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MEDICAL REVIEW

CLINICAL REVIEW

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Established Name amlodipine besylate & valsartan
(Proposed) Trade Name Exforge
Therapeutic Class Dihydropyridine CCB/ARB
Applicant Novartis

Priority Designation S

Formulation Combination tablets
Dosing Regimen Once daily
Indication Hypertension
Intended Population Adults

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1 EXECUTIVE SUMMARY

Hypertension has been described as a lifestyle syndrome. It is estimated that hypertension is present in at least 35% of the population of an industrialized nation. The incidence is increasing in the U.S. with the aging of the population and in the world with the economic development of other nations.

There are advocates of combination treatments being utilized from the beginning in the treatment of hypertension especially in patients with an initial high blood pressure (BP). This submission however states that amlodipine/valsartan combination tablets (Exforge) are intended for use in patients with mild to moderate hypertension who do not respond to either valsartan or amlodipine alone

In this NDA submission the Sponsor has taken two established drugs, amlodipine and valsartan, which have been utilized for 10 or more years for the treatment of hypertension, and has combined them at various doses. Both medications have individual good efficacy and safety records. The Sponsor has demonstrated that combined, these drugs safely improve the control of hypertension over the individual medications. Also, the edema seen with amlodipine is less with the combination and there is no apparent occurrence of orthostatic events.

This Medical Reviewer recommends that valsartan/amlodipine (Exforge) be approved in the Sponsor's dose range of combination tablets.

1.1 Recommendation on Regulatory Action

This Medical Reviewer recommends that the combination tablets containing amlodipine and valsartan in the following doses: — 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg be approved.

1.2 Recommendation on Postmarketing Actions

Not applicable (N/A)

1.2.1 Risk Management Activity

N/A

1.2.2 Required Phase 4 Commitments

N/A

1.2.3 Other Phase 4 Requests

N/A

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Sponsor has submitted electronically a number of clinical studies. However, only two studies were designed as multicenter, double-blind, randomized, multifactorial, placebo-controlled, parallel group trials. Therefore, these two trials were evaluated for efficacy. Five studies were reviewed for safety; they included the two placebo-controlled trials and three active-controlled studies. Also mentioned with the safety review are two long-term, open-label extension studies of the two placebo-controlled trials reviewed for efficacy.

1.3.2 Efficacy

The combination of valsartan/amlodipine generally provided additive diastolic and systolic blood pressure lowering effects compared to valsartan or amlodipine alone in patients with essential hypertension. Both components contributed to the antihypertensive effect of the combination in the overall population. The combination produced a successful blood pressure response at endpoint (defined as a mean sitting diastolic blood pressure <90 mmHg or a ≥ 10 mmHg decrease compared to baseline) in approximately 80-90% of patients and achieved blood pressure control (mean sitting diastolic blood pressure <90 mmHg) in approximately 70-80% of patients at the higher doses. The combination was effective regardless of gender, age and race. A positive dose response relationship was demonstrated within the studied dose range of the combination.

1.3.3 Safety

At least 2613 patients received the combination valsartan/amlodipine in the safety population which was comprised of two placebo-controlled trials and three active-controlled studies. The overall incidence of Adverse Events (AEs) showed no significant differences between valsartan/amlodipine combination therapy and valsartan monotherapy and amlodipine monotherapy. The most common AEs regardless of relationship to treatment in the valsartan/amlodipine group ($\geq 2\%$) were peripheral edema, headache, and nasopharyngitis. The incidence of peripheral edema was significantly reduced in patients receiving valsartan/amlodipine compared to amlodipine monotherapy. There was a general trend toward an increase in the incidence of peripheral edema as the dose of amlodipine in the combination increased. The most frequent AEs ($\geq 1\%$) suspected related to study drug in the valsartan/amlodipine group were peripheral edema and headache. The overall incidence of serious AEs and AEs leading to study discontinuation in the valsartan/amlodipine group was low and generally comparable to placebo. No significant new adverse events were observed with long-term treatment. Valsartan/amlodipine was generally well-tolerated regardless of gender, age, or race.

1.3.4 Dosing Regimen and Administration

The combination tablets will be available in the following doses of amlodipine/valsartan: 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg. They are to be taken once a day.

1.3.5 Drug-Drug Interactions

N/A

1.3.6 Special Populations

N/A

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Amlodipine besylate, a calcium channel blocker (CCB), is approved for the treatment of hypertension (Norvasc®, NDA 19-787). It was originally approved in the U.S. on July 31, 1992. Valsartan, an angiotensin receptor blocker (ARB), is also approved for the treatment of hypertension (Diovan, NDAs 20-665 and 21-283). It was first approved in the U.S. December 23, 1996.

Approved combination drug products for hypertension include a CCB combined with an angiotensin-converting enzyme (ACE) inhibitor: Lotrel (Amlodipine/benazepril hydrochloride), Lexxel (Enalapril maleate/ felodipine), and Tarka (Tranolapril/verapamil). This submission, if approved, will be the first combination of a CCB with an ARB. Valsartan and amlodipine fixed-dose combinations have not been marketed anywhere in the world. Although both valsartan and amlodipine are currently approved in many countries worldwide. It is not possible to estimate the exposure to the use of the combination of valsartan and amlodipine. Co-packaging of valsartan and amlodipine is approved in Brazil (March 2004), Ecuador (March 2005), Venezuela (June 2005), Argentina (September 2005), as well as in the Central American and the Caribbean Regions (November 2005).

2.2 Currently Available Treatment for Indications

There are many choices of treatments, at least 100, available for hypertension including combination drugs which include: ACE inhibitors with CCBs, ACE inhibitors with diuretics, ARBs with diuretics, β -Blockers with diuretics, centrally acting drugs with diuretics, and a diuretic with another diuretic.

2.3 Availability of Proposed Active Ingredient in the United States

Both Diovan (40 mg, 80 mg, 160 mg, and 320 mg) and Norvasc® (2.5 mg, 5 mg, and 10 mg) are currently marketed in the U.S.

2.4 Important Issues with Pharmacologically Related Products

ACEs and ARBs have a Black box warning regarding drugs which act on the rennin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected they should be discontinued as soon as possible.

Many CCBs have a warning about their use in patients with heart failure especially in conjunction with beta adrenergic blockers.

2.5 Presubmission Regulatory Activity

Health Authority meetings include the following:

- **Pre-IND Meeting with the FDA on 20 February 2002**
- Scientific Advice meeting with Swedish MPA on 1 October 2002
- Scientific Advice meeting with UK MHRA on 3 December 2002
- Scientific Advice meeting with French AFSSAPS on 21 February 2003
- Meeting with UK MHRA on 19 October 2004
- Meeting with Swedish MPA on 26 October 2004
- Meeting with French AFSSAPS on 2 November 2004
- Meeting with Dutch MEB on 11 November 2004
- **Pre-NDA Meeting with the FDA on 14 April 2005**
- Pre-submission meeting with Dutch MEB on 6 October 2005
- Pre-submission meeting with UK MHRA on 14 October 2005
- Pre-submission meeting with Danish DMA on 17 October 2005
- Pre-submission meeting with Spanish Health Authority 19 October 2005
- Pre-submission meeting with Swedish MPA on 20 October 2005

2.6 Other Relevant Background Information

Not applicable (N/A)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

N/A

3.2 Animal Pharmacology/Toxicology

N/A

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Sponsor has submitted electronic submissions to the EDR dated February 22, 2006; March 31, 2006; April 11, 2006; April 25, 2006; June 22, 2006; July 2, 2006; August 1, 4, 15 and 22, 2006; and September 22, 2006.

4.2 Tables of Clinical Studies

Table 1 Summary of placebo controlled trials

Study No.	Study objective	Patients randomized	Treatment duration	Treatment/dose (mg)	Efficacy endpoint
A2201	Efficacy and safety of various valsartan/amlodipine combinations compared to their monotherapy components and to placebo, in patients with mild to moderate essential hypertension	1911	2-4 weeks 8 weeks	placebo run-in placebo valsartan 40 valsartan 80 valsartan 160 valsartan 320 amlodipine 2.5 amlodipine 5 valsartan/amlodipine 40/2.5 valsartan/amlodipine 40/5 valsartan/amlodipine 80/2.5 valsartan/amlodipine 80/5 valsartan/amlodipine 160/2.5 valsartan/amlodipine 160/5 valsartan/amlodipine 320/2.5 valsartan/amlodipine 320/5	Primary: change from baseline in MSDBP Secondary/other: change from baseline in MSSBP; standing SBP and DBP; sitting and standing pulse; responder rate; control rate
A2307	As for Study A2201	1250	2-4 weeks 8 weeks	placebo run-in placebo valsartan 160 valsartan 320 amlodipine 10 valsartan/amlodipine 160/10 valsartan/amlodipine 320/10	As for Study A2201

Page 13 Summary of Clinical Efficacy

Table 2 Summary of active-controlled trials

Study No.	Study objective, population	Patients randomized	Treatment duration	Dosage (mg)	Efficacy endpoint
A2305	Efficacy/safety of the combinations of valsartan/amlodipine 160/10 or 160/5 mg, compared to valsartan 160 mg alone in patients with essential hypertension not adequately controlled on valsartan 160 mg monotherapy	947	4 weeks 8 weeks	Valsartan 160 run-in Valsartan/amlodipine 160/10 Valsartan/amlodipine 160/5 Valsartan 160	Primary: MSDBP Secondary: MSSBP, responder rate, control rate, standing DBP and SBP, and sitting and standing pulse
A2306	Efficacy/safety of the combination of valsartan/amlodipine 160/10 mg compared to amlodipine 10 mg alone in patients with essential hypertension not adequately controlled on amlodipine 10 mg monotherapy	944	4 weeks 8 weeks	Amlodipine 10 run-in Valsartan/amlodipine 160/10 Amlodipine 10	As for Study A2305
A2308	Safety/efficacy of valsartan/amlodipine compared to lisinopril/HCTZ in severe hypertensive patients (MSDBP \geq 110 mmHg and $<$ 120 mmHg)	130	1-2 weeks 6 weeks	Placebo run-in Valsartan/amlodipine 160/5 titrated to valsartan/amlodipine 160/10 Lisinopril/HCTZ 10/12.5 titrated to lisinopril/HCTZ 20/12.5	Safety was the primary endpoint. With respect to efficacy, the variables analyzed were identical to those in Study A2305.

Page 14, Summary of Clinical Efficacy

Table 3 Summary of long-term trials

Study No.	Study objective, population	Patients enrolled	Treatment duration	Treatment/dose (mg)	Efficacy endpoints
A2201E1	Long-term open-label efficacy/safety in hypertensive patients	1246	52 weeks	valsartan/amlodipine 80/2.5 (4 weeks) forced titrated to 160/5 OR valsartan/amlodipine 80/5 (4 weeks) forced titrated to 160/10. Optional addition of HCTZ 12.5 permitted. Back titration allowed following up titration.	Primary: MSDBP. Secondary: MSSBP, standing DBP and SBP, and sitting and standing pulse
A2307E1	Long-term open-label safety/efficacy in hypertensive patients	403	54 weeks	valsartan/amlodipine 160/2.5 (2 weeks); forced titration to valsartan/amlodipine 320/5	As for Study A2201E1

Page 15, Summary of Clinical Efficacy

4.3 Review Strategy

A number of clinical studies were submitted electronically. However only two studies, A2201 and A2307, were designed as multicenter, double-blind, randomized, multifactorial, placebo-controlled, parallel group trials. Therefore, these two trials were evaluated for efficacy. Five studies were reviewed for safety; they included the two placebo-controlled trials and three active-controlled studies. Also mentioned with the Safety Review are two long-term, open-label extension studies of the two placebo-controlled trials reviewed for efficacy.

4.4 Data Quality and Integrity

The Review Team decided that a DSI inspection was not warranted as there was no investigational site that had an undue influence on the two studies evaluated for efficacy.

4.5 Compliance with Good Clinical Practices

The studies were performed in accordance with standard operating procedures of the Sponsor. They were designed to ensure adherence to GCP and to ensure the protection of the patients as required by the following directives:

1. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients).
2. Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning Informed Patient Consent and IRB approval.

The Sponsor states they did not use the services of any person debarred under section 306 (a and b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

4.6 Financial Disclosures

None of the clinical investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. _____ and its extension _____ received from Novartis more than \$25,000 in honoraria and travel expenses for educational activities. The Sponsor states that any bias was minimized by the independent data monitoring by Novartis, by the use of multiple investigators, and by the use of double-blind placebo-controlled trials.

5 CLINICAL PHARMACOLOGY

As per Dr. Elena Mishina, Exforge was evaluated in five controlled clinical trials. Valsartan and amlodipine were administered as capsules (clinical service forms) and as free combinations. In order to bridge the clinical efficacy and safety data obtained with the clinical service forms as free combination to the intended fixed combination tablet products, the sponsor performed the bioequivalence studies with the dose strengths 80/2.5 mg, 160/10 mg, and 320/5 mg of valsartan/amlodipine. A drug-drug interaction study and a food effect study were also performed. The sponsor requested biowaivers for the following dose strengths: 80/5 mg, 160/5 mg and 320/10 mg of valsartan/amlodipine based on the tablet dissolution information.

The Office of Clinical Pharmacology and Biopharmaceutics reviewed and found the clinical pharmacology and biopharmaceutics acceptable. The requested biowaivers for the 5/80mg, 5/160mg and 10/320mg dosage strength were granted.

5.1 Pharmacokinetics

N/A

5.2 Pharmacodynamics

N/A

5.3 Exposure-Response Relationships

N/A

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication requested in this submission is for mild to moderate hypertension which is not controlled by either amlodipine besylate or valsartan alone.

6.1.1 Methods

Studies A2201 and A2307 were multicenter, double-blind, randomized, multifactorial, placebo-controlled, parallel group trials. Both of these trials were reviewed for efficacy. They employed a 2 week washout in order to allow patients to taper off previous antihypertensives, followed by a 2-4 week single-blind placebo run-in period, and 8 weeks of double-blind treatment. Both trials enrolled male and female outpatients at least 18 years of age with mild to moderate essential diastolic hypertension.

Table 4 Summary of placebo-controlled trials

Study No.	Study objective	Patients randomized	Treatment duration	Treatment/dose (mg)	Efficacy endpoint
A2201	Efficacy and safety of various valsartan/amlodipine combinations compared to their monotherapy components and to placebo, in patients with mild to moderate essential hypertension	1911	2-4 weeks 8 weeks	placebo run-in placebo valsartan 40 valsartan 80 valsartan 160 valsartan 320 amlodipine 2.5 amlodipine 5 valsartan/amlodipine 40/2.5 valsartan/amlodipine 40/5 valsartan/amlodipine 80/2.5 valsartan/amlodipine 80/5 valsartan/amlodipine 160/2.5 valsartan/amlodipine 160/5 valsartan/amlodipine 320/2.5 valsartan/amlodipine 320/5	Primary: change from baseline in MSDBP Secondary/other: change from baseline in MSSBP; standing SBP and DBP; sitting and standing pulse; responder rate; control rate
A2307	As for Study A2201	1250	2-4 weeks 8 weeks	placebo run-in placebo valsartan 160 valsartan 320 amlodipine 10 valsartan/amlodipine 160/10 valsartan/amlodipine 320/10	As for Study A2201

Page 18, Clinical overview

6.1.2 General Discussion of Endpoints

Information and ideas concerning the control of hypertension are evolving. Stated in JNC 6 is the control of the diastolic blood pressure. In JNC 7, the control of the systolic blood pressure gains more importance with special groups such as diabetics requiring even stricter control. The studies in this submission utilized the JNC 6 endpoint of reducing and controlling the diastolic blood pressure. However, as a secondary endpoint the Sponsor has evaluated the systolic blood pressure. Therefore, this submission does evaluate the two most important endpoints as of today in the control of hypertension.

6.1.3 Study Design

6.1.3.1 Study A2201

Title: A randomized, double-blind, multicenter, multifactorial, placebo-controlled, parallel group study to evaluate the efficacy and safety of valsartan and amlodipine combined and alone in hypertensive patients.

Study centers: 169 centers in 6 countries: 7 in Belgium, 10 in Canada, 7 in France, 32 in Germany, 5 in Mexico and 108 in the US.

Study dates: January 28, 2003 to February 27, 2004.

Target population: Patients with mild to moderate essential hypertension, grades 1 and 2 according to the WHO classification. Patients with severe hypertension classification, sitting diastolic blood pressure (MSDPB) ≥ 110 mmHg or sitting systolic blood pressure (MSSBP) ≥ 180 mmHg were excluded for safety reasons. Eligible patients may or may not have been taking antihypertensive medications prior to enrollment; these medications had to be discontinued during the washout (week -4 to -6).

Objectives:

The primary objective of this trial was to assess the blood pressure lowering effects of a once daily regimen of various combinations of valsartan and amlodipine, compared to their monotherapy components and placebo, in patients with WHO classification grades 1 and 2 uncomplicated diastolic essential hypertension (mean sitting diastolic blood pressure [MSDBP] ≥ 95 mmHg and < 110 mmHg).

The secondary objectives were to determine the best dose combination of valsartan and amlodipine as compared to monotherapy, and assess the safety and tolerability of the combination of valsartan and amlodipine in patients with grades 1 to 2 essential diastolic hypertension.

Study design:

This was a multicenter, randomized, double-blind, placebo controlled, parallel group trial in mild to moderate hypertensive patients (WHO classification grades 1 and 2). A single-blind placebo run-in period of two to four weeks preceded an 8-week double-blind active treatment period. Eligible patients were randomized to receive valsartan monotherapy 40 mg, 80 mg, 160 mg, or 320 mg once daily (OD); amlodipine monotherapy 2.5 mg, or 5 mg OD; the combination of valsartan/amlodipine 40/2.5 mg, 40/5 mg, 80/2.5 mg, 80/5 mg, 160/2.5 mg, 160/5 mg, 320/2.5 mg, 320/5 mg OD or placebo OD. The first week post randomization was a forced titration period for patients randomized to the valsartan/amlodipine 320/5 mg OD treatment group. During this period, patients randomized to the valsartan/amlodipine 320/5 mg OD treatment group received valsartan/amlodipine 160/2.5 mg OD, while patients randomized to the remaining 14 treatment groups received their respective final doses. From the second post randomization week through the end of the trial (week 8), all treatment groups received their final dose giving a minimum of 7 weeks on each of the final doses.

The study design is shown in the diagram below.

Figure 1 Study design

Washout (2 weeks)	Single-blind run-in (2-4 weeks)	Double-blind treatment (8 weeks)						
Visit 0	1	2	3	4	5	6	7*	
Week -4 to -6	-2 to -4	0	1	2	4	6	8	
		↓ Randomization						
		Placebo						
		Valsartan 40 mg OD						
		Valsartan 80 mg OD						
		Valsartan 160 mg OD						
		Valsartan 320 mg OD						
		Amlodipine 2.5 mg OD						
		Amlodipine 5 mg OD						
	Placebo	Valsartan/Amlodipine 40/2.5 mg OD						
		Valsartan/Amlodipine 40/5 mg OD						
		Valsartan/Amlodipine 80/2.5 mg OD						
		Valsartan/Amlodipine 80/5 mg OD						
		Valsartan/Amlodipine 160/2.5 mg OD						
		Valsartan/Amlodipine 160/5 mg OD						
		Valsartan/Amlodipine 320/2.5 mg OD						
		Valsartan/Amlodipine 160/2.5mg OD			Valsartan/Amlodipine 320/5mg OD			
*At the end of the 8 week double-blind treatment phase, patients at selected centers who completed all the double-blind visits without serious adverse experiences were eligible to enroll in a one-year open-label extension.								

Page 20, Study A2201

Inclusion criteria:

Eligible patients fulfilled the following inclusion criteria:

1. Male or female patients 18 years and older were eligible. Female patients had to be either post-menopausal for one year, or surgically sterile, or using an effective contraceptive method. Hormonal contraceptive use was disallowed.
2. Patients with mild to moderate essential diastolic hypertension (grades 1 and 2 WHO classification) measured by calibrated standard sphygmomanometer. Patients had to have a MSDBP \geq 90 mmHg and $<$ 110 mmHg at Visit 1 (week - 2 to - 4), and a MSDBP \geq 95 mmHg and $<$ 110 mmHg at Visit 2 (week 0).
3. Patients had to have an absolute difference of \leq 10 mmHg in their average sitting diastolic blood pressure between Visits 1 and 2.
4. Patients who were eligible and able to participate in the study, and consented to do so after the purpose and nature of the investigation had been clearly explained to them (written informed consent).

Exclusion criteria:

Patients with the following physiological states or concomitant medical conditions were excluded:

1. Severe hypertension (grade 3 WHO classification; MSDBP \geq 110 mmHg diastolic and/or MSSBP \geq 180 mmHg systolic).
2. Inability to discontinue all prior anti-hypertensive medications safely for a period of 14 weeks.
3. Known Keith-Wagener grade III or IV hypertensive retinopathy.

4. History of hypertensive encephalopathy or cerebrovascular accident at anytime prior to Visit 1 (week -2 to -4).
5. Transient ischemic cerebral attack during the last 12 months prior to Visit 1 (week -2 to -4).
6. Evidence of a secondary form of hypertension, such as coarctation of the aorta, hyperaldosteronism, unilateral renal artery stenosis, or pheochromocytoma, etc.
7. Type 1 Diabetes Mellitus.
8. Type 2 Diabetes Mellitus with poor glucose control as defined by fasting glycosylated hemoglobin (HbA1c) >8% at Visit 1 (week -2 to -4).
9. Administration of any agent indicated for the treatment of hypertension within a minimum 4 weeks prior to randomization into the study (Visit 2, week 0), with the permitted exception of those anti-hypertensive medications requiring tapering down commencing at Visit 0 (week -4 to -6).
10. Known or suspected contraindications, including history of allergy to angiotensin receptor blockers, calcium channel blockers, hydrochlorothiazide, or hypersensitivity to other sulfonamide-derived drugs.
11. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug including but not limited to any of the following:
 - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
 - Currently active or active inflammatory bowel syndrome within 12 months prior to Visit 1 (week -2 to -4).
 - Currently active gastritis, ulcers or gastrointestinal/rectal bleeding.
 - Any history of pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury as indicated by abnormal lipase or amylase.
 - Evidence of hepatic disease as determined by any one of the following: SGOT or SGPT values 2 x ULN at Visit 1 (week -2 to -4), a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt.
 - Evidence of renal impairment as determined by any one of the following: serum creatinine > 1.5 ULN at Visit 1 (week -2 to -4), a history of dialysis, or a history of nephrotic syndrome.
 - Current obstruction of the urinary tract or difficulty in voiding due to mechanical as well as inflammatory conditions which is likely to require intervention during the course of the study or is regarded as clinically meaningful by the investigator.
12. History of heart failure.
13. History of myocardial infarction within the 12 months prior to Visit 1 (week -2 to -4).
14. Second or third degree heart block without a pacemaker.
15. Concomitant refractory angina pectoris.
16. Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.
17. Clinically significant valvular heart disease.
18. Sodium depletion.
19. History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the past five years.
20. History of any severe, life-threatening disease.
21. Any condition that in the opinion of the investigator or the Novartis monitor would jeopardize the evaluation of efficacy or safety.

22. Any surgical or medical conditions which, at the discretion of the investigator, placed the patient at higher risk from his/her participation in the study, or were likely to prevent the patient from complying with the requirements of the study or completing the trial period.
23. History of drug or alcohol abuse within the last 2 years.
24. History of noncompliance to medical regimens, or patients unwilling to comply with the study protocol.
25. Participation in any investigational drug trial within one month prior to Visit 1 (week -2 to -4).
26. Unwillingness or inability to give informed consent.
27. Persons directly involved in the execution of this protocol.

Discontinuation:

Reasons for permanent discontinuation included the following:

- MSDBP \geq 110 mmHg or MSSBP \geq 180 mmHg at any time during the single-blind or double-blind treatment phases
- Signs and symptoms of hypotension with a MSDBP $<$ 60 mmHg and/or a MSSBP $<$ 100 mmHg at any time during the single-blind or double-blind treatment phases
- Pregnancy.

Treatment:

During the single-blind and double-blind treatment phases, patients were instructed to take one capsule from each of three bottles with water in the morning at 8:00 am, except on the morning of their next office visit. Therefore, the blood pressure evaluations were done at the trough level. Patients had to return medication from the previous treatment phase before receiving medication for the next treatment period.

Patients randomized to the valsartan 80 mg treatment group received two 40 mg valsartan capsules, and patients randomized to the 320 mg treatment group received two 160 mg valsartan capsules. To accommodate the combination valsartan/amlodipine 80/2.5 mg, 80/5 mg, 320/2.5 mg, and 320/5 mg treatment arms, all patients were required to take three capsules at each dosing interval (i.e. the valsartan/amlodipine 320/2.5 mg dose was supplied as two 160 mg valsartan capsules and one 2.5 mg amlodipine capsule).

Randomization:

Randomization was performed by an IVRS vendor using a validated system. At randomization (Visit 2, week 0), following a call to IVRS, patients who met all inclusion/exclusion criteria received a medication pack containing medication for the first week of the double-blind treatment period.

Concomitant medications:

Medications having the potential to interfere with the evaluation of efficacy were excluded throughout the trial and included:

- Drugs approved for the treatment of hypertension even if prescribed for another indication. (Beta-blocker ophthalmic preparations were permitted.)

- Any antidepressant drugs in the class MAO inhibitors and tricyclics. Other psychotropic drugs such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) were allowed if well tolerated when previously taken.
- Any systemic use of corticosteroids. Topical and nasal steroid preparations were allowed.
- Use of hormonal contraceptives within 4 weeks prior to Visit 1 (week -2 to -4) and during trial.
- Thyroid medication and/or estrogen replacement therapy, unless these were stable maintenance replacement doses for the 6 months preceding Visit 1 (week -2 to -4).
- Insulin.
- Chronic administration of sympathomimetic drugs such as those found in nasal decongestants, oral decongestants and bronchodilators.
- Antacids in amounts greater than package labeling.
- Ergot and serotonin (5-hydroxytryptamine) receptor agonist preparations.
- Antiarrhythmic drugs. (Digoxin was permitted provided serum levels had been stable and no dose adjustments had been made during the 6 months preceding Visit 1 (week -2 to -4)).
- Diuretics of any kind.
- Nitrates of any kind.

Visit schedule:

The patients' scheduled visits and evaluations are shown in the following table. A range of ± 3 days was allowed.

Table 5 Visit Schedule

Visit	0 ¹	1	2	3	4	5	6	7 ²
Week ³	-4 to -6	-2 to -4	0	1	2	4	6	8
Inclusion/Exclusion Criteria	X	X	X					
Informed Consent	X							
IVRS	X	X	X	X	X	X	X	X
Medical History/Background Information		X						
Physical Examination – Complete		X						
Physical Examination – Interim			X	X	X	X	X	X
Weight and Height ¹¹		X	X	X	X	X	X	X
Blood Pressure and Pulse ⁴		X	X	X	X	X	X	X
Chest X-ray ⁵ (optional)		X						
ECG ⁶		X						
Laboratory Evaluations ⁷		X	X					X
Serum Pregnancy Test ⁸		X	X					X
Pharmacogenetic Sample ⁹			X					
Prior/Concomitant Medications		X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X
Screening Log ¹⁰	X	X						
Randomization			X					
Dispense Study Medications		X	X	X	X	X	X	
Drug Accountability			X	X	X	X	X	X
Termination								X

¹ Washout- Patients discontinued or tapered down anti-hypertensive medications, according to manufacturer's recommendations at Visit 0.
² Or sooner for premature termination.
³ +/-3 days.
⁴ Taken at the same time, by the same person, at every study visit, between 7 am and 10 am.
⁵ Chest X-ray performed at the discretion of the investigator based on the patient's medical history and/or symptoms.
⁶ Test results were kept with the source documents at the investigational site.
⁷ Blood and urine samples were obtained in a fasting state (7 hours for diabetics; 12 hours for non-diabetics).
⁸ Women of child bearing potential only. Performed on serum samples by central laboratory at Visits 1, 2, and 7.
⁹ Participating patients signed a separate pharmacogenetic specific consent form.
¹⁰ Completed for patients not entering the double-blind treatment phase. Maintained at the investigational site.
¹¹ Height measured only at Visit 1.

Source: page 20, Study VAA489A2201

Efficacy assessments:

The primary efficacy parameter was the sitting diastolic blood pressure (MSDBP). The secondary efficacy parameters were the sitting systolic blood pressure (MSSBP), standing diastolic and systolic blood pressures, and sitting and standing pulse. Pulse rate was measured for 30 seconds just prior to blood pressure measurements in both the sitting and standing positions.

Blood pressure measurement:

Blood pressure was measured using a calibrated standard sphygmomanometer and the appropriate size cuff. The arm in which the highest sitting diastolic pressures were found was the arm used for all subsequent readings throughout the study. An attempt to obtain each patient's blood pressure measurements by the same staff member, at the same time of day, using the same equipment, was made at every visit. At each study visit, after having the patient in a sitting position for five minutes, systolic/diastolic blood pressure was measured three times. The repeat measurements were made at one - to - two minute intervals. The patient then stood up, and after standing for two minutes, one

blood pressure measurement was taken. The mean of all three sitting measurements was used for the study. No up or down rounding of blood pressure was allowed.

Drug levels:

No drug levels or pharmacokinetics were assessed during this study.

Protocol amendments:

The original protocol dated April 15, 2002 was amended once, February 13, 2003. The changes included: hormonal contraceptive use was disallowed; patients with known allergies to hydrochlorothiazide, or hypersensitivity to other sulfonamide-derived drugs were added to the exclusions; patients with signs and symptoms of hypotension with a MSDBP <60 mmHg and/or a MSSBP <100 mmHg at any time during the treatment phases were permanently discontinued from the trial; a chest x-ray was done only at the discretion of the investigator; blood samples could be taken after a fast of 7 hours for diabetics rather than the 12 hours; and a breast examination was included only if indicated.

Statistical methods:

The global assessment was considered primary. To assess whether both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment, the primary efficacy variable at endpoint was analyzed using an ANCOVA model with valsartan, amlodipine and region as 3 factors and the baseline as a covariate. Regions in this study are the trial regions in Belgium, Canada, France, North Germany, South Germany, Mexico, and in the US: Northeast, Mid-Atlantic, Southeast, Great Lakes, Great Plains, Mid-South, Northwest, and Southwest. The valsartan-by-amlodipine interaction was included in the model. The model was fitted using the SAS PROC GLM procedure. The test for each term (i.e. valsartan, amlodipine, region and the interaction) was performed at a two-sided significance level of 0.05. These were considered as global tests to assess the overall contribution of the two monotherapy components. The pattern of the interaction was further examined using least-squares means. It was considered that both monotherapy treatments contribute to the effect for the combination treatment if both tests for valsartan and amlodipine terms were statistically significant. The significance level of 0.05 was used since it requires both tests to be statistically significant.

A responder was defined as a patient with a MSDBP < 90 mmHg or a ≥ 10 mmHg reduction from baseline (pre-dose measurement at the randomization Visit 2). A controlled patient was defined as a patient with a MSDBP < 90 mmHg. The proportion of patients in each treatment group achieving a successful response or control at endpoint during the double-blind period was compared as a secondary analysis using a logistic model with treatment and region as factors for all ITT patients.

The change from baseline at Week 4 and Week 8 in MSDBP and MSSBP were analyzed for the ITT population using similar models as specified for the primary efficacy analysis for pairwise comparisons. A LOCF (last observation carried forward) approach was employed for those patients who did not complete the Week 8 efficacy assessment.

The changes from baseline at endpoint for standing blood pressures as well as sitting and standing pulses were analyzed for the ITT population using similar models as specified for the primary efficacy

analysis for pairwise comparisons. A LOCF (last observation carried forward) approach was employed for those patients who did not complete the Week 8 efficacy assessment.

Patient disposition:

A total of 1738 patients, 90.9% of the randomized population which was 1911 patients, completed the study. The placebo group had the smallest proportion of completed patients (78.1%) compared to the other 14 groups. The treatment groups are shown in the table below with regard to numbers of patients who were randomized to each group.

Table 6 Size of Treatment Groups

Treatment Group	Randomized ²	Completed n (%)	Discontinued n (%)
Valsartan/Amlodipine 320/5 mg	127	121 (95.3)	6 (4.7)
Valsartan/Amlodipine 320/2.5 mg	129	121 (93.8)	8 (6.2)
Valsartan/Amlodipine 160/5 mg	127	115 (90.6)	12 (9.4)
Valsartan/Amlodipine 160/2.5 mg	127	112 (88.2)	15 (11.8)
Valsartan/Amlodipine 80/5 mg	128	122 (95.3)	6 (4.7)
Valsartan/Amlodipine 80/2.5 mg	130	124 (95.4)	6 (4.6)
Valsartan/Amlodipine 40/5 mg	125	116 (92.8)	9 (7.2)
Valsartan/Amlodipine 40/2.5 mg	129	122 (94.6)	7 (5.4)
Valsartan 320 mg	128	116 (90.6)	12 (9.4)
Valsartan 160 mg	128	118 (92.2)	10 (7.8)
Valsartan 80 mg	124	113 (91.1)	11 (8.9)
Valsartan 40 mg	127	115 (90.6)	12 (9.4)
Amlodipine 5 mg	128	113 (88.3)	15 (11.7)
Amlodipine 2.5 mg	128	110 (87.3)	16 (12.7)
Placebo	128	100 (78.1)	28 (21.9)
Total (N=2478 Enrolled¹)	1911	1738 (90.9)	173 (9.1)

¹visit (single-blind), ²Visit 2 (double-blind)
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Unsatisfactory therapeutic effect was the most common reason for discontinuation and it occurred at 13.3% in the placebo group and 0 to 5.5% in the other treatment groups. The other reasons for discontinuation which primarily included withdrawal of consent and adverse events occurred at similar frequencies across the treatment groups.

Table 7 Number of randomized patients who discontinued prematurely

Treatment Group	Total n (%)	Adverse Event(s) n (%)	Unsatisfactory Therapeutic Effect n (%)	Withdrawal of consent n (%)	Others ¹ n (%)
Val/ Aml 320/5 mg	6 (4.7)	2 (1.6)	0 (0.0)	2 (1.6)	2 (1.6)
Val/ Aml 320/2.5 mg	8 (6.2)	1 (0.8)	3 (2.3)	3 (2.3)	1 (0.8)
Val/ Aml 160/5 mg	12 (9.4)	3 (2.4)	1 (0.8)	5 (3.9)	3 (2.4)
Val/ Aml 160/2.5 mg	15 (11.8)	1 (0.8)	4 (3.1)	0 (0.0)	10 (7.9)
Val/ Aml 80/5 mg	6 (4.7)	2 (1.6)	2 (1.6)	1 (0.8)	1 (0.8)
Val/ Aml 80/2.5 mg	6 (4.6)	1 (0.8)	2 (1.5)	3 (2.3)	0 (0.0)
Val/ Aml 40/5 mg	9 (7.2)	1 (0.8)	1 (0.8)	3 (2.4)	4 (3.2)
Val/ Aml 40/2.5 mg	7 (5.4)	3 (2.3)	0 (0.0)	2 (1.6)	2 (1.6)
Val 320 mg	12 (9.4)	3 (2.3)	3 (2.3)	4 (3.1)	2 (1.6)
Val 160 mg	10 (7.8)	0 (0.0)	5 (3.9)	4 (3.1)	1 (0.8)
Val 80 mg	11 (8.9)	1 (0.8)	3 (2.4)	3 (2.4)	4 (3.2)
Val 40 mg	12 (9.4)	0 (0.0)	7 (5.5)	2 (1.6)	3 (2.4)
Am 5 mg	15 (11.7)	2 (1.6)	4 (3.1)	6 (4.7)	3 (2.3)
Aml 2.5 mg	16 (12.7)	4 (3.2)	5 (4.0)	4 (3.2)	3 (2.4)
Placebo	28 (21.9)	3 (2.3)	17 (13.3)	3 (2.3)	5 (3.9)
Total	173 (9.1)	27 (1.4)	57 (3.0)	45 (2.4)	44 (2.3)

¹Others include abnormal laboratory value(s), abnormal test procedure result(s), subject's condition no longer requires study drug, protocol violation, lost to follow-up and administrative problems
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May 2, 2003, a sudden, unexpected and total depletion of study medication for two out of 15 treatment arms occurred in the US and Germany requiring the immediate suspension of enrollment in these two countries. The same situation occurred in France and Belgium. It took 4 months to manufacture and redistribute new supplies to reinitiate enrollment. During this time, patients enrolled in the washout or single blind were discontinued. Randomized patients were continued; however, if patients were randomized to one of the two depleted treatment arms and there was no more drug available to treat them, they were terminated. Sixteen randomized patients were discontinued due to the depletion of study drug. The investigators were instructed that the reason for discontinuation of affected patients was to be indicated as "Administrative reasons" in the CRF. Of the 167 patients discontinued from the single-blind period for administrative reasons, 151 discontinuations were due to depletion of study drug. Patients who were discontinued from the washout or single-blind were permitted to re-enroll once enrollment resumed in September of 2003. A total of 44 patients who were discontinued from the single-blind phase due to depletion of study drug were re-enrolled. These patients were counted twice (43 patients) or three times (one patient) in the denominator for enrolled patients.

Protocol deviations:

A total of 151 randomized patients (7.9%) were protocol violators. Major violations occurred in 74 patients (3.9%). The most common major protocol violations were no cuff blood pressure measurements after Visit 2 (33 patients; 1.7%), use of other antihypertensive medications at or after Visit 1 (11 patients; 0.6%), and not fulfilling the blood pressure criteria at Visit 1 or 2 (19 patients; 1.0%). In addition, 9 patients (0.5%) received the wrong treatment allocation for more than two weeks after Visit 2.

The most common other violations (i.e. non-major) were Type 2 diabetes mellitus with poor glucose control (21 patients; 1.1%) and use of systemic corticosteroids (14 patients; 0.7%).

Three patients were unblinded during the course of the study, all due to adverse events.

(PID 0040/00005 in the val 80 mg group; PID 0076/00007 in the val/aml 40/2.5 mg group, and PID 0062/00001 in the val/aml 80/5 mg group)

The numbers of patients included in each analysis population are shown in the following table.

Table 8 Number (%) of patients in the analysis populations

Treatment group	Population			
	Randomized n (%)*	Intent-to-treat n (%)*	Safety n (%)*	Per-protocol n (%)*
Val/Aml 320/5 mg	127 (100)	126 (99)	127 (100)	118 (93)
Val/Aml 320/2.5 mg	129 (100)	128 (99)	129 (100)	118 (91)
Val/Aml 160/5 mg	127 (100)	127 (100)	126 (99)	113 (89)
Val/Aml 160/2.5 mg	127 (100)	125 (98)	126 (99)	111 (87)
Val/Aml 80/5 mg	128 (100)	126 (98)	128 (100)	121 (95)
Val/Aml 80/2.5 mg	130 (100)	129 (99)	129 (99)	121 (93)
Val/Aml 40/5 mg	126 (100)	123 (98)	124 (99)	114 (91)
Val/Aml 40/2.5 mg	129 (100)	128 (99)	129 (100)	119 (92)
All Combo	1022 (100)	1012 (99)	1018 (100)	935 (91)
Val 320 mg	128 (100)	128 (100)	128 (100)	116 (91)
Val 160 mg	128 (100)	127 (99)	128 (100)	116 (91)
Val 80 mg	124 (100)	123 (99)	123 (99)	110 (89)
Val 40 mg	127 (100)	127 (100)	127 (100)	115 (91)
Val Mono	507 (100)	505 (100)	506 (100)	457 (90)
Aml 5 mg	128 (100)	128 (100)	128 (100)	110 (86)
Aml 2.5 mg	126 (100)	126 (100)	125 (99)	109 (87)
Aml Mono	254 (100)	254 (100)	253 (100)	219 (86)
Placebo	128 (100)	127 (99)	128 (100)	99 (77)
Total	1911 (100)	1898 (99)	1905 (99)	1710 (89)

Denominator is from randomized population

*Percentages (%) were rounded to the nearest integer

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Demographics:

The demographics were comparable for each of the groups as shown in the following table. The majority of the patients were Caucasian; Black patients accounted for 10.4% of the study population. There was a slight majority of male patients. The mean age was 54.4 years, with most patients, 81.8%, younger than 65 years of age. This is a representative group of the population who would be taking the medication, except for not including a number of patients older than 75. However, this older age group is difficult to study because of the number of medications they frequently take.

Table 9 Demographics

Treatment Group	N	Age (yrs) Mean	Sex n (%)		Race n (%)			
			Male	Female	Caucasian	Black	Oriental	Other
Val/Aml 320/5 mg	127	55.3	71 (55.9)	56 (44.1)	103 (81.1)	9 (7.1)	4 (3.1)	11 (8.7)
Val/Aml 320/2.5 mg	129	55.1	75 (58.1)	54 (41.9)	103 (79.8)	13 (10.1)	3 (2.3)	10 (7.8)
Val/Aml 160/5 mg	127	54.9	58 (45.7)	69 (54.3)	104 (81.9)	12 (9.4)	1 (0.8)	10 (7.9)
Val/Aml 160/2.5 mg	127	55.1	67 (52.8)	60 (47.2)	102 (80.3)	10 (7.9)	2 (1.6)	13 (10.2)
Val/Aml 80/5 mg	128	54.2	57 (44.5)	71 (55.5)	99 (77.3)	15 (11.7)	2 (1.6)	12 (9.4)
Val/Aml 80/2.5 mg	130	54.1	79 (60.8)	51 (39.2)	100 (76.9)	17 (13.1)	3 (2.3)	10 (7.7)
Val/Aml 40/5 mg	125	53.4	71 (56.8)	54 (43.2)	102 (81.6)	12 (9.6)	1 (0.8)	10 (8.0)
Val/Aml 40/2.5 mg	129	54.5	76 (58.9)	53 (41.1)	105 (81.4)	10 (7.8)	3 (2.3)	11 (8.5)
Val 320 mg	128	56.8	67 (52.3)	61 (47.7)	100 (78.1)	16 (12.5)	0 (0.0)	12 (9.4)
Val 160 mg	128	53.0	69 (53.9)	59 (46.1)	105 (82.0)	9 (7.0)	2 (1.6)	12 (9.4)
Val 80 mg	124	53.1	56 (45.2)	68 (54.8)	95 (76.6)	19 (15.3)	2 (1.6)	8 (6.5)
Val 40 mg	127	55.0	72 (56.7)	55 (43.3)	97 (76.4)	16 (12.6)	0 (0.0)	14 (11.0)
Aml 5 mg	128	53.8	68 (53.1)	60 (46.9)	106 (82.8)	10 (7.8)	3 (2.3)	9 (7.0)
Aml 2.5 mg	126	54.4	66 (52.4)	60 (47.6)	95 (75.4)	19 (15.1)	1 (0.8)	11 (8.7)
Placebo	128	53.7	70 (54.7)	58 (45.3)	103 (80.5)	12 (9.4)	3 (2.3)	10 (7.8)
Total	1911	54.4	1022 (53.5)	889 (46.5)	1519 (79.5)	199 (10.4)	30 (1.6)	163 (8.5)

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The following table shows that the treatment groups were comparable with regard to mean blood pressure and pulse values at baseline.

Table 10 Baseline sitting blood pressures and pulses

Treatment Group	No. of Pts	Mean Sitting Diastolic BP (mmHg)	Mean Sitting Systolic BP (mmHg)	Sitting Pulse (bpm)
		Mean (SD)	Mean (SD)	Mean (SD)
Val/Aml 320/5 mg	127	99.3 (3.75)	152.5 (12.25)	71.8 (8.95)
Val/Aml 320/2.5 mg	129	99.4 (3.71)	162.3 (12.49)	74.8 (9.77)
Val/Aml 160/5 mg	127	99.4 (3.59)	153.0 (13.07)	73.4 (10.14)
Val/Aml 160/2.5 mg	127	99.0 (3.42)	152.1 (13.29)	73.2 (9.18)
Val/Aml 80/5 mg	128	99.1 (3.32)	153.2 (12.75)	72.6 (8.94)
Val/Aml 80/2.5 mg	130	99.5 (3.88)	151.8 (13.71)	72.8 (9.06)
Val/Aml 40/5 mg	125	99.4 (3.48)	153.0 (13.68)	71.5 (9.46)
Val/Aml 40/2.5 mg	129	99.6 (3.84)	153.1 (13.21)	74.0 (9.55)
Val 320 mg	128	99.3 (3.59)	154.6 (11.41)	72.7 (9.05)
Val 160 mg	128	98.9 (3.54)	152.0 (14.19)	73.4 (9.29)
Val 80 mg	124	99.2 (3.55)	153.2 (11.63)	73.1 (8.71)
Val 40 mg	127	99.2 (3.22)	153.7 (12.56)	73.8 (10.67)
Aml 5 mg	128	99.0 (3.49)	152.6 (12.70)	72.6 (10.15)
Aml 2.5 mg	126	99.5 (3.73)	153.9 (12.86)	73.4 (9.79)
Placebo	128	99.4 (3.72)	151.6 (12.57)	72.5 (9.38)
Total	1911	99.3 (3.59)	152.8 (12.83)	73.0 (9.49)

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Most patients had hypertension for at least two years. The mean duration of hypertension was similar across treatment groups, 6.3-8.7 years, except for the valsartan 40 mg group which had a slightly longer mean duration of 10.4 years.

Table 11 Duration of Hypertension

Treatment Group	Number of Patients	Duration (months)			Mean years (SD)
		< 12 n (%)	12 - < 24 n (%)	≥ 24 n (%)	
Val/Aml 320/5 mg	127	25 (19.7)	16 (12.6)	86 (67.7)	7.0 (7.39)
Val/Aml 320/2.5 mg	129	24 (18.6)	14 (10.9)	91 (70.5)	6.5 (7.05)
Val/Aml 160/5 mg	126	20 (15.7)	9 (7.1)	97 (76.4)	7.0 (7.37)
Val/Aml 160/2.5 mg	127	22 (17.3)	11 (8.7)	94 (74.0)	8.2 (8.94)
Val/Aml 80/5 mg	128	25 (19.5)	14 (10.9)	89 (69.5)	6.4 (6.78)
Val/Aml 80/2.5 mg	130	31 (23.8)	7 (5.4)	92 (70.8)	6.6 (6.75)
Val/Aml 40/5 mg	125	19 (15.2)	9 (7.2)	97 (77.6)	7.4 (7.88)
Val/Aml 40/2.5 mg	129	20 (15.5)	8 (6.2)	101 (78.3)	7.7 (8.14)
Val 320 mg	128	19 (14.8)	6 (4.7)	103 (80.5)	8.7 (8.11)
Val 160 mg	128	26 (20.3)	13 (10.2)	89 (69.5)	6.5 (7.32)
Val 80 mg	124	24 (19.4)	17 (13.7)	83 (66.9)	6.3 (6.77)
Val 40 mg	127	11 (8.7)	14 (11.0)	102 (80.3)	10.4 (11.15)
Aml 5 mg	128	22 (17.2)	9 (7.0)	97 (75.8)	7.6 (8.26)
Aml 2.5 mg	126	20 (15.9)	16 (12.7)	90 (71.4)	6.7 (6.86)
Placebo	128	18 (14.1)	10 (7.8)	100 (78.1)	7.0 (5.91)
Total	1910	326 (17.1)	173 (9.1)	1411 (73.8)	7.3 (7.78)

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One past or concurrent medical condition was reported in 94.4% of the patients. The most frequently reported conditions which occurred in similar frequencies across treatment groups were metabolic and nutrition disorders (46.3%), musculoskeletal and connective tissue disorders (44.1%), surgical and medical procedures (37.6%), nervous system disorders (31.7%), and gastrointestinal disorders (30.5%).

Medication:

Eligible patients were randomized to one of 15 treatment groups for 8 weeks of double-blind therapy. For safety reasons, patients who were randomized to the valsartan/amlodipine 320/5 mg group received valsartan/amlodipine 160/2.5 mg for one week before being force-titrated to their final dose. No other dose adjustments were permitted. The mean exposure of only 48.6 days in the placebo group was consistent with the observed discontinuation rate in that group.

Three patients had excessively long durations of exposure:

- Patient PID 0069/00044 (valsartan/amlodipine 160/5 mg) appeared to have had 103 days of exposure. This patient interrupted study medication for 6 weeks (while on holiday), and was prescribed alternate antihypertensive therapy during this period (a protocol violation).
- Two patients were lost to follow up and no date for last dose of medication was recorded: patient PID 0563/00009 (valsartan 80 mg), with 132 days of exposure and patient PID 0563/00013 (amlodipine 2.5 mg), with 135 days of exposure. The date of last dose was recorded as the last attempted contact with the patients.

Table 12 Overall treatment exposure

Treatment Group	Number of Patients	Exposure (Days)		
		Mean (SD)	Median	Range
Valsartan/Amlodipine 320/5 mg	127	55.3 (7.66)	56	7 - 69
Valsartan/Amlodipine 320/2.5 mg	129	55.7 (10.30)	56	3 - 84
Valsartan/Amlodipine 160/5 mg	127	54.0 (11.99)	56	2 - 103
Valsartan/Amlodipine 160/2.5 mg	127	53.4 (12.28)	56	4 - 81
Valsartan/Amlodipine 80/5 mg	128	55.3 (9.38)	56	8 - 77
Valsartan/Amlodipine 80/2.5 mg	130	55.3 (8.52)	56	9 - 80
Valsartan/Amlodipine 40/5 mg	125	55.1 (9.90)	56	1 - 70
Valsartan/Amlodipine 40/2.5 mg	129	55.6 (10.81)	56	1 - 84
Valsartan 320 mg	128	54.4 (9.54)	56	6 - 70
Valsartan 160 mg	128	54.8 (10.70)	56	1 - 84
Valsartan 80 mg	124	54.3 (13.10)	56	7 - 132
Valsartan 40 mg	127	52.5 (12.29)	56	4 - 64
Amlodipine 5 mg	128	53.9 (9.96)	56	14 - 88
Amlodipine 2.5 mg	126	54.0 (14.95)	56	5 - 135
Placebo	128	48.6 (16.99)	56	1 - 83
Total	1911	54.1 (11.55)	56	1 - 135

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Concomitant medication:

Concomitant medication use was generally similar across all treatment groups. Overall, 59.3% of the randomized population took at least one concomitant medication before starting the run-in period. The most frequently used medications prior to the start of run-in treatment were plain ACE inhibitors (14.7%), plain angiotensin II antagonists (9.7%), selective beta blocking agents (9.4%), dihydropyridine derivatives (7.6%), angiotensin II antagonists and diuretics (7.1%) and plain thiazides (6.9%).

Of the randomized patients, 77.9% took at least one concomitant medication after starting the run-in treatment. The most frequently used medications after the start of the run-in period were salicylic acid and derivatives (17.8%), non-steroidal anti-inflammatory preparations for topical use (17.3%), platelet inhibitors excluding heparin (16.7%), other agents for local oral treatment (16.3%, almost all of which was aspirin), and anilides (15.7%). Aspirin, which fell into one or more of these categories, was used by 16.2% of the randomized population.

6.1.3.2 Study 2307

Title: A randomized, double-blind, multicenter, multifactorial, placebo-controlled, parallel group study to evaluate the efficacy and safety of valsartan (160 mg and 320 mg) and amlodipine (10 mg) combined and alone in hypertensive patients.

Study centers: 133 centers in 10 countries: 2 Egypt, 9 France, 84 Germany, 10 Korea, 2 Malaysia, 4 Norway, 6 Peru, 1 Portugal, 10 Spain and 5 in Taiwan.

Study dates: January 28, 2004 to July 29, 2004.

Objectives:

The primary objective of this trial was to assess the blood pressure lowering effects of a once daily regimen of various combinations of valsartan (160 and 320 mg) and amlodipine (10 mg), compared to their monotherapy components and placebo, in patients with uncomplicated diastolic essential hypertension (mean sitting diastolic blood pressure [MSDBP] ≥ 95 mmHg and < 110 mmHg).

The secondary objectives were to determine the blood pressure lowering effects of a once daily regimen of various combinations of valsartan (160 and 320 mg) and amlodipine (10 mg), compared to their monotherapy components and placebo on systolic blood pressure, and assess the safety and tolerability of the combination of valsartan and amlodipine in patients with essential diastolic hypertension.

An open-label extension study, A2307E1, to this protocol was conducted in order to obtain long-term safety data on valsartan and amlodipine 320/5 mg and is included in the safety review.

Study design:

This was a multicenter, randomized, double-blind, placebo controlled, parallel group trial in hypertensive patients with MSDBP ≥ 95 mmHg and < 110 mmHg. A single-blind placebo run-in period of two to four weeks preceded an 8-week double-blind active treatment period. Eligible patients were randomized in a double-blind fashion to receive valsartan monotherapy 160 mg or 320 mg OD, amlodipine monotherapy 10 mg OD, the combination of valsartan/amlodipine 160/10 mg or 320/10 mg OD, or placebo OD. The first week post randomization was a forced titration period for patients randomized to the valsartan/amlodipine 320/10 mg OD treatment group. During this period, patients randomized to the valsartan/amlodipine 320/10 mg OD treatment group received valsartan/amlodipine 160/5 mg OD, while patients randomized to the remaining 5 treatment groups received their respective final doses. From the second post randomization week through the end of the trial (week 8), all treatment groups received their final dose giving a minimum of 7 weeks on each of the final doses. The study design is illustrated below.

Figure 2 Study design

Washout (2 weeks)	Single-blind run-in (2-4 weeks)	Double-blind treatment (8 weeks)					
Visit 0	1	2	3	4	5	6	7*
Week -6 to -4	-4 to -2	0	1	2	4	6	8
		↓ Randomization					
	Placebo	Placebo					
		Valsartan 160 mg OD					
		Valsartan 320 mg OD					
		Amlodipine 10 mg OD					
		Valsartan/Amlodipine 160/10 mg OD					
		Valsartan/Amlodipine 160/5 mg OD			Valsartan/Amlodipine 320/10 mg OD		
*At the end of the 8 week double-blind treatment phase, the first 400 patients to complete all double-blind visits, with no drug related serious adverse experiences during the trial, were eligible to enroll in a one-year open-label extension.							

The Agency requested that the valsartan/amlodipine clinical program evaluate the full range of approved doses of valsartan and amlodipine as a prerequisite for approval. Six treatment arms were evaluated in this trial; two of the approved valsartan doses (valsartan 160 mg and 320 mg), one of the approved amlodipine doses (amlodipine 10 mg), all combinations of these approved doses and placebo. The remaining approved doses and their combinations were evaluated in study VAA489A2201 previously reviewed.

For safety reasons, in particular during the washout period, patients with severe hypertension (MSDPB ≥ 110 mmHg or MSSBP ≥ 180 mmHg) were excluded from the study. Moreover, patients developing severe hypertension at any time during the single-blind or double-blind treatment phases had to be permanently discontinued from the study.

Population studied:

In order to complete 900 patients (150 per treatment arm), it was estimated that approximately 1100 patients with uncomplicated essential diastolic hypertension (MSDBP ≥ 95 mmHg and < 110 mmHg) would have to be randomized in this study.

The inclusion and exclusion criteria were essentially the same as the above reviewed study A2201.

Treatment:

To accommodate the valsartan/amlodipine combination (160/10 and 320/10 mg) treatment arms, all patients were required to take four capsules at each dosing interval during both the single-blind and double-blind treatment phases. Medication was taken with water in the morning at 8:00 am, except on the morning of their next office visit. The table below outlines the dosing scheme for the 6 treatment groups:

Table 13 Dosing scheme

Treatment Group	2-4 week Single-blind phase	8-week Double-blind phase
Placebo		2 capsules valsartan placebo 2 capsules amlodipine placebo
Valsartan 160 mg		2 capsules valsartan 80 mg 2 capsules amlodipine placebo
Valsartan 320 mg		2 capsules valsartan 160 mg 2 capsules amlodipine placebo
Amlodipine 10 mg	2 capsules valsartan placebo 2 capsules amlodipine placebo	2 capsules valsartan placebo 2 capsules amlodipine 5 mg
Valsartan/Amlodipine 160/10 mg		2 capsules valsartan 80 mg 2 capsules amlodipine 5 mg
Valsartan/Amlodipine 320/10 mg (Valsartan/Amlodipine 160/5 mg - week 0 to week 1)		2 capsules valsartan 80 mg 2 capsules amlodipine 2.5 mg
Valsartan/Amlodipine 320/10 mg (week 1 to week 8)		2 capsules valsartan 160 mg 2 capsules amlodipine 5 mg

Randomization was performed by an IVRS vendor and concomitant medication which could interfere with the evaluation of efficacy was excluded throughout the trial as in the previously discussed study. The visit schedule and evaluations in this study were also similar study A2201.

Efficacy:

The primary efficacy parameter was sitting diastolic blood pressure. The secondary efficacy parameters were sitting systolic blood pressure, standing diastolic and systolic blood pressures, and sitting and standing pulse.

At each study visit, after having the patient in a sitting position for five minutes, systolic/diastolic blood pressure was measured three times. The repeat measurements were made at one- to two minute intervals. The patient then stood up, and after standing for two minutes, one blood pressure measurement was taken. The mean of all three sitting measurements was decisive for the study specific procedures. No up or down rounding was allowed. Pulse rate was measured for 30 seconds just prior to blood pressure measurements; once in the sitting and once in the standing position. Ideally, each patient's blood pressure measurements were obtained by the same staff member, at the same time of day, using the same equipment, at every visit.

Drug levels:

Drug levels and pharmacokinetics were not assessed.

Protocol amendments:

There were no protocol amendments.

Efficacy variables:

Primary efficacy variable: Changes from baseline (Visit 2/Week 0) in mean sitting diastolic blood pressure (CMSDBP)

Secondary efficacy variables:

- Changes from baseline (Visit 2/Week 0) in mean sitting systolic blood pressure (CMSSBP)
- Responder rate for achieving mean sitting diastolic blood pressure (MSDBP) < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline
- Control rate for achieving mean sitting diastolic blood pressure (MSDBP) < 90 mmHg

Global assessment of primary efficacy variable CMSDBP at endpoint:

To assess whether both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment, the primary efficacy variable at endpoint was analyzed using an ANCOVA model with valsartan, amlodipine, and region as three factors and the baseline as a covariate. In this study regions are trial regions in North Germany, South Germany, Spain, Czech Republic, Portugal, Peru, Argentina, Norway, Egypt, Korea, Taiwan, Malaysia, and Singapore. The valsartan-by-amlodipine interaction was also included in the model. The model was fitted using the SAS PROC GLM procedure. The test for each term (i.e. valsartan, amlodipine, region, and the interaction) was performed at a two-sided significance level of 0.05. These were considered as global tests to assess the overall contribution of the two monotherapy components. It was considered that both monotherapy treatments contribute to the effect for the combination treatment if both tests for

valsartan and amlodipine terms were statistically significant. The significance level of 0.05 was used since it requires both tests to be statistically significant. The global assessment was considered primary.

Patients studied:

A total of 1407 patients were enrolled into the single-blind period of the study. A total of 1338 patients completed the single-blind period; 69 were discontinued. The most common reasons for discontinuation from the single-blind period were withdrawal of consent (21 patients) and abnormal laboratory value (19 patients).

There were 1250 randomized patients. The treatment groups were balanced with regard to numbers of randomized patients. A total of 1167 patients (93.4% of the randomized population) completed the study. The completion rates were similar across treatment groups.

Table 14 Patient disposition by treatment group

Treatment Group	Randomized ²	Completed n (%)	Discontinued n (%)
Val/Aml 320/10 mg	210	192 (91.4)	18 (8.6)
Val/Aml 160/10 mg	209	199 (95.2)	10 (4.8)
Val 320 mg	208	193 (92.8)	15 (7.2)
Val 160 mg	207	192 (92.8)	15 (7.2)
Aml 10 mg	207	196 (94.7)	11 (5.3)
Placebo	209	195 (93.3)	14 (6.7)
Total (N= 1407 Enrolled¹)	1250	1167 (93.4)	83 (6.6)

¹Visit 1 (single-blind), ²Visit 2 (double-blind)
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The most common reasons for discontinuation from the double-blind period were adverse event(s), unsatisfactory therapeutic effect and withdrawal of consent. The reasons for discontinuation generally occurred at similar frequencies across treatment groups as shown in the following table.

Table 15 Number (%) of patients who discontinued prematurely during treatment phase

Treatment Group	Total n (%)	Adverse Event(s) n (%)	Unsatisfactory Therapeutic Effect n (%)	Withdrawal of consent n (%)	Others ¹ n (%)
Val/Aml 320/10 mg (N=210)	18 (8.6)	5 (2.4)	2 (1.0)	4 (1.9)	7 (3.3)
Val/Aml 160/10 mg (N=209)	10 (4.8)	7 (3.3)	0 (0.0)	1 (0.5)	2 (1.0)
Val 320 mg (N=208)	15 (7.2)	2 (1.0)	6 (2.9)	4 (1.9)	3 (1.4)
Val 160 mg (N=207)	15 (7.2)	2 (1.0)	4 (1.9)	3 (1.4)	6 (2.9)
Aml 10 mg (N=207)	11 (5.3)	8 (3.9)	0 (0.0)	2 (1.0)	1 (0.5)
Placebo (N=209)	14 (6.7)	5 (2.4)	5 (2.4)	2 (1.0)	2 (1.0)
Total (N=1250)	83 (6.6)	29 (2.3)	17 (1.4)	16 (1.3)	21 (1.7)

¹Others include abnormal laboratory value(s), abnormal test procedure result(s), subject's condition no longer required study drug, protocol violation, lost to follow-up and administrative problems
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Protocol deviations:

122 randomized patients (9.8%) were protocol violators. Major violations occurred in 63 patients (5.0%). The most common major protocol violations were patients whose blood pressure evaluations

were performed <20 or >30 hours after their last dose of study medication (47 patients; 3.8%), and wrong treatment allocation for more than 2 weeks (7 patients; 0.6%). Sixty-five patients (5.2%) had other (i.e. non-major) violations. These were primarily patients who took prohibited concomitant medications; the most common was use of systemic corticosteroids (19 patients; 1.5%). Nine patients (0.7%) had MSDBP that increased >10 mmHg between visits 1 and 2.

No patients were unblinded during the course of the study.

The following table shows similar proportions of patients in each treatment group for each population.

Table 16 Number (%) of patients in the analysis populations by treatment group

Treatment group	Randomized n (%)	Intent-to-treat n (%)	Safety n (%)	Per-protocol n (%)
Val/Aml 320/10 mg	210 (100.0)	208 (99.0)	210 (100.0)	184 (87.6)
Val/Aml 160/10 mg	209 (100.0)	209 (100.0)	209 (100.0)	198 (94.7)
Val 320 mg	208 (100.0)	207 (99.5)	208 (100.0)	188 (90.4)
Val 160 mg	207 (100.0)	207 (100.0)	207 (100.0)	187 (90.3)
Aml 10 mg	207 (100.0)	206 (99.5)	207 (100.0)	191 (92.3)
Placebo	209 (100.0)	209 (100.0)	209 (100.0)	186 (89.0)
Total	1250 (100.0)	1246 (99.7)	1250 (100.0)	1134 (90.7)

-Denominator is from randomized population.
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One hundred sixteen randomized patients were excluded from the per protocol population. These were patients who either did not complete the study, or had major protocol violations.

Demographics:

The treatment groups were generally comparable with respect to the demographic characteristics. In all treatment groups, the majority of the patients were Caucasian. Overall, and in 4 of the 6 treatment groups, there was a slight majority of male patients. The overall mean age was 56.9 years, with most patients (71.4% overall) younger than 65 years of age. Similar characteristics were observed in the per protocol population.

Table 17 Demographics

Treatment Group	N	Age (yrs)		Sex n (%)		Race n (%)			
		Mean	Male	Female	Caucasian	Black	Oriental	Other	
Val/Aml 320/10 mg	210	58.0	113 (53.8)	97 (46.2)	163 (77.6)	1 (0.5)	30 (14.3)	16 (7.6)	
Val/Aml 160/10 mg	209	56.7	109 (52.2)	100 (47.8)	167 (79.9)	0 (0.0)	26 (13.4)	14 (6.7)	
Val 320 mg	208	56.7	108 (51.9)	100 (48.1)	170 (81.7)	0 (0.0)	28 (13.5)	10 (4.8)	
Val 160 mg	207	56.8	92 (44.4)	115 (55.6)	163 (78.7)	2 (1.0)	27 (13.0)	15 (7.2)	
Aml 10 mg	207	55.4	114 (55.1)	93 (44.9)	164 (79.2)	1 (0.5)	29 (14.0)	13 (6.3)	
Placebo	209	58.0	93 (44.5)	116 (55.5)	165 (78.9)	1 (0.5)	29 (13.9)	14 (6.7)	
Total	1250	56.9	629 (50.3)	621 (49.7)	992 (79.4)	5 (0.4)	171 (13.7)	82 (6.6)	

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The treatment groups were also comparable with regard to mean blood pressure and pulse values at baseline in the randomized population as shown in the following table.

Table 18 Baseline mean sitting blood pressures and pulse by treatment group

Treatment Group	Number of Patients	Mean Sitting Diastolic BP (mmHg) Mean (SD)	Mean Sitting Systolic BP (mmHg) Mean (SD)	Sitting Pulse (bpm) Mean (SD)
Val/Aml 320/10 mg	210	99.2 (3.5)	157.2 (12.0)	74.6 (9.1)
Val/Aml 160/10 mg	209	99.3 (3.6)	157.4 (11.5)	73.9 (9.1)
Val 320 mg	208	99.1 (3.6)	157.5 (11.5)	74.0 (8.9)
Val 160 mg	207	98.9 (3.3)	155.6 (11.3)	73.2 (8.5)
Aml 10 mg	207	98.8 (3.2)	156.2 (12.6)	72.7 (8.5)
Placebo	209	99.0 (3.3)	156.4 (11.5)	73.2 (8.6)
Total	1250	99.1 (3.4)	156.7 (11.7)	73.6 (8.8)

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Across treatment groups, most patients had hypertension for at least two years. The mean duration of hypertension was similar across treatment groups (5.1 - 5.8 years) as shown in the following table.

Table 19 Duration of Hypertension

Treatment Group	Number of Patients	Duration (months)			Mean years (SD)
		< 12 n (%)	12 - < 24 n (%)	≥ 24 n (%)	
Val/Aml 320/10 mg	210	52 (24.8)	16 (7.6)	142 (67.6)	5.8 (6.1)
Val/Aml 160/10 mg	209	49 (23.4)	25 (12.0)	135 (64.6)	5.5 (6.3)
Val 320 mg	208	42 (20.2)	30 (14.4)	136 (65.4)	5.3 (5.5)
Val 160 mg	207	52 (25.1)	19 (9.2)	136 (65.7)	5.1 (5.0)
Aml 10 mg	207	58 (28.0)	21 (10.1)	128 (61.8)	5.1 (6.1)
Placebo	209	55 (26.3)	29 (13.9)	125 (59.8)	5.5 (6.7)
Total	1250	308 (24.6)	140 (11.2)	802 (64.2)	5.4 (6.0)

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Study medication:

Eligible patients were randomized to one of 6 treatment groups for 8 weeks of double-blind therapy. For safety reasons, patients randomized to the valsartan/amlodipine 320/10 mg group received valsartan/amlodipine 160/5 mg for one week before being force-titrated to their final dose.

Some patients enrolled at Site 0022 had excessively long durations of exposure. It was found that the investigator at that site had an extended illness that prevented him from complying with the protocol defined visit intervals. As a result, the patients at this site did not have an adequate supply of study medication on hand to treat them for the full duration of their study participation. Patients were instructed to take their study medication until one dose of medication remained, and to save that last dose of medication for the day prior to the next study visit date. No alternate antihypertensive medication was taken during the lapse in treatment, and because the patients took the last dose of study medication on the day prior to their next study visit, no major protocol violations were triggered.

At least one concomitant medication was taken by 63.0% of the randomized patients after starting the run-in treatment. The most frequently used medications after the start of the run-in period were HMG

CoA reductase inhibitors (13.3%), non-drug therapies and procedures (11.3%), anti-inflammatory preparations for topical use (9.3%), thyroid hormones (6.7%), platelet inhibitors excluding heparin (5.9%) and salicylic acid and derivatives (5.8%). Aspirin, which fell into one or more of these categories, was used by 4.3% of the randomized population.

Demographics:

In both studies, A2201 and A2307, the majority of the patients were Caucasian, but there were some inter-study differences with regard to the other racial categories: Black patients accounted for 10.4% of the study population in Study A2201, but only 0.4% in Study A2307. Oriental patients made up 13.7% of the population in Study A2307, but only 1.6% of the population in Study A2201. This was due to the fact that most of the study centers for Study A2201 were in North America, and most of the study centers for Study A2307 were in Europe and Asia. Overall, and in most treatment groups, there was a slight majority of male patients. Most patients were also younger than 65 years of age (81.8% overall in Study A2201; 71.4% in Study A2307).

6.1.3.3 Study A2305

Title: A randomized, double-blind, multicenter, active-controlled, parallel design trial to evaluate the safety and efficacy of the combination of valsartan/amlodipine 160/5 mg or 160/10 mg versus valsartan 160 mg alone for 8 weeks in hypertensive patients who are not adequately controlled on valsartan 160 mg monotherapy.

Study centers: 83 enrolling centers in Estonia (8), France (5), Germany (5), Ireland (8), Lithuania (16), the Netherlands (13), Poland (10), Slovenia (5), Spain (5) and the UK (8).

Dates: October 14, 2004 to June 27, 2005

Objectives:

The primary objective was to demonstrate the efficacy of the combinations of valsartan/amlodipine 160/10 mg or 160/5 mg in patients with essential hypertension not adequately controlled on valsartan 160 mg monotherapy by testing the hypothesis that either combination of valsartan/amlodipine 160/10 mg or 160/5 mg produces a superior reduction in mean sitting diastolic blood pressure (MSDBP) from baseline to 8 weeks compared to valsartan 160 mg alone.

Secondary objectives:

- The combination of valsartan/amlodipine 160/10 mg produces superior reductions in MSDBP from baseline to 8 weeks compared to the combination of valsartan/amlodipine 160/5 mg;
- The combinations of valsartan/amlodipine 160/10 or 160/5 mg produces superior reductions in mean sitting systolic blood pressure (MSSBP) from baseline to 8 weeks compared to valsartan 160 mg alone;
- The combination of valsartan/amlodipine 160/10 mg produces superior reductions in MSSBP from baseline to 8 weeks compared to the combination of valsartan/amlodipine 160/5 mg;
- To explore responder rates at the end of the study;
- To explore the safety and tolerability of the three treatments.

Design:

This was a multicenter, double-blind, active-controlled, randomized, parallel-group, study in patients with essential hypertension. Eligible patients at Visit 1 entered a washout period of 1- 4 weeks, followed at Visit 2 by a 4-week single-blind valsartan 160 mg OD (once a day) run-in phase. Patients at Visit 3 were then randomized, in a double-blind manner, to receive valsartan 160 mg, valsartan/amlodipine 160/5 mg or valsartan/amlodipine 160/10 mg OD for 8 weeks.

Indication:

Male and female adult patients with essential diastolic hypertension measured by calibrated standard aneroid or mercury sphygmomanometer. At Visit 1 (Week -8 to -4), patients not treated with antihypertensive medications had to have a MSDBP of ≥ 95 mmHg and < 110 mmHg; those patients treated with antihypertensive medication had to have a MSDBP of < 110 mmHg. At Visit 2 (Week -4), all patients had to have a MSDBP of ≥ 95 mmHg and < 110 mmHg. At Visit 3 (Week 1, baseline), all patients had to have a MSDBP of ≥ 90 mmHg and < 110 mmHg. Patients with severe hypertension (MSDBP ≥ 110 mmHg and/or MSSBP ≥ 180 mmHg) were excluded.

Duration of treatment:

This study began with a 1-4 week washout phase, followed by a 4-week single-blind valsartan run-in period, and 8 weeks of double-blind treatment. The maximum trial duration was 16 weeks.

Efficacy:

The primary efficacy variable was the change from baseline in MSDBP. Secondary efficacy variables were the change from baseline in MSSBP, the responder rate (defined as achieving a MSDBP < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline) and the control rate (defined as a patient with a MSDBP < 90 mmHg). Other variables were the change from baseline in standing DBP, change from baseline in standing SBP, change from baseline in sitting pulse rate, and change from baseline in standing pulse rate.

This study was included in the Safety Review.

6.1.3.4 Study A2306

Title: A randomized, double-blind, multi-center, active-controlled, parallel design trial to evaluate the safety and efficacy of the combination of valsartan/amlodipine 160/10 mg versus amlodipine 10 mg alone for 8 weeks in hypertensive patients who are not adequately controlled on amlodipine 10 mg monotherapy.

Study centers: 85 centers in France (14), Germany (8), Hungary (6), Israel (11), Italy (3), Latvia (14), Poland (11), Romania (13) and the UK (5).

Dates: November 1, 2004 to June 28, 2005

Objectives:

The primary objective was to demonstrate the efficacy of the combination of valsartan/amlodipine 160/10 mg in patients with essential hypertension not adequately controlled on amlodipine 10 mg monotherapy by testing the hypothesis that the combination of valsartan/amlodipine 160/10 mg produces a superior reduction in mean sitting diastolic blood pressure (MSDBP) from baseline to 8 weeks compared to amlodipine 10 mg alone.

The secondary objectives were:

- To explore the efficacy of the combination of valsartan/amlodipine 160/10 mg in patients with essential hypertension not adequately controlled on amlodipine 10 mg monotherapy by testing the hypothesis that the combination of valsartan/amlodipine 160/10 mg produces superior reductions in mean sitting systolic blood pressure (MSSBP) from baseline to 8 weeks compared to amlodipine alone;
- To explore responder rates at the end of the study;
- To explore the safety and tolerability of the two treatments.

Study design:

This was a multi-center, randomized, double-blind, active controlled parallel group study in patients with essential hypertension. Eligible patients at Visit 1 entered a 1-4 week washout phase followed at Visit 2 by a 4 week single-blind 10 mg OD (once a day) amlodipine run-in phase. Patients were then randomized at Visit 3, in a double-blind manner, to receive amlodipine 10 mg OD, or valsartan/amlodipine 160/10 mg OD for 8 weeks.

Indication inclusion:

The study population consisted of male and female patients ≥ 18 years of age with essential diastolic hypertension measured by calibrated standard aneroid or mercury sphygmomanometer. At Visit 1 (Week -8 to -4), patients not treated with antihypertensive medications had to have a MSDBP of ≥ 95 mmHg and < 110 mmHg; those patients treated with antihypertensive medication had to have a MSDBP of < 110 mmHg. At Visit 2 (Week -4), all patients had to have a MSDBP of ≥ 95 mmHg and < 110 mmHg. At Visit 3 (Week 1, baseline), all patients had to have a MSDBP of ≥ 90 mmHg and < 110 mmHg.

Duration of treatment:

Duration of single-blind treatment (amlodipine 10 mg OD) was 4 weeks. Duration of double-blind treatment (amlodipine 10 mg OD, or valsartan/amlodipine 160/10 mg OD) was 8 weeks. The maximum trial duration was 16 weeks, including the washout phase.

Efficacy:

The primary efficacy variable was change from baseline in MSDBP. Secondary efficacy variables were change from baseline in MSSBP, responder rate (defined as achieving a MSDBP < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline) and control rate (defined as a patient with a MSDBP < 90 mmHg). Other variables were changes from baseline in standing DBP, standing SBP, sitting pulse rate, and standing pulse rate.

This study was included in the Safety Review.

6.1.3.5 Study A2308

Title: A randomized, double-blind, multicenter, active-controlled, parallel-group study to evaluate the safety and efficacy of valsartan/amlodipine compared to lisinopril/hydrochlorothiazide given once daily for 6 weeks in patients with severe hypertension.

Study centers: 15 centers in 3 countries; 4 in Netherlands, 5 in Peru and 6 in Russia.

Dates: October 21, 2004 to April 27, 2005

Objectives:

The primary objective of this trial was to evaluate the overall safety profile of a valsartan/amlodipine treatment regimen compared to a lisinopril/hydrochlorothiazide (HCTZ) treatment regimen in patients with severe hypertension (mean sitting diastolic blood pressure [MSDBP] ≥ 110 mmHg and <120 mmHg).

The secondary objective was to evaluate the blood pressure (BP) lowering effects of a valsartan/amlodipine treatment regimen compared to a lisinopril/HCTZ treatment regimen in patients with severe hypertension. Additional safety data such as laboratory test data and vital signs including orthostatic hypotension was assessed as a secondary objective.

Study design: This was a multicenter, randomized, double-blind, active-controlled, parallel-group trial in adult patients with severe hypertension (MSDBP ≥ 110 mmHg and <120 mmHg). Eligible patients were randomized to valsartan/amlodipine 160/5 mg or lisinopril/HCTZ 10/12.5 mg (1:1 ratio) for a period of 2 weeks. Following this period, patients with a MSDBP ≥ 90 mmHg received higher dose levels. Patients randomized to the valsartan/amlodipine 160/5 mg OD treatment group received valsartan/amlodipine 160/10 mg and patients randomized to the lisinopril/HCTZ 10/12.5 mg OD treatment group received lisinopril/HCTZ 20/12.5 mg for the remainder of the study.

Indication for inclusion: The study population consisted of male and female outpatients at least 18 years of age with severe hypertension (MSDBP ≥ 95 mmHg and <120 mmHg at Visit 2 and MSDBP ≥ 110 mmHg and <120 mmHg at Visit 3).

Duration of treatment: Total study duration was up to 9 weeks (1-week washout, 1 to 2 weeks single-blind run-in; 6 weeks double-blind treatment).

Efficacy: The efficacy assessments consisted of sitting and standing BP and pulse.

This study was included in the Safety Review.

6.1.4.6 Study A2201E1

Title: A 52-week open-label extension to the randomized, double-blind, multicenter, multifactorial, placebo-controlled, parallel group study to evaluate the efficacy and safety of valsartan and amlodipine combined and alone in hypertensive patients.

Study centers: 139 centers in 6 countries (6 in Belgium, 7 in Canada, 6 in France, 30 in Germany, 5 in Mexico, and 85 in the US)

Dates: April 10, 2003 to March 8, 2005

Objectives: The primary objective of this 52-week open label extension was to further evaluate the safety, tolerability and long-term efficacy of once daily administration of the combination of valsartan/amlodipine 80/2.5, 80/5, 160/5, or 160/10 mg, alone or in combination with hydrochlorothiazide (HCTZ) 12.5 mg.

Study design: This was a 52-week, multicenter, open-label extension study to Study A2201. Patients were enrolled directly from the double-blind phase into the open-label extension, with no intervening washout period and with no prior knowledge of treatment they received in the core protocol. Eligible patients were randomized in an open-label fashion to receive either valsartan/amlodipine 80/2.5 mg OD (low dose group) or 80/5 mg OD (high dose group) for a period of four weeks. Subsequently, patients without symptomatic hypotension or significant peripheral edema were force titrated to valsartan/amlodipine 160/5 mg OD (low dose group) or 160/10 mg OD (high dose group), respectively, for the remainder of the trial. Patients whose MSDBP remained ≥ 90 mmHg or whose MSSBP remained ≥ 140 mmHg with no signs of hypovolemia, at any dose following the initial titration period, could have added HCTZ 12.5 mg. Patients who experienced intolerable adverse experiences at any point following up-titration to the higher doses (i.e. valsartan/amlodipine 160/5 or 160/10 mg) could be back titrated to a prior dose combination of valsartan/amlodipine, with or without HCTZ.

Indications for inclusion: Patients with mild to moderate uncomplicated essential diastolic hypertension (grades 1 and 2 WHO classification) who successfully completed Study 2201 with no serious drug related adverse experiences were eligible for entry into this trial.

Duration of treatment: Planned duration of treatment was up to 52 weeks.

Efficacy: Primary efficacy parameter: Changes from baseline (Visit 2) in mean sitting diastolic blood pressure (MSDBP) at trough measured by calibrated standard sphygmomanometer. Secondary efficacy parameters: Changes from baseline (Visit 2) in mean sitting systolic blood pressure (MSSBP) at trough. Other variables to be analyzed were change from baseline in standing diastolic and systolic blood pressures, and sitting and standing pulse.

This study was included in the Safety Review for long-term safety.

6.1.3.7 Study A2307E1

Title: A 54 week open-label extension to the randomized, double-blind, multicenter, multifactorial, placebo-controlled, parallel group study to evaluate the efficacy and safety of valsartan (160 mg and 320 mg) and amlodipine (10 mg) combined and alone in hypertensive patients.

Study centers: 73 centers in 5 countries (8 France, 55 Germany, 2 Norway, 5 Peru, 3 Spain)

Dates: April 16, 2004 to June 8, 2005

Objectives: The primary objective of this 54-week open label extension was to further evaluate the safety, tolerability and long-term efficacy of once daily administration of the combination of valsartan/amlodipine 320/5 mg.

Study design: This was a 54 week open-label extension to the randomized, double-blind, multicenter, multifactorial, placebo-controlled, parallel group core study (A2307). Patients were enrolled directly from the double-blind phase into the open-label extension, with no intervening washout period and with no prior knowledge of treatment they received in the core protocol. Eligible patients began treatment with valsartan/amlodipine 160/2.5 mg OD for a period of 2 weeks. Following the initial 2-week treatment period, all patients were force titrated to valsartan/amlodipine 320/5 mg OD for the remainder of the trial.

Indications for inclusion: Male or female outpatients at least 18 years of age with uncomplicated essential diastolic hypertension who had successfully completed the core study without serious drug related adverse experiences.

Duration of treatment: All patients who enrolled in the extension were guaranteed the opportunity to complete 6 months of treatment with valsartan/amlodipine 320/5 mg. Only the first 150 patients (approximately) who successfully completed Visit 11 of the extension (6 months of treatment with valsartan/amlodipine 320/5 mg) were eligible to continue the extension protocol, and were guaranteed the opportunity to complete the full 12 months of treatment.

Efficacy: Primary: mean sitting diastolic blood pressure (MSDBP). Secondary: mean sitting systolic blood pressure (MSSBP), standing diastolic and systolic blood pressures, and sitting and standing pulse.

This study was included in the Safety Review for long-term safety.

6.1.4 Efficacy Findings

The two studies reviewed for efficacy were A2201 and A2307 as they were multicenter, double-blind, randomized, multifactorial, placebo-controlled, parallel group trials.

6.1.4.1 Study A2201

Primary efficacy results:

The change from the baseline in mean sitting diastolic blood pressure (MSDBP) at the endpoint was the primary efficacy variable. Global assessment of MSDBP reduction at the endpoint showed that both monotherapy treatments contributed to the overall effect in blood pressure reduction of the combination treatment, $p < 0.0001$ for both valsartan and amlodipine.

All treatments for both the ITT population and per protocol population produced statistically significant reductions from baseline in MSDBP. The greatest reductions were achieved with valsartan/amlodipine 320/5 mg, and the smallest with the placebo.

Between-treatment groups comparisons of MSDBP:

Combination treatments for both the ITT and per protocol populations were statistically significantly superior to their monotherapy components and to placebo in MSDBP reduction at the endpoint with the exceptions of [val/aml 320/2.5 mg vs. val 320 mg], [val/aml 40/2.5 mg vs. aml 40 mg] and [val/aml 40/2.5 mg vs. aml 2.5 mg]. This is shown for the ITT population in the following table.

Table 20 LS Mean Reduction of MSDBP at Endpoint

LS Mean Reduction of MSDBP (mmHg) at Endpoint		Valsartan (mg)				
		0	40	80	160	320
Amlodipine (mg)	0	6.75	10.13 ^p	9.73 ^p	11.05 ^p	13.40 ^p
	2.5	9.34 ^p	10.85 ^p	13.35 ^{pva}	13.28 ^{pva}	14.17 ^{pa}
	5	11.46 ^p	14.64 ^{pva}	14.52 ^{pva}	14.20 ^{pva}	15.94 ^{pva}

p = statistically significant vs. placebo ($p < 0.05$)
 v = statistically significant vs. valsartan ($p < 0.05$)
 a = statistically significant vs. amlodipine ($p < 0.05$)
 Page 50, Study A2201

The maximum reduction in diastolic blood pressure with the combination doses (after accounting for the placebo response) was generally achieved by 2 weeks.

Mean sitting diastolic blood pressure subgroup results:

Summary statistics for MSDBP by age, sex, and race indicated that the combinations of valsartan/amlodipine generally were effective in comparison with placebo regardless of age, gender, or race. The placebo response in black patients was small relative to Caucasian patients. No definitive conclusions can be made regarding oriental patients since the number of patients was very small, ranging from 0-4 patients per treatment group.

Mean sitting diastolic blood pressure at Weeks 4 and 8:

All treatments produced statistically significant reductions from baseline in MSDBP at Weeks 4 and 8. At Week 4, all combination treatments were statistically superior to their monotherapy components and to placebo except for [val/aml 320/2.5 vs. val 320 mg], [val/aml 40/2.5 vs. val 40 mg] and [aml 2.5 mg vs. placebo]. At Week 8, all combination treatments were statistically superior to their

monotherapy components and placebo except for [val/aml 320/2.5 vs. val 320], [val/aml 40/2.5 vs. val 40 mg], [val/aml 40/2.5 vs. aml 2.5 mg] and [aml 2.5 mg vs. placebo].

Secondary efficacy results:

The secondary efficacy parameters were sitting systolic blood pressure, standing diastolic and systolic blood pressures, and sitting and standing pulse.

Mean sitting systolic blood pressure (MSSBP):

Global assessment of MSSBP reduction at endpoint showed both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment, $p < 0.0001$ for both valsartan and amlodipine.

All treatments produced statistically significant reductions from baseline in MSSBP at endpoint. The greatest reductions were achieved with valsartan/amlodipine 320/5 mg, and the smallest with placebo.

Between-treatment groups analysis of MSSBP:

The between-treatment analysis showed the combination treatments to be statistically significantly superior to their monotherapy components and placebo in MSSBP reduction at endpoint with the only exceptions being [val/aml 320/2.5 mg vs. val 320 mg] and [val/aml 160/2.5 mg vs. val 160 mg] as shown in the following table.

Table 21 LS Mean Reduction of MSSBP at Endpoint

LS Mean Reduction of MSSBP (mmHg) at Endpoint	Valsartan (mg)					
	0	40	80	160	320	
Amlodipine (mg)	0	6.74	11.76 ^p	12.94 ^p	15.06 ^p	15.68 ^p
	2.5	12.41 ^p	15.54 ^{pva}	17.04 ^{pva}	16.74 ^{pa}	18.34 ^{pa}
	5	15.07 ^p	19.62 ^{pva}	20.75 ^{pva}	19.49 ^{pva}	22.74 ^{pva}

p = statistically significant vs. placebo ($p < 0.05$)
 v = statistically significant vs. valsartan ($p < 0.05$)
 a = statistically significant vs. amlodipine ($p < 0.05$)
 Page 58, Study A2201

Subgroup results for mean sitting systolic blood pressure:

Summary statistics for MSSBP by age, sex, and race indicate that the combinations of valsartan/amlodipine generally were effective in comparison with placebo regardless of age, sex, or race. The placebo response in black patients was small relative to Caucasian patients. No definitive conclusions can be made regarding oriental patients since the number of patients was very small, ranging from 0-4 patients per treatment group.

MSSBP at Weeks 4 and 8:

All treatments produced statistically significant reductions from baseline in MSSBP at Weeks 4 and 8. At Week 4, all combination treatments were statistically superior to their individual components except for [val/aml 80/2.5 mg vs. val 80 mg], [val/aml 40/2.5 vs. val 40 mg] and [val/aml 40/2.5 vs. aml 2.5 mg]. At Week 8, all combination treatments were statistically superior to their individual components except for [val/aml 160.2.5 vs. val 160 mg] and [val/aml 40/2.5 vs. aml 2.5 mg].

Responder rates:

A successful response was defined as a mean sitting diastolic blood pressure < 90 mmHg or a ≥ 10 mmHg decrease compared to the baseline. The highest responder rates were achieved with valsartan/amlodipine 320/5 mg (91.3%), and the lowest with placebo (40.9%) which is shown in the following table.

Table 22 Proportion of successful responders at endpoint

BP Reduction Success Rate (%) at Endpoint		Valsartan (mg)				
		0	40	80	160	320
Amlodipine (mg)	0	40.9	59.1 ^p	57.7 ^p	67.7 ^p	73.4 ^p
	2.5	60.3 ^p	57.0 ^p	77.5 ^{pva}	74.4 ^{pv}	79.7 ^{pv}
	5	71.9 ^p	83.7 ^{pva}	84.9 ^{pva}	81.1 ^{pv}	91.3 ^{pva}

p = statistically significant vs. placebo (p < 0.05)
 v = statistically significant vs. valsartan (p < 0.05)
 a = statistically significant vs. amlodipine (p < 0.05)
 Page 61, Study A2201

In the following table similar trends were observed for control rate (defined as MSDBP < 90 mmHg). The highest control rates were achieved with valsartan/amlodipine 320/5 mg (82.5%), and the lowest with placebo (33.9%).

Table 23 Proportion of controlled patients at endpoint

BP Reduction Control Rate (%) at Endpoint		Valsartan (mg)				
		0	40	80	160	320
Amlodipine (mg)	0	33.9	52.0 ^p	48.8 ^p	58.3 ^p	67.2 ^p
	2.5	50.0 ^p	46.9 ^p	67.4 ^{pva}	72.8 ^{pva}	68.0 ^{pv}
	5	64.8 ^p	70.7 ^{pv}	73.0 ^{pv}	70.1 ^{pv}	82.5 ^{pva}

p = statistically significant vs. placebo (p < 0.05)
 v = statistically significant vs. valsartan (p < 0.05)
 a = statistically significant vs. amlodipine (p < 0.05)
 Page 61, Study A2201

Combination treatments were statistically significantly superior to their monotherapy components and placebo in responder rates at endpoint with the only exceptions being [val/aml 320/2.5 mg vs. val 320 mg], [val/aml 160/5 mg vs. aml 5 mg], [val/aml 160/2.5 mg vs. val 160 mg], [val/aml 40/2.5 mg vs. val 40 mg] and [val/aml 40/2.5 mg vs. aml 2.5 mg].

Standing diastolic BP:

All treatments produced statistically significant reductions from baseline in standing diastolic blood pressure at the endpoint. The greatest reductions were achieved with valsartan/amlodipine 320/5 mg (14.2 mmHg) and the smallest with placebo (4.0 mmHg). All combination treatments were statistically superior to their monotherapy components and placebo except for [val/aml 320/2.5 vs. val 320 mg], [val/aml 160/2.5 vs. val 160 mg] and [val/aml 40/2.5 vs. val 40 mg].

Standing systolic BP:

All treatments produced statistically significant reductions from baseline in standing systolic blood pressure at the endpoint. The greatest reductions were achieved with valsartan/amlodipine 320/5 mg (21.4 mmHg) and the smallest with placebo (6.1 mmHg). All combination treatments were

statistically superior to their monotherapy components and placebo except for [val/aml 320/2.5 vs. val 320 mg] and [val/aml 160/2.5 vs. val 160 mg].

Pulse:

Only small changes from baseline were observed for sitting and standing pulses. For sitting pulse, the mean changes from baseline at endpoint ranged from -1.66 to +1.37 bpm in the active treatment groups, vs. +1.48 bpm for placebo. For standing pulse, the mean changes from baseline at endpoint ranged from -1.89 to +1.42 bpm in the active treatment groups, vs. +1.57 bpm for placebo. The few statistically significant differences between treatments were not clinically relevant.

6.1.4.2 Study A2307

Efficacy results:

The primary efficacy variable was the change from baseline in mean sitting diastolic blood pressure (MSDBP) at endpoint. Global assessment of MSDBP reduction at endpoint showed both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment $p < 0.0001$ for both valsartan and amlodipine.

Within-treatment comparisons of MSDBP:

All treatments produced statistically significant reductions from baseline in MSDBP in the ITT population. The greatest reductions were achieved with valsartan/amlodipine 320/10 mg and the smallest with placebo. Similar results were observed in the per protocol population

In the ITT population, both combination treatments were statistically significantly superior to their monotherapy components and placebo in MSDBP reduction at endpoint which is in the following tables. Similar results were observed in the per protocol population

Table 24 LS Mean Reduction of MSDBP (mmHg) at Endpoint

LS Mean Reduction of MSDBP (mmHg) at Endpoint		Valsartan (mg)		
		0	160	320
Amlodipine (mg)	0	8.76	13.31 ^p	13.29 ^p
	10	15.62 ^p	17.62 ^{pv}	18.82 ^{pv}

p = statistically significant vs. placebo (p < 0.05)

v = statistically significant vs. valsartan (p < 0.05)

a = statistically significant vs. amlodipine (p < 0.05)

Page 45, Study A2307

The maximum reduction in diastolic blood pressure (after accounting for the placebo response) was achieved after two weeks with the valsartan/amlodipine 160/10 mg dose and after four weeks with the valsartan/amlodipine 320/10 mg dose because patients in this treatment group had therapy initiated with valsartan/amlodipine 160/5 mg for the first week and then were titrated up to the 320/10 mg dose.

Subgroup results:

No rigorous statistical analysis was performed; summary statistics for MSDBP by age, sex, and race indicate that the combinations of valsartan/amlodipine generally were effective in comparison with placebo regardless of age, gender, or race. No definitive conclusions can be made regarding Black patients since the number of patients was very small, ranging from 0-2 patients per treatment group.

All treatments produced statistically significant reductions from baseline in MSDBP at Weeks 4 and 8. Both combination treatments were statistically superior to their monotherapy components and placebo at both timepoints.

Secondary efficacy results:

The secondary efficacy parameters were sitting systolic blood pressure, standing diastolic and systolic blood pressures, and sitting and standing pulse.

Global assessment of Mean Sitting Systolic Blood Pressure (MSSBP) reduction at endpoint showed both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment $p < 0.0001$ for both valsartan and amlodipine. All treatments produced statistically significant reductions from baseline in MSSBP at endpoint. The greatest reductions were achieved with valsartan/amlodipine 320/10 mg, and the smallest with placebo.

The between-treatment analysis showed the combination treatments to be statistically significantly superior to their monotherapy components and placebo in MSSBP reduction at endpoint. This is shown in the following table.

Table 25 LS Mean Reduction of MSSBP at Endpoint

LS Mean Reduction of MSSBP (mmHg) at Endpoint		Valsartan (mg)		
		0	160	320
Amlodipine (mg)	0	12.88	20.19 ^p	19.84 ^p
	10	24.11 ^p	27.81 ^{pva}	28.36 ^{pva}

p = statistically significant vs. placebo ($p < 0.05$)
 v = statistically significant vs. valsartan ($p < 0.05$)
 a = statistically significant vs. amlodipine ($p < 0.05$)
 Page 49 Study A2307

Subgroup results:

Summary-statistics for MSSBP by age, sex, and race indicate that the combinations of valsartan/amlodipine generally were effective in comparison with placebo regardless of age, sex, or race. No definitive conclusions can be made regarding Black patients since the number of patients was very small, ranging from 0-2 patients per treatment group.

All treatments produced statistically significant reductions from baseline in MSSBP at Weeks 4 and 8. Both combination treatments were statistically superior to their individual components and placebo at both timepoints.

Responder and control rates:

A successful response was defined as a mean sitting diastolic blood pressure < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline. The highest responder rate was achieved with

valsartan/amlodipine 160/10 mg (88.5%), and the lowest with placebo (49.3%) as seen in the following table.

Table 26 Proportion of successful responders at endpoint (ITT population)

BP Reduction Responder Rate (%) at Endpoint		Valsartan (mg)		
		0	160	320
Amlodipine (mg)	0	49.3	74.9 ^p	72.0 ^p
	10	86.9 ^p	88.5 ^{pv}	87.5 ^{pv}

p = statistically significant vs. placebo (p <0.05)
 v = statistically significant vs. valsartan (p <0.05)
 a = statistically significant vs. amlodipine (p <0.05)
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Similar trends were observed for control rate (defined as MSDBP < 90 mmHg). Control rates of 81.8-84.1% were observed with combination therapy compared with a rate of 63.8-70.5% with valsartan monotherapy, 80% with amlodipine 10 mg, and 42.6% with placebo shown in the following table.

Table 27 Proportion of controlled patients at endpoint (ITT population)

BP Reduction Control Rate (%) at Endpoint		Valsartan (mg)		
		0	160	320
Amlodipine (mg)	0	42.6	70.5 ^p	63.8 ^p
	10	80.1 ^p	81.8 ^{pv}	84.1 ^{pv}

p = statistically significant vs. placebo (p <0.05)
 v = statistically significant vs. valsartan (p <0.05)
 a = statistically significant vs. amlodipine (p <0.05)
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Both combination treatments were statistically significantly superior to their respective valsartan monotherapy component and placebo, but not the amlodipine component, in responder and control rates at endpoint as seen in the following table.

Table 28 Between-treatment comparisons of responder and control rates at endpoint

Comparison	Responder rate p-value	Control rate p-value
[Val/Aml 320/10 mg] vs [Val 320 mg]	0.0001*	<0.0001*
[Val/Aml 320/10 mg] vs [Aml 10 mg]	0.8459	0.2793
[Val/Aml 320/10 mg] vs Placebo	<0.0001*	<0.0001*
[Val/Aml 160/10 mg] vs [Val 160 mg]	0.0004*	0.0074*
[Val/Aml 160/10 mg] vs [Aml 10 mg]	0.6112	0.6565
[Val/Aml 160/10 mg] vs Placebo	<0.0001*	<0.0001*
[Val 320 mg] vs Placebo	<0.0001*	<0.0001*
[Val 160 mg] vs Placebo	<0.0001*	<0.0001*
[Aml 10 mg] vs Placebo	<0.0001*	<0.0001*

A successful response was defined as a mean sitting diastolic blood pressure <90 mmHg or a ≥ 10 mmHg decrease compared to baseline. Control was defined as a mean sitting diastolic blood pressure < 90 mmHg

* indicates statistical significance at 0.05 level.

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Standing diastolic BP:

All treatments produced statistically significant reductions from baseline in standing diastolic blood pressure at endpoint. The greatest reductions were achieved with valsartan/amlodipine 320/10 mg (16.25 mmHg) and the smallest with placebo (7.28 mmHg). Both combination treatments were statistically superior to their monotherapy components and placebo except for [val/aml 160/10 mg vs. aml 10 mg].

Standing systolic BP:

All treatments produced statistically significant reductions from baseline in standing systolic blood pressure at endpoint. The greatest reductions were achieved with valsartan/amlodipine 320/10 mg (27.04 mmHg) and the smallest with placebo (9.96 mmHg). Both combination treatments were statistically superior to their monotherapy components and placebo.

Pulse:

Only small changes from baseline were observed for sitting and standing pulse. For sitting pulse, the mean changes from baseline at endpoint ranged from -1.07 to +0.44 bpm in the active treatment groups, vs. -0.60 bpm for placebo. For standing pulse, the mean changes from baseline at endpoint ranged from -0.98 to +0.84 bpm in the active treatment groups, vs. +0.11 bpm for placebo. There were no statistically significant differences between treatments.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

- The combination of valsartan/amlodipine generally provided additive diastolic and systolic blood pressure lowering effects compared to valsartan and amlodipine administered as monotherapy in patients with essential hypertension.
- The combination of valsartan/amlodipine generally produced clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy in the studied dose range.
- Both individual monotherapy components contributed to the antihypertensive effect of the combination of valsartan/amlodipine in the overall population.
- The combination of valsartan/amlodipine produced a successful blood pressure response at endpoint (defined as a mean sitting diastolic blood pressure <90 mmHg or a ≥ 10 mmHg decrease compared to baseline) in approximately 80-90% of patients and achieved blood pressure control (mean sitting diastolic blood pressure <90 mmHg) in approximately 70-80% of patients at the higher doses.
- The combination of valsartan/amlodipine was effective regardless of gender, age and race and both individual monotherapy components contributed to the antihypertensive effect of the

combination in all subgroups including males and females, elderly and younger patients, and both black and white patients.

- A positive dose response relationship was demonstrated within the studied dose range of the combination of valsartan/amlodipine.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The Sponsor's submission is divided into three categories of studies: placebo-controlled studies which were reviewed for efficacy, three active-controlled studies, and two long-term studies. The Safety Review pertains to five studies: the two placebo-controlled studies and the three active-controlled studies. Also, safety in the two long-term studies is reviewed. These long-term studies, A2201E1 and A2307E1, were extensions of the two placebo-controlled studies reviewed for efficacy. The extension studies were open label and included 1649 patients.

A summary of the overall duration of exposure of the five studies is shown in the following table. This dataset included 5175 patients, 2613 of whom received the combination valsartan/amlodipine treatment.

Table 29 Duration of exposure to study drug after randomization

Duration of exposure (weeks)	Valsartan/ amlodipine	Valsartan	Amlodipine	Lisinopril/ HCTZ	Placebo	Total
Total population	2613	1229	930	66	337	5175
Exposure n (%)						
<2 Weeks	48 (1.8)	30 (2.4)	12 (1.3)	1 (1.5)	13 (3.9)	104 (2.0)
2 - <4 Weeks	29 (1.1)	20 (1.6)	17 (1.8)	0 (0.0)	18 (5.3)	84 (1.6)
4 - <8 Weeks	653 (25.0)	270 (22.0)	201 (21.6)	65 (98.5)	71 (21.1)	1260 (24.3)
≥ 8 Weeks	1883 (72.1)	909 (74.0)	700 (75.3)	0 (0.0)	235 (69.7)	3727 (72.0)
Exposure (Weeks)						
n	2613	1229	930	66	337	5175
Mean (SD)	7.8 (1.35)	7.8 (1.47)	7.9 (1.39)	6.0 (0.63)	7.5 (2.03)	7.8 (1.45)
Median	8.0	8.0	8.0	6.0	8.0	8.0
Range	0.1 - 17.3	0.1 - 18.9	0.4 - 18.6	1.3 - 6.7	0.1 - 17.0	0.1 - 18.9

Source: page 34, Overview of Clinical Safety

The number and percentage of patients who received each dose level within the valsartan/amlodipine treatment groups for the five studies are shown in the following table.

Table 30 Patients who received valsartan/amlodipine combinations

	Valsartan/amlodipine (mg)										Total N
	320/10 n (%)	320/5 n (%)	320/2.5 n (%)	160/10 n (%)	160/5 n (%)	160/2.5 n (%)	80/5 n (%)	80/2.5 n (%)	40/5 n (%)	40/2.5 n (%)	
Active or placebo-controlled	210 (8.0)	127 (4.9)	129 (4.9)	999 (38.2)	512 (19.6)	126 (4.8)	128 (4.9)	129 (4.9)	124 (4.7)	129 (4.9)	2613
Placebo-controlled	210 (14.6)	127 (8.8)	129 (9.0)	209 (14.5)	126 (8.8)	126 (8.8)	128 (8.9)	129 (9.0)	124 (8.6)	129 (9.0)	1437

Page 34, Overview of Clinical Safety

An overview of the five studies is shown in the following table. Greater than 90% of patients completed the studies, with the highest rate of discontinuations seen in the placebo group, primarily due to an unsatisfactory therapeutic effect. The rate of discontinuations due to AEs was similar in the valsartan/amlodipine combination group, the amlodipine monotherapy group and the placebo group. In the valsartan monotherapy group, the rate was somewhat lower. Comparison across the dose groups did not suggest a greater discontinuation rate in patients who received higher doses of valsartan/amlodipine, valsartan or amlodipine.

Table 31 Patient participation and withdrawals

	Valsartan/ amlodipine	Valsartan	Amlodipine	Lisinopril/ HCTZ	Placebo	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total population	2613	1229	930	66	337	5175
Completed	2456 (94.0)	1144 (93.1)	865 (93.0)	65 (98.5)	295 (87.5)	4825 (93.2)
Discontinued	157 (6.0)	85 (6.9)	65 (7.0)	1 (1.5)	42 (12.5)	350 (6.8)
Main reason for discontinuation						
Abnormal laboratory value(s)	4 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)
Abnormal test procedure result(s)	2 (0.1)	3 (0.2)	0 (0.0)	1 (1.5)	2 (0.6)	8 (0.2)
Administrative problems	13 (0.5)	4 (0.3)	3 (0.3)	0 (0.0)	1 (0.3)	21 (0.4)
AE(s)	64 (2.4)	10 (0.8)	30 (3.2)	0 (0.0)	8 (2.4)	112 (2.2)
SAE(s)	10 (0.4)	1 (0.1)	2 (0.2)	0 (0.0)	2 (0.6)	15 (0.3)
Death	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Lost to follow-up	14 (0.5)	5 (0.4)	6 (0.6)	0 (0.0)	3 (0.9)	28 (0.5)
Protocol violation	11 (0.4)	5 (0.4)	2 (0.2)	0 (0.0)	1 (0.3)	19 (0.4)
Subject's condition no longer requires study drug	3 (0.1)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.1)
Subject withdrew consent	28 (1.1)	22 (1.8)	15 (1.6)	0 (0.0)	5 (1.5)	70 (1.4)
Unsatisfactory therapeutic effect	17 (0.7)	31 (2.5)	9 (1.0)	0 (0.0)	22 (6.5)	79 (1.5)

Page 22, Summary of Clinical Safety

In the two long term studies a total of 1136 patients were exposed to valsartan/amlodipine for approximately 6 months and 425 patients were exposed for one year or more. In Study A2201E1

approximately 90% of patients had at least 270 days of exposure. Similar exposure was achieved in both dose groups at each time interval (6 months, 9 months and one year).

Table 32 Long-term exposure to study drug by treatment duration in Study A2201E1

	High dose valsartan/amlodipine 80/5 mg – 160/10 mg ± HCTZ n (%)	Low dose valsartan/amlodipine 80/2.5 mg – 160/5 mg ± HCTZ n (%)	Total n (%)
Total population	627	619	1246
Duration			
180 days or longer	560 (89.3)	576 (93.1)	1136 (91.2)
270 days or longer	544 (86.8)	561 (90.6)	1105 (88.7)
365 days or longer	219 (34.9)	206 (33.3)	425 (34.1)

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In Study A2307E1 mean exposure to valsartan/amlodipine 320/5 mg was 245.6 days. Of the 396 patients exposed to valsartan/amlodipine 320/5 mg, 310 patients were exposed to valsartan/amlodipine 320/5 mg for 180 days (approximately 6 months) or longer, and 115 patients were exposed to valsartan/amlodipine 320/5 mg for 362 days (approximately 12 months) or longer.

Table 33 Long-term duration of exposure to study drug in Study A2307E1

	Valsartan/amlodipine 320/5 mg
Total population	396*
Duration of exposure	
Mean (SD)	245.6 (95.78)
Median	183.0
Range	8.0 – 378.0
Duration (days)	
< 25 Days	2 (0.5%)
25 - < 53 Days	5 (1.3%)
53 - < 180 Days	79 (19.9%)
180 - < 271 Days	154 (38.9%)
271 - < 362 Days	41 (10.4%)
≥ 362 Days	115 (29.0%)

*All patients who discontinued prior to being titrated (Visit 8) to valsartan/amlodipine 320/5 mg were excluded
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7.1.1 Deaths

Two deaths occurred during the on-study treatment or follow-up periods of the five studies and the two long-term extension studies included in this submission. A summary of the two deaths is described below. Both deaths occurred in patients treated with valsartan/amlodipine, one in the 160/10 mg group and the second in the 160/5 mg group. Neither death was suspected to be related to study treatment.

In Study A2306, an active-control study, a 55 year old Caucasian female who was receiving valsartan/amlodipine 160/10 mg died on day 54 of study treatment due to a myocardial infarction. This event was not suspected by the investigator to be related to the study medication.

In Study A2201E1, the long-term extension of the placebo-controlled study, a 70 year old Caucasian female who received valsartan/amlodipine 160/5 mg for 107 days, died 42 days after discontinuing study treatment following diagnosis and surgical treatment for pancreatic carcinoma with hepatic metastases. This event was not suspected by the investigator to be related to the study medication.

Two deaths also occurred in the single-blind placebo run-in phases of studies included in the submission. In Study A2201, a 62 year old Caucasian male who was enrolled into the single-blind placebo phase but was discontinued for failing to meet the inclusion criteria, died 10 days after discontinuation from the study as a result of a myocardial infarction. In Study A2307, a 66 year old Caucasian male died following an acute cardiac arrest on day 15 of placebo treatment. In addition, one patient died during the washout phase of Study A2308 and was therefore not randomized. None of these patients received active treatment.

7.1.2 Other Serious Adverse Events

Thirty-six (0.7%) patients of whom 32 were on active treatment in the five studies experienced a serious adverse event (SAE). The most common SAE were cardiac disorders, musculoskeletal and connective tissue disorders, and respiratory, thoracic and mediastinal disorders. The overall incidence of SAEs in the total valsartan/amlodipine group was slightly lower than that for placebo. No SAEs were reported for patients who received lisinopril/HCTZ treatment.

In the total valsartan/amlodipine group, four patients experienced a cardiac disorder for a SAE. Of these events, there were three patients who experienced a myocardial infarction, two in the valsartan/amlodipine 160/5 mg group and one in the valsartan/amlodipine 40/2.5 mg group. A fourth cardiac disorder SAE was coronary artery disease, which occurred in one of the patients in the valsartan/amlodipine 160/5 mg group, who experienced a myocardial infarction. In the amlodipine monotherapy group, two patients in the 10 mg dose group experienced SAEs which were in the cardiac disorders category. The two SAEs were myocardial infarction and pericarditis. There were no cardiac disorders SAEs reported for valsartan monotherapy.

In the total valsartan/amlodipine group, there were three SAEs in the musculoskeletal and connective tissue disorders, all of which occurred in patients who received the 160/10 mg dose. The SAEs were cervical spinal stenosis, spinal osteoarthritis and back pain. For valsartan monotherapy, three patients also experienced SAEs in this category. These SAEs were arthralgia (320 mg), osteoarthritis (160 mg) and monoarthritis (40 mg). No similar events were reported in the amlodipine monotherapy or placebo treatment groups.

For the respiratory, thoracic and mediastinal disorders, three patients who were treated with valsartan/amlodipine experienced SAEs. Two of these patients had pulmonary embolism, one in the 320/10 mg group and one in the 320/2.5 mg group. One patient in the 160/10 mg group had SAEs of nasal septum deviation and a vocal cord polyp.

Three patients treated with valsartan monotherapy experienced vascular disorders SAEs. Two of these patients had hypertensive crisis, one in the 160 mg group and one in the 80 mg group. The third patient (40 mg group) had a hematoma.

One SAE of prostate cancer was reported in the valsartan/amlodipine 320/10 mg group and one case of meningioma was reported in the valsartan/amlodipine 160/10 mg group. Neither event occurred in the valsartan or amlodipine monotherapy groups.

Overall, no discernible pattern of events was observed across treatment groups and none of the events was unexpected in the study population. An over-view of serious disorders is shown on the following table.

Table 34 Serious events in placebo-control and active controlled studies

	Valsartan/ amlodipine	Valsartan	Amlodipine	Lisinopril/ HCTZ	Placebo	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total population	2613	1229	930	66	337	5175
Any primary system organ class	18 (0.7)	10 (0.8)	4 (0.4)	0 (0.0)	4 (1.2)	36 (0.7)
Cardiac disorders	4 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.3)	7 (0.1)
Musculoskeletal & connective tissue disorders	3 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.1)
Respiratory, thoracic & mediastinal disorders	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	4 (0.1)
Gastrointestinal disorders	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Infections & infestations	2 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	5 (0.1)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.1)
General disorders & administration site conditions	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Hepatobiliary disorders	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Metabolism & nutrition disorders	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Renal & urinary disorders	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Vascular disorders	1 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Immune system disorders	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Injury, poisoning & procedural complications	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.6)	3 (0.1)

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Serious adverse events in the two long-term populations:
Study A2201E1

In this one year long-term extension study, a similar proportion of patients in the high and low dose groups experienced SAEs. The most common disorders were gastrointestinal disorders and benign, malignant & unspecified neoplasms (including cysts & polyps). For gastrointestinal disorders, SAEs were reported for the same number of patients in both the high and low dose groups, and there was no clear pattern of events indicative of a treatment-emergent or dose-related effect.

Benign, malignant & unspecified neoplasms also occurred in eight patients, three in the high dose group and five in the low dose group. In the high dose group, there were laryngeal cancer, uterine leiomyoma and brain neoplasm. Those in the low dose group included bladder neoplasm, colon cancer, pancreatic carcinoma and breast carcinoma (in two patients).

A total of six patients, all in the high dose group, experienced musculoskeletal and connective tissue disorders SAEs. One of these events was muscle hemorrhage. The other events were spinal stenosis, worsening of osteoarthritis (2 patients), herniated cervical disk and rheumatoid arthritis.

A total of 4 patients in the high dose group experienced general disorders and administration site conditions SAEs. Of these patients, two of these experienced chest pain, one experience pyrexia and the fourth had a pelvic mass.

Study A2307E1

In this one year extension study, the incidence of SAEs (4.2%) was similar to that seen in Study A2201E1 above. There was no particular pattern or clustering of events according either to system organ class or preferred term. The SAEs according to preferred term were epigastric herniation, hernia umbilicalis, urinary incontinence, kidney stone, urosepsis due to prostate hypertrophy, acute pancreatitis, prostatic cancer, depression, worsening of headache, cerebral apoplexy, fracture of vertebral body and serious back pain, fracture of the left arm, left coxarthrosis, worsening of arterial occlusive disease, hypertensive crisis, angina pectoris and allergic skin reaction. There were no cases of edema which were considered serious.

7.1.3 Dropouts and Other Significant Adverse Events

Only 15 (0.3%) patients of whom 13 were on active treatment in the double-blind, active- or placebo-controlled population discontinued due to an SAE. The small number of patients who discontinued due to SAEs precludes making any definitive comparisons between treatment groups. The 13 SAEs which led to discontinuation of 10 patients in the valsartan/amlodipine group were myocardial infarction (3 patients), coronary artery disease, abdominal pain, bacteremia, pneumonia, gout, back pain, prostate cancer, pulmonary embolism (2 patients) and hypertensive crisis. In the valsartan monotherapy group, the one SAE discontinuation was due to hypertensive crisis and in the amlodipine monotherapy group, the two SAE discontinuations were due to myocardial infarction and diverticulitis.

7.1.3.1 Overall profile of dropouts

The overall incidence of AE discontinuations was low and similar in the valsartan/amlodipine, amlodipine monotherapy and placebo groups. The rate in the valsartan monotherapy group was slightly lower. The substantially smaller number of patients in the lisinopril/HCTZ group does not allow meaningful comparisons to be made with the other treatment groups.

The most common AEs which led to discontinuation in both the valsartan/amlodipine and amlodipine monotherapy groups were primarily edema-related, in particular peripheral edema.

The incidence of discontinuations due to peripheral edema was lower in patients treated with valsartan/amlodipine (0.9%) than in those treated with amlodipine monotherapy (1.8%). The low incidence of AEs which led to discontinuation showed no clear relationship to dose.

7.1.3.2 Adverse events associated with dropouts

The adverse events associated with the dropouts are shown in the following table.

Table 35 Adverse events assoc. with discontinuation

	Valsartan/ amlodipine	Valsartan	Amlodipine	Lisinopril/ HCTZ	Placebo	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total population	2613	1229	930	66	337	5175
Any primary system organ class	10 (0.4)	1 (0.1)	2 (0.2)	0 (0.0)	2 (0.6)	15 (0.3)
Cardiac disorders	3 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)	5 (0.1)
Respiratory, thoracic & mediastinal disorders	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.1)
Gastrointestinal disorders	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Infections & infestations	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.0)
Metabolism & nutrition disorders	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Musculoskeletal & connective tissue disorders	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Vascular disorders	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.0)

Source: Page 192 Summary of Clinical Safety

SAE discontinuations in the two long-term populations:

Study A2201E1

In total, 8 (0.6%) patients discontinued due to SAEs. Of these, 7 were in the high dose group and included possible anteroseptal myocardial infarction, septic shock, pancreatic carcinoma with hepatic metastases, hypertensive crisis and melena, suspicion of myocardial infarction, acute myocardial infarction and pelvic mass. The event in the low dose group was gastrointestinal bleeding due to diverticulitis.

Study A2307E1

A total of 4 patients (1.0%) were discontinued due to SAEs which included depression, allergic dermatitis, cerebrovascular accident, and hypertensive crisis.

7.1.4 Other Search Strategies

N/A

7.1.5 Common Adverse Events

7.1.5.1 Incidence of common adverse events

For the active- and placebo-controlled safety population, the most frequently affected system organ class (SOCs) in the total valsartan/amlodipine group was infections & infestations, general disorders and administration site conditions, nervous system disorders and gastrointestinal disorders.

Comparison of the valsartan/amlodipine group with the respective monotherapy and placebo group, showed that the incidence and pattern of events were generally similar in each of the active treatment groups and placebo. The most notable difference between treatment groups was the higher incidence of events in the general disorders and administration site conditions SOC for amlodipine, primarily resulting from edema-related events.

7.1.5.2 Common adverse event table

Table 36 Adverse events regardless of relationship to treatment

	Valsartan/ amlodipine n (%)	Valsartan n (%)	Amlodipine n (%)	Lisinopril/ HCTZ n (%)	Placebo n (%)	Total n (%)
Total population	2613	1229	930	66	337	5175
Patients with ≥ 1 AE	970 (37.1)	445 (36.2)	319 (34.3)	21 (31.8)	129 (38.3)	1884 (36.4)
System organ class						
Infections & infestations	305 (11.7)	132 (10.7)	85 (9.1)	8 (12.1)	38 (11.3)	568 (11.0)
General disorders & administration site conditions	225 (8.6)	59 (4.8)	117 (12.6)	1 (1.5)	23 (6.8)	425 (8.2)
Nervous system disorders	190 (7.3)	109 (8.9)	65 (7.0)	4 (6.1)	35 (10.4)	403 (7.8)
Gastrointestinal disorders	158 (6.0)	88 (7.2)	48 (5.2)	7 (10.6)	20 (5.9)	321 (6.2)
Musculoskeletal & connective tissue disorders	142 (5.4)	80 (6.5)	34 (3.7)	2 (3.0)	18 (5.3)	276 (5.3)
Respiratory, thoracic & mediastinal disorders	74 (2.8)	42 (3.4)	15 (1.6)	2 (3.0)	9 (2.7)	142 (2.7)
Skin & subcutaneous tissue disorders	52 (2.0)	21 (1.7)	14 (1.5)	2 (3.0)	11 (3.3)	100 (1.9)
Psychiatric disorders	48 (1.8)	18 (1.5)	13 (1.4)	1 (1.5)	10 (3.0)	90 (1.7)
Vascular disorders	41 (1.6)	13 (1.1)	12 (1.3)	0 (0.0)	8 (2.4)	74 (1.4)
Cardiac disorders	40 (1.5)	16 (1.3)	13 (1.4)	0 (0.0)	3 (0.9)	72 (1.4)
Injury, poisoning & procedural complications	40 (1.5)	18 (1.5)	10 (1.1)	0 (0.0)	6 (1.8)	74 (1.4)
Investigations	36 (1.4)	14 (1.1)	10 (1.1)	1 (1.5)	5 (1.5)	66 (1.3)
Ear & labyrinth disorders	25 (1.0)	24 (2.0)	5 (0.5)	0 (0.0)	3 (0.9)	57 (1.1)
Metabolism & nutrition disorders	24 (0.9)	13 (1.1)	16 (1.7)	0 (0.0)	1 (0.3)	54 (1.0)
Renal & urinary disorders	22 (0.8)	12 (1.0)	11 (1.2)	0 (0.0)	6 (1.8)	51 (1.0)
Eye disorders	18 (0.7)	13 (1.1)	11 (1.2)	1 (1.5)	4 (1.2)	47 (0.9)
Immune system disorders	13 (0.5)	5 (0.4)	9 (1.0)	0 (0.0)	1 (0.3)	28 (0.5)
Reproductive system & breast disorders	12 (0.5)	7 (0.6)	5 (0.5)	0 (0.0)	3 (0.9)	27 (0.5)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	6 (0.2)	3 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	10 (0.2)
Blood & lymphatic system disorders	5 (0.2)	2 (0.2)	0 (0.0)	1 (1.5)	2 (0.6)	10 (0.2)
Endocrine disorders	3 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.1)
Hepatobiliary disorders	3 (0.1)	3 (0.2)	1 (0.1)	0 (0.0)	2 (0.6)	9 (0.2)
Congenital, familial & genetic disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.0)
Surgical & medical procedures	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

Source: page 33 Summary of Clinical Safety

7.1.5.3 Identifying common and drug-related adverse events

The overall AE rate in the total valsartan/amlodipine group was similar to that for valsartan monotherapy, amlodipine monotherapy and placebo as seen in the above table. The most frequently occurring AE in the total valsartan/amlodipine group was peripheral edema, but it occurred at a significantly lower incidence than in the amlodipine monotherapy group but was higher compared to valsartan monotherapy and placebo.

For the other most common AEs of headache, nasopharyngitis, dizziness and upper respiratory tract infection, there was no significant difference between the incidence in the valsartan/amlodipine group and the valsartan monotherapy, amlodipine monotherapy, or placebo groups. The slightly greater incidence of influenza, diarrhea and cough in the valsartan/amlodipine group compared to the amlodipine monotherapy group, as well as the lower incidence of back pain compared to the valsartan monotherapy group, all achieved statistical significance. There was a low incidence of flushing in the valsartan/amlodipine group (0.5%), but this was lower than that reported in the amlodipine monotherapy group (1.0%) or placebo group (0.9%).

Table 37 Adverse events regardless of relationship to study drug

	Valsartan/ amlodipine n (%)	Valsartan n (%)	Amlodipine n (%)	Lisinopril/ HCTZ n (%)	Placebo n (%)	Total n (%)
Total population	2613	1229	930	66	337	5175
Patients with ≥ 1 AE	970 (37.1)	445 (36.2)	319 (34.3)	21 (31.8)	129 (38.3)	1884 (36.4)
Preferred term						
Edema peripheral	151 (5.8)	23 (1.9)	84 (9.0)	1 (1.5)	10 (3.0)	269 (5.2)
Headache	98 (3.8)	52 (4.2)	49 (5.3)	2 (3.0)	20 (5.9)	221 (4.3)
Nasopharyngitis	71 (2.7)	37 (3.0)	25 (2.7)	0 (0.0)	6 (1.8)	139 (2.7)
Dizziness	45 (1.7)	25 (2.0)	11 (1.2)	0 (0.0)	3 (0.9)	84 (1.6)
Upper RTI	43 (1.6)	13 (1.1)	12 (1.3)	0 (0.0)	7 (2.1)	75 (1.4)
Influenza	40 (1.5)	12 (1.0)	6 (0.6)	2 (3.0)	2 (0.6)	62 (1.2)
Diarrhea	36 (1.4)	16 (1.3)	4 (0.4)	4 (6.1)	5 (1.5)	65 (1.3)
Bronchitis	32 (1.2)	16 (1.3)	6 (0.6)	0 (0.0)	4 (1.2)	58 (1.1)
Cough	27 (1.0)	13 (1.1)	2 (0.2)	2 (3.0)	0 (0.0)	44 (0.9)
Back pain	25 (1.0)	25 (2.0)	13 (1.4)	1 (1.5)	2 (0.6)	66 (1.3)
Fatigue	25 (1.0)	11 (0.9)	10 (1.1)	0 (0.0)	5 (1.5)	51 (1.0)
Sinusitis	25 (1.0)	8 (0.7)	4 (0.4)	1 (1.5)	4 (1.2)	42 (0.8)

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The suspected relationship to study treatment of AEs was based on the opinion of the investigator.

Events suspected to be drug related:

The incidence of AEs suspected to be related to study treatment in the double-blind, active- or placebo-controlled safety population ranged from 7.0-14.2% across all pooled treatment groups. The incidence rate in the total valsartan/amlodipine group was lower than that observed in the amlodipine monotherapy group and higher than for valsartan monotherapy and placebo, primarily due to the incidence of peripheral edema and other edema-related events. The incidence of peripheral edema was significantly lower in the valsartan/amlodipine group compared to the amlodipine monotherapy group, albeit higher than in the valsartan and placebo groups.

Table 38 Suspected drug-related adverse events

	Valsartan/ amlodipine n (%)	Valsartan n (%)	Amlodipine n (%)	Lisinopril/ HCTZ n (%)	Placebo n (%)	Total n (%)
Total population	2613	1229	930	66	337	5175
Patients with ≥ 1 AE	306 (11.7)	86 (7.0)	132 (14.2)	7 (10.6)	27 (8.0)	558 (10.8)
Preferred term						
Edema peripheral	124 (4.7)	13 (1.1)	70 (7.5)	1 (1.5)	3 (0.9)	211 (4.1)
Headache	32 (1.2)	16 (1.3)	18 (1.9)	0 (0.0)	7 (2.1)	73 (1.4)
Dizziness	22 (0.8)	13 (1.1)	4 (0.4)	0 (0.0)	0 (0.0)	39 (0.8)
Diarrhea	12 (0.5)	3 (0.2)	2 (0.2)	0 (0.0)	2 (0.6)	19 (0.4)
Fatigue	12 (0.5)	6 (0.5)	5 (0.5)	0 (0.0)	0 (0.0)	23 (0.4)
Edema	11 (0.4)	1 (0.1)	5 (0.5)	0 (0.0)	0 (0.0)	17 (0.3)
Flushing	10 (0.4)	0 (0.0)	6 (0.6)	0 (0.0)	2 (0.6)	18 (0.3)
Joint swelling	10 (0.4)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	13 (0.3)
Somnolence	6 (0.2)	3 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	11 (0.2)
Vertigo	6 (0.2)	5 (0.4)	1 (0.1)	0 (0.0)	1 (0.3)	13 (0.3)
Asthenia	5 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	7 (0.1)
Cough	5 (0.2)	2 (0.2)	0 (0.0)	1 (1.5)	0 (0.0)	8 (0.2)
Dry mouth	5 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.1)
Nausea	5 (0.2)	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	9 (0.2)
Orthostatic hypotension	5 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)
Pitting edema	5 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)	7 (0.1)
Abdominal pain	4 (0.2)	2 (0.2)	1 (0.1)	0 (0.0)	1 (0.3)	8 (0.2)
Erythema	4 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.3)	7 (0.1)
Hot flush	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Tachycardia	4 (0.2)	2 (0.2)	3 (0.3)	0 (0.0)	0 (0.0)	9 (0.2)

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Events suspected to be drug related in the two long-term populations:

Study A2201E1

AEs that were suspected to be related to study treatment occurred in 23.2% of the total population in this long-term extension population. The incidence was greater in the high dose group (30.0%) than in the low dose group (16.3%). This difference was primarily due to the incidence of peripheral edema, which occurred in 9.5% of the total population (13.2% of the high dose group and 5.7% of the low dose group).

Study A2307E1

AEs that were suspected to be study drug related occurred in 4.7% of the total extension population. The most frequently reported AE suspected to be study drug related was peripheral edema, which occurred in only 1.0% of the total population.

7.1.5.4 Additional analyses and explorations

For the valsartan/amlodipine group, there was no clear dose response relationship for the overall incidence of adverse events as the dose of either valsartan or amlodipine was increased while the dose of the other component was kept constant. For peripheral edema, there was a general trend toward an increase in the incidence as the dose of amlodipine in the combination increased. The amlodipine 2.5 mg and 10 mg groups had relatively high incidence rates of peripheral edema, but the incidence was lower in the amlodipine 5 mg group. As a result, significant attenuation of peripheral edema with the combination was observed with the valsartan/amlodipine 2.5 mg and valsartan/amlodipine 10 mg

combinations. This is seen in the following table. For the other common AEs, there was no clear indication of any relationship to dose.

A comparison by treatment and dose of the incidence of edema (pooled) in the valsartan/amlodipine, valsartan monotherapy and amlodipine monotherapy groups is shown in the following table. Consistent with the results for the combined treatment groups, in patients who received either 2.5 or 10 mg amlodipine, the incidence of edema (pooled) was lower when amlodipine was administered in combination with valsartan compared to amlodipine monotherapy. In patients who received amlodipine 5 mg monotherapy, the incidence of edema was unexpectedly low and therefore, the attenuation of edema could not be detected for the valsartan/amlodipine 5 mg combination doses.

Table 39 Incidence of Edema by treatment and dose

Amlodipine (mg)	Valsartan (mg)					All n/N (%)
	0 n/N (%)	40 n/N (%)	80 n/N (%)	160 n/N (%)	320 n/N (%)	
0	12/337 (3.6)	7/127 (5.5)	4/123 (3.3)	10/335 (3.0)	5/336 (1.5)	26/921 (2.8)
2.5	11/125 (8.8)	5/129 (3.9)	7/129 (5.4)	4/126 (3.2)	7/129 (5.4)	-
5	4/128 (3.1)	6/124 (4.8)	4/128 (3.1)	7/126 (5.6)	4/127 (3.1)	-
10	31/207 (15.0)	-	-	27/209 (12.9)	20/210 (9.5)	-
All	46/460 (10.0)	-	-	-	-	91/1437 (6.3)*

Source: page 48 Summary of Clinical Safety

7.1.6 Less Common Adverse Events

N/A

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The hematology variables evaluated in all studies were hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential and platelet count. Biochemistry variables evaluated in all studies were alkaline phosphatase (AlkPhos), alanine aminotransferase (ALT), aspartamine aminotransferase (AST), total bilirubin, creatinine, blood urea nitrogen (BUN), sodium, potassium, and glucose. Additional biochemistry variables evaluated in selective studies were LDH, creatinine kinase, chloride, calcium, phosphorous, total protein, albumin and uric acid. All available laboratory data was pooled.

For all of the clinical laboratory variables, the following were analyzed:

- mean change from baseline to final visit
- shift analysis of number of patients who experienced a shift from baseline to any postbaseline visit of low/normal to high, or normal/high to low values.

In addition, the percentage of patients who experienced pre-specified percentage changes from baseline to any post-baseline visit were evaluated for hemoglobin, hematocrit, RBC count, WBC count, platelet count, AlkPhos, ALT, AST, total bilirubin, creatinine kinase, creatinine, BUN, sodium, potassium, calcium, chloride, glucose and uric acid.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Hematology

No clinically meaningful changes from baseline were observed for any variable in the double-blind active and placebo-controlled populations. Increased WBC count was the most common finding in the valsartan/amlodipine group and the valsartan and amlodipine monotherapy groups. The incidence was similar in the placebo group. The long-term studies also revealed no clinically meaningful changes in hematology. As was seen in the short-term studies, the most common finding was increased WBC count.

Clinical chemistry

Mean changes from baseline in biochemistry variables were generally unremarkable for the valsartan/amlodipine, valsartan monotherapy and amlodipine monotherapy groups. Compared to the placebo group, there were small increases in BUN in the valsartan/amlodipine and valsartan monotherapy groups. In the lisinopril/HCTZ group, increases in ALT, creatinine, BUN, uric acid and calcium were observed and a decrease in serum chloride was observed. These changes are consistent with the known effects of either an ACEI or diuretic.

Study A2201E1

In this long-term study of valsartan/amlodipine 80/2.5 mg titrated to 160/5 mg (low dose) or 80/5 mg titrated to 160/10 mg (high dose) with the optional addition of HCTZ, mean and median changes from baseline at endpoint were clinically unremarkable for the biochemistry parameters with the exception of uric acid, potassium, and BUN. Uric acid increased in both the high and low dose groups for patients who received HCTZ in addition to their valsartan/amlodipine treatment regimen. The addition of HCTZ also resulted in slight decreases from baseline in potassium. Increased BUN was seen in patients who received HCTZ in addition to valsartan/amlodipine.

Analysis of shifts in biochemistry values from baseline to any extension visit showed that the vast majority of patients had normal values at baseline and post-baseline. There were no clinically important differences in the incidence of shifts to abnormal values between treatment groups with the exception of uric acid. A greater incidence of patients with a shift from normal to high uric acid values was observed in patients receiving HCTZ compared those patients not receiving HCTZ in both the low dose group (9.7% and 4.3%, respectively) and the high dose (7.0% and 4.3%, respectively) group.

Study A2307E1

In this long-term study of valsartan/amlodipine 320/5 mg, mean and median changes in biochemistry values from baseline and at endpoint were clinically unremarkable.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

There were no clinically significant changes from baseline in body weight or sitting and standing pulse rate in any of the treatment groups for the studies included in this submission.

7.1.9 Electrocardiograms (ECGs)

ECG measurements were not performed post-baseline in any of the studies included in this submission.

7.1.9.1 Additional analyses and explorations

Orthostatic blood pressure changes

Orthostatic blood pressure changes were defined as a decrease of at least 20 mmHg in systolic pressure, or a decrease of at least 10 mmHg in diastolic blood pressure when rising from a sitting to standing position. The overall incidence of such changes at any timepoint postbaseline in the active- or placebo-controlled population was generally lower in the valsartan/amlodipine group than in the valsartan or amlodipine monotherapy groups. In the valsartan/amlodipine group, the overall incidence was lower than for placebo and there was no clear dose response in any of the treatment groups. There were very few AE reports of orthostatic hypotension or postural dizziness. Orthostatic hypotension was reported as an AE for only 5 (0.2%) patients receiving valsartan/amlodipine, one in each of the 320/10 mg, 160/10 mg and 160/5 mg groups, and two in the 40/2.5 mg group. Postural dizziness was reported for only 3 (0.1%) patients treated with valsartan/amlodipine, one in the 160/5 mg group and two in the 80/5 mg group.

Study A2201E1

In this long-term study, orthostatic blood pressure changes occurred at an incidence of 8.6% in the low dose group (valsartan/amlodipine 80/2.5 mg titrated to 160/5 mg \pm HCTZ) and 10.2% in the high dose group (valsartan/amlodipine 80/5 mg titrated to 160/10 mg \pm HCTZ). The vast majority of cases were isolated, occurring at more than one visit in only 1.9% of patients. A total of 1.3% and 0.3% of patients reported orthostatic hypotension as an AE in the high and low dose groups, respectively. One patient discontinued due to orthostatic hypotension reported as an AE, but no cases were considered serious.

Study A2307E1

In this long-term study in which patients received valsartan/amlodipine 320/5 mg, the incidence of orthostatic blood pressure changes occurring at one or more study visit was 5.5% over the one year

study period. The majority of cases were isolated, occurring at more than one visit in only 0.7% of patients. Orthostatic hypotension was not reported as an AE in this trial.

7.1.10 Immunogenicity

N/A

7.1.11 Human Carcinogenicity

N/A

7.1.12 Special Safety Studies

N/A

7.1.13 Withdrawal Phenomena and/or Abuse Potential

N/A

7.1.14 Human Reproduction and Pregnancy Data

N/A

7.1.15 Assessment of Effect on Growth

N/A

7.1.16 Overdose Experience

N/A

7.1.17 Postmarketing Experience

Although co-packaging of valsartan and amlodipine is approved in Brazil, Ecuador, Venezuela, Argentina, and in the Central American and Caribbean Regions, valsartan/amlodipine fixed combinations are not currently marketed. Therefore, only limited data are available. The most frequently reported events according to preferred term were dizziness (n = 85), angina (n= 42), edema peripheral (n= 41), chest pain (n= 41), cerebral infarction (n= 41), dyspnea (n= 40), and cough (n= 40). All other events had a frequency of less than 40. These are events already labeled for the monotherapies or events in which causality can be explained by co-medications, co-morbidities or underlying disease.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A wide age range of the adult population, including the elderly was studied (range 19-92 years, mean 54.7 years for valsartan/amlodipine). Women comprised almost half of the population in both the valsartan/amlodipine group (46.5%) and overall (47.3%). Of the patients in the total valsartan/amlodipine group, 87.6% were Caucasian, a similar proportion to that in the overall population (86.3%). Black and Oriental patients each represented approximately 4% of the population both in the valsartan/amlodipine group and in the overall population. The high proportion of patients in this group whose race was categorized as "Other" was due to approximately one third of the population in Study A2308 being recruited at centers in Latin America.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

N/A

7.2.3 Adequacy of Overall Clinical Experience

Since amlodipine and valsartan have been individually marketed for almost 10 years, the postmarketing experience and the data submitted in this submission is adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

N/A

7.2.5 Adequacy of Routine Clinical Testing

N/A

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

N/A

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

N/A

7.2.8 Assessment of Quality and Completeness of Data

N/A

7.2.9 Additional Submissions, Including Safety Update

N/A

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This clinical summary of safety considers data obtained in 5182 randomized patients with essential hypertension in well-controlled, double-blind studies. Of these patients, 5175 received at least one dose of study medication and were included in the safety population. Of these patients, 2613 received valsartan/amlodipine, 1229 received valsartan alone, 930 received amlodipine alone, 337 received placebo and 66 received lisinopril/hydrochlorothiazide (HCTZ). In addition, 1649 patients from two long-term open-label studies and 717 patients from two additional short-term studies were also considered.

- The overall incidence of AEs regardless of relationship to treatment showed no statistically significant differences between valsartan/amlodipine combination therapy and valsartan monotherapy, amlodipine monotherapy, or placebo in the active- or placebo-controlled studies.
- In the active- or placebo-controlled studies, the most common AEs regardless of relationship to treatment in the valsartan/amlodipine group ($\geq 2\%$) were peripheral edema, headache, and nasopharyngitis with the incidence of peripheral edema and nasopharyngitis being greater than with placebo.
- The incidence of peripheral edema was significantly reduced in patients receiving valsartan/amlodipine compared to amlodipine monotherapy in both the active- or placebo-controlled.
- The overall incidence of adverse events was not dose dependent among the valsartan/amlodipine doses. There was a general trend toward an increase in the incidence of peripheral edema as the dose of amlodipine in the combination increased.
- The most frequent AEs ($\geq 1\%$) suspected related to study drug in both the active- or placebo-controlled and the placebo-controlled studies in the valsartan/amlodipine group were peripheral edema and headache.
- The overall incidence of serious AEs and AEs leading to study discontinuation in the valsartan/amlodipine group was low and generally comparable to placebo across datasets.
- No significant new adverse events were observed with long-term treatment compared to short-term treatment and the known effects of the monotherapy components.
- Valsartan/amlodipine was generally well-tolerated regardless of gender, age, or race.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

N/A

7.4.2 Causality Determination

N/A

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The combination tablets will be available in the following doses of amlodipine/valsartan: _____
5/160 mg, 10/160 mg, 5/320 mg, 10/320 mg. These tablets are to be taken once a day.

8.2 Drug-Drug Interactions

N/A

8.3 Special Populations

N/A

8.4 Pediatrics

During the pre-NDA meeting for Exforge on April 14, 2005, the Sponsor requested a waiver of the pediatric requirement for the combination product based on the fact that pediatric data was available for amlodipine besylate and that there was an ongoing pediatric program for valsartan. The Agency confirmed at that meeting that a waiver would be granted for the combination product.

8.5 Advisory Committee Meeting

N/A

8.6 Literature Review

A review of the literature included how to measure blood pressure, what the acceptable current values are, blood pressure treatment in special populations, various agents used in the treatment of hypertension, and combination drug treatment of hypertension.

8.7 Postmarketing Risk Management Plan

N/A

8.8 Other Relevant Materials

N/A

9 OVERALL ASSESSMENT

9.1 Conclusions

Hypertension has been described as a lifestyle syndrome. It is estimated that hypertension is present in at least 35% of the population of an industrialized nation. The incidence is increasing in the U.S. with the aging of the population and in the world with the economic development of other nations.

There are advocates of combination treatments being utilized from the beginning in the treatment of hypertension especially in patients with an initial high blood pressure (BP). This submission however states that amlodipine/valsartan combination tablets (Exforge) are intended for use in patients with mild to moderate hypertension who do not respond to either valsartan or amlodipine alone.

In this submission the Sponsor has taken two established drugs, amlodipine and valsartan, which have been utilized for 10 or more years for the treatment of hypertension and has combined them at various doses. Both medications have individual good efficacy and safety records. The Sponsor has demonstrated that combined, these drugs improve the control of hypertension over the individual medications. Also, the edema seen with amlodipine is less and with the combination there is no apparent occurrence of orthostatic events.

The Sponsor submitted electronically a number of clinical studies. However, only two studies were designed as multicenter, double-blind, randomized, multifactorial, placebo-controlled, parallel group trials. Therefore, these two trials were evaluated for efficacy. Five studies were reviewed for safety; they included the two placebo-controlled trials and three active-controlled studies. Also mentioned with the safety review are two long-term, open-label extension studies of the two placebo-controlled trials reviewed for efficacy.

The combination of valsartan/amlodipine generally provided additive diastolic and systolic blood pressure lowering effects compared to valsartan or amlodipine alone in patients with essential hypertension. Both components contributed to the antihypertensive effect of the combination in the overall population. The combination produced a successful blood pressure response at endpoint (defined as a mean sitting diastolic blood pressure <90 mmHg or a ≥ 10 mmHg decrease compared to baseline) in approximately 80-90% of patients and achieved blood pressure control (mean sitting diastolic blood pressure <90 mmHg) in approximately 70-80% of patients at the higher doses. The combination was effective regardless of gender, age and race. A positive dose response relationship was demonstrated within the studied dose range of the combination.

At least 2613 patients received the combination valsartan/amlodipine in the safety population which was comprised of two placebo-controlled trials and three active-controlled studies. The overall

incidence of Adverse Events (AEs) showed no significant differences between valsartan/amlodipine combination therapy and valsartan monotherapy and amlodipine monotherapy. The most common AEs regardless of relationship to treatment in the valsartan/amlodipine group ($\geq 2\%$) were peripheral edema, headache, and nasopharyngitis. The incidence of peripheral edema was significantly reduced in patients receiving valsartan/amlodipine compared to amlodipine monotherapy. There was a general trend toward an increase in the incidence of peripheral edema as the dose of amlodipine in the combination increased. The most frequent AEs ($\geq 1\%$) suspected related to study drug in the valsartan/amlodipine group were peripheral edema and headache. The overall incidence of serious AEs and AEs leading to study discontinuation in the valsartan/amlodipine group was low and generally comparable to placebo. No significant new adverse events were observed with long-term treatment. Valsartan/amlodipine was generally well-tolerated regardless of gender, age, or race.

9.2 Recommendation on Regulatory Action

This Medical Reviewer recommends that the combination tablets containing amlodipine and valsartan in the following doses: ~~5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg~~ be approved.

9.3 Recommendation on Postmarketing Actions

N/A

9.3.1 Risk Management Activity

N/A

9.3.2 Required Phase 4 Commitments

N/A

9.3.3 Other Phase 4 Requests

N/A

9.4 Labeling Review

To be completed with the Review Team and submitted separately.

9.5 Comments to Applicant

N/A

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