NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis

Generic Drug Name

Valsartan and amlodipine

Trial Indication(s)

Hypertension

Protocol Number

CVAA489A2305

Protocol 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.

Clinical Trial Phase

Phase III

Study Start/End Dates

14 Oct 2004 to 27 Jun 2005

Reason for Termination

Not applicable.

Study Design/Methodology

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 o.d. (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 o.d. for 8 weeks.

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))

Objectives:

Primary objective(s)

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 objective(s)

To explore the efficacy of the combination of valsartan/amlodipine 160/10 mg compared to 160/5 mg in patients with essential hypertension not adequately controlled on valsartan 160 mg monotherapy by testing the hypothesis that 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;

To explore 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 superior reductions in mean sitting systolic blood pressure (MSSBP) from baseline to 8 weeks compared to valsartan 160 mg alone;

To explore the efficacy of the combination of valsartan/amlodipine 160/10 mg compared to 160/5 mg in patients with essential hypertension not adequately controlled on valsartan 160 mg monotherapy by testing the hypothesis that 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.

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 a.m. 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 there was no treatment difference in the reduction of MSDBP among all three groups of valsartan/amlodipine 160/10 mg, valsartan/amlodipine 160/5 mg and valsartan 160 mg. The alternative hypothesis was that there was a treatment difference in at least one of the following: (1) valsartan/amlodipine 160/10 mg and valsartan 160 mg; (2) valsartan/amlodipine 160/5 mg and valsartan 160 mg.

The Dunnett multiple comparison procedure was used to adjust for the two comparisons of valsartan/amlodipine combination treatment versus valsartan monotherapy to ensure an overall two-sided significance level of 0.05. The multiple comparisons in the reduction of MSDBP at endpoint for the primary efficacy population (i.e. ITT population) were considered as the primary analysis.

The change from baseline in MSDBP was analyzed using analysis of covariance model (ANCOVA) with treatment and pooled center as factors, centered baseline MSDBP as a covariate, and treatmentby-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 analysis. 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 out patients ≥ 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. A diagnosis of essential diastolic hypertension as 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 1-4 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 that required 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 who required 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 that required 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	Val/Aml 160/5 mg	Val 160 mg	Total
	n (%)	n (%)	n (%)	n (%)
Enrolled [1]			1136	1136
Discontinued During Single-blind Period			189	189 (16.6)
Randomized [2]	317	322	308	947
Discontinued During Double-blind Period	20 (6.3)	12 (3.7)	11 (3.6)	43 (4.5)
Completed Double-blind Period	297 (93.7)	310 (96.3)	297 (96.4)	904 (95.5)

[1] Visit 2 (excluding 1 patient who did not receive at least one dose of single-blind run-in medication)

[2] Visit 3-5 (Double-blind study drug treatment)

Baseline Characteristics

Demographics by treatment group (Randomized population)

Demographic Variable	Val/Aml 160/10 mg n (%)	Val/Aml 160/5 mg n (%)	Val 160 mg n (%)	Total n (%)
Number of Patients	317	322	308	947
Age (years)				
Mean (SD)	53.9 (10.8)	55.4 (10.3)	54.5 (9.9)	54.6 (10.4)
Sex				
Male	171 (53.9)	174 (54.0)	172 (55.8)	517 (54.6)
Female	146 (46.1)	148 (46.0)	136 (44.2)	430 (45.4)
Race				
Caucasian	314 (99.1)	320 (99.4)	305 (99.0)	939 (99.2)
Black	2 (0.6)	1 (0.3)	3 (1.0)	6 (0.6)
Oriental	0	1 (0.3)	0	1 (0.1)
Other	1 (0.3)	0	0	1 (0.1)
Unknown	0	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	316	96.6	-11.4	(-12.13, -10.64)	< 0.0001
Val/Aml 160/5 mg	322	96.8	-9.6	(-10.47, -8.82)	< 0.0001
Val 160 mg	308	96.2	-6.6	(-7.40, -5.74)	< 0.0001

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

Comparison	Between-treatment LSM difference (SE)	95% CI	P-value
Dunnett Multiple Comparison			
[Val/Aml 160/10 mg] vs. [Val 160 mg]	-4.78 (0.547)	(-5.99, -3.57)	<0.0001
[Val/Aml 160/5 mg] vs. [Val 160 mg]	-2.93 (0.545)	(-4.13, -1.72)	<0.0001
Pairwise Comparison			
[Val/Aml 160/10 mg] vs. [Val/Aml 160/5 mg]	-1.85 (0.541)	(-2.91, -0.79)	0.0006

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	316	149.1	-13.9	(-15.25, -12.53)	< 0.0001
Val/Aml 160/5 mg	322	149.6	-12.0	(-13.45, -10.56)	< 0.0001
Val 160 mg	308	149.8	- 8.2	(-9.63, -6.67)	< 0.0001

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

Comparison	Between-treatment LSM difference (SE)	95% CI	P-value
Dunnett Multiple Comparison			
[Val/Aml 160/10 mg] vs. [Val 160 mg]	-6.04 (0.885)	(-8.00, -4.08)	<0.0001
[Val/Aml 160/5 mg] vs. [Val 160 mg]	-3.94 (0.880)	(-5.89, -1.99)	<0.0001
Pairwise Comparison			
[Val/Aml 160/10 mg] vs. [Val/Aml 160/5 mg]	-2.10 (0.875)	(-3.82, -0.39)	0.0164

Proportion of successful responders at endpoint (ITT population)

Treatment Group	N[1]	n[2]	Responder Rate (%)
Val/Aml 160/10 mg	316	256	81.0
Val/Aml 160/5 mg	322	219	68.0
Val 160 mg	308	175	56.8

[1] N represents the number of patients with non-missing baseline and endpoint
[2] n represents the number of responders
Responder is defined as achieving a MSDBP < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline

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

Comparison	Odds Ratio	95% CI	P-value
[Val/Aml 160/10 mg] vs. [Val 160 mg]	3.76	(2.56, 5.52)	<0.0001
[Val/Aml 160/5 mg] vs. [Val 160 mg]	1.74	(1.23, 2.47)	0.0018
[Val/Aml 160/10 mg] vs. [Val/Aml 160/5 mg]	2.16	(1.47, 3.18)	<0.0001

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

Treatment Group	N[1]	n[2]	Control Rate (%)
Val/Aml 160/10 mg	316	238	75.3
Val/Aml 160/5 mg	322	201	62.4
Val 160 mg	308	162	52.6

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

Comparison	Odds Ratio	95% CI	P-value
[Val/Aml 160/10 mg] vs. [Val 160 mg]	3.18	(2.20, 4.57)	<0.0001
[Val/Aml 160/5 mg] vs. [Val 160 mg]	1.59	(1.13, 2.24)	0.0074
[Val/Aml 160/10 mg] vs. [Val/Aml 160/5 mg]	1.99	(1.39, 2.86)	0.0002

[1] N represents the number of patients with non-missing baseline and endpoint
[2] n represents the number of responders
controlled MSDBP is defines as MSDBP <90 mmHg

Summary of Safety

Safety Results

Two patients experienced SAEs and 20 patients 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 SAEs or discontinued due to adverse events during double-blind treatment period (safety population)

	Val/Aml 160/10 mg N=317 n (%)	Val/Aml 160/5 mg N=322 n (%)	Val 160 mg N=308 n (%)	Total N=947 n (%)
Any adverse experience	120 (37.9)	78 (24.2)	78 (25.3)	276 (29.1)
Deaths	0	0	0	0
SAEs	1 (0.3)	2 (0.6)	3 (1.0)	6 (0.6)
AEs led to discontinuation	17 (5.4)	3 (0.9)	2 (0.6)	22 (2.3)

A total of 160 patients (14.1%) experienced at least one AE during the single-blind treatment period. The most frequently effected primary system organ classes were infections and infestations (4.6%) and nervous system disorders (4.5%); all others occurred in no more than 1.8% of patients overall. The most frequent AE by preferred term was headache (3.3%), followed by influenza (1.1%), dizziness (0.9%) and nasopharyngitis (0.7%).

Number (%) of patients with AEs overall and by primary system organ class (>= 1% in the total treatment group) during double-blind treatment period (Safety population)

Primary System Organ Class	Val/Aml 160/10 mg N=317 n (%)	Val/Aml 160/5 mg N=322 n (%)	Val 160 mg N=308 n (%)	Total N=947 n (%)
Any adverse experience	120 (37.9)	78 (24.2)	78 (25.3)	276 (29.1)
Infections and infestations	28 (8.8)	22 (6.8)	22 (7.1)	72 (7.6)
General disorders and administration site conditions	37 (11.7)	4 (1.2)	9 (2.9)	50 (5.3)
Nervous system disorders	16 (5.0)	15 (4.7)	16 (5.2)	47 (5.0)
Musculoskeletal and connective tissue disorders	18 (5.7)	12 (3.7)	14 (4.5)	44 (4.6)
Gastrointestinal disorders	14 (4.4)	7 (2.2)	14 (4.5)	35 (3.7)
Psychiatric disorders	6 (1.9)	6 (1.9)	6 (1.9)	18 (1.9)
Cardiac disorders	5 (1.6)	6 (1.9)	2 (0.6)	13 (1.4)
Vascular disorders	7 (2.2)	3 (0.9)	2 (0.6)	12 (1.3)
Respiratory, thoracic and mediastinal disorders	3 (0.9)	2 (0.6)	5 (1.6)	10 (1.1)
Skin and subcutaneous tissue disorders	6 (1.9)	3 (0.9)	1 (0.3)	10 (1.1)
Investigations	3 (0.9)	3 (0.9)	3 (1.0)	9 (1.0)

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

Preferred Term	Val/Aml 160/10 mg N=317	Val/Aml 160/5 mg N=322	Val 160 mg N=308	Total N=947
	n (%)	n (%)	n (%)	n (%)
Any adverse experience	120 (37.9)	78 (24.2)	78 (25.3)	276 (29.1)
Edema peripheral	29 (9.1)	3 (0.9)	4 (1.3)	36 (3.8)
Headache	6 (1.9)	9 (2.8)	8 (2.6)	23 (2.4)
Influenza	7 (2.2)	3 (0.9)	6 (1.9)	16 (1.7)
Back pain	4 (1.3)	4 (1.2)	6 (1.9)	14 (1.5)
Bronchitis	7 (2.2)	4 (1.2)	2 (0.6)	13 (1.4)
Dizziness	6 (1.9)	2 (0.6)	3 (1.0)	11 (1.2)
Fatigue	4 (1.3)	1 (0.3)	3 (1.0)	8 (0.8)
Joint swelling	6 (1.9)	2 (0.6)	0	8 (0.8)
Flushing	4 (1.3)	1 (0.3)	0	5(0.5)
Nasopharyngitis	4 (1.3)	1 (0.3)	0	5 (0.5)

Date of Clinical Trial Report

19-Dec-2005