Sponsor

Novartis

Generic Drug Name

Valsartan and amlodipine

Trial Indication(s)

Hypertension

Protocol Number

CVAA489A2306

Protocol 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

Clinical Trial Phase

Phase III

Study Start/End Dates

01 Nov 2004 to 28 Jun 2005

Reason for Termination

Not applicable.

Study Design/Methodology

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 o.d. (once a day) amlodipine run-in phase. Patients were then randomized at Visit 3, in a double-blind manner, to receive amlodipine 10 mg o.d., or valsartan/amlodipine 160/10 mg o.d for 8 weeks.

Centers

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

Objectives:

Primary objective(s)

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.

Secondary objective(s)

• 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.

Test Product (s), Dose(s), and Mode(s) of Administration

Identically appearing capsules of valsartan, amlodipine and placebo; for oral administration, once daily at 8 AM with water. Each dose (monotherapy or combination therapy) consisted of 3 capsules (one from each bottle).

Statistical Methods

For the primary analysis, the null hypothesis was that the mean change from baseline in MSDBP at endpoint was the same for amlodipine 10 mg and valsartan/amlodipine 160/10 mg. The alternative hypothesis was that the mean change from baseline in MSDBP at endpoint was different.

The comparison of valsartan/amlodipine combination treatment versus amlodipine monotherapy was tested at a two-sided significance level of 0.05. The comparison in the reduction of MSDBP at endpoint for the primary efficacy population (i.e. ITT population) was considered as the primary analysis.

The change from baseline in MSDBP at endpoint was analyzed using an analysis of covariance model (ANCOVA) with treatment and pooled center as factors, centered baseline MSDBP as a covariate, and treatment-by-centered-baseline as an interaction for the ITT population. This analysis was also repeated using the per-protocol population.

Change from baseline MSSBP was analyzed in the same way as the primary efficacy variable. Responder rate and control rate were analyzed using a logistic regression model including treatment and pooled center as factors.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Male or female outpatients ≥ 18 years. Female patients had to be either post-menopausal for one year or surgically sterile, or using effective contraceptive methods such as barrier method with spermicide or an intra-uterine device. Hormonal contraceptive use was disallowed.
2. Patients with essential diastolic hypertension measured by calibrated standard aneroid or mercury sphygmomanometer. At Visit 1, 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, all patients had to have a MSDBP of ≥ 95 mmHg and < 110 mmHg. At Visit 3, all patients had to have a MSDBP of ≥ 90 mmHg and < 110 mmHg.

Exclusion Criteria:

1. Severe hypertension (MSDBP ≥ 110 mmHg and/or MSSBP ≥ 180 mmHg).
2. Inability to completely discontinue all prior antihypertensive medications safely for a period of 1 to 4 weeks as required by the protocol.
3. Known Keith-Wagener grade III or IV hypertensive retinopathy.
4. History of hypertensive encephalopathy or cerebrovascular accident at any time prior to Visit 1 (week -8 to -4).
5. Transient ischemic attack, myocardial infarction, all types of revascularization procedures at any time prior to Visit 1 (week -8 to -4).
6. Heart failure requiring treatment.
7. Second or third degree heart block without a pacemaker.
8. Concomitant refractory angina pectoris.
9. Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.
10. Clinically significant valvular heart disease.
11. Evidence of a secondary form of hypertension
12. Diabetic patients requiring insulin treatment.
13. Type 2 diabetics with poor glucose control defined as a glycosylated hemoglobin (HbA1c) > 7% at Visit 1.
14. Administration of any agent indicated for the treatment of hypertension within a minimum of 1 week prior to enrolling into the single-blind run-in phase of the study (Visit 2, week -4), with the permitted exception of those antihypertensive medications requiring tapering down commencing at Visit 1 (week -8 to -4).
15. Known or suspected contraindications, including a history of allergy to ARBs or calcium channel blockers.
16. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug.
17. Any history of pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury within 12 months of Visit 1 (week -8 to -4).
18. Evidence of significant hepatic disease or renal disease
19. Sodium depletion.
20. History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the past five years.

Participant Flow Table

Patient disposition by treatment group

	Val/Aml 160/10 mg n (%)	Aml 10 mg n (%)	Total n (%)
Enrolled[1]		1283	1283
Discontinued During Single-blind Period		339	339 (26.4)
Randomized [2]	473	471	944
Discontinued During Double-blind Period	31 (6.6)	25 (5.3)	56 (5.9)
Completed Double-blind Period	442 (93.4)	446 (94.7)	888 (94.1)

[1]Visit 2 (excluding 1 patient who did not receive at least one dose of single-blind run-in medication)
[2]Visit 3 to 5 (Double-blind study drug treatment)

Baseline Characteristics

Demographics by treatment group (Randomized population)

Demographic Variable	Val/Aml 160/10 mg n (%)	Aml 10 mg n (%)	Total n (%)
Number of Patients	473	471	944
Age (years)			
Mean (SD)	54.1 (12.0)	54.1 (12.2)	54.1 (12.1)
Sex			
Male	251 (53.1)	253 (53.7)	504 (53.4)
Female	222 (46.9)	218 (46.3)	440 (46.6)
Race			
Caucasian	472 (99.8)	471 (100.0)	943 (99.9)
Black	1 (0.2)	0	1 (0.1)
Oriental	0	0	0
Other	0	0	0
Unknown	0	0	0

Summary of Efficacy

Primary Outcome Result(s)

Within-treatment analyses for changes from baseline in MSDBP (mmHg) at endpoint by treatment group (ITT population)

Treatment Group	N	Baseline mean (mmHg)	Mean change from baseline	95% CI for mean change from baseline	p-value
Val/Aml 160/10 mg	472	94.8	-11.8	(-12.50, -11.06)	< 0.0001
Aml 10 mg	468	95.3	-10.0	(-10.73, -9.26)	< 0.0001

Between-treatment comparisons of MSDBP (mmHg) at endpoint (ITT population)

Comparison	Between-treatment difference (SE)	95% CI	P-value
[Val/Aml 160/10 mg] vs. [Aml 10 mg]	-2.11 (0.438)	(-2.97, -1.25)	<0.0001

Secondary Outcome Result(s)

Within-treatment analyses for changes from baseline in MSSBP (mmHg) at endpoint by treatment group (ITT population)

Treatment Group	N	Baseline mean (mmHg)	Mean change from baseline	95% CI for mean change from baseline	p-value
Val/Aml 160/10 mg	472	146.0	-12.7	(-13.81, -11.52)	< 0.0001
Aml 10 mg	468	148.0	-10.8	(-11.88, -9.68)	< 0.0001

Between-treatment comparisons of MSSBP (mmHg) at endpoint (ITT population)

Comparison	Between-treatment difference (SE)	95% CI	P-value
Val/Aml 160/10 mg vs. Aml 10 mg	-2.87 (0.665)	(-4.17, -1.56)	<0.0001

Proportion of successful responders at endpoint (ITT population)

Treatment Group	N	n*	Responder Rate (%)
Val/Aml 160/10 mg	472	373	79.03
Aml 10 mg	468	328	70.09

Between-treatment comparisons of successful responders at endpoint (ITT population)

Comparison	Odds Ratio	95% CI	P-value
[Val/Aml 160/10 mg] vs. [Aml 10 mg]	1.66	(1.22, 2.24)	0.0011

*A responder was defined as a patient with MSDBP < 90 mmHg, or a ≥ 10 mmHg decrease compared to baseline

Proportion of patients with controlled MSDBP at endpoint (ITT population)

Treatment Group	N	n*	Control Rate (%)
Valsartan/Amlodipine 160/10 mg	472	367	77.8
Amlodipine 10 mg	468	311	66.5

Between-treatment comparison of patients with controlled MSDBP at endpoint (ITT population)

Comparison	Odds Ratio	95% CI	P-value
[Val/Aml 160/10 mg] vs. [Aml 10 mg]	1.83	(1.36, 2.46)	< 0.0001

n*: n represents the number of successful responders. A responder was defined as a patient with MSDBP < 90 mmHg, or a ≥ 10 mmHg decrease compared to baseline

Summary of Safety

Safety Results

Four patients (0.3%) experienced SAEs and 88 patients (6.9%) were discontinued due to AEs during the single-blind run-in period. No deaths occurred during this treatment period.

Number (%) of patients who died, had serious AEs or discontinued due to AEs during double-blind treatment period (Safety population)

	Val/Aml 160/10 mg N=473 n (%)	Aml 10 mg N=470 n (%)	Total N=943 n (%)
Any adverse experience	110 (23.3)	109 (23.2)	219 (23.2)
Deaths	1 (0.2)	0	1 (0.1)
SAEs	4 (0.8)	1 (0.2)	5 (0.5)
AEs that led to discontinuation	16 (3.4)	16 (3.4)	32 (3.4)

19.6% of patients reported AEs during the single-blind period. The most frequent AEs by primary system organ class were general disorders and administrative site conditions (10.0%), nervous system disorders (3.6%), and infections and infestations (2.3%). AEs for the single-blind period are presented for the enrolled population by preferred term. The most frequent AEs by preferred term were peripheral edema (8.0%), headache (2.8%), and edema (1.4%).

Number (%) of patients with AEs overall and by primary system organ class (> or = 1% for the valsartan/amlodipine 160/10 mg treatment group) during double-blind treatment period (Safety population)

Primary System Organ Class	Val/Aml 160/10 mg N=473 n (%)	Aml 10 mg N=470 n (%)	Total N=943 n (%)
Any adverse experience	110 (23.3)	109 (23.2)	219 (23.2)
General disorders and administration site conditions	42 (8.9)	54 (11.5)	96 (10.2)
Nervous system disorders	24 (5.1)	18 (3.8)	42 (4.5)
Infections and infestations	14 (3.0)	21 (4.5)	35 (3.7)
Gastrointestinal disorders	10 (2.1)	10 (2.1)	20 (2.1)
Investigations	10 (2.1)	6 (1.3)	16 (1.7)
Musculoskeletal and connective tissue disorders	8 (1.7)	6 (1.3)	14 (1.5)
Cardiac disorders	6 (1.3)	6 (1.3)	12 (1.3)
Skin and subcutaneous tissue disorders	5 (1.1)	4 (0.9)	9 (1.0)

Number (%) of patients with most frequent AEs (>or = 1% for the valsartan/amlodipine 160/10 mg treatment group) during double-blind treatment period (Safety population)

Preferred Term	Val/Aml 160/10 mg N=473 n (%)	Aml 10 mg N=470 n (%)	Total N=943 n (%)
Any adverse experience	110 (23.3)	109 (23.2)	219 (23.2)
Edema peripheral	36 (7.6)	44 (9.4)	80 (8.5)
Headache	14 (3.0)	14 (3.0)	28 (3.0)
Dizziness	7 (1.5)	4 (0.9)	11 (1.2)
Influenza	7 (1.5)	4 (0.9)	11 (1.2)
Increased alanine aminotransferaminase	7 (1.5)	4 (0.9)	11 (1.2)
Edema	5 (1.1)	5 (1.1)	10 (1.1)

Date of Clinical Trial Report

19-Dec-2005