

2 INTRODUCTION AND BACKGROUND

Hypertension affects approximately 1 billion individuals worldwide. As the population ages, the prevalence of hypertension will increase. The relationship between blood pressure and risk of cardiovascular disease events is continuous, consistent, and independent of other risk factors. In clinical trials, antihypertensive therapy has been generally associated with a 35% to 40% mean reduction in stroke incidence, a 20% to 25% mean reduction in the incidence of myocardial infarction, and a >50% reduction in the incidence of heart failure, as well as the delay in new onset diabetes. Meta-analyses of 61 prospective, observational studies in 1 million adults indicate that for every 2 mmHg decrease in systolic blood pressure there is an associated 7% reduction in risk of cardiovascular disease mortality and 10% reduction in risk of stroke mortality. Current control rates for hypertension are far below expectation; 30% are still unaware they have hypertension, only 60% of patients with hypertension are being treated, and only 30% of patients with hypertension are treated to a target blood pressure of <140/90 mmHg..

Recent clinical trials have demonstrated that effective blood pressure control can be achieved in most patients with hypertension, but the majority of patients will require two or more antihypertensive medications.

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

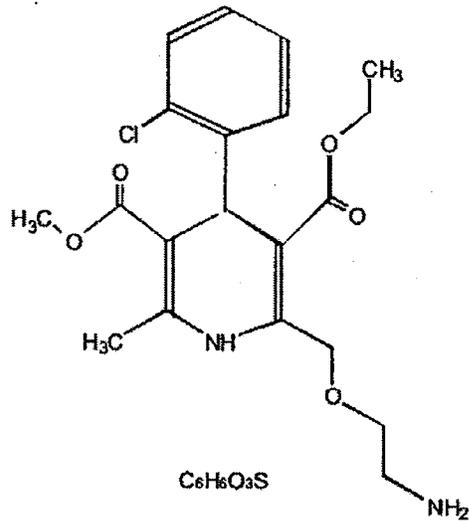
The antihypertensive effect of olmesartan medoxomil was demonstrated in 7 placebo-controlled studies at doses ranging from 2.5 mg to 80 mg for 6 to 12 weeks. The response in terms of reductions in peak and trough blood pressure was dose related; however, olmesartan medoxomil doses greater than 40 mg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

Amlodipine besylate is a calcium ion influx inhibitor of the dihydropyridine group and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to arteriolar vasodilatation. The mode of action of amlodipine thus differs from, and is complementary to, that of olmesartan medoxomil. The drug was granted approval by the FDA in 1992 (Norvasc®) and is currently available as 2.5, 5, and 10 mg tablets. The experience derived from the clinical trials conducted with amlodipine is accounted for by the version of the US package insert (June 2003) in existence when designing the study.

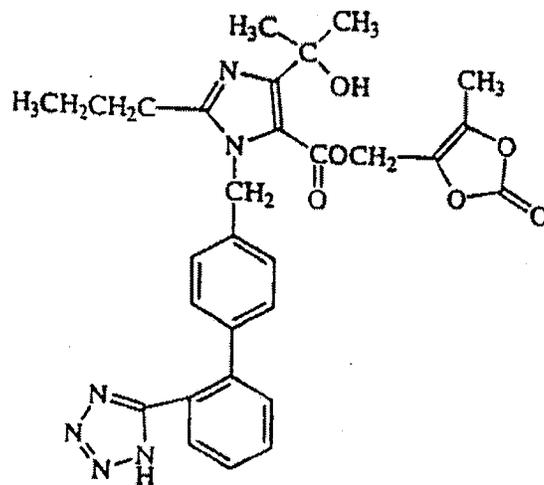
A pilot study was conducted to assess the effects of concomitant dosing of olmesartan medoxomil 20 mg and amlodipine 5 mg on pharmacokinetics, safety and tolerability in healthy, male patients. The results of this study indicated that the pharmacokinetic properties of each drug were essentially unaffected by co-administration of both drugs. In addition, the safety profile was unremarkable (Clin Pharm review by Dr L.Velaquez).

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The structural formula for amlodipine besylate is:



The structural formula for olmesartan medoxomil is:



Amlodipine besylate and Olmesartan Medoxomil NDA22-100

AZOR contains amlodipine besylate, a white to off-white crystalline powder, and olmesartan medoxomil, a white to light yellowish-white powder or crystalline powder. The molecular weights of amlodipine besylate and olmesartan medoxomil are 567.1 and 558.59, respectively. Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol. Olmesartan medoxomil is practically insoluble in water and sparingly soluble in methanol.

Each tablet of AZOR contains the following inactive ingredients: silicified microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, and magnesium stearate. The color coatings contain polyvinyl alcohol, macrogol/polyethylene glycol 3350, titanium dioxide, talc, iron oxide yellow (5/40 mg, 10/20 mg, 10/40 mg tablets), iron oxide red (10/20 mg and 10/40 mg tablets), and iron oxide black (10/20 mg tablets).

2.2 Currently available treatment for indications

See Section 10 - References

2.3 Availability of proposed active ingredients in the United States

The ingredients are available in the United States.

2.4 Important issues with pharmacologically related products

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.

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].

Valsartan and amlodipine Exforge has recently been approved by the Agency under NDA 21-990. Exforge® (amlodipine and valsartan) is a fixed combination of amlodipine and valsartan. Similarly, AZOR is a fixed combination of amlodipine and olmesartan. AZOR tablets are formulated in four strengths for oral administration with a combination of amlodipine besylate, equivalent to 5mg and 10 mg of amlodipine free-base, with 20 mg, or 40 mg of olmesartan providing for the following available combinations: 5/20, 10/20, 5/40, and 10/40 mg.

In a double-blind, active-controlled study, a total of 944 patients with mild to moderate hypertension who were not adequately controlled on amlodipine 10 mg received a combination of amlodipine and valsartan (10/160 mg), or amlodipine alone (10 mg). At week 8, the combination treatment was statistically significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures.

In a double-blind, placebo controlled study, a total of 1250 patients with mild to moderate hypertension received treatments of two combinations of amlodipine and valsartan

Medical Reviewer (AZOR)

Amlodipine besylate and Olmesartan Medoxomil NDA22-100

(10/160, 10/320 mg), or amlodipine alone (10 mg), valsartan alone (160 or 320 mg) or placebo. At week 8, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures.

In a double-blind, active-controlled study, a total of 947 patients with mild to moderate hypertension who were not adequately controlled on valsartan 160 mg received treatments of two combinations of amlodipine and valsartan (10/160, 5/160 mg), or valsartan alone (160 mg). At week 8, the combination treatments were statistically significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic blood pressure, usually with little or no orthostatic change. Valsartan has indications other than hypertension which can be found in the Diovan® package insert.

Similar to Exforge® AZOR contains the besylate salt of amlodipine, a dihydropyridine calcium channel blocker (CCB). Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate's chemical name is 3-Ethyl-5- methyl (4RS)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1, 4-dihydropyridine- 3, 5-dicarboxylate benzenesulphonate; its structural formula is Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and its molecular weight is 567.1.

Valsartan's chemical name is N-(1-oxopentyl)-N- [[2'-(1H-tetrazol-5-yl) [1, 1'-biphenyl]-4-yl] methyl]-L-valine; its structural formula is Its empirical formula is $C_{24}H_{29}N_5O_3$ and its molecular weight is 435.5. Valsartan is a nonpeptide, orally active and specific angiotensin II antagonist acting on the AT1 receptor subtype. Valsartan is a white to practically white fine powder, soluble in ethanol and methanol and slightly soluble in water.

Studies with valsartan

There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan.

Studies with valsartan: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease.

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Valsartan

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available. Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed. In multiple dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

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

2.5 Pre-submission regulatory activity

The present study was based on Sankyo protocol CS8663-A-U301, 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."

Several changes were made to Version 1 of the final study protocol (7 January 2005) including additional accepted methods of antihypertensive medication withdrawal, changes in visit dates for the pharmacokinetic substudy evaluations, adjustments to the description of blood pressure measurements during the pharmacokinetic substudy, additional safety assessments of peripheral edema and body weight, and changes to the requirements for removal of patients from the study.

These changes were incorporated into Version 2 of the study protocol (30 June 2005). In addition, a response letter from the FDA (23 February 2005 noted below), specified changes to the statistical analysis plan in Version 1 of the protocol. The statistical

methods were revised within Version 2 of the protocol to reflect these FDA-specified changes. Further details regarding these protocol changes are provided in Section 9.8 of this report.

The Division of Cardio-Renal Drug Products and Sankyo Pharma Development had the guidance meeting on 20 December 2004, during which the design of clinical study was discussed. Sankyo Pharma Development submitted protocol CS8663-A-U301 for a Special Protocol Assessment to the FDA on 24 January 2005, and feedback from the FDA was received on 23 February 2005, regarding the results of the special protocol assessment. Following the letter from the FDA, Sankyo Pharma Development submitted

“Comments on the FDA responses to special protocol assessment for the clinical study protocol” on 15 March 2005, and Ms. Denise Hinton, FDA project manager, informed Sankyo that the Special Protocol Assessment was approved on 11 April 2005. Sankyo Pharma Development submitted the revised protocol with several minor changes, dated 30 June 2005.

Other relevant background information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC and product microbiology

Please refer to CMC review. Both component drugs have been approved.

3.2 Clinical pharmacology/Biopharm

Based on the package insert information of Benicar[®], olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours.¹ Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing. The absolute bioavailability of olmesartan is approximately 26%.¹ After oral administration, the peak plasma concentration (C_{max}) of olmesartan is reached after 1 to 2 hours.^{1,4} Bioavailability is not altered by the presence of food.¹

Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.¹

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In patients with renal insufficiency, serum concentrations of olmesartan were elevated compared to subjects with normal renal function. One study found a significant negative correlation between renal dysfunction and both C_{max} and AUC. After repeated dosing, the AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <20 mL/min).⁵ Therefore, authors recommended that the daily dose for patients with severe renal impairment should not exceed 20 mg.⁵ The pharmacokinetics of olmesartan in patients undergoing hemodialysis has not been studied.¹

Following oral administration of olmesartan, C_{max} values in patients with mild and moderate hepatic impairment were similar to those in healthy controls. Values of AUC, however, increased by 30% in patients with mild liver disease, and 48% in patients with moderate liver disease.^{5,6} The increase in patients with moderate impairment of liver function was significant.

When amlodipine was administered in a fixed-dose combination with olmesartan, the rate and extent of bioavailability of amlodipine were similar to those observed when amlodipine and olmesartan were coadministered as separate tablets.

Table 48: Bioequivalence of 40 mg olmesartan vs Formulation H 40/10

Parameters	Geometric LSM		Ratio (T/R) of LSM (%)	90% CI (Lower, Upper) (%)
	Test ^a (n=27)	Reference ^b (n=28)		
AUC ₀₋₁₂ (ng·h/mL)	5120.5	4754.1	107.71	(102.0, 113.8)
AUC ₀₋₂₄ (ng·h/mL)	5201.7*	4805.9**	108.24	(102.5, 114.3)
C_{max} (ng/mL)	858.9	748.2	114.80	(107.5, 122.6)

^a CS-8663 Formulation H Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)
^b Olmesartan medoxomil 40 mg (Olmecor[®]) oral tablet in combination with amlodipine besylate 10 mg (Amlodipine[®]) oral tablet
 *Test: n = 26; **Reference: n = 27
 Source: CS8663-A-U113 Final Report

3.3 Animal pharmacology/Toxicology

Mechanism of Action

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic 2 :3 interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. Please refer to Pharmtox review

4 DATA SOURCES, REVIEW STRATEGY AND DATA INTEGRITY

4.1 Sources of Clinical data

- Electronic submission for NDA 22100
- NDA for amlodipine – 19-787
- NDA for olmesartan – 21-286
- NDA for Avalide – 20-758
- NDA for combined Amlodipine and Valsartan (Exforge) – 21-990
- Minutes of Cardio-Renal Advisory committee for Avalide - initial therapy-2007
- Package inserts for Amlodipine and Olmesartan
- JNC7 recommendations

4.2 Tables of Clinical Studies

Table 49: Summary of clinical studies -PK

Study No. (No. of Centers) Investigators	Study Design	Study Title	Formulation	Treatments Dose Regimen	Randomized (Completed)	Key Entry Criteria	Age Range (Years) Sex % (M) Race % (A, B, C, H, O)
Pivotal Clinical Pharmacology Studies							
CS8663-A-U101 (1) Shenouda, ML	3-way CO, OL, MD, DDI	A Randomized, Open-Label 3- Way Crossover Multiple Dose Study to Determine the Pharmacokinetic Interaction of Olmesartan Medoxomil and Amlodipine Besylate in Healthy Subjects	OM 40-mg tablet (Lot No. 442299) AML 10-mg tablet (Lot No. 4QL171A)	Trt A: OM 40 mg tablet QD for 10 days (21 day washout) Trt B: AML 10 mg tablet QD for 10 days (21 day washout) Trt C: OM 40 mg tablet + AML 10 mg tablet QD for 10 days (21 day washout) (Fasted on Days 1, 8, and 10)	24 (23)	Healthy male and female subjects	19-52 Years 66.7% M 58.3% B 25.0% C 12.5% H 4.2% O
CS8663-A-E102 (1) Golor, G	3-way CO, OL, SD, BE	A Randomized, Open-Label, Single-Dose, Three-Way Crossover Study to Determine the Bioequivalence of 10 mg Amlodipine Besylate, Istin® (UK) vs. 10 mg Amlodipine Besylate Norvasc® (US) and Amlodipine Besylate, Antacal® (Italy)	AML 10-mg tablet (Lot No. 0405081A 1) AML 10-mg tablet (Lot No. 4QL 166E) AML 10-mg tablet (Lot No. 410190231)	Trt A: AML 10 mg (Istin®) Single-Dose (14 day washout) (8:00 a.m. in fasted state) Trt B: AML 10 mg (Norvasc®) Single-Dose (14 day washout) (8:00 a.m. in fasted state) Trt C: AML 10 mg (Antacal®) Single-Dose (14 day washout) (8:00 a.m. in fasted state)	18 (18)	Healthy male and female subjects	19-55 Years 55.6% M 88.9% C 11.1% H
AML=amlodipine, BA=bioavailability, BE = bioequivalence, CO=cross-over, OL=open-label, OM=olmesartan medoxomil, DDI=drug-drug interaction, DP=dose-proportionality, MD=multi-dose, SD=single-dose, Trt=treatment Race (A=Asian, B=Black, C=Caucasian, H=Hispanic, O=Other) Sex (M=male) Source: Individual Clinical Trial Reports							

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Table 50: Summary of clinical studies-PK

Study No. (No. of Centers) Investigators	Study Design	Study Title	Formulation	Treatments; Dose Regimen	Randomized (Completed)	Key Entry Criteria	Age Range (Years) Sex % (M) Race % (A, B, C, H, O)
CS8663-A-U109 (1) Allison, M	2-way CO, OL, SD, BA	A Randomized, Single-Dose, Open-Label 2- Way Crossover Study to Determine the Bioavailability of Olmesartan and Amlodipine from a Fifth Fixed- Dose Combination Formulation Relative to Olmecet [®] and Antacal [®] in Healthy Subjects	Fixed Dose OM/AML 40/10-mg tablet (Lot No. 3223V05003) OM 40-mg tablet (Lot No. 337610) AML 10-mg tablet (Lot No. 410190130)	Trt A: OM/AML 40/10 mg fixed-dose tablet [Formulation G] Single-dose (14 day washout) Trt B: OM 40 mg tablet (Olmecet [®]) + AML 10 mg tablet (Antacal [®]) Single-dose (14 day washout) (Fasted on days of dosing)	28 (26)	Healthy male and female subjects	19-44 Years 46.4% M 3.6% C 96.4% H

AML=amlodipine, BA=bioavailability, BE = bioequivalence, CO=cross-over, OL=open-label, OM=olmesartan medoxomil, DDI=drug-drug interaction, DP=dose-proportionality,
 MD=multi-dose, SD=single-dose, Tri=treatment
 Race (A=Asian, B=Black, C=Caucasian, H=Hispanic, O=Other)
 Sex (M=male)
 Source: Individual Clinical Trial Reports

Table 51: Clinical Studies-NDA 22100

Study No. (No. of Centers)	Study Design (Period)	Primary Objectives of the Study	Study Status (Start Date)	Test Products; Dose Regimen; Route of Administration	No. and Type of Patients Randomized (Completed)	Discontinued	
						Due to AE	Other
CS8663-A-U301 (172)	(Period II) Double-Blind 8 Weeks	To demonstrate that OM + AML co-administration was more efficacious for seated diastolic blood pressure lowering than each of its corresponding monotherapy components.	C (05/05)	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 5mg, OM 40 mg + AML 5 mg, OM 10 mg + AML 10 mg, OM 20 mg + AML 10 mg, or OM 40 mg + AML 10 mg Route of Administration: Oral	Male and female patients with mild to severe hypertension 1940 (1689)	114	137
CS8663-A-U301 (172)	(Period III) Open-Label Extension 44 Weeks	1. To gain long-term efficacy and safety experience with co-administration of OM + AML (plus the addition of hydrochlorothiazide [HCTZ], if needed) while minimally treating patients to blood pressure goal (<140/90 mmHg, <130/80 mmHg for diabetic patients). 2. To evaluate the number (%) of patients achieving blood pressure goal (defined as blood pressure <140/90 mmHg, <130/80 mmHg for diabetic patients).	Ongoing	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) Route of Administration: Oral	Male and female patients with mild to severe hypertension 1684 (232 as of 14 July 2006)	67	161

AE = adverse event, AML = amlodipine, BA = bioavailability, BE = bioequivalent, C = complete, CO = cross-over, DDI = drug-drug interaction, DP = dose-proportionality,
 MD = multiple dose, OL = open-label, OM = olmesartan medoxomil, QD = once daily, SD = single-dose, Tri = treatment

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Table 52: Clinical studies - PK

Study No. (No. of Centers)	Study Design (Period)	Primary Objectives of the Study	Study Status (Start Date)	Test Products; Dose Regimen; Route of Administration	No. and Type of Patients Randomized (Completed)	Discontinued	
						Due to AE	Other
CS8663-A-U114 (1)	2-way CO, OL, SD, BA	To determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination monolayer tablet formulation (Formulation E) intended for commercial use relative to coadministration of the separate entities as their marketed formulations.	C (4/06)	OM/AML 10/10 mg fixed-dose tablet [Formulation E] OM 10 mg tablet (Olmecet [®]) + AML 10 mg tablet (Antacal [®]) Route of Administration: Oral	Healthy male and female subjects 28 (28)	0	0
CS8663-A-E102 (1)	3-way CO, OL, SD, BE	To determine the bioequivalence of three marketed amlodipine besylate formulations: Istia [®] 10 mg (Pfizer UK) vs. Nervac [®] 10 mg (Pfizer US) vs. Antacal [®] 10 mg (Pfizer Italy), each equivalent to 10 mg amlodipine.	C (12/04)	AML 10 mg (Istia [®]) AML 10 mg (Nervac [®]) AML 10 mg (Antacal [®]) Route of Administration: Oral	Healthy male and female subjects 18 (18)	0	0
CS8663-A-U103 (1)	2-way CO, OL, SD, BA	To determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation relative to coadministration of the separate entities as their marketed formulations (Olmecet [®] and Antacal [®] , respectively).	C (5/05)	OM 40 mg/AML 10 mg fixed-dose tablet [Formulation A] OM 40 mg tablet + AML 10 mg tablet Route of Administration: Oral	Healthy male subjects 28 (26)	2	0
CS8663-A-U104 (1)	2-way CO, OL, SD, BA	To determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation relative to co-administration of the separate entities as their marketed formulations (Olmecet [®] and Antacal [®] , respectively).	C (9/05)	OM 40/AML 10 mg fixed-dose tablet [Formulation B] OM 40 mg tablet + AML 10 mg tablet Route of Administration: Oral	Healthy male and female subjects 28 (28)	0	0

Table 53: Clinical studies - PK

Study No. (No. of Centers)	Study Design (Period)	Primary Objectives of the Study	Study Status (Start Date)	Test Products; Dose Regimen; Route of Administration	No. and Type of Patients Randomized (Completed)	Discontinued	
						Due to AE	Other
CS8663-A-U105 (1)	2-way CO, OL, SD, BA	To determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation relative to coadministration (free combination) of the separate entities as their marketed formulations (Olmecet [®] and Antacal [®] , respectively).	C (9/05)	OM/AML 40/10 mg fixed dose tablet [Formulation C] OM 40 mg tablet + AML 10 mg tablet Route of Administration: Oral	Healthy male and female subjects 28 (26)	0	2
CS8663-A-U106 (1)	2-way CO, OL, SD, BA	To determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation relative to coadministration (free combination) of the separate entities as their marketed formulations (Olmecet [®] and Antacal [®] , respectively).	C (9/05)	OM/AML 40/10 mg fixed-dose tablet [Formulation D] OM 40 mg tablet + AML 10 mg tablet Route of Administration: Oral	Healthy male and female subjects 28 (26)	0	2
CS8663-A-U109 (1)	2-way CO, OL, SD, BA	To determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation relative to co-administration (free combination) of the separate entities as their marketed formulations (Olmecet [®] and Antacal [®] , respectively).	C (10/05)	OM/AML 40/10 mg fixed-dose tablet [Formulation G] OM 40 mg tablet + AML 10 mg tablet Route of Administration: Oral	Healthy male and female subjects 28 (26)	1	1

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Table 54: Clinical studies - PK

Study No. (No. of Centers)	Study Design (Period)	Primary Objectives of the Study	Study Status (Start Date)	Test Products; Dose Regimen; Route of Administration	No. and Type of Patients Randomized (Completed)	Discontinued	
						Due to AE	Other
CS8663-A-U111 (1)	CO, OL, SD, BA	To determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation intended for commercial use relative to coadministration of the separate entities as their marketed formulations. The bioavailability was determined for the following 2 tablet strengths: <ul style="list-style-type: none"> • olmesartan 10 mg and amlodipine 5mg • olmesartan 40 mg and amlodipine 10 mg 	C (01/06)	<u>Cohort 1 (30 subjects)</u> Trt A (Test): OM/AML 10/5 mg fixed-dose tablet Trt B (Reference) OM 10 mg tablet (Olmetec [®]) + AML 5 mg tablet (Antacal [®]) <u>Cohort 2 (30 subjects)</u> Trt C (Test): OM/AML 40/10 mg fixed-dose tablet Trt D (Reference) OLM 40 mg tablet (Olmetec [®]) + AML 10 mg tablet (Antacal [®]) Route of Administration: Oral	Healthy male and female subjects 60 (58)	1	1

Table 55: Clinical studies - PK

Study No. (No. of Centers)	Study Design (Period)	Primary Objectives of the Study	Study Status (Start Date)	Test Products; Dose Regimen; Route of Administration	No. and Type of Patients Randomized (Completed)	Discontinued	
						Due to AE	Other
CS8663-A-U112 (1)	3-way CO, OL, SD, DP	To determine the dose proportionality of olmesartan and amlodipine from different strengths of olmesartan medoxomil and amlodipine besylate fixed-dose combination tablet intended for commercialization. Dose proportionality will be determined for the following 6 tablet strengths: <ul style="list-style-type: none"> • olmesartan medoxomil 40 mg and amlodipine besylate 10 mg • olmesartan medoxomil 20 mg and amlodipine besylate 5 mg • olmesartan medoxomil 10 mg and amlodipine besylate 10 mg • olmesartan medoxomil 40 mg and amlodipine besylate 5 mg • olmesartan medoxomil 20 mg and amlodipine besylate 10 mg • olmesartan medoxomil 10 mg and amlodipine besylate 5 mg 	C (01/06)	<u>Cohort 1 (30 subjects)</u> Trt A: OM/AML 40/10 mg fixed-dose tablet Trt B: OM/AML 20/5 mg fixed-dose tablet Trt C: OM/AML 10/10 mg fixed-dose tablet <u>Cohort 2 (30 subjects)</u> Trt D: OM/AML 40/5 mg fixed-dose tablet Trt E: OM/AML 20/10 mg fixed-dose tablet Trt F: OM/AML 10/5 mg fixed-dose tablet Route of Administration: Oral	Healthy male and female subjects 60 (57)	0	3

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Table 56: Clinical studies - PK

Study No. (No. of Centers)	Study Design (Period)	Primary Objectives of the Study	Study Status (Start Date)	Test Products; Dose Regimen; Route of Administration	No. and Type of Patients Randomized (Completed)	Discontinued	
						Due to AE	Other
CS8663-A-U113 (1)	2-way CO, OL, SD, BA	To determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation relative to co-administration (free combination) of the separate entities as their marketed formulations (Olmtec [®] and Antacal [®] , respectively).	C (1/06)	OM/AML 40/10 mg fixed-dose tablet [Formulation H] OM 40 mg tablet (Olmtec [®]) + AML 10 mg tablet (Antacal [®]) Route of Administration: Oral	Healthy male and female subjects 28 (27)	0	1
CS8663-A-U101 (1)	3-way CO, OL, MD, DDI	To investigate the pharmacokinetic interaction between olmesartan and amlodipine when administered concomitantly in healthy subjects.	C (10/04)	Tri A: OM 40 mg tablet QD for 10 days Tri B: AML 10 mg tablet QD for 10 days Tri C: OM 40 mg tablet + AML 10 mg tablet QD for 10 days Route of Administration: Oral	Healthy male and female subjects 24 (23)	0	1
CS8663-A-U110 (1)	2-way CO, OL, SD, BA Food Effect	To determine the effect of food on the bioavailability of olmesartan and amlodipine from a fixed-dose combination tablet.	C (2/06)	OM/AML 40/10 mg fixed-dose tablet OM/AML 40/10 mg fixed-dose tablet Route of Administration: Oral	Healthy male and female subjects 28 (27)	0	1

4.3 Review Strategy

The overall efficacy review was to ascertain that the efficacy of the fixed dose combination was better than its component tablets and that the blood pressure goals were reached before those of the monotherapy components.

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. Furthermore this review assessed the dose related adverse events of Amlodipine with the fixed dose combination particularly the frequencies of edema, laboratory abnormalities and hypotension.

The review also ascertain that adequate numbers of patients of all ages, races and patients with co-morbidities are randomized in order to be able to recommend whether this fixed dose combination can be used as initial therapy.

4.4 Data Quality and Integrity

This was found to be acceptable. Following Week 8 through a data cut-off date of 14 July 2006, the database was cleaned and locked, and a separate Period III commenced. On completion of Week 52, the database was again cleaned and locked and a complete Period III report was generated. Analyses of these reports and other sources of information form the basis of this review.

Although formulation G has been selected as the primary formulation for commercial use for many reasons, data from formulation H were used to validate bioequivalence (Table 48).

There is evidence of compliance and good clinical practice. An investigators meeting was held on 10-11 March 2005 to prepare investigators for the study and standardize performance. A clinical research associate (CRA) conducted periodic on-site visits to assure adherence to the protocol, review CRFs and patient records for accuracy and completeness of information, examine site records for documentation of drug receipt and administration, observe the progress of the trial, and review investigator files for required documents.

After the CRFs were received , the data were double-entered into the database, where specially designed computer checks (as well as manual checks) were used to identify any data entry errors and other errors. Data were reviewed and corrections were made on an ongoing basis, as needed. When necessary, requests for clarifications or corrections were sent to the investigator via data queries.

b(4)

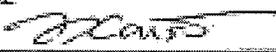
A central laboratory performed all study-related laboratory tests. The investigator reviewed all laboratory reports and filed a copy with the patient's chart and CRFs.

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.

4.6 Financial Disclosures

The investigators disclosed their financial interests. See Certificate below. The certificate of financial interest has been signed on behalf of all 59 investigators. A list of the investigators is attached to the certificate but has not been replicated in this review. The reviewer accepts this certificate signed by the Manager for Regulatory affairs of the sponsor's company to the effect that none of the investigators had received any form of remuneration that might compromise the results of the trials in this NDA.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	Form Approved: DMB No. 0210-0284 Expiration Date: April 30, 2009.						
TO BE COMPLETED BY APPLICANT							
<p>With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).</p>							
Please mark the applicable selection.							
<p><input checked="" type="checkbox"/> (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).</p>							
Clinical Investigator	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">See attached list</td> <td style="width: 20%;"></td> </tr> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> </table>	See attached list					
See attached list							
<p><input type="checkbox"/> (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).</p>							
<p><input type="checkbox"/> (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.</p>							
NAME Tetsuya Kase	TITLE Manager, Regulatory Affairs						
FIRM / ORGANIZATION Daiichi Sankyo, Inc							
SIGNATURE 	DATE 8/15/2006						
Paperwork Reduction Act Statement							
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, to the address on the right.	Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 1H1-01 Rockville, MD 20857						

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5 CLINICAL PHARMACOLOGY

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The objectives of the clinical pharmacology program for the fixed dose combination include the following:

- To define the PK properties of the various formulations of the fixed dose olmesartan/amlodipine combination in order to identify the optimal formulation based on the resulting bioavailability data from these studies.
- To verify the lack of drug-drug interaction of the constituents of the fixed dose combination
- To determine the bioequivalence between the formulation to be marketed and the drug products used in the pivotal safety and efficacy trials
- To verify a lack of food effect with the fixed dose combination and
- To establish the dose proportionality of each agent when administered as a fixed dose combination.

The summary of results of clinical pharmacology studies are presented in Tables 57 to 60. Overall, the clinical pharmacology studies would suggest that olmesartan and amlodipine taken in a fixed dose combination is bioequivalent to taking these same compounds concomitantly as separate tablets. Please refer to Biopharm review for more details. Although formulation G has been selected as the primary formulation for commercial use for many reasons, data from formulation H were used to validate bioequivalence (Table 48).

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Amlodipine besylate and Olmesartan Medoxomil NDA22-100

Table 57: Summary of results of clinical pharmacology studies - NDA 22100

Study No. Dose Information (Other Information)	Pharmacokinetic Results							
	C _{max} (ng/mL) Arithmetic Mean ± SD		T _{max} (h) Median		AUC _{0-∞} (ng • h/mL) Arithmetic Mean ± SD *0-48 hours *0-72 hours *0-96 hours *0-144 hours *0-192 hours		t _{1/2} (h)	
	OM	AML	OM	AML	OM	AML	OM	AML
Pivotal Clinical Pharmacology Studies								
CS8663-A-U101								
OM 40 mg (QD) - Benicar [®]	1084 ± 283		1.5		6794 ± 1707 ^a		13.7 ± 5.6	
AML 10 mg (QD) - Norvasc [®]		19.8 ± 6.7		8.0		359 ± 129 ^c		51.2 ± 10.9
OM 40 mg + AML 10 mg (Separate tablets) (QD)	1038 ± 312	20.1 ± 7.7	2.0	8.0	6891 ± 1918 ^a	389 ± 155 ^c	13.5 ± 5.4	50.6 ± 11.7
CS8663-A-E102								
AML 10 mg - Irtin [®] (After overnight fast)		3.7 ± 0.9		8.0		168 ± 43 ^e		43.6 ± 11.0
AML 10 mg - Norvasc [®] (After overnight fast)		3.5 ± 0.8		8.6		168 ± 45 ^e		41.9 ± 7.4
AML 10 mg - Antacal [®] (After overnight fast)		3.8 ± 0.8		8.6		171 ± 48 ^e		42.4 ± 6.2
CS8663-A-U109								
OM/AML 40/10 mg (Fixed dose: Formulation G)	858 ± 208	7.7 ± 1.6	2.0	8.0	5554 ± 1315 ^b	434 ± 99 ^d	10.7 ± 2.8	54.4 ± 13.6
OM 40 mg + AML 10 mg (Separate tablets)	836 ± 198	7.6 ± 1.8	2.0	8.0	5571 ± 1308 ^b	423 ± 104 ^d	11.7 ± 4.3	51.6 ± 12.9
CS8663-A-U110								
OM/AML 40/10 mg (Fixed dose: fed state)	898 ± 180	6.5 ± 1.4	2.5	8.0	5402 ± 1267 ^b	313 ± 59 ^d	14.2 ± 4.1	40.0 ± 7.6
OM/AML 40/10 mg (Fixed dose: fasted state)	995 ± 313	6.6 ± 1.5	2.0	8.0	6317 ± 2056 ^b	309 ± 67 ^d	14.2 ± 4.1	40.2 ± 8.1

AML=amlodipine, OM=olmesartan medoxomil, QD=once daily, SD=standard deviation
 Source: Individual Clinical Trial Reports

Table 58: Summary of results of clinical pharmacology continued – NDA 22100

Study No. Dose Information (Other Information)	Pharmacokinetic Results							
	C _{max} (ng/mL) Arithmetic Mean ± SD		T _{max} (h) Median		AUC _{0-∞} (ng • h/mL) Arithmetic Mean ± SD *0-48 hours *0-72 hours *0-96 hours *0-144 hours *0-192 hours		t _{1/2} (h)	
	OM	AML	OM	AML	OM	AML	OM	AML
Pivotal Clinical Pharmacology Studies (Continued)								
CS8663-A-U111								
OM/AML 10/5 mg (Fixed dose: Trt A)	348 ± 80	3.2 ± 0.8	1.6	8.0	1872 ± 407 ^b	152 ± 42 ^d	14.3 ± 7.5	40.7 ± 9.7
OM 10 mg (Olmotec [®]) + AML 5 mg (Antacal [®]) (Separate tablets: Trt B)	306 ± 81	3.2 ± 0.8	2.0	8.0	1739 ± 391 ^b	150 ± 43 ^d	13.6 ± 5.6	40.5 ± 9.2
OM/AML 40/10 mg (Fixed dose: Trt C)	939 ± 240	6.8 ± 1.5	2.0	6.1	5995 ± 1782 ^b	319 ± 79 ^d	15.6 ± 7.0	40.2 ± 7.5
OM 40 mg (Olmotec [®]) + AML 10 mg (Antacal [®]) (Separate tablets: Trt D)	859 ± 182	6.2 ± 1.4	1.5	8.0	5383 ± 1297 ^b	310 ± 69 ^d	17.3 ± 8.1	40.8 ± 7.1
CS8663-A-U112								
OM/AML 40/10 mg (Fixed dose: Trt A)	950 ± 226	7.6 ± 1.3	2.0	8.0	6384 ± 1566 ^b	394 ± 94 ^d	16.3 ± 7.5	54.6 ± 15.6
OM/AML 20/5 mg (Fixed dose: Trt B)	578 ± 117	3.7 ± 0.7	2.0	8.0	3701 ± 762 ^b	190 ± 45 ^d	13.9 ± 5.5	54.6 ± 14.3
OM/AML 10/10 mg (Fixed dose: Trt C)	315 ± 83	7.8 ± 1.3	2.0	8.0	1903 ± 472 ^b	404 ± 85 ^d	15.0 ± 5.9	53.5 ± 12.4
OM/AML 40/5 mg (Fixed dose: Trt D)	906 ± 295	3.5 ± 0.9	2.0	8.0	5616 ± 1801 ^b	163 ± 47 ^d	13.8 ± 5.3	46.1 ± 11.0
OM/AML 20/10 mg (Fixed dose: Trt E)	572 ± 197	7.7 ± 1.7	1.5	8.0	3309 ± 1157 ^b	337 ± 94 ^d	14.2 ± 7.0	46.4 ± 13.0
OM/AML 10/5 mg (Fixed dose: Trt F)	360 ± 151	3.7 ± 0.9	1.5	8.0	1867 ± 585 ^b	165 ± 48 ^d	13.5 ± 5.4	44.6 ± 11.9

AML=amlodipine, OM=olmesartan medoxomil, QD=once daily, SD=standard deviation
 Source: Individual Clinical Trial Reports

Table 59: Summary of results of clinical pharmacology continued – NDA 22100

Study No. Dose Information (Other Information)	Pharmacokinetic Results							
	C _{max} (ng/mL) Arithmetic Mean ± SD		T _{max} (h) Median		AUC _{0-∞} (ng • h/mL) Arithmetic Mean ± SD *0 – 48 hours *0 – 72 hours *0 – 96 hours *0 – 144 hours *0 – 192 hours		t _{1/2} (h)	
	OM	AML	OM	AML	OM	AML	OM	AML
Supportive Bioavailability/Bioequivalence Studies								
CS8663-A-U103								
OM/AML 40/10 mg (Fixed dose: Formulation A)	950 ± 279	6.8 ± 1.1	2.0	8.0	5867 ± 1276 ^b	326 ± 70 ^d	13.6 ± 4.0	40.2 ± 7.9
OM 40 mg + AML 10 mg (Separate tablets)	954 ± 315	6.9 ± 1.5	2.0	8.0	5831 ± 1311 ^b	327 ± 67 ^d	13.5 ± 4.7	39.5 ± 8.7
CS8663-A-U104								
OM/AML 40/10 mg (Fixed dose: Formulation B)	854 ± 306	7.3 ± 1.9	2.0	8.0	5626 ± 1708 ^b	384 ± 108 ^d	13.9 ± 5.0	44.6 ± 9.6
OM 40 mg + AML 10 mg (Separate tablets)	903 ± 307	7.3 ± 1.8	2.0	8.0	5892 ± 1607 ^b	379 ± 108 ^d	15.5 ± 5.4	44.8 ± 13.1
CS8663-A-U105								
OM/AML 40/10 mg (Fixed dose: Formulation C)	648 ± 214	6.7 ± 1.6	2.5	8.0	5098 ± 1666 ^b	337 ± 106 ^d	15.9 ± 6.1	43.0 ± 9.5
OM 40 mg + AML 10 mg (Separate tablets)	837 ± 254	6.6 ± 1.8	2.0	8.0	6106 ± 2201 ^b	339 ± 110 ^d	16.2 ± 6.5	46.3 ± 10.4
CS8663-A-U106								
OM/AML 40/10 mg (Fixed dose: Formulation D)	984 ± 297	6.4 ± 1.4	2.0	8.0	6459 ± 2033 ^b	305 ± 70 ^d	18.5 ± 8.4	42.2 ± 10.1
OM 40 mg + AML 10 mg (Separate tablets)	950 ± 229	6.5 ± 1.4	2.0	6.0	6013 ± 1679 ^b	309 ± 68 ^d	18.0 ± 7.3	41.3 ± 7.6
AML=amlodipine, OM=olmesartan medoxomil, QD=once daily, SD=standard deviation Source: Individual Clinical Trial Reports								

Table 60: Summary of results of clinical pharmacology continued – NDA 22100

Study No. Dose Information (Other Information)	Pharmacokinetic Results							
	C _{max} (ng/mL) Arithmetic Mean ± SD		T _{max} (h) Median		AUC _{0-∞} (ng • h/mL) Arithmetic Mean ± SD *0 – 48 hours *0 – 72 hours *0 – 96 hours *0 – 144 hours *0 – 192 hours		t _{1/2} (h)	
	OM	AML	OM	AML	OM	AML	OM	AML
Supportive Bioavailability/Bioequivalence Studies (Continued)								
CS8663-A-U113								
OM/AML 40/10 mg (Fixed dose: Formulation H)	870 ± 169	6.9 ± 2.0	1.5	8.0	5263 ± 1327 ^b	367 ± 115 ^d	12.7 ± 4.1	50.0 ± 10.2
OM 40 mg (Oimetec [®]) + AML 10 mg (Antacal [®]) (Separate tablets)	768 ± 171	7.2 ± 1.8	2.0	8.0	4868 ± 1029 ^b	376 ± 103 ^d	12.5 ± 5.1	51.0 ± 10.8
Secondary Clinical Pharmacology Studies								
CS8663-A-U114								
OM/AML 10/10 mg (Fixed dose: Formulation H)	305 ± 96	7.7 ± 2.0	2.0	8.0	1962 ± 674 ^b	376 ± 101 ^d	12.1 ± 3.9	44.0 ± 9.2
OM 10 mg (Oimetec [®]) + AML 10 mg (Antacal [®]) (Separate tablets)	292 ± 95	7.5 ± 1.7	2.0	8.0	1912 ± 654 ^b	362 ± 83 ^d	12.5 ± 4.8	45.7 ± 10.8
AML=amlodipine, OM=olmesartan medoxomil, QD=once daily, SD=standard deviation Source: Individual Clinical Trial Reports								

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Amlodipine

Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food. The apparent volume of distribution of amlodipine is 21 L. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Elimination of amlodipine 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.

Population PK Sub-study

Data from 4 clinical pharmacology studies and one phase III study were used for the population PK analysis. The population included 170 healthy volunteers (115 males and 55 females) in clinical pharmacology trials and 546 patients (276 males and 270 females) with mild to severe hypertension in Phase III study. Data from the Phase III trial alone was used to conduct the exposure response analysis.

The Clinical Pharmacology studies carried out intensive sampling for PK profiles that were conducted after a steady state dose and after a single dose in the other 3 Clinical Pharmacology studies. The exposure response analysis used trough SeDBP measurements taken at the start of visit 3 and end of visit 7 in the Period II study.

Patients were instructed to delay taking study medication on the days of their scheduled study visits until after the pharmacokinetics sample had been drawn. Prior to all pharmacokinetic blood draws, blood pressure and pulse measurements were taken. Three blood pressure measurements were obtained at least 1 minute apart, with the patient seated utilizing the provided calibrated Omron device. The 3 results were averaged. Heart rate was measured once manually. The time of the blood pressure measurement and blood draw were recorded on the CRF. Patients enrolled in this portion of the study contributed 4 extra blood samples including one trough sample 24 hours post-dose at Visit 6, one trough sample pre-dose at Visit 7, one blood sample between 0.5 and 2 hours post-dose Visit 7, and one blood sample 4-10 hours post-dose at Visit 7. Blood samples were taken anytime during the specified time interval.

Population Pharmacokinetics

The purpose of the population pharmacokinetic (popPK) study was to characterize the pharmacokinetic interactions and corresponding pharmacodynamic correlation (i.e., blood pressure lowering) between olmesartan and amlodipine using population pharmacokinetic sampling, pharmacodynamic responses, and modeling. The specific objectives of this study were to:

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Develop popPK models of olmesartan and amlodipine using the data collected in studies CS8663-A-U101, CS8663-A-U110, CS8663-A-U111, CS8663-A-U112, and CS8663-A-U301.

Characterize and quantify the effects of covariates on the oral clearances of the compounds. For both olmesartan and amlodipine, investigate age, weight, gender, serum creatinine, race, and patient/volunteer status in the covariate analysis. For amlodipine, also investigate alanine aminotransferase (ALT), aspartate aminotransferase, and total bilirubin in the covariate analysis.

The following conclusions were drawn from the popPK analysis:

- Olmesartan PK was adequately characterized by a two-compartmental model with first-order absorption and time lag; sex, weight, serum creatinine, and hypertensive status were predictors of the apparent oral clearance of olmesartan.
- Amlodipine PK was adequately characterized by a one-compartmental model with first-order absorption and a time lag; weight, age, and ALT were predictors of the apparent oral clearance of amlodipine.
- Neither compound had a clinically significant impact on the clearance of the other, based on the definition of clinically significant interaction as that which causes at least a 1.25-fold change in a parameter (i.e., outside of the bioequivalence range of 80% to 125%).
- The estimates of the covariate impacts on the clearances of olmesartan and amlodipine did not change between monotherapy and combination therapy.
- The drug effect of olmesartan exposure on ΔSeDBP was described by an E_{max} model, whereas the drug effect of amlodipine exposure on ΔSeDBP was described by a linear model.
- In the exposure-response model, black race was the most important covariate, decreasing the maximal possible effect on blood pressure of olmesartan while increasing the effect of amlodipine, without influencing PK parameters.
- The drug effect for combination therapy was defined on the basis of exposures to both compounds, and it was greater than either of the monotherapy arms alone.

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The 3 different marketed formulations of amlodipine besylate (equivalent to amlodipine 10 mg) are considered bioequivalent. This would indicate that the conclusions drawn from the Clinical Pharmacology program bioequivalence/bioavailability studies regarding the comparisons of the fixed-dose formulation of amlodipine vs. Antacal[®] are applicable to the other 2 commercially available formulations of amlodipine (i.e., Istin[®] and Norvasc[®]). Antacal[®] was the formulation of amlodipine besylate used in the pivotal efficacy study, CS8663-A-U301.

Food Interaction

The bioavailability of olmesartan and amlodipine is unaffected by food.^{1,2} Study CS8663-A-U110 demonstrated that the pharmacokinetics of olmesartan and amlodipine were equivalent when olmesartan and amlodipine were administered as a fixed-dose combination (olmesartan/amlodipine 40/10 mg: Formulation G) during the fasting state and following a high fat meal.

Since food did not affect the pharmacokinetic profiles of the fixed-dose combination, the presence of food should not alter efficacy results with Formulation G, which is the formulation to be marketed.

Dose-Proportionality

The purpose of study CS8663-A-U112 was to determine the dose proportionality of olmesartan and amlodipine from different strengths of olmesartan and amlodipine fixed-dose combination tablets intended for commercial use.

The total systemic exposure of olmesartan (AUC), following oral administration of 10 mg, 20 mg, and 40 mg dose levels, increased in a dose-proportional manner when administered in a fixed-dose combination with either 5 mg or 10 mg of amlodipine.

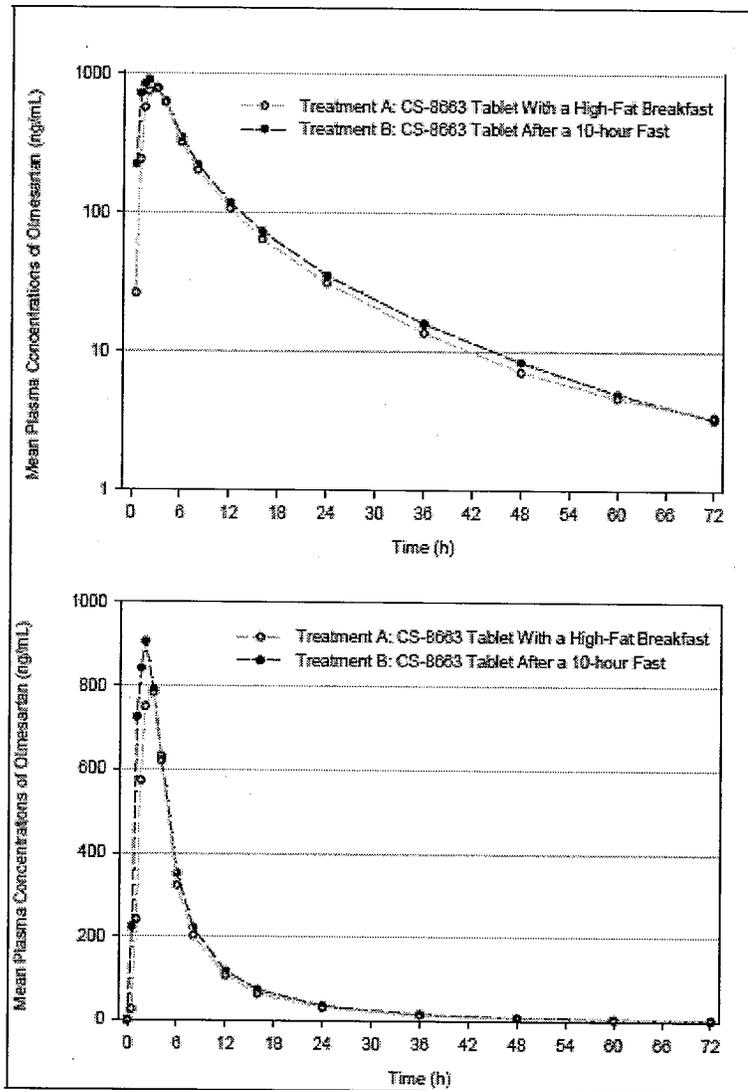
Elderly

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

Food Effect: Olmesartan- No food effect.

**Figure 9: PK graphs to show no food effect with Olmesartan
: Pharmacokinetic study - Food Effect- Olmesartan**



Source: CS8663-A-U110 Final Report

The C_{max} values of olmesartan, following oral administration of 10 mg, 20 mg, and 40 mg dose levels, increased in a slightly less than dose-proportional manner when administered in a fixed-dose combination with either 5 mg or 10 mg of amlodipine. This observation was not considered to be of clinical significance.

The systemic exposure of amlodipine (AUC and C_{max}), following oral administration of 5 mg and 10 mg dose levels, increased in a dose-proportional manner when administered in a fixed-dose combination with 10 mg, 20 mg, or 40 mg of olmesartan.

The rate and extent of bioavailability of amlodipine were also similar when the fixed-dose combination was administered with or without food. In addition, the ratio of LSM and 90% CIs for AUC_{0-t} , AUC_{0-inf} and C_{max} of amlodipine were within the bioequivalence range of 80.0% to 125.0%. Therefore, the rate and extent of bioavailability of amlodipine after oral administration of this fixed-dose combination were bioequivalent under fed and fasting conditions.

5.2 Pharmacodynamics

Amlodipine

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilatation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina. With chronic once daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria. As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in 6 normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects of electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce

higher degrees of AV blocks. Amlodipine has indications other than hypertension which can be found in the Norvasc® package insert.

Olmesartan

Olmesartan doses of 2.5 mg to 40 mg inhibit the pressor effects of angiotensin I infusion. The duration of the inhibitory effect was related to dose, with doses of olmesartan >40 mg giving >90% inhibition at 24 hours.

Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity (PRA) increase after single and repeated administration of olmesartan to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg olmesartan had minimal influence on aldosterone levels and no effect on serum potassium.

5.3 Exposure response relationship

Exposure-Response Analysis for Seated Diastolic Blood Pressure (SeDBP)

The final exposure-response model for change from baseline in SeDBP related the drug effects of both olmesartan (OM) and amlodipine (AML) to their systemic exposures, AUC_{OM} and AUC_{AML} , respectively. The drug effect for olmesartan was described by an E_{max} model, whereas the drug effect for amlodipine was described by a linear model. The drug effect of combination therapy was greater than either of the drug effects in monotherapy, but slightly less than their additive sum. This finding was modeled via an interaction term that consisted of a constant (0.05) multiplied by the product of the drug effects. The final model for change from baseline in SeDBP was:

$$\Delta SeDBP = Intercept + DEff_{OM} + DEff_{AML} + 0.05 * DEff_{OM} * DEff_{AML} + \eta + \varepsilon$$

where Intercept describes the placebo effect, η is an additive random effect, and ε is residual error.

The most important covariate was black race, as it modified both drug effects, but in opposite directions. Persons of black race ($KB = 1$) realized about 20% greater reduction in SeDBP from amlodipine than other races, but only half of the reduction in SeDBP from olmesartan, as shown in the two equations below:

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$$DEff_{OM} = (-18 + KB * 9.5) * \left(\frac{AUC_{OM}}{AUC_{OM} + 1630} \right)$$

$$DEff_{AM} = (-0.00488 * KB + -0.02220) * AUC_{AM}$$

where AUC has units of ng/mL*h. The placebo effect was estimated as a 3.59 mmHg reduction in SeDBP, with Hispanics (KH = 1) having a larger placebo effect than non-Hispanics, and subjects with higher baseline SeDBP (Baseline) having a larger placebo effect (approximately 3 mmHg additional change per 10 mmHg higher baseline).

$$Intercept = -3.59 + -4.84 * KH + -0.33 * (Baseline - 100.5)$$

To determine the impact of coadministration on the covariate analysis for the exposure-response relationship, the initial covariate estimates were obtained from a dataset containing the monotherapy and placebo arms. The final estimates were obtained from a full dataset containing all of the arms in the trial. The monotherapy estimates based on the data subset were not significantly different from the final estimates obtained from the full dataset. In addition, each covariate not in the final model was added back to the final model one at a time to retest for significance. In both cases, coadministration did not influence the covariate relationships in the exposure-response model (see Table 38).

Table 61: Exposure response

Parameter		
	Estimate	SE ^a (% CV)
Placebo	-3.59	19
Hispanic on Placebo	-4.84	28
Baseline on Placebo	-0.33	21
E _{max} (OM) [mmHg]	-18.1	30
Black race on E _{max}	9.51	46
EAUC ₀ (OLM) [h*ng/mL]	1630	37
Slope (AML) [mL/(ng*h)]	-0.0222	13
Black race on Slope	-0.00488	55
Interaction coefficient	0.05	19
IV (SD of Eta) [mmHg]	8.0 ^b	25 ^c
Sigma [mmHg] ^d	3.5	69.3
^a Coefficient of variation of the estimates (100SE _{estimate} /estimate). ^b Square root of ETA _{estimate} . ^c Percent square root of the relative standard error of the coefficient of variation. $100 \sqrt{\frac{SE_{Estimate}}{ETA_{estimate}}}$ ^d Residual intra-subject variability.		

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Table 62: Comparisons in Diastolic BP in Non-Blacks versus blacks Source Dr S. Bai

Label	Estimate	Standard Error	Pr > t	Lower	Upper
W40/10-40 vs. B40/10-40	1.7025	2.3201	0.4632	-2.8478	6.2528
W40/10-10 vs. B40/10-10	-6.6841	2.3626	0.0047	-11.3177	-2.0505
W40/5-40 vs. B40/5-40	4.5646	2.2679	0.0443	0.1167	9.0126
W40/5-5 vs. B40/5-5	-0.6373	2.2859	0.7804	-5.1206	3.8459
W20/10-20 vs. B20/10-20	3.8448	2.2952	0.0941	-0.6567	8.3462
W20/10-10 vs. B20/10-10	-3.8166	2.2395	0.0885	-8.2088	0.5757
W20/5-20 vs. B20/5-20	3.3847	2.3289	0.1463	-1.1829	7.9523
W20/5-5 vs. B20/5-5	-1.0920	2.2519	0.6278	-5.5087	3.3247
W10/10-10 vs. B10/10-10	3.8867	2.3405	0.0970	-0.7037	8.4772
W10/10-10 vs. B10/10-10	-1.5793	2.2575	0.4843	-6.0070	2.8483
W10/5-10 vs. B10/5-10	-1.2920	2.4433	0.5970	-6.0840	3.5000
W10/5-5 vs. B10/5-5	-3.5734	2.3398	0.1269	-8.1625	1.0156

Table 63: Comparisons in Systolic BP in Non-Blacks versus blacks Source Dr S. Bai

Label	Estimate	Standard Error	Pr > t	Lower	Upper
W40/10-40 vs. B40/10-40	8.3944	3.8580	0.0297	0.8278	15.9611
W40/10-10 vs. B40/10-10	-8.9190	3.9277	0.0233	-16.6224	-1.2156
W40/5-40 vs. B40/5-40	9.8389	3.7715	0.0092	2.4420	17.2357
W40/5-5 vs. B40/5-5	0.8475	3.8042	0.8237	-6.6135	8.3086
W20/10-20 vs. B20/10-20	5.3386	3.8168	0.1621	-2.1471	12.8243
W20/10-10 vs. B20/10-10	-9.2410	3.7234	0.0132	-16.5436	-1.9383
W20/5-20 vs. B20/5-20	8.6520	3.8736	0.0256	1.0549	16.2491
W20/5-5 vs. B20/5-5	2.3945	3.7460	0.5228	-4.9524	9.7414
W10/10-10 vs. B10/10-10	7.7647	3.8932	0.0463	0.1291	15.4003
W10/10-10 vs. B10/10-10	-5.4660	3.7539	0.1455	-12.8285	1.8966
W10/5-10 vs. B10/5-10	2.4216	4.0635	0.5513	-5.5480	10.3912
W10/5-5 vs. B10/5-5	-2.4870	3.8912	0.5228	-10.1186	5.1446

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6 INTEGRATED REVIEW OF EFFICACY

6.1

The two indication. sought by the Sponsor are as follows:

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

6.1.1 Methods

Statistical Analysis

The primary null hypothesis of no difference between the 6 combination therapies and their respective monotherapy components in change from baseline in SeDBP at Week 8 with LOCF in the ITT population was evaluated using Hommel's procedure in order to control the overall one-sided Type I error rate at 0.025 (See Dr Bai's Statistical Review). Table 27 summarizes the p values for all treatment arms adjusted for factorial study.

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

One-sided p-values for testing the primary and secondary null hypotheses were obtained from an Analysis of Covariance (ANCOVA) model that had fixed effects for treatment group, diabetic status (with or without diabetes) and age group (age ≥ 65 years or age < 65 years), and study baseline blood pressure as a covariate. Least-squares (LS) means, corresponding standard errors and 95% two-sided confidence intervals, as well as the difference in LS means, corresponding standard error and two-sided 95% confidence intervals were also derived from the ANCOVA model and presented.

Summary statistics were provided for baseline, endpoint and mean change in SeDBP and SeSBP at Week 8 with LOCF for each level of these subgroup variables. Within-treatment p-values are also presented testing whether there was a significant change from baseline within each treatment group. Three-dimensional plots displaying the mean reduction in SeDBP and SeSBP at Week 8 with LOCF are also presented for the primary subgroups (Black versus non-Black, gender, diabetic status, and age group).

One-sided p-values for testing the significance of the combination therapy against each monotherapy component were derived from an ANCOVA model that had treatment group, subgroup (e.g., age subgroup), and treatment-by-subgroup interaction as fixed effects and study baseline blood pressure as a covariate. Least-squares means, corresponding standard errors and 95% 2-sided confidence intervals, as well as the difference in LS means, corresponding standard error, and 2-sided 95% confidence interval were also derived from this ANCOVA model and presented. Given the exploratory nature of these analyses, no adjustments for multiple comparisons were made.

Due to the large number of investigational sites in this study, resulting in approximately 13 patients per site for this 12 treatment arm study, center as a factor was not included in this model.

The resulting p-values from Hommel's procedure were compared to a significance level of 0.025 to determine whether the given combination therapy could be declared statistically significantly better than both respective monotherapy components. The same analysis was applied to the secondary efficacy variable, change from baseline in SeSBP at Week 8 with LOCF in the ITT population and change from baseline for SeDBP and SeSBP at Weeks 2, 4, 6, and 8, all without LOCF imputation.

In addition, summary statistics are provided for baseline, endpoint, and mean change in each efficacy variable at each time point. Within treatment p-values are also presented testing whether there was a significant mean change from baseline within each treatment group.

The ANCOVA model was also used for the comparison of each monotherapy against placebo. Least-squares means, standard errors, LS mean of the treatment difference, its corresponding standard error and 95% confidence interval, and 2-sided p-value are also presented for the monotherapy versus placebo comparisons. This ANCOVA model was also used to obtain placebo-subtracted LS mean changes in SeDBP and SeSBP at Week 8 with LOCF for each active treatment group.

The number and percentage of patients achieving blood pressure goal at Week 8 with LOCF within each treatment group and in total are presented. Similar summaries are presented for patients achieving various blood pressure thresholds (<120/80 mmHg, <130/80 mmHg, <130/85 mmHg, and <140/90 mmHg). For the number and percentage of patients achieving blood pressure goal at Week 8, a chi-square test was used to test for significant differences among treatment groups.

The same treatment group comparisons that were described for the SeDBP and SeSBP analyses for each combination therapy versus its respective monotherapy components as well as each monotherapy versus placebo were performed. Hommel's procedure was also applied to the set of p-values obtained from the combination therapy versus monotherapy Haenszel tests stratified by age group and diabetic status for the given comparison. P-values for the monotherapy versus placebo comparisons were similarly obtained.

Interim analysis was neither planned nor performed during the double-blind treatment period of the study. As planned, the database was cleaned, treatment groups were unblinded, and data analyses were performed after all patients completed Week 8 (Visit 7). This report only provides the results of the double-blind treatment period.

Multiplicity Control of the Type I error level at a one-sided significance level of 0.025 was achieved through the application of Hommel's multiple comparison procedure.

Hypothesis

The primary null hypothesis of no difference between the 6 combination therapies and their respective monotherapy components in change from baseline in SeDBP at Week 8 with LOCF in the ITT population was evaluated using Hommel's procedure²⁹ in order to control the overall one-sided Type I error rate at 0.025.

Hommel's procedure requires computing $j = \max \{i: P(n-i+k) > \alpha / i \text{ for } k=1, \dots, i\}$, where $P(1) = P(2) = P(3) = \dots = P(n)$ are the n ordered p-values in ascending order, n is the number of comparisons and $i=1, \dots, n$. If the maximum does not exist, reject all H_i ($i=1, \dots, n$); otherwise reject all H_i with $P_i = \alpha / j$. This test is based on the principle of closed test procedures as proposed by Marcus, Peritz, and Gabriel.

In order to apply Hommel's procedure, the larger p-value of each pair of p-values obtained from comparing each combination with its components was used. This decision was justified because a combination was considered better than its components only if both p-values from comparing the combination to its components were both statistically significant, and if the larger of the 2 p-values was smaller than the significance level, the smaller p-value was also smaller than the significance level as well. Therefore, it was justified to select the larger p-value from the pair and use the resulting 6 p-values to go through Hommel's procedure rather than using all 12 p-values.

The resulting 6 p-values were arranged from the smallest, $P(1)$, to the largest, $P(6)$, each with its corresponding null hypothesis $H_0(1)$ to $H_0(6)$, and Hommel's procedure was applied. A combination was concluded as better than its 2 individual components if the corresponding null hypothesis was rejected.

Subgroup analyses

Subgroup analyses were performed for each level of the following dichotomous variables: age group (<65 years, ≥ 65 years), diabetic status (yes, no), gender (male, female), race (Black, non-Black), ethnicity (Hispanic/Latino, non-Hispanic/Latino), hypertension class (Stage 1 hypertension, Stage 2 hypertension), prior antihypertensive medication use (naïve to antihypertensive medication, not naïve to antihypertensive medication), and baseline BMI ($> 30 \text{ kg/m}^2$, $\geq 30 \text{ kg/m}^2$).

6.1.2 General Discussion of Endpoints

The primary efficacy variable was the change from baseline in SeDBP at the end of Period II. If a patient withdrew from the study prior to Week 8, the last observed value during the randomized double-blind treatment period was carried forward for the primary efficacy analysis. This is acceptable for statistical evaluation of treatment effect.

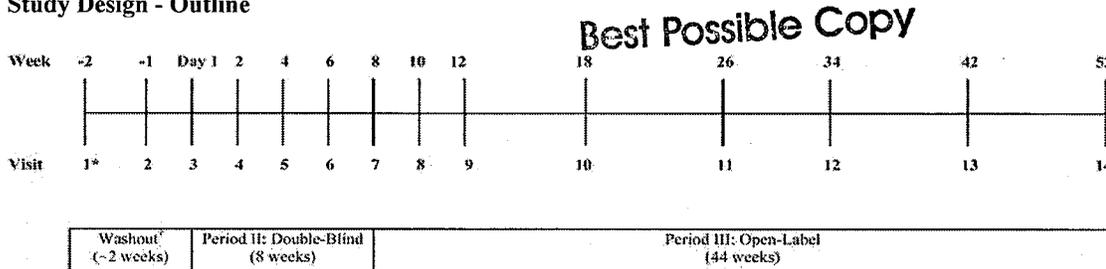
Change from baseline in SeSBP at the end of Period II with LOCF was the secondary efficacy variable. These endpoints are usual and are acceptable for this type of anti-hypertensive drug trial.

6.1.3 Study Design

The trial consisted of 3 periods. Period I was a washout of prior antihypertensive medications, Period II was a double-blind treatment period with different doses of

olmesartan medoxomil and amlodipine or combinations of these agents, and Period III was an open-label, long-term extension period with different combinations of olmesartan medoxomil and amlodipine.

Study Design - Outline



*At Visit 1, patients naïve to antihypertensive medications who had a mean SeDBP ≥ 95 mmHg and ≤ 120 mmHg, and who met all other entry criteria, proceeded directly to Visit 3 (randomization) within 7 days (± 3 days).
 †Patients on antihypertensive therapies requiring a washout period > 2 weeks were down-titrated over a period of time, and Visit 2 occurred 7 days (± 3 days) after the last day of the washout dose.
 Source: Study Protocol

Table 64: Treatment scheme - Overall plan – NDA 22-100

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

Study Design

Period I – Washout (approximately 2 weeks):

Period I consisted of a single screening visit for patients not on antihypertensive medications and a washout period with a minimum of 2 and a maximum of 3 visits for patients on antihypertensive medications.

At Visit 1, patients naïve to antihypertensive medications (patients who were never on antihypertensive medication or who had not been on antihypertensive medications for at least 2 weeks prior to Visit 1) who had a mean SeDBP ≥ 95 mmHg and ≤ 120 mmHg, and who met all other entry criteria, proceeded directly to Visit 3 (randomization) within 7 days (± 3 days). Patients naïve to antihypertensive medication (i.e., had not taken

antihypertensive medication for at least 2 weeks prior to screening) who did not have a mean SeDBP ≥ 95 mmHg and ≤ 120 mmHg were discontinued from the study.

At Visit 1, patients on antihypertensive medications who met all other entry criteria began a washout of these medications. Patients either immediately stopped antihypertensive medications or down-titrated antihypertensive medications over a period of time determined by the investigator. All of these patients had a blood pressure evaluation 7 days (± 3 days) after their last dose of antihypertensive medication (Visit 2), as follows:

- If the patient's mean SeDBP was not ≥ 95 mmHg at Visit 2, the patient could return within 1 week for another blood pressure evaluation at the discretion of the investigator (i.e., unscheduled Visit 2.1). If the patient's mean SeDBP was ≥ 95 mmHg and ≤ 120 mmHg at Visit 2.1, the patient proceeded to Visit 3 (randomization) within 3 to 7 days. If the patient's mean SeDBP was not ≥ 95 mmHg and ≤ 120 mmHg at Visit 2.1, the patient was discontinued from the study; or
- If the patient's mean SeDBP was ≥ 95 mmHg and ≤ 120 mmHg at Visit 2, the patient proceeded to Visit 3 within 7 days (± 3 days). If the patient's mean SeDBP was not ≥ 95 mmHg at Visit 3, the investigator could designate this Visit 3 measurement as an unscheduled visit (i.e., unscheduled Visit 2.1) and the patient could return within 3 to 7 days for another Visit 3 measurement.
- To be eligible for randomization, all patients had to have a mean SeDBP ≥ 95 mmHg and ≤ 120 mmHg at Visit 3. In addition, the difference in mean SeDBP measurements from Visits 1 and 3 for patients naïve to antihypertensive medication, and from Visits 2 and 3 (or Visits 2.1 and 3) for patients previously on antihypertensive medications, must have been ≥ 10 mmHg.
- If the difference in mean SeDBP was > 10 mmHg or the patient's mean SeDBP was not in the range and the patient had already been to Visit 2.1, the patient was discontinued from the study.
- If the difference in mean SeDBP was > 10 mmHg and the patient had not had a prior Visit 2.1, this visit was then considered as Visit 2.1 and no additional procedures were performed at this visit. The patient returned within 3 to 7 days for Visit 3. The patient proceeded to randomization only if their SeDBP was ≥ 95 mmHg and ≤ 120 mmHg and the difference between the Visit 2.1 and Visit 3 SeDBP was ≥ 10 mmHg.

Period II – Double-Blind Treatment (Day 1 to Week 8):

Period II consisted of an 8-week treatment period. Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized equally to 1 of the following 12 treatment arms in Table 1 above. The drug supply is presented in Table 3.

Treatment was double-blind, parallel-arm for all randomized patients. To achieve even distribution among treatment groups, the randomization process included stratification for

age (≥ 65 years, ≤ 65 years) and diabetic status. This study targeted approximately 20% of the patients to be ≥ 65 years of age.

Period III – Open-Label Treatment (Week 8 through Week 52)

Period III consisted of a 44-week, open-label treatment period to assess long-term safety and efficacy of various treatment combinations. After completing Period II, all patients were switched to the combination of OM 40 mg + AML 5 mg. Those patients whose blood pressure was not adequately controlled (i.e., did not achieve a minimum blood pressure goal of $<140/90$ mmHg, or $<130/80$ mmHg for diabetic patients) on OM 40 mg + AML 5 mg were titrated to OM 40 mg + AML 10 mg. Patients whose blood pressures were still not adequately controlled were offered HCTZ 12.5 mg or 25 mg, as required, to achieve this blood pressure goal. If a patient experienced symptoms of hypotension or displayed intolerance to study medication at any time during Period III, the patient was back-titrated at the investigator's discretion.

After Week 52, patients were discontinued from the study and treated according to investigators' discretion. A follow-up visit two weeks later (Week 54) was scheduled to examine any safety issues.

Objectives:

Period I is the washout period.

Primary objective - Period II

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.

For approval, the primary efficacy endpoint has to demonstrate that co-administration of olmesartan medoxomil (OM) and amlodipine (AML) is more efficacious for lowering seated diastolic blood pressure (SeDBP) compared to each of the corresponding monotherapy components.

The primary objective of Period II, being the double-blind, factorial, treatment period, was to demonstrate that olmesartan medoxomil (OM) and amlodipine (AML) co-administration was more efficacious for seated diastolic blood pressure (SeDBP) lowering than each of the corresponding monotherapy components.

Secondary Objectives – Period II

- To evaluate the antihypertensive efficacy for seated systolic blood pressure (SeSBP) lowering with co-administration of various doses of OM + AML compared to the corresponding monotherapy component;

- To evaluate the number and percentage of patients achieving blood pressure goal (defined as blood pressure <140/90 mmHg, or <130/80 mmHg for diabetic patients);
- To characterize the pharmacokinetic interactions and corresponding pharmacodynamic correlation (i.e., blood pressure lowering) between OM and AML using population pharmacokinetic sampling and modeling (blood specimens collected at selected clinical sites); and
- To perform exploratory evaluation of 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).

The objectives of Period III are as follows:

- To gain long-term efficacy and safety experience with co-administration of OM + AML (plus the addition of hydrochlorothiazide [HCTZ], if needed) while minimally treating patients to blood pressure goal (<140/90 mmHg, or <130/80 mmHg for diabetic patients); and
- To evaluate the number and percentage of patients achieving blood pressure goal (defined as blood pressure <140/90 mmHg, or <130/80 mmHg for diabetic patients).

Demographic and Baseline Characteristics

Table 65 below summarizes demographic data and other baseline characteristics for the All Randomized Patients population. The treatment groups were comparable with respect to demographics, with no statistically significant differences among the treatment groups.

Demographic and baseline characteristics were summarized for both the All Randomized Patients and ITT populations by treatment group and overall. Age group, gender, ethnicity, race, diabetic status, screening antihypertensive medication status, peripheral edema grade, baseline hypertension class (Stage 1 and Stage 2). Table 66.

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Table 65: Demographics

Baseline Characteristic	Pho (N = 162)	OM10 (N = 161)	OM20 (N = 161)	OM40 (N = 162)	AML5 (N = 161)	AML10 (N = 163)	OM10/ AML5 (N = 163)	OM20/ AML5 (N = 161)	OM40/ AML5 (N = 162)	OM10/ AML10 (N = 162)	OM20/ AML10 (N = 160)	OM40/ AML10 (N = 162)
Age (years)												
N	162	161	161	162	161	163	163	161	162	162	160	162
Mean (SD)	54.7 (10.92)	53.8 (10.97)	53.6 (10.84)	53.9 (10.59)	53.4 (11.40)	54.1 (10.61)	53.7 (11.52)	54.3 (10.86)	53.7 (11.26)	54.3 (10.52)	54.3 (11.59)	54.1 (12.19)
P-value ¹	0.9986											
Age Group (n, %) ¹												
<65 years	130 (80.2)	129 (80.1)	131 (81.4)	130 (80.2)	129 (80.1)	131 (80.4)	131 (80.4)	127 (78.9)	130 (80.2)	131 (80.9)	128 (80.0)	129 (79.6)
≥65 years	32 (19.8)	32 (19.9)	30 (18.6)	32 (19.8)	32 (19.9)	32 (19.6)	32 (19.6)	34 (21.1)	32 (19.8)	31 (19.1)	32 (20.0)	33 (20.4)
P-value ²	1.0000											
Age Group (n, %) ¹												
<50 years	48 (29.6)	58 (36.0)	64 (39.8)	53 (32.7)	65 (40.4)	53 (33.7)	58 (35.6)	54 (33.5)	56 (34.6)	54 (33.3)	55 (34.4)	55 (34.0)
≥50 years and <65 years	82 (50.6)	71 (44.1)	67 (41.6)	77 (47.5)	64 (39.8)	76 (46.6)	73 (44.8)	73 (45.3)	74 (45.7)	77 (47.5)	73 (45.6)	74 (45.7)
≥65 years and <75 years	26 (16.0)	26 (16.1)	27 (16.8)	26 (16.0)	27 (16.8)	30 (18.4)	26 (16.0)	31 (19.3)	27 (16.7)	27 (16.7)	23 (14.4)	26 (16.0)
≥75 years	6 (3.7)	6 (3.7)	3 (1.9)	6 (3.7)	5 (3.1)	2 (1.2)	6 (3.7)	3 (1.9)	5 (3.1)	4 (2.5)	9 (5.6)	7 (4.3)
P-value ³	0.9890											
Gender (n, %) ¹												
Male	93 (57.4)	87 (54.0)	90 (55.9)	82 (50.6)	87 (54.0)	98 (60.1)	84 (51.5)	83 (51.6)	97 (59.9)	94 (58.0)	71 (44.4)	88 (54.3)
Female	69 (42.6)	74 (46.0)	71 (44.1)	80 (49.4)	74 (46.0)	65 (39.9)	79 (48.5)	78 (48.4)	65 (40.1)	68 (42.0)	89 (55.6)	74 (45.7)
P-value ⁴	0.2222											
Ethnicity (n, %) ¹												
Hispanic or Latino	13 (8.0)	23 (14.3)	23 (14.3)	23 (14.2)	20 (12.4)	20 (12.3)	21 (12.9)	21 (13.0)	20 (12.3)	16 (9.9)	25 (15.6)	20 (12.3)
Not Hispanic or Latino	148 (91.4)	138 (85.7)	138 (85.7)	139 (85.8)	141 (87.6)	143 (87.7)	142 (87.1)	140 (87.0)	142 (87.7)	146 (90.1)	134 (83.8)	142 (87.7)
Missing	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)	0 (0.0)	1 (0.6)	0 (0.0)
P-value ⁵	0.8183											
Race (n, %) ^{1,2}												
Caucasian	114 (70.4)	119 (73.9)	118 (73.2)	111 (68.5)	113 (70.2)	120 (73.6)	121 (74.2)	111 (68.9)	115 (71.0)	113 (69.8)	107 (66.9)	123 (75.9)
Black	43 (27.3)	32 (19.9)	36 (22.4)	44 (27.2)	42 (26.1)	39 (23.9)	34 (20.9)	43 (26.7)	40 (24.7)	44 (27.2)	47 (29.4)	35 (21.6)
Asian	1 (0.6)	3 (1.9)	3 (1.9)	3 (1.9)	2 (1.2)	2 (1.2)	3 (1.8)	5 (3.1)	6 (3.7)	3 (1.9)	2 (1.3)	1 (0.6)
Native Hawaiian/Pacific Islander	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)	0 (0.0)	0 (0.0)
American Indian/Alaskan Native	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.6)	2 (1.2)	2 (1.2)	0 (0.0)	2 (1.2)	1 (0.6)	1 (0.6)
Other	2 (1.2)	6 (3.7)	4 (2.5)	2 (1.2)	4 (2.5)	2 (1.2)	5 (3.1)	2 (1.2)	1 (0.6)	1 (0.6)	3 (1.9)	4 (2.5)
P-value ^{3,5}	NS											
Weight (kg)												
N	162	161	161	162	160	163	163	161	162	162	160	162
Mean (SD)	96.3 (22.63)	95.5 (22.30)	95.4 (22.04)	94.3 (21.93)	95.8 (21.47)	96.2 (21.52)	94.3 (21.02)	95.6 (21.14)	93.4 (20.11)	95.9 (22.83)	94.1 (22.43)	94.6 (24.05)
P-value ⁴	0.9867											

Of the 1940 patients in the All Randomized Patients population, 1054 (54.3%) were male, 1385 (71.4%) were Caucasian, 481 (24.8%) were Black, 36 (1.9%) were Asian, and 48 (2.5%) were all other races (including Other, American Indian/Alaskan Native, and Native Hawaiian/Pacific Islander). The mean age was 54.0 years. A total of 384 (19.8%) patients were ≥65 years of age.

Weight, height, and BMI were also similar for the treatment groups, with no statistically significant differences among the treatment groups for these baseline characteristics. Mean weight was 95.1 kg, mean height was 170.1 cm, and mean BMI was 33.5 kg/m². A total of 64.7% of patients were obese (BMI =30 kg/m²), and 13.5% of patients had diabetes.

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.

Hypertension classifications of Stage 1 and Stage 2 were based on JNC7 guidelines with the following definitions:

Table 66: Classification of Hypertension by stage- Source Sponsor

	SeSBP	SeDBP
Stage 1	140-159	90-99
Stage 2	≥160	≥100

According to the sponsor, when a patient was classified at one level on systolic and a different level on diastolic, the higher classification was used for secondary hypertension.

Efficacy Analyses

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 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).

All statistical assessments are presented by randomized treatment group (i.e., by the actual treatment the patient received).

Efficacy parameters

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

Change from baseline in SeSBP at the end of Period II with LOCF was the secondary efficacy variable.

6.1.4 Efficacy findings

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

The findings are presented in Tables 67 – 92.

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Table 67: Mean change in SeDBP from baseline to wk 8 - ITT- NDA 22100

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)			Adjusted p-value
Tmt 1	vs.	Tmt 2	Tmt 1	Tmt 2	Tmt 1	Tmt 2	LS Mean (SE)	95% CI	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	<0.0001
	vs.	AML5		161		-10.0 (0.75)	-4.3 (0.99)	(-6.3, -2.4)	<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	<0.0001
	vs.	AML5		161		-10.0 (0.75)	-4.6 (0.99)	(-6.5, -2.6)	<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	0.0004
	vs.	AML10		163		-13.3 (0.74)	-3.3 (0.99)	(-5.3, -1.4)	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	<0.0001
	vs.	AML10		163		-13.3 (0.74)	-4.4 (0.99)	(-6.3, -2.4)	<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	<0.0001
	vs.	AML10		163		-13.3 (0.74)	-6.1 (0.99)	(-8.0, -4.2)	<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: C38862-A-1301 Final Report (Period II), Post-test Table 14.2.2

Table 68: 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

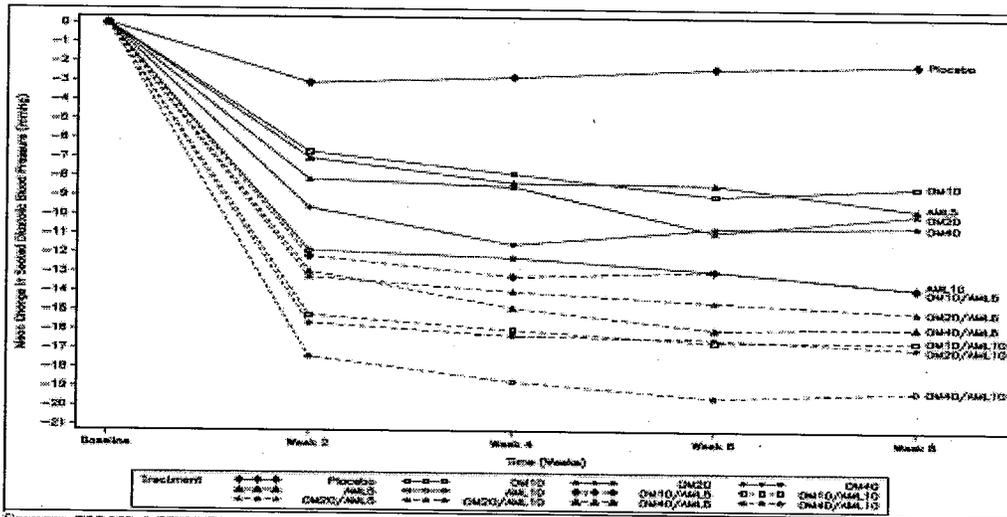
Time course: In the analysis of both SeDBP and SeSBP over time, the greatest mean reductions (70% to 80% of the maximum effect) in blood pressure occurred between baseline and Week 2. At Week 4, continued slight reductions were observed and plateaued in most of the treatment groups. In all of the combination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

Amlodipine besylate and Olmesartan Medoxomil NDA22-100

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.

Mean reduction from baseline in SeDBP over time - ITT- NDA 22100

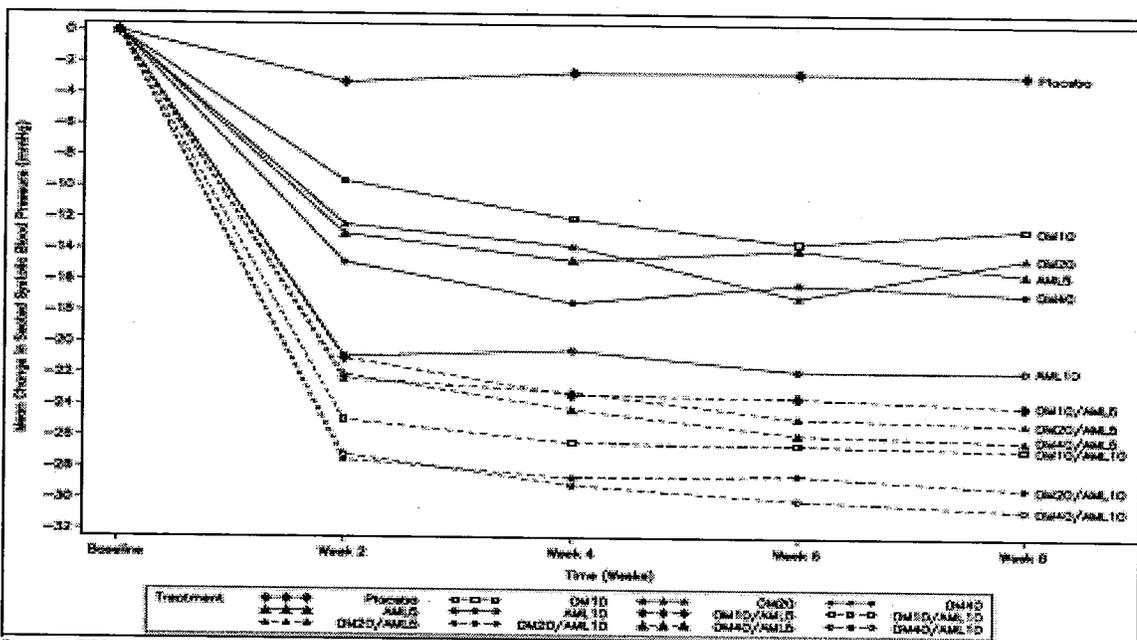
Figure 1: Mean Reduction from Baseline in SeDBP (mmHg) Over Time – All Treatment Groups – Pivotal Study (Double-Blind Treatment Period) – Intent-to-Treat Population



Source: CS8663-A-U301 Final Report (Period II), Post-text Figure 14.2.29

Mean reduction from baseline in SeSBP over time - ITT- NDA 22100

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-U301 Final Report (Period II), Post-text Figure 14.2.30

Table 69: Mean change of SeDBP Change from Baseline to week 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	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	102.3 ± 5.80	83.3 ± 9.77	-19.0 ± 8.90	<0.0001

¹N was the number of patients with values at both time points.
²Baseline for vital signs parameters was defined as the average of the values from the randomization visit (Visit 3) and the visit prior to the randomization visit.
³Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
⁴p-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: C88663-A-11501 Final Report (Period II), Post-text Table 14.2.1

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Table 70: p-values of SeSBP Change from Baseline to week 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

¹N was the number of patients with values at both time points.
²Baseline 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.
³Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
⁴P-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: C28653-A-01001 Final Report (Period II), Post-test Table 14.2.5

Table 71: Placebo-subtracted change in SeSBP- ITT-NDA 22100

		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

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Table 72: Mean change in SeSBP from baseline to week 8 in factorial study- comparisons - ITT-

Treatment Comparison			N		LS Mean (SE)		Difference (Tmt 1 – Tmt 2)			Adjusted p-value
Tmt 1	vs.	Tmt 2	Tmt 1	Tmt 2	Tmt 1	Tmt 2	LS Mean (SE)	95% CI	p-value	
OM10/AML5	vs.	OM10	163	160	-22.6 (1.33)	-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 (1.24)	-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 Bonferroni'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: CRR663-A-1301 Final Report (Period II), Post-text Table 14.2.6

Table 73: Number of patients reaching Blood Pressure goal –Period II - ITT

Table 7: Number (%) of Patients Reaching Blood Pressure Treatment Goal – Pivotal Study (Double-Blind Treatment Period) – Intent-to-Treat Population

Time point Category	Pbo (N = 160)	OM10 (N = 160)	OM20 (N = 159)	OM40 (N = 160)	AML5 (N = 161)	AML10 (N = 163)	OM10/AML5 (N = 163)	OM20/AML5 (N = 160)	OM40/AML5 (N = 157)	OM10/AML10 (N = 161)	OM20/AML10 (N = 153)	OM40/AML10 (N = 161)
Week 8 with LOCF												
Number Exposed (N)	160	160	159	160	161	163	163	160	157	161	153	161
Number Achieving Goal (n)	14	32	42	58	34	53	57	68	80	79	84	79
Percent Achieving Goal (n/N)	(8.8)	(20.0)	(26.4)	(36.3)	(21.1)	(32.5)	(35.0)	(42.5)	(51.0)	(49.1)	(55.2)	(49.1)
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-value was 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.
 Source: CRR663-A-1301 Final Report (Period II), Post-text Table 14.2.7.3

Table 74: Percent of patients reached BP goals at week 8- combination versus monotherapy

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

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

Amlodipine besylate and Olmesartan Medoxomil NDA22-100

Table 75: Comparisons between Combination therapy versus Monotherapy BP Goals-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		p-value	Adjusted p-value
Tmt 1	vs.	Tmt 2	Tmt 1	Tmt 2	Tmt 1 n (%)	Tmt 2 n (%)		
OM10/AML5	vs.	OM10	163	160	57 (35.0)	32 (20.0)	0.0009	0.0045
	vs.	AML5		161		34 (21.1)	0.0023	
OM20/AML5	vs.	OM20	160	159	68 (42.5)	42 (26.4)	0.0009	0.0055
	vs.	AML5		161		34 (21.1)	<0.0001	
OM40/AML5	vs.	OM40	157	160	89 (51.0)	38 (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	0.0044
	vs.	AML10		163		53 (32.3)	0.0013	
OM20/AML10	vs.	OM20	158	159	84 (53.2)	42 (26.4)	<0.0001	0.0002
	vs.	AML10		163		53 (32.5)	<0.0001	
OM40/AML10	vs.	OM40	161	160	79 (49.1)	38 (38.3)	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 Holm'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: CS8663-A-U301 Final Report (Period II), Post-text Table 14.2.74

Table 76: Percent of patients reached BP threshold at week 8

Table 9: Number (%) of Patients Reaching Blood Pressure Thresholds at Week 8 with LOCF – Pivotal Study (Double-Blind Treatment Period) – Intent-to-Treat Population

Treatment	N	Blood Pressure Threshold			
		<120/80 mmHg n (%)	<130/80 mmHg n (%)	<130/85 mmHg n (%)	<140/90 mmHg n (%)
Placebo	160	1 (0.6)	4 (2.5)	6 (3.8)	16 (10.0)
OM10	160	2 (1.3)	6 (3.8)	15 (9.4)	36 (22.5)
OM20	159	5 (3.1)	10 (6.3)	22 (13.8)	43 (27.0)
OM40	160	8 (5.0)	22 (13.8)	32 (20.0)	61 (38.1)
AML5	161	1 (0.6)	3 (1.9)	10 (6.2)	38 (23.6)
AML10	163	2 (1.2)	12 (7.4)	25 (15.3)	57 (35.0)
OM10/AML5	163	7 (4.3)	19 (11.7)	31 (19.0)	63 (38.7)
OM20/AML5	160	11 (6.9)	19 (11.9)	28 (17.5)	71 (44.4)
OM40/AML5	157	14 (8.9)	32 (20.4)	49 (31.2)	84 (53.5)
OM10/AML10	161	14 (8.7)	31 (19.3)	49 (30.4)	86 (53.4)
OM20/AML10	158	22 (13.9)	42 (26.6)	56 (35.4)	89 (56.3)
OM40/AML10	161	22 (13.7)	37 (23.0)	49 (30.4)	87 (54.0)

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 14.2.76

Blood Pressure Goals

The larger blood pressure reductions achieved with the combination treatments compared to the monotherapy treatments translated into a comparatively greater percentage of patients on combination therapy achieving their blood pressure goals. The number of patients achieving their blood pressure goals by Week 8 with LOCF ranged from 20.0% to 36.3% for the groups treated with monotherapy compared with 35.0% to 53.2% for the groups treated with combination therapy. The trend of improved treatment-to-goal benefit with combination therapy was also observed at all time points, beginning at Week 2 of treatment.

As would be expected, the subgroup of patients with Stage 1 hypertension had a greater percentage of patients who reached their blood pressure goals compared with the subgroup of patients with Stage 2 hypertension. Among the subgroups treated with one of the combination therapies, the percentage of patients achieving blood pressure goals at Week 8 with LOCF ranged from 65.6% to 80.0% for the subgroup of patients with Stage 1 hypertension compared with 27.4% to 49.2% for the subgroup of patients with Stage 2 hypertension.

The reductions in both mean SeDBP and mean SeSBP were all statistically significant in both patients with Stage 1 and Stage 2 hypertension. The reductions in both mean SeDBP and mean SeSBP were generally numerically greater in the subgroup of patients with Stage 2 hypertension compared to those patients with Stage 1 hypertension.

Table 77: Proportion of all randomized patients reaching BP Goals

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

A total of 531 patients out of 573 patients with mild to severe hypertension had valid blood pressure measurements. Trough-to-peak ratio for a patient was calculated as the Week 8 trough change from baseline divided by the maximum reduction in blood pressure selected from the following measurements: Week 8 trough change-from-baseline, Week 8 at 0.5-2 hour change-from-baseline, and Week 8 at 4-10 hour change-from-baseline. The ratio was considered missing when the sign of the trough measurement was different from the sign of the peak measurement. The results are presented in Table 78.

Table 78: Trough to Peak ratio for change in BP (Diastolic/Systolic) from the PK substudy

Table 10: Trough-to-Peak Ratio for Change in Blood Pressure (Diastolic/Systolic) from the Pharmacokinetic Substudy

		Olmesartan Medoxomil			
		Placebo Mean Ratio (N)	10 mg Mean Ratio (N)	20 mg Mean Ratio (N)	40 mg Mean Ratio (N)
Amlodipine	Placebo Mean Ratio (N)	0.63/0.68 (24)	0.72/0.75 (39)	0.71/0.74 (36)	0.65/0.73 (36)
	5 mg Mean Ratio (N)	0.71/0.73 (38)	0.73/0.74 (39)	0.72/0.79 (46)	0.71/0.81 (44)
	10 mg Mean Ratio (N)	0.76/0.81 (43)	0.75/0.74 (45)	0.74/0.79 (43)	0.73/0.82 (50)
N was the number of patients with valid trough/peak ratio based on SeDBP measurements. Trough/Peak ratio for a patient was calculated as the Week 8 trough change from baseline divided by the minimum of Week 8 trough change from baseline, Week 8 at 0.5-2 hour change from baseline, and Week 8 at 4-10 hour change from baseline. The ratio was considered missing when the sign of the trough measurement was different from the sign of the peak measurement. Sources: C38663-A-1301 Final Report (Period II), Post-text Tables 14.2.239 and 14.2.241					

Subgroup analyses were carried out on the following:

- Age
- Gender
- Race
- Ethnicity
- Hypertension class
- Diabetic status
- BMI

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The changes in blood pressures in the combination therapy groups were compared to the monotherapy components that made up the combinations and the percentage of patients achieving treatment goals were analyzed by age, diabetic status, gender, race, ethnicity, hypertension class, prior antihypertensive medication use, and baseline BMI. All statistical comparisons made for these subgroups were exploratory in nature and no adjustments for multiple comparisons were made.

Subgroup Analysis by Age

The following is a summary of patients in the clinical development studies for AZOR showing the proportion of the elderly in the development program. About 20% of all randomized patients were over the age of 65 years but discontinuations were relatively common in the elderly as shown below:

- Planned:** 1896 randomized patients (approx. 20% of patients ≥65 years of age)
- Enrolled:** 4234 patients. **Randomized:** 1940 patients (384 patients ≥65 years of age)
- Completed Period II:** 1689 patients (332 patients ≥ 65 years of age)
- Discontinued Period II:** 251 patients (52 patients ≥65 years of age)
- Entered Period III:** 1684 patients (331 patients ≥65 years of age)
- Completed Period III:** 1400 patients (267 patients ≥65 years of age)
- Discontinued Period III :** 284 patients (64 patients ≥ 65 years of age)

The reductions in both mean SeDBP and mean SeSBP were all statistically significant in both patients ≥ 65 years of age and in patients ≤ 65 years of age. The reductions in both mean SeDBP and mean SeSBP were generally numerically greater in the group of patients ≤ 65 years of age. For both age subgroups, the greatest mean blood pressure reductions were observed in the OM 40 mg + AML 10 mg treatment group. When treated with OM 40 mg + AML 10 mg, mean blood pressure was reduced by approximately 29/19 mmHg in patients < 65 years of age and by approximately 34/21 mmHg in patients ≥ 65 years of age (Tables 79 and 80).

In both age categories, combination treatments reduced mean SeDBP and mean SeSBP to a greater extent than the component monotherapies. For the subgroup of patients < 65 years of age, all of the comparisons were highly statistically significant. In the subgroup of patients ≥ 65 years of age, all of the reductions in blood pressure were greater in the combination treatment groups compared to the monotherapy treatment groups although not all of the comparisons between the combination groups and the various monotherapy treatments reached statistical significance. This may be due to the small numbers of patients ≥ 65 years of age in each treatment group.

Table 79: Mean change in SeDBP by Age

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

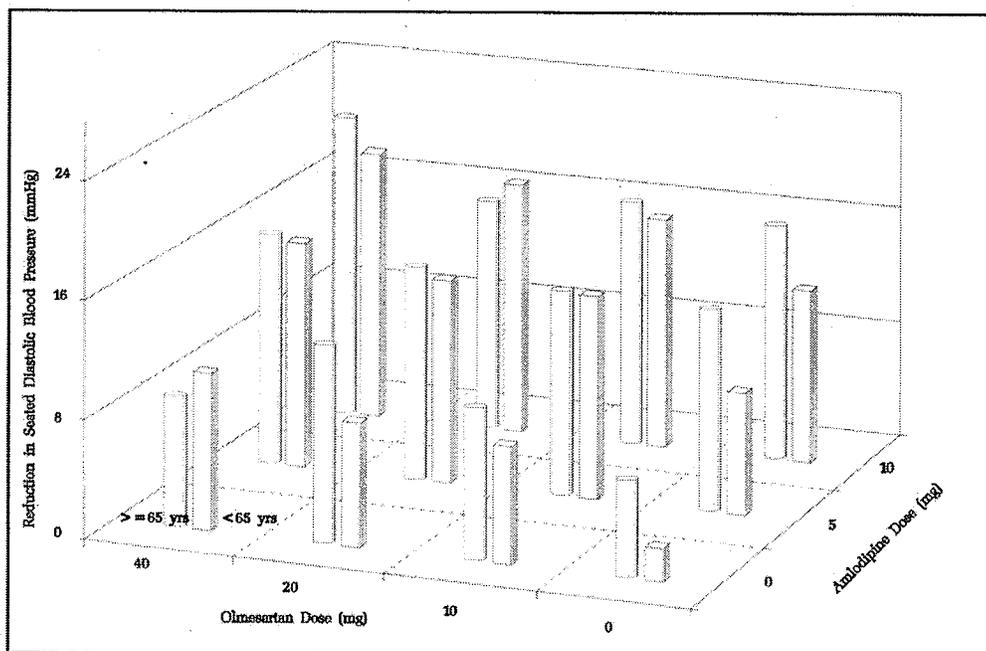
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Table 80: Mean change in SeSBP by Age

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

Figure 10: Mean Reduction in SeDBP from baseline to week 8 by age with LOCF-NDA 22100

Figure 7: Mean Reduction in SeDBP (mmHg) from Baseline to Week 8 with LOCF – Age Subgroups – Intent-to-Treat Population

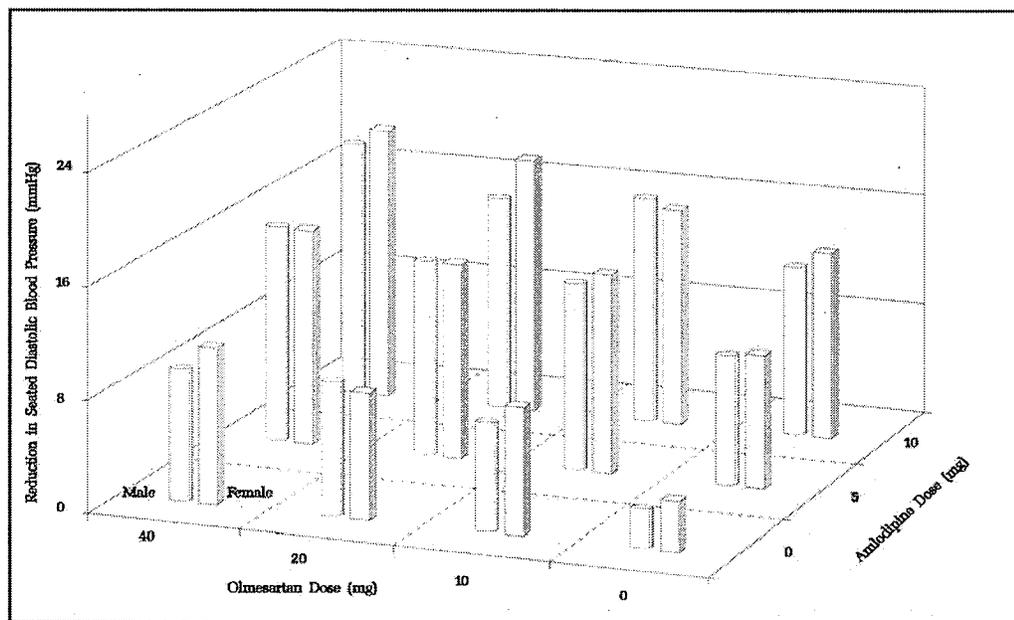


Source: Post-text Figure 14.2.21

Gender

The reductions in both mean SeDBP and mean SeSBP were all statistically significant in both male and female patients. Although the mean reductions in SeDBP were similar in males and females, there did appear to be numerically greater mean reductions in SeSBP in females compared to males (Tables 81 and 82).

Figure 11: Mean reduction in SeDBP (mmHg) from baseline to wk 8 with LOCF- by Gender –ITT



Source: Post-text Figure 14.2.25

In both subgroups, the greatest mean blood pressure reductions were observed in the OM 40 mg + AML 10 mg treatment group with mean reductions of approximately 27/19 mmHg in the subgroup of male patients and approximately 35/20 mmHg in the subgroup of female patients (Tables 84 and 85).

In all comparisons between the combination treatments and the component monotherapies, greater mean reductions in blood pressures were observed in the combination treatments compared to the monotherapy components. These comparisons for both SeDBP and SeSBP were similar between males and females. The comparisons were all highly statistically significant except for the comparison between OM 10 mg + AML 10 mg and AML 10 mg in the female subgroup.

For both subgroups, larger mean blood pressure reductions with the combination therapies resulted in a greater percentage of patients achieving their blood pressure goals compared with monotherapy. Females, because of better responsiveness to the combination treatment, tended to have a greater percentage of patients reaching goal than males (Table 83).

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Table 81: Mean change in SeDBP by Gender

Table 32: Mean Change in Seated Diastolic Blood Pressure (mmHg) from Baseline to Week 8 with LOCF – Gender Subgroups – Intent-to-Treat Population

Treatment	Male Patients			Female Patients		
	N ¹	Change Mean ± SD	p-value ²	N ¹	Change Mean ± SD	p-value ²
Placebo	91	-2.7 ± 10.77	0.0059	69	-3.5 ± 10.60	0.0019
OM10	86	-7.7 ± 8.83	<0.0001	74	-9.0 ± 9.78	<0.0001
OM20	90	-9.5 ± 9.45	<0.0001	69	-8.9 ± 10.15	<0.0001
OM40	81	-9.3 ± 10.32	<0.0001	79	-11.1 ± 11.05	<0.0001
AML5	87	-9.2 ± 8.11	<0.0001	74	-9.5 ± 8.48	<0.0001
AML10	98	-12.2 ± 7.49	<0.0001	65	-13.5 ± 9.28	<0.0001
OM10/AML5	84	-13.4 ± 7.20	<0.0001	79	-14.3 ± 7.77	<0.0001
OM20/AML5	82	-14.0 ± 9.17	<0.0001	78	-14.0 ± 9.03	<0.0001
OM40/AML5	94	-15.5 ± 8.01	<0.0001	63	-15.5 ± 8.43	<0.0001
OM10/AML10	93	-16.3 ± 7.97	<0.0001	68	-15.7 ± 9.49	<0.0001
OM20/AML10	71	-15.3 ± 7.60	<0.0001	87	-18.4 ± 8.18	<0.0001
OM40/AML10	88	-18.5 ± 7.96	<0.0001	73	-19.6 ± 9.94	<0.0001

¹N was the number of patients with values at both time points.
²Two-sided p-values were obtained from an Analysis of Covariance model with treatment, gender subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
 AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.
 Sources: Post-text Tables 14.2.122 and 14.2.124

Table 82: Mean change in SeSBP from baseline to wk 8 with LOCF- Combination versus monotherapy comparisons- Gender subgroups – ITT population

Table 35: Mean Change in Seated Systolic Blood Pressure (mmHg) from Baseline to Week 8 with LOCF – Gender Subgroups – Intent-to-Treat Population

Treatment	Male Patients			Female Patients		
	N ¹	Change Mean ± SD	p-value ²	N ¹	Change Mean ± SD	p-value ²
Placebo	91	-2.9 ± 15.93	0.0657	69	-7.4 ± 21.70	0.0031
OM10	86	-10.3 ± 15.45	<0.0001	74	-12.9 ± 14.96	<0.0001
OM20	90	-13.8 ± 15.90	<0.0001	69	-13.9 ± 16.01	<0.0001
OM40	81	-16.7 ± 15.81	<0.0001	79	-15.4 ± 17.41	<0.0001
AML5	87	-13.6 ± 12.87	<0.0001	74	-16.3 ± 17.06	<0.0001
AML10	98	-16.6 ± 14.56	<0.0001	65	-24.5 ± 18.22	<0.0001
OM10/AML5	84	-22.7 ± 12.27	<0.0001	79	-25.7 ± 15.50	<0.0001
OM20/AML5	82	-20.8 ± 14.33	<0.0001	78	-26.5 ± 14.94	<0.0001
OM40/AML5	94	-23.7 ± 13.53	<0.0001	63	-28.0 ± 16.07	<0.0001
OM10/AML10	93	-24.9 ± 14.60	<0.0001	68	-25.9 ± 15.33	<0.0001
OM20/AML10	71	-23.8 ± 15.40	<0.0001	87	-33.7 ± 16.51	<0.0001
OM40/AML10	88	-26.5 ± 14.82	<0.0001	73	-34.5 ± 16.16	<0.0001

¹N was the number of patients with values at both time points.
²Two-sided p-values were obtained from an Analysis of Covariance model with treatment, gender subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
 AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.
 Sources: Post-text Tables 14.2.126 and 14.2.128

Each combination therapy had a significantly greater mean reduction in SeDBP compared to both of its monotherapy components (p<0.01) for all components). Each combination therapy had a significantly greater mean reduction in SeSBP compared to both of its monotherapy components (p<0.003 for all comparisons).

Tables 83 and 84 below presents the comparisons between combination therapy versus monotherapy with respect to mean change in SeDBP from baseline to week 8 with LOCF for the subgroup of male and female patients.

Table 83: Mean change in SeDBP from baseline to wk 8 with LOCF- Combination versus monotherapy comparisons Male patients – ITT population-NDA 22100

Table 33: Mean Change in Seated Diastolic Blood Pressure (mmHg) from Baseline to Week 8 with LOCF – Combination Therapy Versus Monotherapy Comparisons – Male Patients – 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
OM10/AML5	vs.	OM10	84	86	-13.3 (0.97)	-7.7 (0.96)	-5.6 (1.37)	(-8.3, -3.0)	<0.0001
	vs.	AML5		87		-9.3 (0.96)	-4.0 (1.37)	(-6.7, -1.3)	0.0018
OM20/AML5	vs.	OM20	82	90	-13.9 (0.99)	-9.4 (0.94)	-4.5 (1.36)	(-7.3, -1.8)	0.0005
	vs.	AML5		87		-9.3 (0.96)	-4.6 (1.38)	(-7.3, -1.9)	0.0004
OM40/AML5	vs.	OM40	94	81	-15.7 (0.92)	-9.3 (0.99)	-6.4 (1.35)	(-9.0, -3.7)	<0.0001
	vs.	AML5		87		-9.3 (0.96)	-6.4 (1.33)	(-9.0, -3.8)	<0.0001
OM10/AML10	vs.	OM10	93	86	-16.2 (0.93)	-7.7 (0.96)	-8.6 (1.34)	(-11.2, -5.9)	<0.0001
	vs.	AML10		98		-12.2 (0.90)	-4.0 (1.29)	(-6.5, -1.5)	0.0010
OM20/AML10	vs.	OM20	71	90	-15.5 (1.06)	-9.4 (0.94)	-6.0 (1.42)	(-8.8, -3.2)	<0.0001
	vs.	AML10		98		-12.2 (0.90)	-3.2 (1.39)	(-6.0, -0.5)	0.0100
OM40/AML10	vs.	OM40	88	81	-18.3 (0.95)	-9.3 (0.99)	-9.0 (1.38)	(-11.7, -6.3)	<0.0001
	vs.	AML10		98		-12.2 (0.90)	-6.1 (1.31)	(-8.6, -3.5)	<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 treatment, gender subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 AML = amlodipine, CI = confidence interval, LS = least squares, OM = olmesartan medoxomil, SE = standard error, Tmt = treatment, vs. = versus.
 Source: Post-text Table 14.2.123

Table 84: Mean change in SeDBP from baseline to wk 8 with LOCF- Combination versus monotherapy comparisons Female patients – ITT population - NDA 22100

Table 34: Mean Change in Seated Diastolic Blood Pressure (mmHg) from Baseline to Week 8 with LOCF – Combination Therapy Versus Monotherapy Comparisons – Female Patients – 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
OM10/AML5	vs.	OM10	79	74	-14.2 (1.01)	-8.9 (1.04)	-5.2 (1.45)	(-8.1, -2.4)	0.0001
	vs.	AML5		74		-9.5 (1.04)	-4.7 (1.45)	(-7.5, -1.8)	0.0006
OM20/AML5	vs.	OM20	78	69	-14.0 (1.01)	-9.0 (1.08)	-5.0 (1.48)	(-7.9, -2.1)	0.0004
	vs.	AML5		74		-9.5 (1.04)	-4.6 (1.45)	(-7.4, -1.7)	0.0008
OM40/AML5	vs.	OM40	63	79	-15.6 (1.13)	-11.3 (1.01)	-4.3 (1.31)	(-7.3, -1.4)	0.0021
	vs.	AML5		74		-9.5 (1.04)	-6.1 (1.53)	(-9.1, -3.1)	<0.0001
OM10/AML10	vs.	OM10	68	74	-15.8 (1.08)	-8.9 (1.04)	-6.9 (1.50)	(-9.8, -4.0)	<0.0001
	vs.	AML10		65		-13.5 (1.11)	-2.3 (1.55)	(-5.3, 0.7)	0.0686
OM20/AML10	vs.	OM20	87	69	-18.4 (0.96)	-9.0 (1.08)	-9.4 (1.44)	(-12.2, -6.6)	<0.0001
	vs.	AML10		65		-13.5 (1.11)	-4.9 (1.46)	(-7.8, -2.1)	0.0004
OM40/AML10	vs.	OM40	73	79	-19.5 (1.05)	-11.3 (1.01)	-8.3 (1.45)	(-11.1, -5.4)	<0.0001
	vs.	AML10		65		-13.5 (1.11)	-6.0 (1.52)	(-9.0, -3.0)	<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 treatment, gender subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 AML = amlodipine, CI = confidence interval, LS = least squares, OM = olmesartan medoxomil, SE = standard error, Tmt = treatment, vs. = versus.
 Source: Post-text Table 14.2.123

Table 85 presents the comparisons of combination therapy versus monotherapy with respect to mean change in SeSBP from baseline to week 8 with LOCF for the subgroup of male patients.

Table 85: Mean change in SeSBP – Combination versus Monotherapy – male patients – p value



Table 36: Mean Change in Seated Systolic Blood Pressure (mmHg) from Baseline to Week 8 with LOCF – Combination Therapy Versus Monotherapy Comparisons – Male Patients – 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
OM10/AML5	vs.	OM10	84	86	-22.4 (1.59)	-11.2 (1.57)	-11.2 (2.24)	(-15.6, -6.8)	<0.0001
	vs.	AML5		87		-14.6 (1.56)	-7.9 (2.23)	(-12.3, -3.5)	0.0002
OM20/AML5	vs.	OM20	82	90	-21.7 (1.61)	-14.3 (1.54)	-7.3 (2.23)	(-11.7, -3.0)	0.0005
	vs.	AML5		87		-14.6 (1.56)	-7.1 (2.25)	(-11.5, -2.7)	0.0008
OM40/AML5	vs.	OM40	94	81	-24.9 (1.51)	-16.5 (1.62)	-8.4 (2.21)	(-12.7, -4.0)	<0.0001
	vs.	AML5		87		-14.6 (1.56)	-10.3 (2.17)	(-14.6, -6.1)	<0.0001
OM10/AML10	vs.	OM10	93	86	-25.0 (1.51)	-11.2 (1.57)	-13.7 (2.18)	(-18.0, -9.5)	<0.0001
	vs.	AML10		98		-17.3 (1.47)	-7.7 (2.11)	(-11.9, -3.6)	0.0001
OM20/AML10	vs.	OM20	71	90	-23.8 (1.73)	-14.3 (1.54)	-9.4 (2.32)	(-14.0, -4.9)	<0.0001
	vs.	AML10		98		-17.3 (1.47)	-6.5 (2.27)	(-11.0, -2.0)	0.0021
OM40/AML10	vs.	OM40	88	81	-26.0 (1.56)	-16.5 (1.62)	-9.5 (2.25)	(-13.9, -5.1)	<0.0001
	vs.	AML10		98		-17.3 (1.47)	-8.8 (2.14)	(-13.0, -4.6)	<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 treatment, gender subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 AML = amlodipine, CI = confidence interval, LS = least squares, OM = olmesartan medoxomil, SE = standard error, Tmt = treatment, vs. = versus.
 Source: Post-hoc Table 14.2.127

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Each combination therapy had a significantly greater mean reduction in SeSBP compared to both of its monotherapy components in males (p<0.003).

Table 86 presents the comparisons of combination therapy versus monotherapy with respect to mean change in SeSBP from baseline to Week 8 with LOCF for the subgroup of female patients.

All comparisons between the combination therapy groups and the respective monotherapy component groups were statistically significant (p=0.0001) with the exception of the OM 10 mg + AML 10 mg group compared with the AML 10 mg group. Each combination therapy had a significantly greater mean reduction in SeSBP compared to both of its monotherapy components in females (p<0.0001 with the exception of OM10/AML10).

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Table 86: Mean change in SeSBP – Combination versus Monotherapy – female patients -ITT

Table 37: Mean Change in Seated Systolic Blood Pressure (mmHg) from Baseline to Week 8 with LOCF – Combination Therapy Versus Monotherapy Comparisons – Female Patients – 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
OM10/AML5	vs.	OM10	79	74	-24.8 (1.64)	-12.6 (1.70)	-12.2 (2.36)	(-16.9, -7.6)	<0.0001
	vs.	AML5							
OM20/AML5	vs.	OM20	78	69	-25.7 (1.65)	-13.0 (1.76)	-12.7 (2.41)	(-17.4, -7.9)	<0.0001
	vs.	AML5							
OM40/AML5	vs.	OM40	63	79	-28.0 (1.84)	-16.3 (1.64)	-11.7 (2.46)	(-16.5, -6.8)	<0.0001
	vs.	AML5							
OM10/AML10	vs.	OM10	68	74	-26.8 (1.77)	-12.6 (1.70)	-14.3 (2.45)	(-19.1, -9.5)	<0.0001
	vs.	AML10							
OM20/AML10	vs.	OM20	87	69	-33.5 (1.56)	-13.0 (1.76)	-20.5 (2.35)	(-25.1, -15.9)	<0.0001
	vs.	AML10							
OM40/AML10	vs.	OM40	73	79	-33.6 (1.71)	-16.3 (1.64)	-17.3 (2.37)	(-21.9, -12.6)	<0.0001
	vs.	AML10							

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 treatment, gender subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 AML = amlodipine, CI = confidence interval, LS = least squares, OM = olmesartan medoxomil, SE = standard error, Tmt = treatment, vs. = versus.
 Source: Post-text Table 14.2.129

Race

The reductions in both mean SeDBP and mean SeSBP were not all statistically significant in both Black and non-Black patients. The degree of significance was less in Black patients treated with olmesartan medoxomil monotherapy. The reductions in both mean SeDBP and mean SeSBP were generally numerically less in Black patients compared to non-Black patients, which was particularly evident in the olmesartan medoxomil monotherapy treatment groups. Mean reductions were slightly less in Black patients treated with amlodipine 5 mg monotherapy compared to non-Black patients. However, Black patients treated with amlodipine 10 mg achieved greater mean reductions in both SeDBP and SeSBP compared to non-Black patients (Table 87).

For both race subgroups, the greatest mean blood pressure reductions were observed in the OM 40 mg + AML 10 mg treatment group, with mean reductions of approximately 29/16 mmHg in the subgroup of Black patients and approximately 31/20 mmHg in the subgroup of non- Black patients (Table 87) .

Table 88 below presents the comparisons of combination therapy versus monotherapy with respect to mean change in SeDBP from baseline to Week 8 with LOCF for the subgroup of Black patients.

In the following cases, combination therapy resulted in significantly greater mean reductions in SeDBP compared with one or both of the monotherapy components:

- OM 20 mg + AML 5 mg group compared with both the OM 20 mg group (LS mean treatment difference of -7.6 mmHg; p<0.0001) and the AML 5 mg group (LS mean treatment difference of -4.1 mmHg; p=0.0163);

- OM 40 mg + AML 5 mg group compared with both the OM 40 mg group (LS mean treatment difference of -8.5 mmHg; $p < 0.0001$) and the AML 5 mg group (LS mean treatment difference of -5.8 mmHg; $p = 0.0018$);
- OM 10 mg + AML 10 mg group compared only with the OM 10 mg group (LS mean treatment difference of -10.4 mmHg; $p < 0.0001$);
- OM 20 mg + AML 10 mg group compared only with the OM 20 mg group (LS mean treatment difference of -10.8 mmHg; $p < 0.0001$); and
- OM 40 mg + AML 10 mg group compared only with the OM 40 mg group (LS mean treatment difference of -9.9 mmHg; $p < 0.0001$).

Table 87: Mean change in SeDBP by Race –Black versus non black

Treatment	Black			Non-Black		
	N ¹	Change Mean \pm SD	p-value ²	N ¹	Change Mean \pm SD	p-value ²
Placebo	45	-1.3 \pm 9.55	0.4587	115	-3.8 \pm 11.04	<0.0001
OM10	32	-5.3 \pm 8.44	0.0012	128	-9.0 \pm 9.35	<0.0001
OM20	34	-4.5 \pm 9.98	0.0032	125	-10.5 \pm 9.30	<0.0001
OM40	44	-5.5 \pm 9.51	<0.0001	116	-12.0 \pm 10.61	<0.0001
AML5	42	-8.3 \pm 8.66	<0.0001	119	-9.7 \pm 8.11	<0.0001
AML10	39	-13.4 \pm 8.40	<0.0001	124	-12.5 \pm 8.22	<0.0001
OM10/AML5	34	-9.4 \pm 6.94	<0.0001	129	-15.0 \pm 7.20	<0.0001
OM20/AML5	43	-12.4 \pm 9.17	<0.0001	117	-14.6 \pm 9.00	<0.0001
OM40/AML5	38	-13.9 \pm 8.35	<0.0001	119	-16.0 \pm 8.06	<0.0001
OM10/AML10	43	-15.5 \pm 8.45	<0.0001	118	-16.2 \pm 8.71	<0.0001
OM20/AML10	46	-15.2 \pm 7.92	<0.0001	112	-17.8 \pm 8.01	<0.0001
OM40/AML10	34	-15.7 \pm 9.05	<0.0001	127	-19.9 \pm 8.68	<0.0001

¹N was the number of patients with values at both time points.
²Two-sided p-values were obtained from an Analysis of Covariance model with treatment, race subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.
Sources: Post-text Tables 14.2.130 and 14.2.132

The other comparisons between the combination therapy groups and the respective monotherapy component groups were not statistically significant (Table 88).

This phenomenon is attributed to the higher incidence of low-renin-producers in the Black population.

Although Black patients treated with combination therapies had generally less mean reduction in SeDBP and SeSBP compared to non-Black patients, the combination of olmesartan medoxomil with amlodipine produced almost but not as good an effect as in the non-Black groups. In all likelihood, this was due to the effect of the amlodipine component in the combination treatment groups.

Table 88: Mean change in SeDBP from baseline to wk 8 with LOCF : Combined versus monotherapy- comparisons -blacks ITT

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
OM10/AML5	vs.	OM10	34	32	-9.0 (1.51)	-5.0 (1.56)	-4.0 (2.17)	(-8.3, 0.2)	0.0322
	vs.	AML5		42		-8.0 (1.36)	-1.0 (2.03)	(-5.0, 3.0)	0.3066
OM20/AML5	vs.	OM20	43	34	-12.1 (1.34)	-4.4 (1.51)	-7.6 (2.02)	(-11.6, -3.7)	<0.0001
	vs.	AML5		42		-8.0 (1.36)	-4.1 (1.91)	(-7.8, -0.3)	0.0163
OM40/AML5	vs.	OM40	38	44	-13.8 (1.43)	-5.3 (1.33)	-8.5 (1.95)	(-12.3, -4.7)	<0.0001
	vs.	AML5		42		-8.0 (1.36)	-5.8 (1.97)	(-9.6, -1.9)	0.0018
OM10/AML10	vs.	OM10	43	32	-15.5 (1.34)	-5.0 (1.56)	-10.4 (2.05)	(-14.5, -6.4)	<0.0001
	vs.	AML10		39		-13.5 (1.41)	-2.0 (1.94)	(-5.8, 1.8)	0.1549
OM20/AML10	vs.	OM20	46	34	-15.2 (1.30)	-4.4 (1.51)	-10.8 (1.99)	(-14.7, -6.9)	<0.0001
	vs.	AML10		39		-13.5 (1.41)	-1.7 (1.91)	(-5.5, 2.0)	0.1851
OM40/AML10	vs.	OM40	34	44	-15.2 (1.51)	-5.3 (1.33)	-9.9 (2.01)	(-13.9, -6.0)	<0.0001
	vs.	AML10		39		-13.5 (1.41)	-1.7 (2.07)	(-5.8, 2.3)	0.2023

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 treatment, race subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 AML = amlodipine, CI = confidence interval, LS = least squares, OM = olmesartan medoxomil, SE = standard error, Tmt = treatment, vs. = versus.
 Source: Post-text Table 14.2.131

Table 89: Mean change in SeDBP from baseline to wk 8 with LOCF : Combined versus monotherapy- comparisons Non-blacks ITT

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
OM10/AML5	vs.	OM10	129	128	-14.9 (0.77)	-9.0 (0.78)	-5.9 (1.10)	(-8.0, -3.7)	<0.0001
	vs.	AML5		119		-9.9 (0.81)	-5.0 (1.12)	(-7.2, -2.9)	<0.0001
OM20/AML5	vs.	OM20	117	125	-14.7 (0.81)	-10.6 (0.79)	-4.1 (1.13)	(-6.3, -1.9)	0.0002
	vs.	AML5		119		-9.9 (0.81)	-4.8 (1.15)	(-7.0, -2.5)	<0.0001
OM40/AML5	vs.	OM40	119	116	-16.3 (0.81)	-12.2 (0.82)	-4.1 (1.15)	(-6.3, -1.8)	0.0002
	vs.	AML5		119		-9.9 (0.81)	-6.4 (1.14)	(-8.6, -4.2)	<0.0001
OM10/AML10	vs.	OM10	118	128	-16.3 (0.81)	-9.0 (0.78)	-7.2 (1.12)	(-9.4, -5.0)	<0.0001
	vs.	AML10		124		-12.5 (0.79)	-3.8 (1.13)	(-6.0, -1.6)	0.0004
OM20/AML10	vs.	OM20	112	125	-17.9 (0.83)	-10.6 (0.79)	-7.3 (1.14)	(-9.6, -5.1)	<0.0001
	vs.	AML10		124		-12.5 (0.79)	-5.4 (1.15)	(-7.7, -3.2)	<0.0001
OM40/AML10	vs.	OM40	127	116	-19.8 (0.78)	-12.2 (0.82)	-7.6 (1.13)	(-9.8, -5.4)	<0.0001
	vs.	AML10		124		-12.5 (0.79)	-7.3 (1.11)	(-9.5, -5.1)	<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 treatment, race subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 AML = amlodipine, CI = confidence interval, LS = least squares, OM = olmesartan medoxomil, SE = standard error, Tmt = treatment, vs. = versus.
 Source: Post-text Table 14.2.133

Table 89 shows comparisons of combination therapy versus monotherapy with respect to mean change in SeDBP from baseline to Week 8 with LOCF for the subgroup of non-Black patients.

For the subgroup of non-Black patients, each combination therapy had a significantly greater mean reduction in SeDBP compared to both of its monotherapy components (p<0.001 for all comparisons).

Each combination therapy had a significantly greater mean reduction in SeSBP compared to both of its monotherapy components in non blacks (tables 90 – 92).

Table 90: Mean change in SeSBP by Race –Black versus non-black

Treatment	Black Patients			Non-Black Patients		
	N ¹	Change Mean ± SD	p-value ²	N ¹	Change Mean ± SD	p-value ²
Placebo	45	-4.3 ± 21.29	0.2150	115	-5.0 ± 17.69	0.0017
OM10	32	-6.0 ± 12.30	0.0322	128	-12.9 ± 15.62	<0.0001
OM20	34	-5.5 ± 17.06	0.0139	125	-16.1 ± 14.84	<0.0001
OM40	44	-8.2 ± 16.07	0.0008	116	-19.1 ± 15.83	<0.0001
AML5	42	-11.9 ± 13.40	<0.0001	119	-15.9 ± 15.39	<0.0001
AML10	39	-22.1 ± 15.12	<0.0001	124	-19.0 ± 16.93	<0.0001
OM10/AML5	34	-18.8 ± 12.53	<0.0001	129	-25.6 ± 14.02	<0.0001
OM20/AML5	43	-23.7 ± 12.57	<0.0001	117	-23.5 ± 15.66	<0.0001
OM40/AML5	38	-24.7 ± 13.84	<0.0001	119	-25.7 ± 15.01	<0.0001
OM10/AML10	43	-24.1 ± 16.10	<0.0001	118	-25.8 ± 14.45	<0.0001
OM20/AML10	46	-25.3 ± 13.76	<0.0001	112	-30.9 ± 17.59	<0.0001
OM40/AML10	34	-28.7 ± 14.85	<0.0001	127	-30.5 ± 16.22	<0.0001

¹N was the number of patients with values at both time points.
²Two-sided p-values were obtained from an Analysis of Covariance model with treatment, race subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 Week 8 with LOCF was defined as the last available measurement during the double-blind, active treatment period.
 AML = amlodipine, OM = olmesartan medoxomil, SD = standard deviation.
 Sources: Post-text Tables 14.2.134 and 14.2.136

Table 91 Mean change in SeSBP from baseline to wk 8 with LOCF : Combined versus monotherapy comparisons-blacks ITT

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
OM10/AML5	vs.	OM10	34	32	-18.6 (2.49)	-5.5 (2.57)	-13.1 (3.58)	(-20.1, -6.0)	0.0001
	vs.	AML5		42		-13.4 (2.25)	-5.2 (3.36)	(-11.8, 1.4)	0.0605
OM20/AML5	vs.	OM20	43	34	-22.7 (2.22)	-6.1 (2.49)	-16.6 (3.34)	(-23.1, -10.0)	<0.0001
	vs.	AML5		42		-13.4 (2.25)	-9.3 (3.16)	(-15.5, -3.1)	0.0016
OM40/AML5	vs.	OM40	38	44	-24.4 (2.36)	-7.3 (2.19)	-17.1 (3.22)	(-23.4, -10.8)	<0.0001
	vs.	AML5		42		-13.4 (2.25)	-11.1 (3.26)	(-17.4, -4.7)	0.0004
OM10/AML10	vs.	OM10	43	32	-25.2 (2.22)	-5.5 (2.57)	-19.7 (3.40)	(-26.4, -13.1)	<0.0001
	vs.	AML10		39		-23.3 (2.33)	-1.9 (3.22)	(-8.2, 4.4)	0.2759
OM20/AML10	vs.	OM20	46	34	-26.2 (2.14)	-6.1 (2.49)	-20.0 (3.29)	(-26.5, -13.6)	<0.0001
	vs.	AML10		39		-23.3 (2.33)	-2.8 (3.17)	(-9.0, 3.4)	0.1848
OM40/AML10	vs.	OM40	34	44	-27.2 (2.50)	-7.3 (2.19)	-19.9 (3.32)	(-26.4, -13.4)	<0.0001
	vs.	AML10		39		-23.3 (2.33)	-3.9 (3.42)	(-10.6, 2.8)	0.1255

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 treatment, race subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 AML = amlodipine, CI = confidence interval, LS = least squares, OM = olmesartan medoxomil, SE = standard error, Tmt = treatment, vs. = versus.
 Source: Post-text Table 14.2.135

Table 92: Mean change in SeSBP from baseline to wk 8 with LOCF : Combined versus monotherapy- comparisons Non-blacks ITT

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
OM10/AML5	vs.	OM10	129	128	-24.9 (1.28)	-13.4 (1.29)	-11.4 (1.82)	(-15.0, -7.9)	<0.0001
	vs.	AML5		119		-16.0 (1.33)			
OM20/AML5	vs.	OM20	117	125	-23.9 (1.34)	-15.8 (1.30)	-8.1 (1.87)	(-11.8, -4.5)	<0.0001
	vs.	AML5		119		-16.0 (1.33)			
OM40/AML5	vs.	OM40	119	116	-26.7 (1.33)	-19.9 (1.35)	-6.8 (1.90)	(-10.6, -3.1)	0.0002
	vs.	AML5		119		-16.0 (1.33)			
OM10/AML10	vs.	OM10	118	128	-26.0 (1.34)	-13.4 (1.29)	-12.5 (1.86)	(-16.2, -8.9)	<0.0001
	vs.	AML10		124		-18.8 (1.31)			
OM20/AML10	vs.	OM20	112	125	-30.3 (1.37)	-15.8 (1.30)	-14.5 (1.89)	(-18.2, -10.8)	<0.0001
	vs.	AML10		124		-18.8 (1.31)			
OM40/AML10	vs.	OM40	127	116	-30.0 (1.29)	-19.9 (1.35)	-10.2 (1.87)	(-13.8, -6.5)	<0.0001
	vs.	AML10		124		-18.8 (1.31)			

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 treatment, race subgroup, and treatment-by-subgroup interaction as fixed effects and baseline blood pressure as a covariate.
 AML = amlodipine, CI = confidence interval, LS = least squares, OM = olmesartan medoxomil, SE = standard error, Tmt = treatment, vs. = versus.
 Source: Post-text Table J4.2.137

All of the combination treatment groups had greater mean reductions in both SeDBP and SeSBP compared to the monotherapy components. In the non-Black subgroup, all of the comparisons were highly statistically significant. In the comparisons between the combination treatment groups and the monotherapy treatment groups in Black patients, the greatest difference and the most statistical significance was seen when the combinations were compared to monotherapy with olmesartan medoxomil.

In the comparisons between the combinations and amlodipine monotherapy, not all comparisons reached statistical significance.

For both race subgroups, larger blood pressure reductions with the combination therapies resulted in a greater percentage of patients achieving their blood pressure goals compared with monotherapy. Across all combination therapies other than the OM 10 mg + AML 10 mg combination, the non-Black subgroup had a greater percentage of patients who reached their 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 39.5% to 56.3% for the non- Black subgroup compared with 17.6% to 51.2% for the Black subgroup. This is reflected in the exposure response analysis (Table 61) and the two tables below (Source Dr Bai).

Comparisons in diastolic and systolic BP by dose and combination tablets:

There are statistically significant difference between the two racial groups: diastolic p=0.0047 for 40/10 and systolic p=0.0297; p= 0.0233 and p=0.0092 for 40/10vs 40, 40/10vs10 and 40/5vs40, respectively. Also 20/10 vs 10; 20/5 vs 20 and 10/10 vs 10 ; p=0.0132; p=0.0256; p=0.0463, respectively. The differences are more in the systolic BP than in the diastolic BP (Tables 93 and 94).

Table 93: Comparisons in Diastolic BP Non-Blacks versus Blacks- Period II Source Dr Bai

Label	Estimate	Standard Error	Pr > t	Lower	Upper
W40/10-40 vs. B40/10-40	1.7025	2.3201	0.4632	-2.8478	6.2528
W40/10-10 vs. B40/10-10	-6.6841	2.3626	0.0047	-11.3177	-2.0505
W40/5-40 vs. B40/5-40	4.5646	2.2679	0.0443	0.1167	9.0126
W40/5-5 vs. B40/5-5	-0.6373	2.2859	0.7804	-5.1206	3.8459
W20/10-20 vs. B20/10-20	3.8448	2.2952	0.0941	-0.6567	8.3462
W20/10-10 vs. B20/10-10	-3.8166	2.2395	0.0885	-8.2088	0.5757
W20/5-20 vs. B20/5-20	3.3847	2.3289	0.1463	-1.1829	7.9523
W20/5-5 vs. B20/5-5	-1.0920	2.2519	0.6278	-5.5087	3.3247
W10/10-10 vs. B10/10-10	3.8867	2.3405	0.0970	-0.7037	8.4772
W10/10-10 vs. B10/10-10	-1.5793	2.2575	0.4843	-6.0070	2.8483
W10/5-10 vs. B10/5-10	-1.2920	2.4433	0.5970	-6.0840	3.5000
W10/5-5 vs. B10/5-5	-3.5734	2.3398	0.1269	-8.1625	1.0156

Table 94: Comparisons of Systolic BP in Non-blacks vs. Black Period II Source Dr Bai

Label	Estimate	Standard Error	Pr > t	Lower	Upper
W40/10-40 vs. B40/10-40	8.3944	3.8580	0.0297	0.8278	15.9611
W40/10-10 vs. B40/10-10	-8.9190	3.9277	0.0233	-16.6224	-1.2156
W40/5-40 vs. B40/5-40	9.8389	3.7715	0.0092	2.4420	17.2357
W40/5-5 vs. B40/5-5	0.8475	3.8042	0.8237	-6.6135	8.3086
W20/10-20 vs. B20/10-20	5.3386	3.8168	0.1621	-2.1471	12.8243
W20/10-10 vs. B20/10-10	-9.2410	3.7234	0.0132	-16.5436	-1.9383
W20/5-20 vs. B20/5-20	8.6520	3.8736	0.0256	1.0549	16.2491
W20/5-5 vs. B20/5-5	2.3945	3.7460	0.5228	-4.9524	9.7414
W10/10-10 vs. B10/10-10	7.7647	3.8932	0.0463	0.1291	15.4003
W10/10-10 vs. B10/10-10	-5.4660	3.7539	0.1455	-12.8285	1.8966
W10/5-10 vs. B10/5-10	2.4216	4.0635	0.5513	-5.5480	10.3912
W10/5-5 vs. B10/5-5	-2.4870	3.8912	0.5228	-10.1186	5.1446

Hypertension class

The reductions in both mean SeDBP and mean SeSBP were all statistically significant in both patients with Stage 1 and Stage 2 hypertension. The reductions in both mean SeDBP and mean SeSBP were generally numerically greater in the subgroup of patients with Stage 2 hypertension compared to those patients with Stage 1 hypertension.

In the comparisons between the combination treatment groups and the component monotherapy treatment groups, the mean reductions in blood pressure were significantly greater in most of the combination treatment groups compared to the monotherapy treatment groups, for patients with both Stage 1 and Stage 2 hypertension. In patients with Stage 1 hypertension, comparisons between the higher dose combinations and monotherapy with olmesartan medoxomil 40 mg did not reach statistical significance.

As would be expected, the subgroup of patients with Stage 1 hypertension had a greater percentage of patients who reached their blood pressure goals compared with the subgroup of patients with Stage 2 hypertension. Among the subgroups treated with one of the combination therapies, the percentage of patients achieving blood pressure goals at Week 8 with LOCF ranged from 65.6% to 80.0% for the subgroup of patients with Stage 1 hypertension compared with 27.4% to 49.2% for the subgroup of patients with Stage 2 hypertension.

The reductions in both mean SeDBP and mean SeSBP were all statistically significant in both patients with Stage 1 and Stage 2 hypertension. The reductions in both mean SeDBP and mean SeSBP were generally numerically greater in the subgroup of patients with Stage 2 hypertension compared to those patients with Stage 1 hypertension (Tables 95-96)

In the comparisons between the combination treatment groups and the component monotherapy treatment groups, the mean reductions in blood pressure were significantly greater in most of the combination treatment groups compared to the monotherapy treatment groups, for patients with both Stage 1 and Stage 2 hypertension.

In patients with Stage 1 hypertension, comparisons between the higher dose combinations and monotherapy with olmesartan medoxomil 40 mg did not reach statistical significance for SeDBP and for SeSBP p value = /////.

As would be expected, the subgroup of patients with Stage 1 hypertension had a greater percentage of patients who reached their blood pressure goals compared with the subgroup of patients with Stage 2 hypertension. Among the subgroups treated with one of the combination therapies, the percentage of patients achieving blood pressure goals at Week 8 with LOCF ranged from 65.6% to 80.0% for the subgroup of patients with Stage 1 hypertension compared with 27.4% to 49.2% for the subgroup of patients with Stage 2 hypertension.

The reductions in both mean SeDBP and mean SeSBP were all statistically significant in both patients with Stage 1 and Stage 2 hypertension. The reductions in both mean SeDBP

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and mean SeSBP were generally numerically greater in the subgroup of patients with Stage 2 hypertension compared to those patients with Stage 1 hypertension (Tables 95 and 96).

In the comparisons between the combination treatment groups and the component monotherapy treatment groups, the mean reductions in blood pressure were significantly greater in most of the combination treatment groups compared to the monotherapy treatment groups, for patients with both Stage 1 and Stage 2 hypertension. In patients with Stage 1 hypertension, comparisons between the higher dose combinations and monotherapy with olmesartan medoxomil 40 mg did not reach statistical significance.

As would be expected, the subgroup of patients with Stage 1 hypertension had a greater percentage of patients who reached their blood pressure goals compared with the subgroup of patients with Stage 2 hypertension. Among the subgroups treated with one of the combination therapies, the percentage of patients achieving blood pressure goals at Week 8 with LOCF ranged from 65.6% to 80.0% for the subgroup of patients with Stage 1 hypertension compared with 27.4% to 49.2% for the subgroup of patients with Stage 2 hypertension.

Table 95: Mean change in SeDBP by hypertension class-ITT population

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

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Hypertension class

Table 96: Mean change in SeSBP by hypertension class- ITT- NDA 22100

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

Diabetes

The reductions in both mean SeDBP and mean SeSBP were all statistically significant in both patients with and without diabetes. There did not appear to be any differences in the overall mean reductions in blood pressures between these 2 subgroups. In diabetic and non-diabetic patients, comparisons between the reductions in blood pressure observed in the combination treatment groups and the monotherapy treatment groups were also not meaningfully different. The numbers of diabetics included in this study were small and, hence, not all of the comparisons between combination treatments and monotherapies in the diabetics were in the same direction or reached statistical significance. The subgroup of diabetic patients who were treated with placebo had a large mean reduction in seated blood pressure (-15.3/-8.2 mmHg). The difference in mean reductions in both SeDBP and SeSBP between diabetic and non-diabetic patients receiving placebo is attributed to a small sample size for diabetics (n=23) and one extreme value among the subgroup of diabetic patients

Thus, given the small sample size, one or two unusually large or small values can have considerable influence on observed mean changes. Examination of these figures demonstrates a high degree of overlap or similarity among the distributions for change in both SeDBP and SeSBP for patients with and without diabetes, indicating overall similar response in both groups of patients.

For both subgroups, the greatest mean blood pressure reductions were seen in the OM 40 mg + AML 10 mg treatment group, with mean reductions of approximately 30/18 mmHg in the subgroup of patients with diabetes and approximately 30/19 mmHg in the subgroup of patients without diabetes (Tables 97 and 98).

Table 97: Mean change in SeDBP by Diabetes versus non diabetes

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

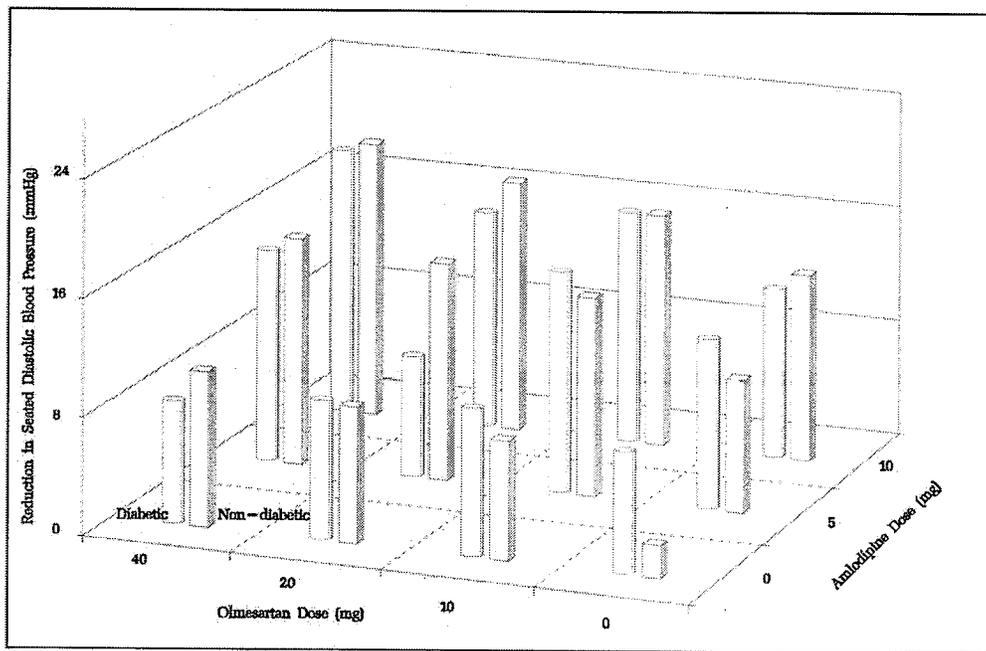
Table 98: Mean change in SeSBP by Diabetes versus non-diabetes

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

For the patients treated with one of the combination therapies, the percentage without diabetes that reached goal blood pressure was similar to the total population. At Week 8 with LOCF, only a small percentage of diabetic patients reached their blood pressure treatment goal, ranging from 0% to 13.6% across all treatment groups. As the blood pressure treatment goal for diabetics is <130/80 mmHg, this result was not unexpected. If the threshold was set at <140/90 mmHg, diabetic patients reached threshold in 33% to 46% with the combinations including AML 10 mg.

Figure 12: Mean reduction in SeDBP from baseline to week 8- Diabetics

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



Source: Post-text Figure 14.2.23

For both subgroups, the greatest mean blood pressure reductions were seen in the OM 40 mg + AML 10 mg treatment group, with mean reductions of approximately 30/18 mmHg in the subgroup of patients with diabetes and approximately 30/19 mmHg in the subgroup of patients without diabetes. For the patients treated with one of the combination therapies, the percentage without diabetes that reached goal blood pressure was similar to the total population. At Week 8 with LOCF, only a small percentage of diabetic patients reached their blood pressure treatment goal, ranging from 0% to 13.6% across all treatment groups. As the blood pressure treatment goal for diabetics is <130/80 mmHg, this result was not unexpected. If the threshold was set at <140/90 mmHg, diabetic patients reached threshold in 33% to 46% with the combinations including AML 10 mg.

Ethnicity

The numbers of Hispanic/Latino patients entered into the study was relatively small and, therefore, it is difficult to draw definitive conclusions. The mean reductions in both

SeDBP and SeSBP were all statistically significant in both Hispanic/Latino patients and non-Hispanic/Latino patients. There were generally numerically greater mean reductions in blood pressure across the treatment groups in the Hispanic/Latino groups, particularly for SeDBP. For both ethnicity subgroups, the greatest blood pressure reductions were observed in the OM 40 mg + AML 10 mg treatment group, with mean reductions of approximately 29/21 mmHg in the subgroup of Hispanic/Latino patients and approximately 30/19 mmHg in the subgroup of non- Hispanic/Latino patients.

For Hispanic/Latino and non-Hispanic/Latino groups all combination treatments resulted in greater mean blood pressure lowering compared to the component monotherapy treatment groups. However, due to the small numbers, not all of the comparisons in the Hispanic/Latino groups reached statistical significance. There did not appear to be any difference in the comparisons between the combination treatments and the monotherapy treatments between these two subgroups.

Among the groups treated with combination therapy, the percentage achieving blood pressure goals at Week 8 with LOCF ranged from 42.9% to 66.7% for the Hispanic/Latino subgroup compared with 30.3% to 52.6% for the non- Hispanic/Latino subgroup.

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.

BMI

The number of patients reaching their goals by BMI is presented in Tables 99-102.

The reductions in both mean SeDBP and mean SeSBP were all statistically significant in patients with a BMI ≥ 30 kg/m² and a BMI < 30 kg/m². Although the numbers are smaller, it did appear that the patients with a BMI < 30 kg/m² achieved numerically greater mean reductions in blood pressure compared to patients with a BMI ≥ 30 kg/m². For both BMI subgroups, the greatest blood pressure reductions were observed in the OM 40 mg + AML 10 mg treatment group, with mean reductions of approximately 30/18 mmHg in the subgroup of patients with a BMI ≥ 30 kg/m² approximately 31/21 mmHg in the subgroup of patients with a BMI of < 30 kg/m².

In the comparisons between the combination treatment groups and the component monotherapy treatment groups, the mean reductions in blood pressure were significantly greater in all of the combination treatment groups compared to the monotherapy treatment groups, for patients with both a BMI ≥ 30 kg/m² and patients with a BMI < 30 kg/m².

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 40.9% to 55.0% for the subgroup of patients with a BMI < 30 kg/m² compared with 28.4% to 52.0% for the subgroup of patients with a BMI ≥ 30 kg/m² (Tables 99 – 102).

Table 99: Number of patients by BMI >30 reaching their target blood pressure goals at week 8-ITT

Table 14.2.198
 Number (%) of Patients Reaching Blood Pressure Treatment Goal by Week
 Subgroup Analyses - Patients With Baseline BMI >= 30 kg/m²
 Intent-to-Treat Population

Timepoint Category	Placebo (N=105)	OM10 (N=106)	OM20 (N=105)	OM40 (N=110)	OM15 (N=104)	OM10 (N=95)
Week 8 With LOCF						
Number Exposed (N)	109	106	105	110	104	95
Number Achieving Goal (n)	8	14	25	33	23	33
Percent Achieving Goal (n/N)	7.3	13.2	26.7	30.0	22.1	34.4
Treatment p-value	<.0001					
Week 8						
Number Exposed (N)	79	94	89	97	91	83
Number Achieving Goal (n)	4	13	24	31	20	33
Percent Achieving Goal (n/N)	5.1	13.8	27.3	32.0	22.0	39.8
Treatment p-value	<.0001					
Week 6						
Number Exposed (N)	84	93	89	99	95	87
Number Achieving Goal (n)	3	15	29	30	19	23
Percent Achieving Goal (n/N)	3.6	16.1	32.6	30.3	20.0	26.4
Treatment p-value	<.0001					
Week 4						
Number Exposed (N)	89	97	92	101	96	90
Number Achieving Goal (n)	6	17	29	33	21	26
Percent Achieving Goal (n/N)	6.7	17.5	21.7	32.7	21.9	28.9
Treatment p-value	<.0001					
Week 2						
Number Exposed (N)	100	101	100	106	100	90
Number Achieving Goal (n)	3	7	22	25	15	22
Percent Achieving Goal (n/N)	3.0	6.9	21.6	24.5	15.0	24.4
Treatment p-value	<.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 100: Number of patients by BMI >30 reaching their target blood pressure goals at week 8-ITT

Table 14.2.198
 Number (%) of Patients Reaching Blood Pressure Treatment Goal by Week
 Subgroup Analyses - Patients With Baseline BMI >= 30 kg/m²
 Intent-to-Treat Population

Timepoint Category	OM10/OM15 (N=103)	OM10/OM10 (N=104)	OM20/OM15 (N=115)	OM20/OM10 (N=95)	OM40/OM15 (N=95)	OM40/OM10 (N=100)
Week 8 With LOCF						
Number Exposed (N)	106	104	115	96	95	100
Number Achieving Goal (n)	31	49	59	51	45	46
Percent Achieving Goal (n/N)	28.4	47.1	43.5	32.0	48.4	46.0
Week 8						
Number Exposed (N)	103	83	105	90	89	89
Number Achieving Goal (n)	31	42	50	45	33	39
Percent Achieving Goal (n/N)	30.1	50.6	47.6	50.0	48.9	43.8
Week 6						
Number Exposed (N)	105	87	108	91	90	96
Number Achieving Goal (n)	34	43	43	45	43	43
Percent Achieving Goal (n/N)	32.4	49.4	39.8	50.5	47.8	45.7
Week 4						
Number Exposed (N)	106	90	109	94	90	96
Number Achieving Goal (n)	35	47	39	47	42	37
Percent Achieving Goal (n/N)	33.0	52.2	35.8	50.0	46.7	38.5
Week 2						
Number Exposed (N)	106	97	114	96	90	98
Number Achieving Goal (n)	22	42	33	45	31	47
Percent Achieving Goal (n/N)	20.8	43.3	29.0	46.9	33.7	48.0

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Table 101: Number of patients by BMI < 30 reaching their target blood pressure goals at week 8-ITT

Table 14.2.300
 Number (%) of Patients Reaching Blood Pressure Treatment Goal by Week
 Subgroup Analysis - Patients With Baseline BMI < 30 kg/m²
 Intent-to-Treat Population

Timepoint Category	Placebo (N=50)	OM10 (N=53)	OM20 (N=53)	OM40 (N=49)	AMLE (N=55)	AMLEO (N=65)
Week 8 With LACE						
Number Exposed (N)	50	51	53	48	55	65
Number Achieving Goal (n)	6	17	14	23	11	20
Percent Achieving Goal (n/N)	12.0	33.3	26.4	47.9	19.8	30.8
Treatment p-value	<.0001					
Week 8						
Number Exposed (N)	41	44	46	44	48	60
Number Achieving Goal (n)	5	14	13	21	10	19
Percent Achieving Goal (n/N)	12.2	31.8	28.3	47.7	20.8	31.7
Treatment p-value	<.0001					
Week 6						
Number Exposed (N)	43	44	47	45	48	60
Number Achieving Goal (n)	5	16	14	19	8	19
Percent Achieving Goal (n/N)	11.6	36.4	29.8	42.2	16.7	31.7
Treatment p-value	<.0001					
Week 4						
Number Exposed (N)	44	45	48	45	51	60
Number Achieving Goal (n)	2	13	10	21	8	16
Percent Achieving Goal (n/N)	4.5	28.9	20.8	46.7	17.6	26.7
Treatment p-value	<.0001					
Week 2						
Number Exposed (N)	47	49	50	46	53	65
Number Achieving Goal (n)	2	12	11	20	7	21
Percent Achieving Goal (n/N)	4.3	24.5	22.0	43.5	13.2	32.3
Treatment p-value	<.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 102: Number of patients by BMI < 30 reaching target blood pressure goals at week 8-ITT

Table 14.2.300
 Number (%) of Patients Reaching Blood Pressure Treatment Goal by Week
 Subgroup Analysis - Patients With Baseline BMI < 30 kg/m²
 Intent-to-Treat Population

Timepoint Category	OM10/AMLE (N=53)	OM10/AMLEO (N=55)	OM20/AMLE (N=44)	OM20/AMLEO (N=50)	OM40/AMLE (N=61)	OM40/AMLEO (N=60)
Week 8 With LACE						
Number Exposed (N)	53	56	44	48	61	60
Number Achieving Goal (n)	26	30	18	23	23	23
Percent Achieving Goal (n/N)	49.1	53.6	40.9	47.9	37.7	38.3
Week 8						
Number Exposed (N)	50	50	40	53	54	53
Number Achieving Goal (n)	25	28	18	30	31	30
Percent Achieving Goal (n/N)	50.0	56.0	45.0	56.6	57.4	56.6
Week 6						
Number Exposed (N)	51	51	41	56	54	53
Number Achieving Goal (n)	25	20	20	29	25	32
Percent Achieving Goal (n/N)	49.0	39.2	48.8	51.8	46.3	60.4
Week 4						
Number Exposed (N)	52	51	42	57	55	55
Number Achieving Goal (n)	23	26	17	30	24	24
Percent Achieving Goal (n/N)	44.2	51.0	40.5	52.6	43.6	43.6
Week 2						
Number Exposed (N)	53	55	43	58	59	59
Number Achieving Goal (n)	22	27	17	30	26	31
Percent Achieving Goal (n/N)	41.5	49.1	39.5	51.7	44.1	52.5

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.

6.1.5 Clinical Microbiology

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The results from the double-blind study period demonstrated in the overall population that :

- the combination therapy lowered both diastolic and systolic blood pressure to a significantly greater extent compared to each of the monotherapy that made up the combination.
- The combination of olmesartan medoxomil and amlodipine reduced both mean SeDBP and mean SeSBP to a significantly greater extent compared to the component monotherapies that made up each combination.
- The combination of OM 40 mg + AML 10 mg resulted in the greatest mean reductions in both SeDBP and SeSBP .
- Although there were minor differences in some of the subgroups, similar reductions in blood pressure were observed in all of the subgroups analyzed.
- 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. This additional blood pressure lowering achieved with the combination treatments compared to the monotherapy components is clearly in a range that is considered to be clinically meaningful.
- 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.
- 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

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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).

- Similar results 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, and $p<0.0001$ for the rest of the comparisons).
- 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 + AML 10 mg group).
- Among the groups that were treated with a combination therapy, mean reductions in SeDBP were about 2 to 3 mmHg greater when olmesartan medoxomil doses (10 mg, 20 mg, and 40 mg) were combined with amlodipine 10 mg rather than amlodipine 5 mg. This trend also held true for SeSBP; mean reductions in SeSBP were about 1 to 5 mmHg greater when olmesartan medoxomil doses were combined with amlodipine 10 mg rather than amlodipine 5 mg.
- 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. 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.
- The mean reductions in SeDBP and SeSBP observed with the 6 combination treatments brought approximately 50% of the patients to a goal blood pressure of <140/90 mmHg for non-diabetics, or <130/80 mmHg for diabetics. The mean baseline SeDBP in the group of patients that received OM 40 mg + AML 10 mg was 102.3 mmHg. With a mean reduction in SeDBP of 19.0 mmHg it would appear that more than 50% of the patients treated with this combination should reach a goal diastolic blood pressure of <90 mmHg. However, the analysis of the

percentage of patients achieving blood pressure goals was based on patients achieving both a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg (or for diabetics, a systolic blood pressure goal of <130 mmHg and a diastolic blood pressure goal of <80 mmHg). The OM 40 mg + AML 10 mg-treatment group had a baseline mean SeSBP of 165.7 mmHg. Mean SeSBP was reduced by 30.1 mmHg. In all likelihood, fewer patients in this treatment group achieved the systolic blood pressure goal threshold of <140 mmHg compared to the achievement of the diastolic blood pressure goal, which would explain the result of 50% of patients reaching goal.

- 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.

Efficacy Evaluation by Subgroup

- Changes in blood pressures in the combination therapy groups compared to the monotherapy components that made up the combinations and the percentage of patients achieving treatment goals were analyzed by age, diabetic status, gender, race, ethnicity, hypertension class, prior antihypertensive medication use, and baseline BMI. All statistical comparisons made for these subgroups were exploratory in nature and no adjustments for multiple comparisons were made. In the absence of adjustments for multiple comparisons, no valid conclusions can be made with confidence.

OPEN LABEL - END OF Week 8 – week 52

After the end of Period II all patients were given OM40/AML5. After 2 weeks of open label treatment period (week10) 1640 patients remained on OM40mg/AML5mg with a mean SeDBP of 86.00mmHg. A total of 48.3% (792/1640) reached their blood pressure goal within 2 weeks of treatment. The patients were titrated upwards to higher doses with a greater percentage reaching their blood pressure goals (Tables 103 -).

At week 52, or early termination, a total of 525 patients remained on OM40/AML5 and had a mean SeDBP of 81.0 and a mean SeSBP of 127.6 mmHg. 80% of these patients reached their goals.

A total of 378 patients were on OM40/AML10 and had a mean SeDBP of 82.4 and a mean of 130.9 mmHg.;70.6% of these patients reached their goal (Table 104).

Table 103: Number of patients achieving BP threshold s all patients entering Period III

Treatment	Number of patients Exposed	Patients achieving BP Treatment goal	
		N	%
OM40/AML5	1678	861	51.3
OM40/AML10	1100	530	48.2
OM40/AML10/HCTZ12.5	732	358	48.9
OM40/AML10/HCTZ25	434	244	56.2
Percentage calculated using total number of patients exposed to the given dose regimen as denominator			

Table 104: Number of patients achieving BP treatment goal –Period III

Week 8-52/ET	N (%)	Mean SeDBP	Mean SeSBP	% reaching goal
Week 8-10 OM40/AM5	792/1640 (48.3)	86.00		
Week 52/ET OM40/AML5	525	81.00	127.6	80
Week 52 Om40/AML10	378	82.4	130.9	70.6
Week 52 OM40/AML10/HCTZ12.5	287	81	130.7	66.6
Week 52 OM40/AML10/HCTZ25	419	83.4	136.8	46.3
Others	63	79.4	126.2	68.3

It is evident that at week 52, patients who were more resistant to the initial open label treatment and therefore required uptitration had higher mean SeDBP values. Therefore a smaller percentage of these treatment resistant patients reached their blood pressure goals. Up-titration resulted in further mean reductions in SeDBP and with additional HCTZ this became more evident (Tables 105-106).

Table 105: Titration Effect – Blood Pressure change – All patients entering Period III

Parameter	OM40/AML5 To OM40/AML10	OM40/AML10 To OM40/AML10/HCTZ12.5	OM40/AML10/HCTZ12.5 To OM40/AML10/HCTZ25
Change in SeDBP			
N	1053	646	378
Mean±SD	-5.2±7.89	-4.4±7.90	-5.8±7.92
Change in SeSBP			
N	1053	646	378
Mean±SD	-7.6±12.60	-7.5±13.51	-9.7±12.98
Titration effect was calculated as blood pressure at last visit on new dose regimen minus BP at last visit of previous dose regimen			

Table 106 Number of patients reaching blood pressure thresholds-All patients entering Period III

Table 15: Number of Patients Reaching Blood Pressure Thresholds – All Patients Entering Period III

Treatment	N	Blood Pressure Threshold			
		<120/90 mmHg n (%)	<130/80 mmHg n (%)	<130/85 mmHg n (%)	<140/90 mmHg n (%)
OM40/AML5	1678	342 (20.4)	528 (31.5)	641 (38.2)	907 (54.1)
OM40/AML10	1100	131 (11.9)	268 (24.4)	352 (32.0)	579 (52.6)
OM40/AML10/HCTZ12.5	732	83 (11.3)	163 (22.3)	228 (31.1)	402 (54.9)
OM40/AML10/HCTZ25	434	46 (10.6)	107 (24.7)	156 (35.9)	292 (67.3)

N is the number of patients exposed.
 Percentage was calculated by using the total number of patients exposed to the given dosing regimen as the denominator.
 AML = amlodipine, HCTZ = hydrochlorothiazide, OM = olmesartan medoxomil.
 Source: CS6663-A-11301 Interim Report (Period III), Post-text Table 14.2.27

The following efficacy findings during the open label component of the double blind study in patients on combination tablets are presented in Tables 107 to 108:

Table 107: Seated Diastolic Blood Pressure by week and dosing regimen- Open label

Table 11: Seated Diastolic Blood Pressure (mmHg) by Week and Dosing Regimen – Pivotal Study (Open-Label Treatment Period) – All Patients Entering Period III

Week	OM40/ AML5	OM40/ AML10	OM40/ AML10/ HCTZ12.5	OM40/ AML10/ HCTZ25	Other ³
Baseline¹					
N	1683				
Mean ± SD	101.5 ± 4.97				
Week 10					
N	1637	13			3
Mean ± SD	86.0 ± 9.29	92.1 ± 7.68			75.3 ± 3.61
n (%) to BP goal ²	790 (48.3)	3 (23.1)			3 (100.0)
Week 12					
N	882	681	46		13
Mean ± SD	82.3 ± 7.69	87.0 ± 8.29	90.6 ± 8.31		82.2 ± 7.77
n (%) to BP goal ²	643 (72.9)	246 (36.1)	2 (4.3)		10 (76.9)
Week 18					
N	698	428	396	31	21
Mean ± SD	81.7 ± 7.67	83.7 ± 7.99	85.8 ± 8.64	84.8 ± 7.33	84.7 ± 7.84
n (%) to BP goal ²	326 (46.6)	245 (57.2)	147 (37.1)	7 (22.6)	15 (81.9)
Week 26					
N	564	381	317	233	32
Mean ± SD	80.9 ± 7.72	82.5 ± 7.64	83.8 ± 8.00	84.9 ± 8.18	84.3 ± 7.56
n (%) to BP goal ²	449 (79.6)	270 (70.9)	168 (53.0)	68 (29.2)	17 (53.1)
Week 26/ET					
N	642	420	333	242	35
Mean ± SD	81.7 ± 8.33	82.9 ± 7.99	83.9 ± 8.06	85.3 ± 8.43	83.9 ± 8.09
n (%) to BP goal ²	483 (75.2)	281 (66.9)	174 (52.3)	69 (28.3)	18 (51.4)
Week 34					
N	448	332	268	310	34
Mean ± SD	80.2 ± 7.70	81.9 ± 6.94	81.7 ± 7.69	83.7 ± 8.04	82.5 ± 7.57
n (%) to BP goal ²	387 (86.4)	246 (74.1)	183 (68.3)	128 (41.3)	22 (64.7)
Week #2					
N	333	243	197	277	40
Mean ± SD	79.5 ± 7.00	81.1 ± 7.42	81.1 ± 7.10	83.4 ± 7.91	81.8 ± 6.39
n (%) to BP goal ²	299 (89.8)	193 (79.3)	150 (76.1)	138 (49.3)	32 (80.0)
Week 52					
N	93	64	56	77	10
Mean ± SD	79.5 ± 7.47	81.1 ± 6.89	80.5 ± 7.65	84.6 ± 7.24	79.5 ± 9.30
n (%) to BP goal ²	83 (89.2)	50 (78.1)	43 (76.8)	38 (49.4)	8 (80.0)

¹ Period III baseline blood pressure was defined as the average of the visit values from the randomization visit (Visit 3) and the visit prior to the randomization visit. Each blood pressure visit value was the mean of 3 measurements.
² BP goal was defined as BP <140/90 mmHg (<130/80 mmHg for diabetics). Percentage was calculated using the number of patients within the dosing regimen with a BP measurement at the given time point.
³ Other includes the following regimens: HCTZ25, AML5, OM40/AML10, OM40/AML12.5, OM40/AML5, OM40/AML5/HCTZ12.5, OM40/AML10/HCTZ12.5, OM40/AML12.5/HCTZ12.5, OM40/AML5/HCTZ12.5, and OM40/AML5/HCTZ25.
 AML = amlodipine, BP = blood pressure, ET = early termination, HCTZ = hydrochlorothiazide, OM = olmesartan medoxomil, SD = standard deviation.
 Source: CS6663-A-11301 Interim Report (Period III), Post-text Table 14.2.1

Table 108: Seated systolic BP by week and dosing during open label extension period – Pivotal study

Table 12: Seated Systolic Blood Pressure (mmHg) by Week and Dosing Regimen – Pivotal Study (Open-Label Treatment Period) – All Patients Entering Period III

Week	OM40/ AML5	OM40/ AML10	OM40/ AML10/ HCTZ12.5	OM40/ AML10/ HCTZ25	Other ³
Baseline¹					
N	1683				
Mean ± SD	163.6 ± 15.74				
Week 10					
N	1637	13			3
Mean ± SD	137.9 ± 16.60	145.4 ± 18.37			124.3 ± 4.70
n (%) to BP goal ²	790 (48.3)	3 (23.1)			3 (100.0)
Week 12					
N	882	681	46		13
Mean ± SD	129.9 ± 12.03	141.5 ± 14.38	146.2 ± 13.48		126.7 ± 11.84
n (%) to BP goal ²	643 (73.9)	246 (36.1)	2 (4.3)		10 (76.9)
Week 18					
N	698	428	396	31	21
Mean ± SD	129.4 ± 11.99	135.0 ± 12.90	140.3 ± 15.60	141.6 ± 13.73	132.8 ± 18.07
n (%) to BP goal ²	326 (73.4)	245 (57.2)	147 (37.1)	7 (22.6)	13 (61.9)
Week 26					
N	564	381	317	233	32
Mean ± SD	127.7 ± 11.66	131.4 ± 10.84	135.4 ± 13.34	141.3 ± 14.75	132.1 ± 16.55
n (%) to BP goal ²	449 (79.6)	270 (70.9)	168 (53.0)	68 (29.2)	17 (53.1)
Week 26:ET					
N	642	420	333	242	33
Mean ± SD	129.4 ± 13.33	132.5 ± 11.91	135.8 ± 13.73	142.0 ± 15.17	133.6 ± 18.45
n (%) to BP goal ²	485 (75.5)	281 (66.9)	174 (52.3)	69 (28.5)	18 (54.4)
Week 34					
N	448	332	268	310	34
Mean ± SD	125.8 ± 11.20	131.1 ± 10.34	131.2 ± 12.60	137.7 ± 12.95	127.8 ± 11.42
n (%) to BP goal ²	387 (86.4)	246 (74.1)	183 (68.3)	128 (41.3)	22 (64.7)
Week 42					
N	333	245	197	277	40
Mean ± SD	124.6 ± 9.82	129.5 ± 10.09	128.6 ± 10.34	135.5 ± 13.33	126.1 ± 11.53
n (%) to BP goal ²	289 (89.8)	193 (78.8)	150 (76.1)	138 (49.8)	32 (80.0)
Week 52					
N	93	64	56	77	10
Mean ± SD	123.3 ± 11.44	129.1 ± 10.24	127.9 ± 11.11	133.1 ± 11.32	123.9 ± 11.01
n (%) to BP goal ²	83 (89.2)	50 (78.1)	43 (76.8)	38 (49.4)	8 (80.0)

¹ Period III baseline BP was defined as the average of the visit values from the randomization visit (Visit 3) and the visit prior to the randomization visit. Each blood pressure visit value was the mean of 3 measurements.

² BP goal was defined as BP <140/90 mmHg (<130/80 mmHg for diabetics). Percentage was calculated using the number of patients within the dosing regimen with a BP measurement at the given time point.

³ Other includes the following regimens: HCTZ25, AML5, OM20/AML10, OM20/AML2.5, OM20/AML5, OM20/AML5/HCTZ12.5, OM20/AML10/HCTZ12.5, OM40/AML2.5/HCTZ12.5, OM40/AML5/HCTZ12.5, and OM40/AML5/HCTZ25.

AML = amlodipine, BP = blood pressure, ET = early termination, HCTZ = hydrochlorothiazide, Omb = olmesartan medoxomil, SD = standard deviation.

Source: C81661-A-1130 Interim Report (Period III), Post-0201 Table 14.2.8

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