Acid (mg/dL)								
Placebo	148	6.07	1.371	6.23	1.521	0.16	0.855	0.0586
OM10	154	6.15	1.583	6.10	1.514	-0.05	0.735	0.4252
OM20	148	6.16	1.375	6.27	1.479	0.11	0.914	0.1285
OM40	157	6.08	1.473	6.31	1.620	0.23	0.871	0.0011
AML5	154	6.08	1.452	5.75	1.507	-0.32	0.741	<.0001
AML10	155	6.12	1.545	5.65	1.483	-0.48	0.902	<.0001
OM10/AML5	154	6.03	1.341	5.87	1.328	-0.16	0.758	0.0035
OM10/AML10	152	6.20	1.550	5.98	1.411	-0.22	0.884	0.0024
OM20/AML5	152	6.01	1.540	6.00	1.581	-0.02	0.908	0.8167
OM20/AML10	148	5.87	1.425	5.55	1.338	-0.31	0.913	<.0001
OM40/AML5	152	6.09	1.463	5.89	1.441	-0.19	0.882	0.1610
OM40/AML10	153	5.94	1.492	5.89	1.538	-0.05	1.002	0.5461

The sponsor claims that transient abnormalities of transaminases are expected in this population of patients who often have "fatty livers" and are often receiving other drugs that can cause elevations in these parameters. The elevated transaminases have not been shown to be transient. In fact the increase in enzyme level appears to be a function of time (Figures 5-7)

There are no data to support the sponsor's claim because the concomitant medications used by the patients do not appear to have produced the elevated transaminases. Furthermore this reviewer is not aware of any literature that supports the statement that "elevated transaminases are expected in this population of patients" because they tend to have "Fatty liver". In fact one of the exclusion criteria prohibits the enrolment of patients with abnormal transaminases.

Figure 5: Mean SGOT (AST) at baseline and at week 8/ET by treatment group-Period II-ITT

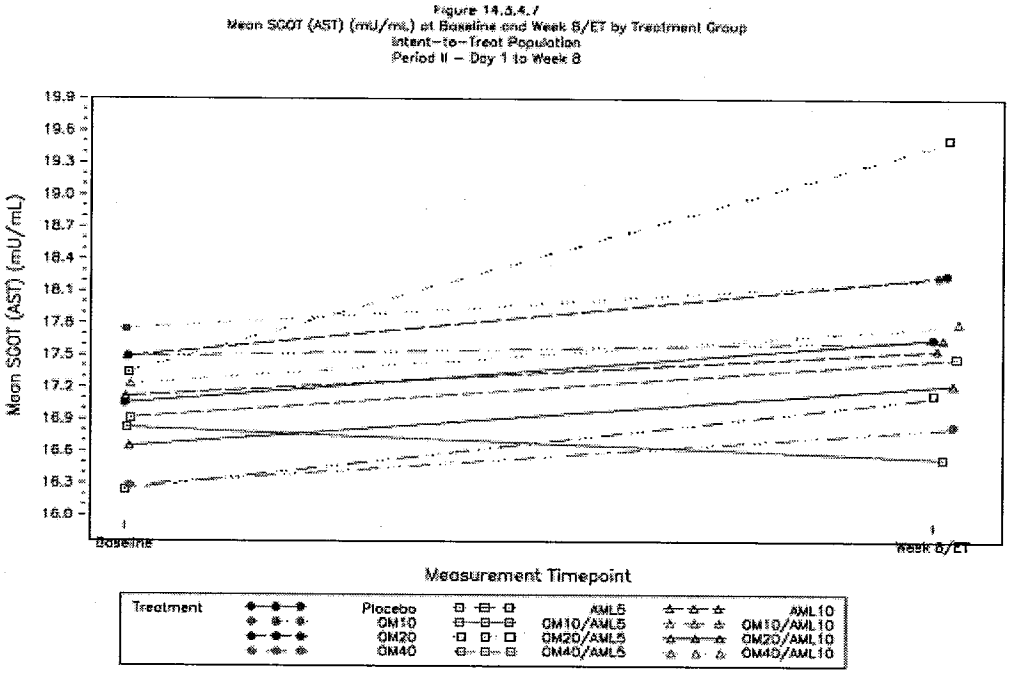
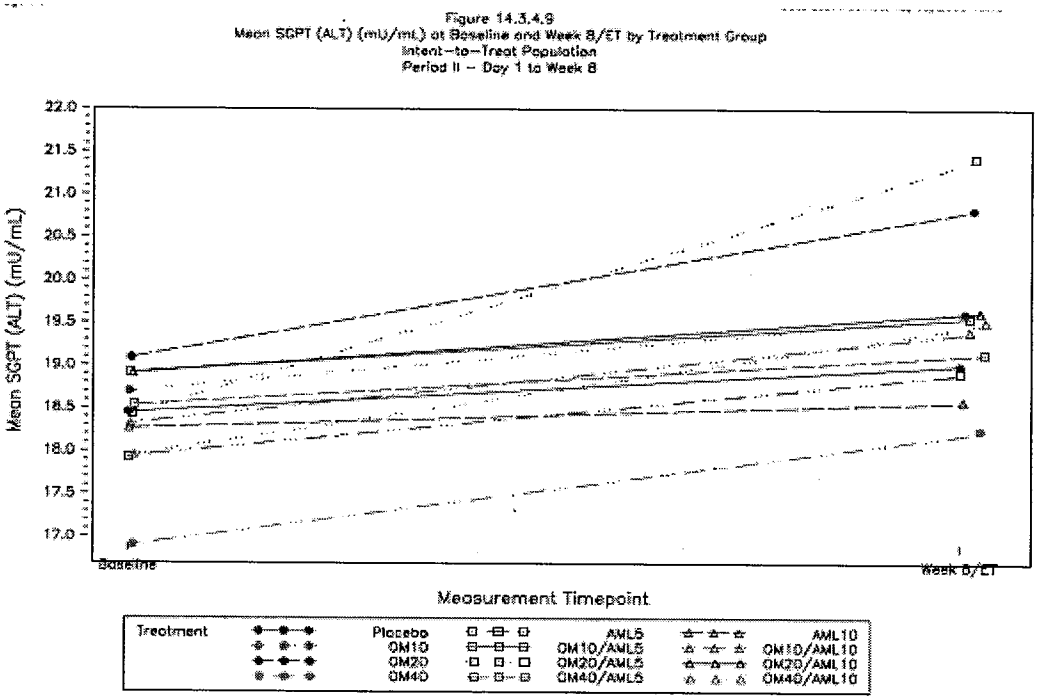
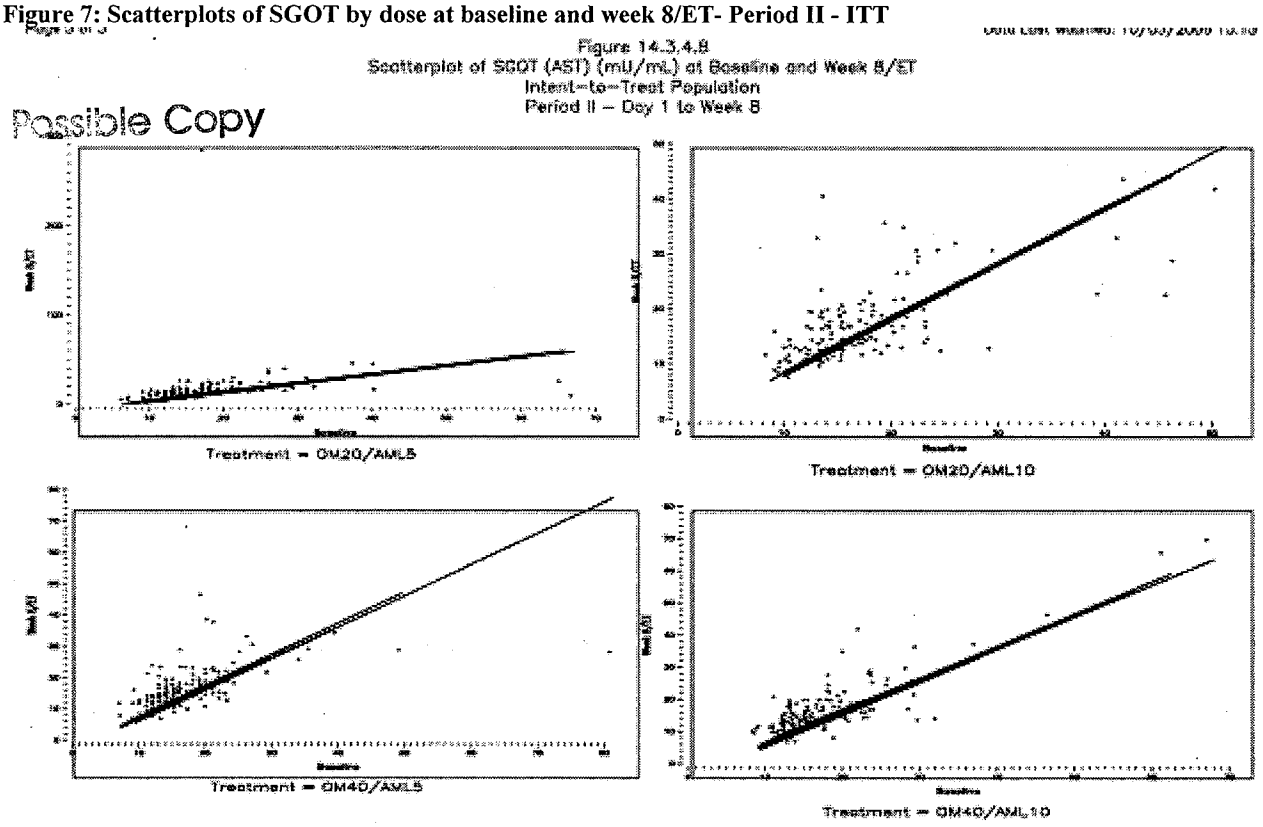


Figure 6:Mean SGPT (ALT) at baseline and at week 8/ET by treatment group-Period II-ITT



Appears This Way
On Original

Figure 7: Scatterplots of SGOT by dose at baseline and week 8/ET- Period II - ITT



3) Hypotension

The numbers of patients experiencing hypotension were small but 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). This is probably a manifestation of the magnitude of the blood pressure lowering by the combination tablet which on one hand predisposes to reaching the target blood pressure earlier and on the other hand predisposes to a higher frequency of hypotension.

Deaths

Two patients died during the study; 1 patient died during the double-blind treatment period while on placebo (murder) and 1 patient died during the washout phase (cerebrovascular accident) of the study. Both deaths were considered unrelated to study medication (Section 7). One other patient died during the open label period making a total or 3 unrelated to drug deaths throughout the entire study.

Serious Adverse events

A total of 25 (1.3%) patients had a treatment-emergent serious adverse event (SAE) during the study: 3 patients in the placebo group, 7 patients in the monotherapy groups, and 15 patients in the combination therapy groups. One patient in the OM 20 mg group experienced a drug-related SAE (cerebrovascular accident). In addition, 1

patient in the OM 10 mg + AML 5 mg group had an SAE (spontaneous incomplete abortion) that occurred 30 days after intake of last dose.

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.

The adverse event profile obtained from 44 weeks of open-label combination therapy with amlodipine plus olmesartan was similar to that observed during the 8-week, double-blind, placebo-controlled period.

The serious adverse events that were observed during the double blind and open label periods are presented in Tables 42 and 43,

Table 42: Patients with serious adverse events during Periods I and II

Table 79: Patients with Serious Adverse Events During the Washout and Double-Blind Treatment Periods

Treatment Group Patient Number	Age/Gender/Race	Adverse Event (Preferred Term)	Severity	Relationship to Study Medication	Duration of the Event	Action Taken	Outcome
Before randomization							
034-015	68/Male/White	Myocardial infarction	Moderate	Unrelated	3 Days	None	Recovered
044-005	43/Female/White	Cardiac failure congestive	Severe	Unrelated	4 Days	None	Recovered
060-028	72/Female/White	Cerebrovascular accident	Severe	Unrelated	1 Day	None	Death
125-015	44/Female/Black	Convulsion	Severe	Unrelated	5 Days	None	Recovered
132-035	75/Female/White	Hypertensive encephalopathy	Moderate	Unrelated	3 Days	None	Recovered
136-048	72/Female/White	Chronic obstructive pulmonary disease	Severe	Unrelated	Continuing	None	Adverse event still present
154-024	65/Female/White	Nephrolithiasis	Severe	Unrelated	2 Days	None	Recovered
160-018	70/Female/White	Cardiac failure congestive	Mild	Unrelated	3 Days	None	Recovered
Placebo							
027-022	41/Female/Black	Adenomyosis	Mild	Unrelated	19 Days	Study medication interrupted	Recovered
		Leiomyoma	Mild	Unrelated	19 Days	Study medication interrupted	Recovered
039-009	49/Male/Black	Murder	Severe	Unrelated	1 Day	Discontinued from study	Death
067-009	55/Male/White	Rash	Moderate	Unrelated	2 Days	None	Recovered
OM10							
123-004	44/Male/White	Chest pain	Moderate	Unrelated	4 Days	Discontinued from study	Recovered
OM20							
046-019	47/Female/Black	Hypertension	Moderate	Unlikely	2 Days	Study medication interrupted	Recovered
082-027	42/Female/Black	Cerebrovascular accident	Moderate	Unlikely	23 Days	Discontinued from study	Recovered
095-023	58/Male/White	Angina unstable	Severe	Unlikely	2 Days	Discontinued from study	Recovered with sequelae
099-017	58/Female/Black	Cerebrovascular accident	Severe	Probable	5 Days	Discontinued from study	Recovered
OM40							
003-034	71/Male/White	Gastrointestinal hemorrhage	Moderate	Unlikely	4 Days	Study medication interrupted	Recovered
AML10							
174-005	55/Male/White	Esophageal cancer metastatic	Severe	Unrelated	11 Days	None	Recovered with sequelae
OM10/AML5							
055-001	30/Female/White	Abortion spontaneous incomplete	Severe	Unrelated	2 Days	None	Recovered

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.

Table 43: Patients with serious adverse events during Periods I and II

Table 79: Patients with Serious Adverse Events During the Washout and Double-Blind Treatment Periods

Treatment Group Patient Number	Age/Gender/Race	Adverse Event (Preferred Term)	Severity	Relationship to Study Medication	Duration of the Event	Action Taken	Outcome
Before randomization							
034-015	68/Male/White	Myocardial infarction	Moderate	Unrelated	3 Days	None	Recovered
044-005	43/Female/White	Cardiac failure congestive	Severe	Unrelated	4 Days	None	Recovered
060-028	72/Female/White	Cerebrovascular accident	Severe	Unrelated	1 Day	None	Death
125-015	44/Female/Black	Convulsion	Severe	Unrelated	5 Days	None	Recovered
132-035	75/Female/White	Hypertensive encephalopathy	Moderate	Unrelated	3 Days	None	Recovered
136-048	72/Female/White	Chronic obstructive pulmonary disease	Severe	Unrelated	Continuing	None	Adverse event still present
154-024	65/Female/White	Nephrolithiasis	Severe	Unrelated	2 Days	None	Recovered
160-018	70/Female/White	Cardiac failure congestive	Mild	Unrelated	3 Days	None	Recovered
Placebo							
027-022	41/Female/Black	Adenomyosis	Mild	Unrelated	19 Days	Study medication interrupted	Recovered
		Leiomyoma	Mild	Unrelated	19 Days	Study medication interrupted	Recovered
039-009	49/Male/Black	Murder	Severe	Unrelated	1 Day	Discontinued from study	Death
067-009	55/Male/White	Rash	Moderate	Unrelated	2 Days	None	Recovered
OM10							
123-004	44/Male/White	Chest pain	Moderate	Unrelated	4 Days	Discontinued from study	Recovered
OM20							
046-019	47/Female/Black	Hypertension	Moderate	Unlikely	2 Days	Study medication interrupted	Recovered
082-027	42/Female/Black	Cerebrovascular accident	Moderate	Unlikely	23 Days	Discontinued from study	Recovered
095-023	58/Male/White	Angina unstable	Severe	Unlikely	2 Days	Discontinued from study	Recovered with sequelae
099-017	58/Female/Black	Cerebrovascular accident	Severe	Probable	5 Days	Discontinued from study	Recovered
OM40							
003-034	71/Male/White	Gastrointestinal hemorrhage	Moderate	Unlikely	4 Days	Study medication interrupted	Recovered
AML10							
174-005	55/Male/White	Esophageal cancer metastatic	Severe	Unrelated	11 Days	None	Recovered with sequelae
OM10/AML5							
055-001	30/Female/White	Abortion spontaneous incomplete	Severe	Unrelated	2 Days	None	Recovered

Table 44:Mean change in key chemistry parameters- safety population

Table 81: Mean Change in the Key Chemistry Parameters of ALT, AST, BUN, Creatinine, Sodium, Potassium, and Bicarbonate from Baseline to Week 8/Early Termination – Safety Population

Parameter (unit)	Pbo	OM10	OM20	OM40	AML5	AML10	OM10/ AML5	OM20/ AML5	OM40/ AML5	OM10/ AML10	OM20/ AML10	OM40/ AML10
ALT (mU/mL)												
N[1]	148	154	148	157	154	155	154	152	152	152	148	153
Baseline[2] Mean (SD)	18.5 (11.8)	18.8 (11.5)	19.3 (8.7)	17.1 (8.6)	18.0 (9.7)	18.1 (9.5)	19.0 (9.0)	18.5 (10.8)	18.7 (11.6)	18.3 (9.9)	19.1 (11.3)	18.2 (10.6)
Week 8/ET Mean (SD)	19.1 (11.4)	19.6 (12.6)	21.8 (17.1)	18.4 (9.5)	19.1 (11.0)	18.8 (8.3)	19.8 (11.0)	21.5 (31.1)	19.4 (10.5)	20.4 (16.7)	19.9 (13.9)	19.6 (13.1)
Mean Change (SD)	0.6 (4.9)	0.8 (8.9)	2.4 (16.4)	1.3 (6.3)	1.1 (5.6)	0.7 (7.0)	0.8 (6.3)	3.0 (30.8)	0.6 (9.4)	2.1 (15.8)	0.8 (9.1)	1.4 (8.4)
AST (mU/mL)												
N[1]	148	154	148	157	154	155	154	152	152	152	148	153
Baseline[2] Mean (SD)	17.1 (7.8)	17.8 (10.8)	17.7 (7.2)	16.4 (6.0)	16.3 (6.4)	17.1 (6.5)	16.9 (5.2)	17.4 (8.1)	17.1 (7.9)	17.5 (10.6)	16.8 (7.0)	17.4 (8.3)
Week 8/ET Mean (SD)	17.6 (7.5)	18.3 (11.3)	18.6 (10.5)	16.9 (5.7)	17.2 (8.6)	17.7 (7.3)	16.8 (5.5)	19.5 (22.7)	17.7 (6.9)	18.4 (10.5)	17.7 (10.5)	18.0 (8.7)
Mean Change (SD)	0.5 (4.0)	0.5 (12.0)	1.0 (9.7)	0.5 (5.5)	0.9 (5.1)	0.6 (5.6)	-0.1 (4.8)	2.1 (22.9)	0.6 (6.7)	0.9 (11.5)	0.9 (8.5)	0.6 (5.1)
BUN (mg/dL)												
N[1]	148	154	148	157	154	155	154	152	152	152	148	153
Baseline[2] Mean (SD)	14.1 (4.1)	15.1 (4.8)	14.1 (4.0)	14.6 (4.1)	14.3 (4.0)	14.7 (4.7)	13.7 (3.8)	15.2 (4.3)	14.8 (4.8)	14.9 (4.3)	14.1 (3.8)	14.1 (4.0)
Week 8/ET Mean (SD)	14.8 (4.4)	15.3 (4.9)	14.9 (4.6)	15.4 (4.5)	13.8 (3.9)	14.6 (4.7)	14.6 (4.1)	15.7 (4.2)	15.5 (5.2)	15.4 (5.0)	15.0 (4.3)	15.0 (3.8)
Mean Change (SD)	0.6 (4.0)	0.2 (3.3)	0.8 (3.6)	0.7 (3.2)	-0.5 (3.4)	-0.0 (3.5)	0.9 (3.3)	0.5 (4.2)	0.7 (3.4)	0.5 (3.6)	0.9 (3.5)	0.9 (3.5)
Creatinine (mg/dL)												
N[1]	148	154	148	157	154	155	154	152	152	152	148	153
Baseline[2] Mean (SD)	1.10 (0.15)	1.09 (0.19)	1.08 (0.17)	1.09 (0.20)	1.07 (0.17)	1.09 (0.20)	1.07 (0.19)	1.08 (0.18)	1.11 (0.22)	1.09 (0.18)	1.07 (0.17)	1.07 (0.16)
Week 8/ET Mean (SD)	1.10 (0.16)	1.08 (0.19)	1.08 (0.17)	1.10 (0.21)	1.05 (0.18)	1.07 (0.22)	1.06 (0.19)	1.08 (0.19)	1.10 (0.23)	1.09 (0.18)	1.07 (0.18)	1.08 (0.17)
Mean Change (SD)	-0.00 (0.1)	-0.01 (0.1)	0.0 (0.1)	0.01 (0.1)	-0.02 (0.1)	-0.02 (0.1)	-0.01 (0.1)	-0.01 (0.1)	-0.01 (0.1)	-0.01 (0.1)	-0.00 (0.1)	0.01 (0.1)
Sodium (meq/L)												
N[1]	148	154	148	157	154	155	154	152	152	152	148	153
Baseline[2] Mean (SD)	141.0 (2.6)	141.2 (2.4)	141.1 (2.0)	140.9 (2.6)	140.8 (2.7)	141.0 (2.5)	141.2 (2.4)	140.9 (2.5)	141.0 (2.8)	141.1 (2.3)	141.3 (2.7)	141.0 (2.4)
Week 8/ET Mean (SD)	140.4 (2.5)	140.4 (2.5)	140.3 (2.6)	140.2 (2.4)	140.5 (2.5)	140.6 (2.8)	140.3 (2.6)	140.4 (2.6)	140.5 (2.7)	140.3 (2.7)	140.4 (2.3)	140.1 (2.7)
Mean Change (SD)	-0.6 (2.8)	-0.9 (2.8)	-0.8 (2.7)	-0.8 (2.8)	-0.3 (3.2)	-0.5 (2.8)	-0.9 (2.7)	-0.4 (3.0)	-0.5 (3.4)	-0.8 (2.9)	-0.9 (3.0)	-0.9 (2.9)
Potassium (meq/L)												
N[1]	148	154	148	156	154	155	154	152	152	152	148	153
Baseline[2] Mean (SD)	4.31 (0.4)	4.28 (0.4)	4.28 (0.4)	4.32 (0.4)	4.30 (0.5)	4.25 (0.4)	4.26 (0.4)	4.36 (0.4)	4.32 (0.4)	4.29 (0.4)	4.29 (0.5)	4.30 (0.4)
Week 8/ET Mean (SD)	4.22 (0.4)	4.33 (0.4)	4.31 (0.4)	4.35 (0.4)	4.21 (0.4)	4.19 (0.4)	4.30 (0.4)	4.35 (0.4)	4.36 (0.5)	4.29 (0.4)	4.30 (0.5)	4.35 (0.4)
Mean Change (SD)	-0.09 (0.4)	0.05 (0.4)	0.03 (0.4)	0.03 (0.4)	-0.9 (0.4)	-0.06 (0.4)	0.04 (0.4)	-0.01 (0.4)	0.04 (0.4)	-0.00 (0.4)	0.01 (0.4)	0.05 (0.4)
Bicarbonate (meq/L)												
N[2]	148	154	148	157	154	155	154	152	152	152	148	153
Baseline[2] Mean (SD)	24.4 (2.3)	24.3 (2.3)	24.2 (2.2)	24.4 (2.3)	24.1 (2.5)	24.4 (2.4)	24.5 (2.5)	24.5 (2.4)	24.2 (2.4)	24.4 (2.3)	24.6 (2.2)	24.3 (2.3)
Week 8/ET Mean (SD)	24.3 (2.6)	24.4 (2.5)	24.3 (2.3)	24.2 (2.2)	24.3 (2.2)	24.5 (2.4)	24.5 (2.1)	24.2 (2.3)	24.0 (2.4)	24.3 (2.4)	24.3 (2.3)	24.2 (2.5)
Mean Change (SD)	-0.1 (2.6)	0.1 (2.3)	0.1 (2.4)	-0.2 (2.6)	0.2 (2.4)	0.1 (2.4)	-0.0 (2.4)	-0.3 (2.6)	-0.2 (2.4)	-0.0 (2.3)	-0.3 (2.3)	-0.0 (2.5)

[1] N was the number of patients with both baseline and Week 8/ET measurements.
[2] Baseline was defined as the last available measurement prior to randomization.
AML = amlodipine, ALT = alanine transaminase, AST = aspartate transaminase, BUN = blood urea nitrogen, ET = early termination, OM = olmesartan medoxomil, Pbo = placebo, SD = standard deviation.
Source: Post-text Table 14.3.4.1

Edema was specifically assessed using a unique CRF.

One of the major tolerability issues associated with the use of amlodipine is the relatively frequent development of peripheral edema, which occurs when amlodipine is used as monotherapy and when it is used in combination with other antihypertensive agents. The high frequency of edema with amlodipine was observed in this study but the addition of Olmesartan reduced the frequency of edema.

For this pivotal study, Sankyo pre-specified the evaluation of edema and used a categorical scale for collecting and assessing the occurrence of edema. This proactive rigorous methodological approach generated adverse event reporting of edema that has not been observed in historical clinical data obtained from passive adverse event observations, nor represented in product labeling for the individual components or combination products that may include these components. Specifically, the results demonstrate the benefits of CS-8663, while at the same time the new methodology reveals a considerably higher incidence of edema in all groups, especially in placebo-treated patients.
The frequency of edema reported in clinical trials with amlodipine is 0.6%, 3.0%, and 10.8% for placebo, the 5 mg dose, and the 10 mg dose, respectively, according to the amlodipine package insert.21 In this study, the frequency of edema reported as a TEAE was 12.3% for placebo, 13.0% for the 5 mg dose, and 36.8% for the 10 mg dose of amlodipine, representing a frequency that is approximately 3 to 4 times higher. Similarly, the frequency rate of peripheral edema for olmesartan medoxomil, as reported in the package insert, 20 is between 0.5% and 1.0% for the various doses of olmesartan medoxomil compared to a frequency rate ranging between 9.9% and 18.5% observed in this study.

The frequency of edema reported in clinical trials with amlodipine is 0.6%, 3.0%, and 10.8% for placebo, the 5 mg dose, and the 10 mg dose, respectively, according to the amlodipine package insert. In this study, the frequency of edema reported as a TEAE was 12.3% for placebo, 13.0% for the 5 mg dose, and 36.8% for the 10 mg dose of amlodipine, representing a frequency that is approximately 3 to 4 times higher. Similarly, the frequency rate of peripheral edema for olmesartan medoxomil, as reported in the package insert, 20 is between 0.5% and 1.0% for the various doses of olmesartan medoxomil compared to a frequency rate ranging between 9.9% and 18.5% observed in this study.

In conclusion, the higher overall rates of edema observed in this study are likely due to the manner in which edema was ascertained and recorded. The group of patients treated with amlodipine 10 mg monotherapy had the highest frequency of edema, and the group of patients treated with olmesartan medoxomil monotherapy and amlodipine 5 mg monotherapy had the lowest frequencies of edema. Using olmesartan medoxomil in combination with amlodipine 10 mg appears to reduce the overall frequency of edema in these treatment groups. The higher the dose of olmesartan medoxomil used in combination with amlodipine 10 mg, the lower the frequency of edema seemed to be.

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. The incidence of edema was not eliminated but attenuated by olmesartan (Tables 127 and 128 and Figure 14).

Safety issues will be discussed in detail in Section 7 - Integrated review of safety .

Postmarketing Safety of Amlodipine

Amlodipine Component of AZOR

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of amlodipine-treated patients and about 1% of placebo-treated patients. The most common side effects were headache and edema. The incidence (%) of dose-related side effects are summarized in Table 45.

Table 45: Dose related incidence (%) of Amlodipine-treated patients

Adverse Event	Placebo N=520	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268
Edema	0.6	1.8	3.0	10.8
Dizziness	1.5	1.1	3.4	3.4
Flushing	0.0	0.7	1.4	2.6
Palpitation	0.6	0.7	1.4	4.5

Edema associated with amlodipine

The frequency of edema reported in clinical trials with amlodipine is 0.6%, 3.0%, and 10.8% for placebo, the 5 mg dose, and the 10 mg dose, respectively, according to the amlodipine package insert. In this study, the frequency of edema reported as a TEAE was 12.3% for placebo, 13.0% for the 5 mg dose, and 36.8% for the 10 mg dose of amlodipine, representing a frequency that is approximately 3 to 4 times higher. Similarly, the frequency rate of peripheral edema for olmesartan medoxomil, as reported in the package insert is between 0.5% and 1.0% for the various doses of olmesartan medoxomil compared to a frequency rate ranging between 9.9% and 18.5% observed in this study.

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. These conclusions were also applicable when the combination was used in patients with Stage 2 hypertension (blood pressure =160/100 mmHg). A positive benefit-risk assessment was confirmed for all combination dosages. In a retrospective analysis of relative risk of edema in combination tablet versus monotherapy components, the attenuating effect of olmesartan at higher doses is demonstrated (Table 46).

Table 46 : Relative risk versus placebo in period II - Retrospective analysis.

		Olmesartan			
		Placebo	10 mg	20 mg	40 mg
Amlodipine					
	0	1.0	1.2	0.8	1.5
	5mg	1.1	1.7	1.5	1.5
	10mg	3.0	2.2	2.1	1.9

Postmarketing Safety of Olmesartan
Olmesartan Component of AZOR
Olmesartan has been evaluated for safety in more than 3825 patients/subjects, including more than 3275 patients treated for hypertension in controlled trials. This experience included about 900 patients treated for at least 6 months and more than 525 for at least 1 year. Treatment with olmesartan was well tolerated, with an incidence of adverse events similar to that seen with placebo. Events were generally mild, transient, and without relationship to the dose of olmesartan.

The overall frequency of adverse events was not dose-related. Analysis of gender, age, and race groups demonstrated no differences between olmesartan and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.4% (i.e., 79/3278) of patients treated with olmesartan and 2.7% (i.e., 32/1179) of control patients. In placebo-controlled trials, the only adverse event that occurred in more than 1% of patients treated with olmesartan and at a higher incidence versus placebo was dizziness (3% vs 1%).

Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes. Therefore interactions with drugs that inhibit induce or are metabolized by those enzymes are not expected. No significant drug interaction were reported in studies in which olmesartan medoxomil was coadministered with digoxin or warfarin in healthy volunteers. In addition the bioavailability of olmesartan was not significantly altered by the co administration of antacids.

AZOR
Outside of an interaction that modified the frequency of peripheral edema there did not appear to be any specific or unexpected safety concerns that were caused by the concomitant use of olmesartan medoxomil with amlodipine. 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.

Overall Conclusions: Safety
There were no new, unexpected safety concerns identified during the double blind period and during the 120 day safety update. The combination tablets, particularly the higher dose combination treatments, did cause an increase in certain safety parameters

Add-on Therapy for Patients with Hypertension Not Adequately Controlled on Amlodipine or Olmesartan Alone

It is usually appropriate to begin therapy with AZOR only after a patient has either (a) failed to achieve the desired antihypertensive effect with amlodipine or olmesartan alone, or (b) demonstrated inability to achieve adequate antihypertensive effect with amlodipine therapy without developing unacceptable edema. In these patients, therapy with AZOR may achieve blood pressure control without unacceptable edema. AZOR may be used to provide additional blood pressure lowering for patients not adequately controlled on amlodipine (or another dihydropyridine) alone or with olmesartan (or another angiotensin receptor blocker) alone. There are no completed studies on AZOR as add-on to amlodipine in patients not adequately controlled by Amlodipine.

Dose selection
This study was designed to support the indication for CS-8663 (medoxomil + amlodipine) as a therapy for control of mild to severe hypertension. The co-administered doses selected for olmesartan medoxomil and amlodipine were based on the approved dose ranges specified within the respective package inserts.

The 10 mg dose of olmesartan medoxomil was used in the pivotal study since this dose has been approved for use in European countries. The doses selected represent the combined recommended dosage range internationally.

1.3.5 Drug – Drug Interactions

No drug interaction studies have been conducted with AZOR and other drugs, although studies have been conducted with the individual amlodipine and olmesartan components of AZOR as described below and no significant drug interactions have been observed.

The pharmacokinetics of amlodipine and olmesartan are not altered when the drugs are co-administered (See Clinical Pharmacology review).

Drug-Drug Interaction

No pharmacokinetic interactions were observed with the concomitant use of olmesartan and amlodipine. One pharmacokinetic study (CS8663-A-U101) demonstrated that coadministration of olmesartan medoxomil and amlodipine besylate did not affect the steady-state maximum and total exposure of either compound at their highest indicated doses and under fasting conditions.

Bioequivalence of Marketed Formulations

The purpose of study CS8663-A-E102 was to determine the bioequivalence of the following 3 amlodipine formulations currently marketed in different countries: Istin® (UK), Norvasc® (US), and Antacal® (Italy).

This has been reviewed by Dr L. Velaquez. See Clinical pharmacology review.

Based on the package insert information of Norvasc®, amlodipine exhibits pharmacokinetic characteristics not seen with other calcium-antagonist drugs. It is predominantly found in the ionized form (pKa = 8.7) at a physiological pH and therefore, possesses a strong affinity for cell membranes. After oral administration of therapeutic doses, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64% and 90%.[2] One study demonstrated that bioavailability was slightly higher in women than in men; authors thought the difference could be explained by the lower body weight of women in the study.[7] Bioavailability is not altered by the presence of food.[2] Grapefruit juice has been shown to interact with certain dihydropyridine calcium channel antagonists; however, coadministration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.[8]

Amlodipine is metabolized in the liver by multiple cytochrome P450 enzymes.[9] It is extensively (about 90%) converted to inactive metabolites with 10% of the parent compound and 60% of the metabolites excreted in the urine. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.[2] Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.[7] One study conducted in healthy volunteers (ages 20-32) found no gender-related differences in drug clearance.[7] A recent study in a population of men (mean age of 72) and women (mean age of 79) currently on stable doses of amlodipine found a faster drug clearance in women.[9]

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%, and a lower initial dose may be required.[2] A similar increase in AUC was observed in patients with moderate to severe heart failure. Sixty-two hypertensive patients aged 6 to 17 years received doses of Norvasc® between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.[2] The pharmacokinetics are not significantly influenced by renal impairment. Hypertensive patients on hemodialysis may therefore receive the usual initial dose.[10,11] The pharmacokinetics of amlodipine are also not altered in hypertensive patients with type II diabetes mellitus when compared to patients without diabetes.[12]

To date, interactions between amlodipine and other concomitant drugs have not been reported. Specifically, the pharmacokinetics of amlodipine was not affected when coadministered with either cimetidine, or Maalox, or sildenafil (Viagra®). Coadministration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin. Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. Finally, *in vitro* data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.[2]

Interaction Studies with Amlodipine
In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Effect of other agents on Amlodipine

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Effect of Amlodipine on other agents

Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Interaction Studies with Olmesartan
No significant drug interactions were reported in studies in which olmesartan was coadministered with digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan was not significantly altered by the co-administration of antacids [$Al(OH)_3/Mg(OH)_2$]. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce, or are metabolized by those enzymes are not expected.

1.3.6 Special Populations

Pregnancy
When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Exforge® (amlodipine and valsartan) should be discontinued as soon as possible. This is also recommended for AZOR
(WARNINGS: Fetal/Neonatal Morbidity and Mortality in label)

Age: Elderly

Geriatric Studies with amlodipine:

Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40%-60%; therefore a lower initial dose of amlodipine may be required.

Elderly patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40% to 60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure. Sixty-two hypertensive patients aged 6-17 years received doses of Norvasc between 1.25mg and 20 mg. Weight-adjusted clearance and volume distribution were similar to values in adults. The PK parameters are not significantly influenced by renal impairment. The PK of amlodipine is not altered in hypertensive patients with type II diabetes mellitus when compared to patients without diabetes.

Coadministration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin and indomethacin.

Renal impaired

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose based on data from amlodipine. There are no studies of AZOR in patients with renal impairment. **(See clinical pharmacology review)**

Renal Impairment: There are no studies of AZOR in patients with renal impairment.

Studies with Amlodipine

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Studies with Olmesartan

Patients with renal insufficiency have elevated serum concentrations of olmesartan compared with patients with normal renal function. After repeated dosing, AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <20 mL/min). No initial dosage adjustment is recommended for patients with moderate to marked renal impairment (creatinine clearance <40 mL/min).

Table 47 shows no statistically significant difference in patients with BP > 160/100 exposed to high doses of AZOR versus monotherapy

Table 47: Creatinine levels High combined vs. Monotherapy- Pts >160/100-ITT

Label	Estimate	Standard Error	Pr > |t|	Lower	Upper
20/10 vs. 20	0.01111	0.05492	0.8398	-0.09707	0.1193
20/10 vs. 10	0.07475	0.05492	0.1748	-0.03344	0.1829
40/10 vs. 40	-0.06900	0.05184	0.1845	-0.1711	0.03312
40/10 vs. 10	0.05964	0.05052	0.2389	-0.03987	0.1591

Source Dr S Bai

Hepatic impaired

Hepatic Insufficiency Studies with amlodipine: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of amlodipine may be required. There are no studies of AZOR in patients with renal impairment (See clinical pharmacology review).

Hepatic Impairment

There are no studies of AZOR in patients with hepatic insufficiency.

Studies with Amlodipine

Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40% to 60%.

Studies with Olmesartan

Increases in $AUC_{0-\infty}$ and C_{max} were observed in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60%.

Pregnancy: Nursing Mothers

It is not known whether the amlodipine or olmesartan components of AZOR are excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. See label.

Pediatric Use

Children: There have been no studies in children.

The safety and effectiveness of AZOR in pediatric patients have not been studied.

Studies with Amlodipine on children

The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Studies with Olmesartan on children

Safety and effectiveness of olmesartan in pediatric patients have not been studied and established.

Geriatric Use

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. No significant differences in safety or effectiveness were observed between subjects 65 years of age or older and younger subjects.

Studies with Amlodipine on the Elderly

Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40% to 60%, and a lower initial dose may be required.

Studies with Olmesartan on the Elderly

Of the total number of hypertensive patients receiving olmesartan in clinical studies, more than 20% were 65 years of age and over, while more than 5% were 75 years of age and older. No overall differences in effectiveness or safety were observed between elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Race: Black Patients

Of the total number of subjects in the double-blind clinical study of AZOR, 25% (481/1940) were black patients. Overall, the mean baseline seated blood pressure was 163.9/102.4 mmHg for the subgroup of Black patients and 163.8/101.4 mmHg for the subgroup of non-Black patients. AZOR was effective in treating black patients (usually a low-renin population), and the magnitude of blood pressure reduction in black patients was not as great as those observed for non-black patients. The test to detect overall treatment differences among the 12 treatment groups was statistically significant ($p<0.0001$) for both subgroups of race.

Other racial/ethnic groups constituted 4% of total population studied in addition to 71% Caucasians. The proportions of blacks reaching their BP goals are in Tables 12, 61-63.

Table 12 presents the number and percentage of patients in each treatment group who reached their blood pressure treatment goal at Week 8 with LOCF for black and non-black subgroups.

For the subgroup of Black patients, approximately 38% to 51% of patients treated with one of the higher dose combination therapies (i.e., OM 10 mg + AML 10 mg, OM 20 mg + AML 10 mg, OM 40 mg + AML 5 mg, and OM 40 mg + AML 10 mg) reached their blood pressure goal. The highest of 51% was in the group of blacks who received 10/10 while the lowest 17.6% was in the group who received OM10/5 AML.

In contrast for these same higher dose combinations, the subgroup of non-Black patients had a percentage of patients who reached their blood pressure goal that ranged from approximately 48% to 56%. The lowest of 39% was in the group of non blacks who received OM10/5 AML and the highest was 56% in the group that received OM20/10AML. The non-blacks had a two fold increase in the percent reaching their BP goals at 8 weeks with the lowest dose of the combined tablet of 10/5.

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 (Tables 12, 61, 62 and 63).