Sponsor

Novartis

Generic Drug Name

Valsartan/ hydrochlorothiazide

Therapeutic Area of Trial

Hypertension

Approved Indication

Indicated for the treatment of hypertension.

Study Number

CVAH631B2406 and CVAH631B2406E1

Title

A randomized, double-blind, parallel group, active-controlled, multi-center, 14-week study and 8-week extension to evaluate the effectiveness of a valsartan- versus an amlodipine-treatment strategy in achieving blood pressure control in patients with stage 1 or stage 2 hypertension or uncontrolled on present monotherapy

An 8-week extension to a randomized, double-blind, parallel group, active-controlled, multi-center, 14-week study to evaluate the effectiveness of a valsartan- versus an amlodipine-treatment strategy in achieving blood pressure control in patients with stage 1 or stage 2 hypertension or uncontrolled on present monotherapy

Phase of Development

Phase IV

Study Start/End Dates

27 Feb 2006 to 19 Jan 2007 (CVAH631B2406)
23 Jun 2006 to 14 Mar 2007 (CVAH631B2406E1)

Study Design/Methodology

The core study was a randomized, double-blind, parallel group, active-controlled, multi-center, mandatory titration (determined by blood pressure), two-arm study.

It comprised two phases:

(1.) Pre-randomization (screening phase): eligibility was assessed and those patients entering the study continued their baseline anti-hypertensive medication (if any) but stopped all medications not allowed by the study protocol.

(2.) Study drug treatment: Patients were randomized in the study in a 1:1 ratio to valsartan treatment strategy or amlodipine treatment strategy.

Valsartan treatment strategy:

Step 1: valsartan 160 mg
Step 2: valsartan 160 mg/hydrochlorothiazide (HCTZ) 12.5 mg
Step 3: valsartan 160 mg/HCTZ 25 mg
Step 4: valsartan 320 mg/HCTZ 25 mg

Amlodipine treatment strategy:

Step 1: amlodipine 5 mg
Step 2: amlodipine 10 mg
Step 3: amlodipine 10 mg/HCTZ 12.5 mg
Step 4: amlodipine 10 mg/HCTZ 25 mg

For both strategies, treatment naïve stage 1 patients started with step 1, treatment naïve stage 2 patients and currently treated but uncontrolled started with step 2.

Patients who had not reached blood pressure (BP) control (mean sitting systolic blood pressure (MSSBP) < 140 mmHg and mean sitting diastolic blood pressure (MSDBP) < 90 mmHg) at Weeks 4, 8 or 11 had to be up titrated to the next appropriate step. During the course of the study down titration to the previous step was permitted if MSSBP < 100 mmHg or if the patient presented with symptomatic hypotension.

The extension study

This was an 8-week double-blind, parallel group, active-controlled, multi-center extension study with two treatment arms. Patients completing the core study with uncontrolled BP could be enrolled in the extension study where they were treated with a triple combination of valsartan, amlodipine and HCTZ. Patients received amlodipine 5 mg or valsartan 160 mg according to their treatment allocation in the core study. After 4 weeks if patients were still not at BP, amlodipine or valsartan had to be up titrated to 10 mg or 320 mg, respectively.

Centres

122 centers in 11 countries: Argentina (9), Brazil (8), Colombia (4), Germany (44), Denmark (5), Ecuador (4), Spain (13), Finland (8), United Kingdom (3), Ireland (3), Italy (21).

Publication

Ongoing

Objectives

Primary objective(s)

Core study:

To evaluate the efficacy of a valsartan treatment strategy compared to an amlodipine treatment strategy by testing the hypothesis of non-inferiority in reaching blood pressure control (MSSBP < 140 mmHg and MSDBP < 90 mmHg) at the end of study (week 14) as determined by the proportion of patients that had completed the study and were controlled. If this can be demonstrated, superiority will be tested between the valsartan treatment strategy group and the amlodipine treatment strategy group.

Extension study:

To assess the incremental rate in blood pressure control for those patients on valsartan 320 mg/HCTZ 25 mg and amlodipine 5/10 mg or amlodipine 10 mg/HCTZ 25 mg and valsartan 160/320 mg at the end of study (Week 22).

Secondary objective(s)

Core study:

- To evaluate the efficacy of a valsartan treatment strategy compared to an amlodipine treatment strategy for the whole study population by testing the hypothesis of non-inferiority in reaching blood pressure control at Weeks 4, 8, and 11 as determined by the proportion of patients that are controlled. If this can be demonstrated, superiority will be tested between the valsartan treatment strategy group and the amlodipine treatment strategy group.
- To evaluate the efficacy in each of the two different patient strata (treatment-naïve and previously treated and uncontrolled on present monotherapy) of a valsartan treatment strategy compared to an amlodipine treatment strategy by testing the hypothesis of non-inferiority in reaching blood pressure control at Weeks 4, 8, 11, and 14 as determined by the proportion of patients that are controlled. If this can be demonstrated, superiority will be tested in the two strata between the valsartan treatment strategy group and the amlodipine treatment strategy group.
- To evaluate MSSBP and MSDBP lowering of the valsartan versus amlodipine treatment strategy in the overall population and in the two strata between baseline (Visit 2) and Weeks 4, 8, 11, and 14.
- To evaluate safety and tolerability as measured by the rate of adverse events of the valsartan versus amlodipine treatment strategy in the overall population and in the two strata between baseline and the end of study (Week 14).

Extension study:

To evaluate the overall number of patients who reached blood pressure control on the valsartan compared to the amlodipine treatment strategy at the end of study including the core and extension phase; and (2) to evaluate safety and tolerability measured by the rate of adverse events between baseline (Week 14) and the end of study (Week 22).

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

Valsartan 160 mg capsules, and hydrochlorothiazide (12.5 mg or 25 mg capsules).

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

Amlodipine 5 mg capsules, and hydrochlorothiazide (12.5 mg or 25 mg capsules).

Criteria for Evaluation

Primary variables

Core study: The proportion of patients who had completed and reached blood pressure (BP) control (<140/90 mmHg) at Week 14.
Extension study: The proportion of patients who had completed and reached BP control at Week 22.

Secondary variables

Core study:

- The proportion of patients who had completed and reached blood pressure (BP) control (<140/90 mmHg) at Week 4, 8, and 11.
- The proportion of patients who had completed and reached blood pressure (BP) control (<140/90 mmHg) for the separate strata:
  - Treatment naïve patients
  - Patients previously treated and uncontrolled on present monotherapy
  - For each stratum at 4, 8, 11 and 14 weeks.
- The change from baseline in MSSBP and MSDBP using analysis of covariance at Week 4, 8, 11, 14, and endpoint.

Extension study:

The overall number of patients who reached BP control at Week 22.

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events, serious adverse events (with their severity and relationship to study drug), and pregnancies; the regular monitoring of hematology, blood chemistry and urine, performed at a central laboratory; and regular assessments of vital signs, physical condition and body weight.

Statistical Methods

Core study primary and secondary analysis

The test for the non-inferiority of the valsartan treatment strategy to amlodipine treatment strategy was based on the following hypothesis and one-sided alternative hypothesis:

H0: 0 <= e versus Ha: 0 > e

Where 0 is the log-odds ratio and e is the log odds ratio non-inferiority limit.

A logistic regression model was fitted including terms for treatment, country and stage of hypertension or failed monotherapy (Treatment naïve stage 1, treatment naïve stage 2 or previously treated on monotherapy and uncontrolled). The percentage of patients controlled in each treatment group, the point estimate for the odds ratio and two-sided 95% confidence interval (Wald) are presented.

Once non-inferiority was demonstrated, superiority was tested in addition using the same confidence interval from which non-inferiority was concluded. The P value associated with the test: H0: 0 = 0 versus Ha: 0 =/ 0, was calculated from the same logistic model.

The primary analysis was performed using the Intent-to-Treat population.

The primary endpoint was also analyzed at Visit 3/Week 4, Visit 4/Week 8, and Visit 5/ Week 11 on the ITT population.

The hypothesis of non-inferiority was tested, and once it was demonstrated superiority was tested.

Analyses for the primary endpoint was performed for the separate strata:

- Treatment naïve patients (stage 1 and stage 2).
- Patients previously treated and uncontrolled on present monotherapy.

A separate logistic regression model was fitted at all core study post-baseline visits. The hypothesis of non-inferiority was tested. Once non-inferiority was evaluated superiority was tested.

Summary statistics for mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic blood pressure (MSDBP) are presented by treatment and overall at all core post-baseline visits and endpoint for the ITT population. Summary statistics of the change from baseline are presented for all post baseline visits including the endpoint visit.

Extension study primary and secondary analysis

The secondary variable was the number and percentage of patients who had completed and reached BP control at Visit 8/Week 22. Data are presented along with the 95% confidence interval for each treatment group and overall for the Extension ITT population.

The secondary analysis was also performed for the core study ITT population.

Summary data for MSSBP and MSDBP are presented by treatment and overall at all core and extension post-baseline visits and endpoint for the extension study ITT population. Summary statistics of the change from baseline are presented for all post baseline visits.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Core study

1. Male or female outpatients between 18-75 years of age inclusive at screening visit.
2. Stage/grade 1 or stage/grade 2 hypertension (MSSBP ≥ 140 mmHg and/or MSDBP = 90 mmHg, based on the JNC-7/ESC/ESH guidelines) at the screening and baseline visits in untreated patients. Untreated was defined as treatment naïve or patients not treated in the past 12 weeks.

   Or

   Patients who were currently treated on monotherapy and uncontrolled (i.e., MSSBP ≥ 140 mm Hg, and/or MSDBP = 90) with a blood pressure = 160/100 mmHg at the screening and baseline visits. Treatment was defined as having taken medication for a minimum of 4 weeks and until = 2 days prior to the screening visit.

   Patients who did not meet the definition of treated or untreated were not eligible for study entry.
3. Written informed consent to participate in the study prior to any study procedures.

Extension study

1. MSSBP ≥ 140 mm Hg, and/or MSDBP = 90 mm Hg and currently treated with either valsartan 320 mg/HCTZ 25 mg or amlodipine 10 mg/HCTZ 25 mg at the end of the core study.
2. Written informed consent to participate in the extension study.

Exclusion criteria

Core study

1. Current treatment with a calcium channel blocker (CCB).
2. MSSBP ≥ 180 mm Hg or MSDBP ≥ 110 mm Hg at any time between the screening and baseline visits.
3. History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures.
4. Evidence of a secondary form of hypertension, such as coarctation of the aorta, hyperaldosteronism, renal artery stenosis, or pheochromocytoma, etc.
5. Cerebrovascular accident or myocardial infarction during the last 12 months, prior to the screening visit.
6. Transient ischemic cerebral attack during the last 6 months, prior to the screening visit.
7. History of/or symptoms consistent with congestive heart failure.
8. Clinically significant valvular heart disease.
9. Second or third degree heart block without a pacemaker.
10. Concomitant angina pectoris.

11. Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.
12. Diabetes mellitus.
13. Serum potassium < 3.5 or > 5.5 mmol/L without medication at the screening visit.
14. Serum creatinine > 1.5 ULN at the screening visit or a history of dialysis or nephrotic syndrome.
15. ALT or AST values > 2 x ULN at the screening visit or a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt.
16. Pregnant or nursing (lactating) women or women of child-bearing age who are not willing to use contraception
17. Any surgical or medical condition which might alter the absorption, distribution, metabolism, or excretion of any drug.
18. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
19. History of any severe or life-threatening disease.

Extension study

1. Premature discontinuation in the core study or failure to comply with the core study protocol.
2. Any patient that should not participate in the extension study based on the discretion of the investigator.

Number of Subjects

Core Study

	Valsartan strategy	Amlodipine strategy
Planned N	622	622
Randomised n	641	644
Intent-to-treat population (ITT) n (%)	632 (98.6)	631 (98.0)
Completed n (%)	595 (92.8)	530 (82.3)
Withdrawn n (%)	46 (7.2)	114 (17.7)
Withdrawn due to adverse events n (%)	22 (3.4)	69 (10.7)
Withdrawn due to lack of efficacy n (%)	1 (<1.0)	5 (<1.0)
Withdrawn for other reasons n (%)	23 (3.6)	40 (6.2)

Extension Study

	Valsartan strategy	Amlodipine strategy
Planned N	112	112
Entered extension study n	36	43
Intent-to-treat population (ITT) n (%)	36 (100)	43 (100)
Completed n (%)	36 (100)	41 (95.3)
Withdrawn n (%)	0	2 (4.7)
Withdrawn due to adverse events n (%)	0	0

Withdrawn due to lack of efficacy n (%)	0	0
Withdrawn for other reasons n (%)	0	2 (4.7)

Demographic and Background Characteristics

Core Study

	Valsartan strategy	Amlodipine strategy
Randomised n	641	644
Gender – n(%) Male Female	 362 (56.5) 279 (43.5)	 347 (53.9) 297 (46.1)
Mean age, years (SD)	54.6 (10.83)	54.3 (11.30)
Mean weight, kg (SD)	80.88 (15.766)	80.99 (16.691)
Predominant race – n (%) Caucasian Black Asian Native American Pacific Islander Unknown Other	 557 (86.9) 10 (1.6) 0 16 (2.5) 0 0 58 (9.0)	 551 (85.6) 17 (2.6) 0 21 (3.3) 0 0 55 (8.5)
Mean BMI, kg/m^2 (SD) (BMI (kg/m^2) = weight(kg) / height$(m)^2$)	28.39 (4.564)	28.43 (4.768)
Mean MSSBP, mmHg (SD)	150.42 (8.970)	150.04 (8.932)
Mean MSDBP, mmHg (SD)	93.88 (6.382)	93.84 (6.239)
Stage of hypertension or failed monotherapy – n (%) Naïve stage 1 Naïve stage 2 Failed monotherapy	 220 (34.3) 90 (14.0) 331 (51.6)	 215 (33.4) 84 (13.0) 345 (53.6)
Mean time (years) since diagnosis of hypertension (SD)	4.50 (6.278)	4.73 (6.222)

Extension Study

	Valsartan strategy	Amlodipine strategy
Entered extension study n	36	43
Gender – n(%) Male Female	 24 (66.7) 2 (33.3)	 37 (86.0) 6 (14.0)
Mean age, years (SD)	56.0 (9.87)	48.1 (13.56)
Mean weight, kg (SD)	82.23 (15.552)	87.42 (16.201)
Predominant race – n (%) Caucasian Black Asian Native American Pacific Islander Unknown Other	 33 (91.7) 1 (2.8) 0 1 (2.8) 0 0 1 (2.8)	 39 (90.7) 1 (2.3) 0 1 (2.3) 0 0 2 (4.7)
Mean BMI, kg/m^2 (SD)	27.75 (4.567)	28.50 (4.921)

Mean MSSBP, mmHg (SD)	158.41 (8.475)	153.98 (11.569)
Mean MSDBP, mmHg (SD)	98.18 (4.860)	97.20 (5.398)
Stage of hypertension or failed monotherapy – n (%) Naïve stage 1 Naïve stage 2 Failed monotherapy	 3 (8.3) 11 (30.6) 22 (61.1)	 10 (23.3) 10 (23.3) 23 (53.5)
Mean time (years) since diagnosis of hypertension (SD)	5.71 (8.269)	3.97 (7.567)

Primary Objective Result(s)

Percentage of patients achieving blood pressure control (<140/90 mmHg) at Week 14 (Intent-to-treat population) (Core Study)

Treatment	n	Incidence rate (%)	Odds ratio Valsartan/Amlodipine	95% CI for odds ratio	p-value for superiority
Valsartan strategy (N=632)	632	498 (78.8)	1.807	1.393, 2.343	<0.0001*
Amlodipine strategy (N=631)	631	428 (67.8)			

N is the number in ITT population; n is the number of ITT patients included in the analysis.
An odds ratio >1 favors the Valsartan strategy. Lower 95% CI > 0.6429 concludes non-inferiority, Lower 95% CI > 1 concludes superiority. * p-value significant at 5 % level.
Logistic regression model with treatment, country and stage of hypertension or failed monotherapy as factors.

Percentage of patients achieving blood pressure control (<140/90 mmHg) at Week 22 (Extension intent-to-treat population) (Extension Study)

Treatment	n	Incidence rate (%)	Exact 95% CI for percentage
Valsartan strategy (N=36)	36	25 (69.4)	53.1, 82.0
Amlodipine strategy (N=43)	43	28 (65.1)	50.2, 77.6
Overall (N=79)	79	53 (67.1)	56.1, 76.4

N is the number in Extension ITT population; n is the number of extension ITT patients included in the analysis.

Secondary Objective Result(s)

Core Study

Percentage of patients achieving blood pressure control (<140/90 mmHg) at Weeks 4, 8 and 11 (Intent-to-treat population)

Week	Treatment	n	Incidence rate (%)	Odds ratio Valsartan/ Amlodipine	95% CI for odds ratio	p-value for superiority
Week 4	Valsartan strategy (N=632)	632	367 (58.1)	1.196	0.952, 1.502	0.1235
	Amlodipine strategy (N=631)	631	340 (53.9)			
Week 8	Valsartan strategy (N=632)	632	444 (70.3)	1.315	1.035, 1.672	0.0252*
	Amlodipine strategy (N=631)	631	407 (64.5)			
Week 11	Valsartan strategy (N=632)	632	478 (75.6)	1.579	1.227, 2.031	0.0004*
	Amlodipine strategy (N=631)	631	421 (66.7)			

N is the number in ITT population; n is the number of ITT patients included in the analysis at each time point.
An odds ratio >1 favors the Valsartan strategy treatment group. Lower 95% CI > 0.6429 concludes non-inferiority, Lower 95% CI > 1 concludes superiority. * p-value significant at 5 % level.
Logistic regression model with treatment, country and stage of hypertension or failed monotherapy as factors.

Change from baseline in MSSBP at Weeks 4, 8, 11, 14 and endpoint (Intent-to-treat population)

Week	Treatment	n	LSM change (SEM)	Difference (Valsartan - Amlodipine)	95% CI for difference	p-value
Week 4	Valsartan strategy (N=632)	632	-15.30 (0.531)	-1.77	-2.94, -0.61	0.0029*
	Amlodipine strategy (N=631)	630	-13.53 (0.528)			
Week 8	Valsartan strategy (N=632)	614	-19.61 (0.542)	-1.61	-2.80, -0.43	0.0078*
	Amlodipine strategy (N=631)	588	-18.00 (0.544)			
Week 11	Valsartan strategy (N=632)	603	-21.36 (0.502)	-1.93	-3.04, -0.83	0.0006*
	Amlodipine strategy (N=631)	553	-19.42 (0.510)			
Week 14	Valsartan strategy (N=632)	600	-22.32 (0.474)	-1.00	-2.05, 0.05	0.0630
	Amlodipine strategy (N=631)	539	-21.32 (0.486)			
Endpoint (1)	Valsartan strategy (N=632)	632	-21.72 (0.498)	-2.11	-3.20, -1.01	0.0002*
	Amlodipine strategy (N=631)	631	-19.61 (0.495)			

N is the number in ITT population; n is the number of ITT patients included in the analysis at each time point.
(1) Endpoint is the value at Week 14 or LOCF value.
Negative values for estimated difference favor Valsartan strategy. * Significant at 5% level.
LSM change=least squares mean change from baseline, SEM=standard error of the least squares mean.
ANCOVA model with treatment, country, baseline MSSBP and stage of hypertension or failed monotherapy as factors.

Change from baseline in MSDBP at Weeks 4, 8, 11, 14 and endpoint (Intent-to-treat population)

Week	Treatment	n	LSM change (SEM)	Difference (Valsartan - Amlodipine)	95% CI for difference	p-value
Week 4	Valsartan strategy (N=632)	632	-8.92 (0.331)	-0.90	-1.62, -0.17	0.0160*
	Amlodipine strategy (N=631)	630	-8.03 (0.330)			
Week 8	Valsartan strategy (N=632)	614	-10.59 (0.353)	-0.84	-1.62, -0.07	0.0328*
	Amlodipine strategy (N=631)	588	-9.75 (0.356)			
Week 11	Valsartan strategy (N=632)	603	-12.05 (0.340)	-0.56	-1.31, 0.20	0.1469

	Amlodipine strategy (N=631)	553	-11.50 (0.347)			
Week 14	Valsartan strategy (N=632)	600	-12.78 (0.327)	-0.68	-1.41, 0.05	0.0672
	Amlodipine strategy (N=631)	539	-12.10 (0.336)			
Endpoint (1)	Valsartan strategy (N=632)	632	-12.53 (0.331)	-1.46	-2.19, -0.73	<0.0001*
	Amlodipine strategy (N=631)	631	-11.07 (0.330)			

N is the number in ITT population; n is the number of ITT patients included in the analysis at each time point.
(1) Endpoint is the value at Week 14 or LOCF value.
Negative values for estimated difference favor Valsartan strategy. * Significant at 5% level.
LSM change=least squares mean change from baseline, SEM=standard error of the least squares mean.
ANCOVA model with treatment, country, baseline MSDBP and stage of hypertension or failed monotherapy as factors.

Percentage of patients achieving blood pressure control (<140/90 mmHg) at Weeks 4, 8, 11 and 14 by prior hypertensive medication history (Intent-to-treat population)

Strata: Treatment naïve (Stage 1 and 2)

Week	Treatment	n	Incidence rate (%)	Odds ratio Valsartan / Amlodipine	95% CI for odds ratio	p-value for superiority
Week 4	Valsartan strategy (N=307)	307	187 (60.9)	1.257	0.905, 1.745	0.1726
	Amlodipine strategy (N=294)	294	163 (55.4)			
Week 8	Valsartan strategy (N=307)	307	215 (70.0)	1.074	0.754, 1.530	0.6925
	Amlodipine strategy (N=294)	294	202 (68.7)			
Week 11	Valsartan strategy (N=307)	307	236 (76.9)	1.230	0.841, 1.800	0.2864
	Amlodipine strategy (N=294)	294	215 (73.1)			
Week 14	Valsartan strategy (N=307)	307	240 (78.2)	1.298	0.887, 1.900	0.1793
	Amlodipine strategy (N=294)	294	216 (73.5)			

N is the number in ITT population; n is the number of ITT patients included in the analysis at each time-point.
An odds ratio >1 favors the Valsartan strategy. Lower 95% CI >0.6429 concludes non-inferiority.
Lower 95% CI >1 concludes superiority. * p-value significant at 5% level.
Logistic regression model with treatment and country as factors.

Percentage of patients achieving blood pressure control (<140/90 mmHg) at Weeks 4, 8, 11 and 14 by prior hypertensivemedication history (Intent-to-treat population)

Strata = Failed monotherapy

Week	Treatment	n	Incidence rate (%)	Odds ratio Valsartan / Amlodipine	95% CI for odds ratio	p-value for superiority
Week 4	Valsartan strategy (N=325)	325	180 (55.4)	1.116	0.818, 1.523	0.4874
	Amlodipine strategy (N=337)	337	177 (52.5)			
Week 8	Valsartan strategy (N=325)	325	229 (70.5)	1.564	1.128, 2.167	0.0073*
	Amlodipine strategy (N=337)	337	205 (60.8)			
Week 11	Valsartan strategy (N=325)	325	242 (74.5)	1.879	1.342, 2.631	0.0002*
	Amlodipine strategy (N=337)	337	206 (61.1)			
Week 14	Valsartan strategy (N=325)	325	258 (79.4)	2.373	1.656, 3.401	<0.0001*
	Amlodipine strategy (N=337)	337	212 (62.9)			

N is the number in ITT population; n is the number of ITT patients included in the analysis at each time-point.
An odds ratio >1 favors the Valsartan strategy. Lower 95% CI >0.6429 concludes non-inferiority.

Lower 95% CI >1 concludes superiority. * p-value significant at 5% level.
Logistic regression model with treatment and country as factors.

Extension Study

Percentage of patients achieving blood pressure control (<140/90 mmHg) at Week 22 (Intent-to-treat population)

Treatment	n	Incidence rate (%)	Exact 95% CI for percentage
Valsartan strategy (N=632)	632	523 (82.8)	79.6, 85.5
Amlodipine strategy (N=631)	631	456 (72.3)	68.6, 75.6
Overall (N=1263)	1263	979 (77.5)	75.1, 79.7

N is the number in ITT population; n is the number of ITT patients included in the analysis.
For patients not entering the extension study, the core study endpoint visit was brought forward to Week 22.

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with AEs reported by system organ class during the core study phase (Safety population)

Primary system organ class	Valsartan strategy (N=632) n(%)	Amlodipine strategy (N=634) n(%)	Total (N=1266) n(%)
Number of patients with any AE	**262 (41.5%)**	**338 (53.3%)**	**600 (47.4%)**
Nervous system disorders	62 (9.8)	70 (11.0)	132 (10.4)
Musculoskeletal and connective tissue disorders	55 (8.7)	55 (8.7)	110 (8.7)
Infections and infestations	52 (8.2)	66 (10.4)	118 (9.3)
Gastrointestinal disorders	45 (7.1)	48 (7.6)	93 (7.3)
General disorders and administration site conditions	42 (6.6)	166 (26.2)	208 (16.4)
Ear and labyrinth disorders	20 (3.2)	9 (1.4)	29 (2.3)
Skin and subcutaneous tissue disorders	18 (2.8)	33 (5.2)	51 (4.0)
Respiratory, thoracic and mediastinal disorders	16 (2.5)	12 (1.9)	28 (2.2)
Vascular disorders	16 (2.5)	19 (3.0)	35 (2.8)
Metabolism and nutrition disorders	15 (2.4)	9 (1.4)	24 (1.9)
Cardiac disorders	13 (2.1)	14 (2.2)	27 (2.1)
Renal and urinary disorders	12 (1.9)	12 (1.9)	24 (1.9)
Reproductive system and breast disorders	12 (1.9)	6 (<1.0)	18 (1.4)
Psychiatric disorders	10 (1.6)	13 (2.1)	23 (1.8)
Injury, poisoning and procedural complications	9 (1.4)	17 (2.7)	26 (2.1)
Eye disorders	8 (1.3)	6 (<1.0)	14 (1.1)
Immune system disorders	3 (<1.0)	0	3 (<1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (<1.0)	1 (<1.0)	4 (<1.0)
Investigations	2 (<1.0)	3 (<1.0)	5 (<1.0)
Endocrine disorders	1 (<1.0)	0	1 (<1.0)
Hepatobiliary disorders	1 (<1.0)	2 (<1.0)	3 (<1.0)
Blood and lymphatic system disorders	0	2 (<1.0)	2 (<1.0)

AEs are ordered by descending frequency of primary system organ class in Valsartan strategy group.

Number (%) of patients with AEs reported by system organ class during the extension study phase (Extension safety population)

Primary system organ class	Valsartan strategy (N=36) n(%)	Amlodipine strategy (N=43) n(%)	Total (N=79) n(%)
Number of patients with any AE	**8 (22.2)**	**9 (20.9)**	**17 (21.5)**
Cardiac disorders	2 (5.6)	1 (2.3)	3 (3.8)
Respiratory, thoracic and mediastinal disorders	2 (5.6)	1 (2.3)	3 (3.8)
Congenital, familial and genetic disorders	1 (2.8)	0	1 (1.3)
Gastrointestinal disorders	1 (2.8)	1 (2.3)	2 (2.5)
Infections and infestations	1 (2.8)	2 (4.7)	3 (3.8)
Musculoskeletal and connective tissue disorders	1 (2.8)	1 (2.3)	2 (2.5)
Nervous system disorders	1 (2.8)	0	1 (1.3)
Renal and urinary disorders	1 (2.8)	0	1 (1.3)
Skin and subcutaneous tissue disorders	1 (2.8)	0	1 (1.3)
Ear and labyrinth disorders	0	1 (2.3)	1 (1.3)
General disorders and administration site conditions	0	1 (2.3)	1 (1.3)
Hepatobiliary disorders	0	1 (2.3)	1 (1.3)
Investigations	0	1 (2.3)	1 (1.3)
Metabolism and nutrition disorders	0	3 (7.0)	3 (3.8)
Reproductive system and breast disorders	0	1 (2.3)	1 (1.3)

AEs are ordered by descending frequency of primary system organ class in Valsartan strategy group.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Core study phase (Safety population)

Primary Preferred term	Valsartan strategy (N=632) n(%)	Amlodipine strategy (N=634) n(%)	Total (N=1266) n(%)
Number Of Patients With Any AE	**262 (41.5%)**	**338 (53.3%)**	**600 (47.4%)**
Headache	25 (4.0)	39 (6.2)	64 (5.1)
Dizziness	24 (3.8)	11 (1.7)	35 (2.8)
Back Pain	16 (2.5)	6 (<1.0)	22 (1.7)
Influenza	14 (2.2)	14 (2.2)	28 (2.2)
Oedema Peripheral	14 (2.2)	142 (22.4)	156 (12.3)
Vertigo	13 (2.1)	6 (<1.0)	19 (1.5)
Diarrhoea	12 (1.9)	6 (<1.0)	18 (1.4)
Fatigue	12 (1.9)	9 (1.4)	21 (1.7)
Asthenia	10 (1.6)	10 (1.6)	20 (1.6)
Nasopharyngitis	10 (1.6)	5 (<1.0)	15 (1.2)

AEs are ordered by descending frequency of primary Preferred term in Valsartan strategy group.

Extension study phase (Extension safety population)

Table -1 Number (%) of patients with AEs reported by system organ class during the extension study phase (Extension safety population)

Primary system organ class	Valsartan strategy (N=36) n(%)	Amlodipine strategy (N=43) n(%)	Total (N=79) n(%)
Number of patients with any AE	**8 (22.2)**	**9 (20.9)**	**17 (21.5)**
Cardiac disorders	2 (5.6)	1 (2.3)	3 (3.8)
Respiratory, thoracic and mediastinal disorders	2 (5.6)	1 (2.3)	3 (3.8)
Congenital, familial and genetic disorders	1 (2.8)	0	1 (1.3)
Gastrointestinal disorders	1 (2.8)	1 (2.3)	2 (2.5)
Infections and infestations	1 (2.8)	2 (4.7)	3 (3.8)
Musculoskeletal and connective tissue disorders	1 (2.8)	1 (2.3)	2 (2.5)
Nervous system disorders	1 (2.8)	0	1 (1.3)
Renal and urinary disorders	1 (2.8)	0	1 (1.3)
Skin and subcutaneous tissue disorders	1 (2.8)	0	1 (1.3)
Ear and labyrinth disorders	0	1 (2.3)	1 (1.3)
General disorders and administration site conditions	0	1 (2.3)	1 (1.3)
Hepatobiliary disorders	0	1 (2.3)	1 (1.3)
Investigations	0	1 (2.3)	1 (1.3)
Metabolism and nutrition disorders	0	3 (7.0)	3 (3.8)
Reproductive system and breast disorders	0	1 (2.3)	1 (1.3)

AEs are ordered by descending frequency of primary system organ class in Valsartan strategy group.

Serious Adverse Events and Deaths

Number (%) of patients who died, had serious or clinically significant AEs or discontinued study drug due to AEs during the core study phase (Safety population)

	Valsartan strategy (N=632) n(%)	Amlodipine strategy (N=634) n(%)	Total (N=1266) n(%)
Deaths	0	0	0
SAEs	8 (1.3)	9 (1.4)	17 (1.3)
SAEs leading to study drug discontinuation	2 (<1.0)	4 (<1.0)	6 (<1.0)
AEs leading to study drug discontinuation	22 (3.5)	71 (11.2)	93 (7.3)

In the core study 8 patients experienced an SAEs in the valsartan strategy (atrial flutter, metrorrhagia & ovarian cyst, cholangitis, myopericarditis, ulcerative colitis, lumbar vertebral fracture, renal cell carcinoma, breast cancer) and 9 in the amlodipine strategy (radius fracture, carpal tunnel syndrome, hypovolaemic shock & anxiety disorder, urinary incontinence, ankle fracture, syncope, myocardial infarction & jaundice, acute pancreatitis, vasovagal syncope)

Number (%) of patients who died, had serious or clinically significant AEs or discontinued study drug due to AEs during the extension study phase (Extension safety population)

	Valsartan strategy (N=36) n(%)	Amlodipine strategy (N=43) n(%)	Total (N=79) n(%)
Deaths	0	0	0
SAEs	0	0	0
SAEs leading to study drug discontinuation	0	0	0
AEs leading to study drug discontinuation	0	0	0

Other Relevant Findings - edema

Number (%) of patients with an AE of edema during the core study phase by preferred term (Safety population)

Category	Valsartan strategy (N=632) n(%)	Amlodipine strategy (N=634) n(%)	Total (N=1266) n(%)
Number of patients with any AE of edema	17 (2.7)	153 (24.1)	170 (13.4)
Edema	2 (<1.0)	6 (<1.0)	8 (<1.0)
Peripheral edema	15 (2.4)	149 (23.5)	164 (13.0)

A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment

Number (%) of patients with an AE of edema during the extension study phase by preferred term (Extension safety population)

Category	Valsartan strategy (N=36) n(%)	Amlodipine strategy (N=43) n(%)	Total (N=79) n(%)
Number of patients with any AE of edema	0	0	0

A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment

Date of Clinical Trial Report

16-May-2008

Date Inclusion on Novartis Clinical Trial Results Database

02-Apr-2008

Date of Latest Update

12-Aug-2008