Sponsor

Novartis

Generic Drug Name

Valsartan

Trial Indication(s)

Hypertension

Protocol Number

CVAL489E0108

Protocol Title

Multinational, multicenter, double-blind, randomized, active controlled, parallel group study comparing the efficacy and safety of long-term treatment with valsartan, captopril and their combination in high-risk patients after myocardial infarction

Clinical Trial Phase

Phase III

Study Start/End Dates

31-Dec-1998 to 23-May-2003

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

VALIANT was a prospective multinational, multicenter, double-blind, randomized, active-controlled phase III study with three parallel treatment groups: valsartan monotherapy, the combination of valsartan and captopril, or captopril monotherapy. The planned study duration was variable, and depended upon the actual accrual rate, the length of the accrual period, and the observed death rate. For planning purposes, the study duration was expected to be approximately 4 years including an enrollment period of 18 months. If the required number of events was not observed after a study duration of 6 years, however, the study was to be closed and considered completed.

Centers

931 centers in 24 countries: Argentina (59), Australia (22), Austria (7), Belgium (7), Brazil (24), Canada (65), Czech Republic (9), Denmark (31), France (24), Germany (38), Hungary (16), Ireland (6), Italy (41), Netherlands (25), New Zealand (12), Norway (2), Poland (20), Russia (80), Slovakia (9), South Africa (10), Spain (9), Sweden (28), United Kingdom (54), United States of America (333).

Publication

Pfeffer MA, McMurray JJ, Velazquez EJ, et al (2003) Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003 Nov 13;349(20):1893-906.

Objectives:

Primary objective:

- To demonstrate that long-term administration of valsartan given as monotherapy is more effective than captopril given as monotherapy in the reduction of total mortality after an acute MI.
- To demonstrate that long-term administration of the combination of valsartan with captopril is more effective than captopril given as monotherapy in the reduction of total mortality after an acute MI.

- If valsartan as monotherapy cannot be shown to be superior to captopril as in objective 1, to demonstrate that long-term administration of valsartan given as monotherapy is at least as effective as captopril given as monotherapy in the reduction of total mortality after an acute MI.

Secondary objective:

- To demonstrate that long-term administration of the combination of valsartan with captopril is more effective than valsartan given as monotherapy in the reduction of total mortality after an acute MI.

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

Valsartan 20 mg, 40 mg, 80 mg, and 160 mg capsules for oral administration. Doses were taken in the morning, at mid-day, and in the evening.

Statistical Methods

The efficacy analyses, unless otherwise mentioned, were carried out using time-to-event analysis. For time-to-event efficacy variables, the date of randomization was used as the baseline. Time-to-event variables were analyzed by the Cox-regression with treatment group and covariates of baseline age (as a continuous variable) and previous Myocardial infarction (MI) (as an indicator: Yes or No). Kaplan-Meier estimate and log-rank test were also performed for each variable as a supportive analysis.

As planned, interim analyses for safety were performed by the independent DSMB statistician after the first 1000 patients were enrolled and twice yearly thereafter. Two of them included formal interim analyses for the primary efficacy endpoint. For each interim analysis the data set analyzed consisted of all patients randomized prior to the cut-off date. No criteria were defined to establish non-inferiority of valsartan relative to captopril based on an interim analysis, as the trial would not be concluded early due to a finding of non inferiority.

There were two primary treatment comparisons: (1) valsartan versus captopril (both superiority and non-inferiority assessments) and (2) valsartan + captopril versus captopril (superiority assessment only). Each comparison used an overall 2.53% significance level

adjusted by Sidak's inequality. Superiority assessment was based on a two-sided test for the null hypothesis of no treatment difference and the corresponding two-sided confidence interval was provided. The significance level used for the final analysis was further adjusted for all interim analyses, using a pre-specified Lan- DeMets alpha spending function with O'Brien-Fleming-type boundaries. Therefore, the 97.82% confidence interval (i.e., 2.18% significance level) for the primary endpoint was provided at the final analysis for the superiority assessment. The non-inferiority assessment was performed at the final analysis based on a one-sided 97.47% confidence interval and the corresponding p-value for testing the null hypothesis of inferiority. The non-inferiority threshold of 1.13 for hazard ratio (valsartan versus captopril) was pre-specified for the primary endpoint. With the non-inferiority threshold, it was estimated to preserve at least 55% of mortality benefit of captopril according to a meta analysis result from the previous placebo-controlled MI studies (SAVE, AIRE, and TRACE) with a similar population.

Similar analyses were performed for the secondary variables and the same non-inferiority threshold was used. Hochberg's step-up procedure was used to make an alpha adjustment for the multiplicity of three variables. Subgroup analyses for treatment comparisons were performed in the subgroups for demographics, baseline disease/risk factors, and baseline medications. Safety assessments consisted of monitoring and recording the pre-defined safety and tolerability parameters, SAEs, and the regular measurement of vital signs.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Patients who had sustained an acute MI and were randomized no earlier than 12 hours, and no later than 10 days after the onset of symptoms.
- Patients also had to have evidence of heart failure and/or left ventricular (LV) systolic dysfunction.

Exclusion Criteria:

- Failure to provide informed consent
- Cardiogenic shock (within the 24 hours prior to randomization)
- Systolic blood pressure < 100 mm Hg
- Serum creatinine > 221 µmol/L (2.5 mg/dL) (most recent value obtained after the qualifying MI and before randomization)
- Known or suspected bilateral renal artery stenosis
- Stroke or transient ischemic attack within the previous one month

- Refractory potentially lethal ventricular arrhythmia
- Refractory angina
- Cardiac surgery planned to occur within the 15 days after randomization
- Known intolerance of, or contra-indication to, an ACE inhibitor or angiotensin receptor blocker (ARB)
- Clinically significant right ventricular qualifying MI
- Pre-existing valvular heart disease likely to require surgery within the next three months
- Obstructive cardiomyopathy
- Serious non-cardiovascular disease severely limiting life expectancy
- Previous major organ (e.g., lung, liver, heart, kidney) transplantation or on transplant waiting list
- Other conditions/circumstances likely to lead to poor treatment adherence (e.g., history of poor compliance, alcohol or drug dependency, psychiatric illness, no fixed abode)
- Current participation in another clinical trial in which a patient was taking an investigational drug. A patient in the follow-up period of another clinical trial but no longer taking the investigational drug, or patients in a clinical trial with a drug already registered in this indication could be considered for inclusion in the study if in accordance with local regulations and if advance permission from Novartis was obtained.
- Current participation in another clinical trial with an investigational medical device except for non-coated or heparin-coated stents.

Participant Flow Table

Patient disposition by treatment (primary analysis population)

	Valsartan	Valsartan + Captopril	Captopril	All
	n (%)	n (%)	n (%)	n (%)
Randomized patients (primary analysis population)	4909 (100.0)	4885 (100.0)	4909 (100.0)	14703 (100)
Total completed [1]	4683 (95.4)	4656 (95.3)	4691 (95.6)	14030 (95.4)
Death [2]	941 (19.2)	911 (18.6)	933 (19.0)	2785 (18.9)
Alive	3742 (76.2)	3745 (76.7)	3758 (76.6)	11245 (76.5)
Premature study termination	226 (4.6)	229 (4.7)	218 (4.4)	673 (4.6)
Subject withdrew consent	195 (4.0)	197 (4.0)	197 (4.0)	589 (4.0)
Death [2]	39 (0.8)	30 (0.6)	25 (0.5)	94 (0.6)
Alive	134 (2.7)	151 (3.1)	155 (3.2)	440 (3.0)
Vital status unknown [3]	53 (1.1)	48 (0.9)	38 (0.8)	139 (0.9)

[1] Completed = Patients whose vital status was known after 01-Oct-2002 and who did not withdraw consent.
[2] One patient in the valsartan group died after the 07-Jan-2003 cut-off date for adjudication and analysis
[3] Vital status was unknown as of 01-Oct-2002. Included are both patients who were lost to follow-up and patients who withdrew consent for whom vital status could not be ascertained.

Reasons for premature permanent discontinuation of study drug by treatment (primary analysis population)

	Valsartan	Valsartan + Captopril	Captopril	Overall
	n (%)	n (%)	n (%)	n (%)
Patients studied				
Total no. of patients randomized	4909	4885	4909	14703
No. who prematurely discontinued study drug but received at least one dose of study drug	1001 (20.4)	1139 (23.3)	1055 (21.5)	3195 (21.7)
Principal reasons:				
Adverse event [1]	282 (5.7)	438 (9.0)	375 (7.6)	1095 (7.4)
Withdrew consent to continue on study drug	380 (7.7)	373 (7.6)	355 (7.2)	1108 (7.5)
Investigator decision	173 (3.5)	145 (3.0)	150 (3.1)	468 (3.2)
Lost to follow-up at time of study drug discontinuations [2]	31 (0.6)	35 (0.7)	30 (0.6)	96 (0.7)
Treatment failure	3 (0.1)	3 (0.1)	2 (0.0)	8 (0.1)
Unknown	132 (2.7)	145 (3.0)	143 (2.9)	420 (2.9)

[1] Including non-AE items associated with MedDRA codes and/or other AE specified.
[2] Vital status was ascertained at study completion for some patients who were lost to follow up at the time of study drug discontinuation.

Baseline Characteristics

Baseline demographics summary by treatment (primary analysis population)

Baseline / demographic characteristic	Valsartan (N=4909)	Valsartan + Captopril (N=4885)	Captopril (N=4909)	All (N=14,703)
	n (%)	n (%)	n (%)	n (%)
Sex N (%)				
Male	3365 (68.5)	3395 (69.5)	3373 (68.7)	10133 (68.9)
Female	1544 (31.5)	1490 (30.5)	1536 (31.3)	4570 (31.1)
Race N (%)				
Caucasian	4604 (93.8)	4553 (93.2)	4591 (93.5)	13748 (93.5)
Black	125 (2.5)	137 (2.8)	145 (3.0)	407 (2.8)
Asian	44 (0.9)	53 (1.1)	44 (0.9)	141 (1.0)
Other	136 (2.8)	142 (2.9)	129 (2.6)	407 (2.8)
Age (years)				
N	4909	4885	4909	14703
Mean	64.5	64.1	64.4	64.3
SD	11.80	11.92	11.76	11.83
Median	65.0	65.0	65.0	65
Age group N (%)				
< 65 years	2313 (47.1)	2370 (48.5)	2305 (47.0)	6988 (47.5)
≥ 65 years	2596 (52.9)	2515 (51.5)	2604 (53.0)	7715 (52.5)
Height (cm)				
N	4819	4778	4804	14401
Mean	169.4	169.8	169.6	169.6
SD	9.44	9.74	9.50	9.56
Median	170.0	170.0	170.0	170

Baseline / demographic characteristic	Valsartan (N=4909)	Valsartan + Captopril (N=4885)	Captopril (N=4909)	All (N=14,703)
	n (%)	n (%)	n (%)	n (%)
Weight (kg) at baseline				
N	4839	4801	4833	14473
Mean	80.5	80.4	80.1	80.4
SD	16.59	16.40	16.35	16.45
Median	79.0	79.0	78.0	79
Systolic BP (mmHg) at baseline				
N	4905	4882	4909	14696
Mean	122.7	122.5	122.8	122.7
SD	16.85	17.10	16.99	16.98
Median	120.0	120.0	120.0	120
Diastolic BP (mmHg) at baseline				
N	4899	4879	4909	14687
Mean	72.3	72.3	72.4	72.3
SD	11.29	11.35	11.18	11.27
Median	70.0	70.0	70.0	70
Heart rate (bpm) at baseline				
N	4897	4872	4900	14669
Mean	76.2	76.2	76.2	76.2
SD	12.98	12.74	12.76	12.83

Median	75.0	75.0	75.0	75.0
Serum creatinine (mg/dL) at baseline				
N	4903	4882	4904	14689
Mean	1.1	1.1	1.1	1.1
SD	0.31	0.31	0.35	0.33
Median	1.1	1.1	1.1	1.1

Summary of Efficacy

Primary Outcome Result(s)

Analysis results for the primary endpoint – all cause mortality (primary analysis population)

	Valsartan vs. Captopril (N=4909) (N=4909)			Valsartan + Captopril vs. Captopril (N=4885) (N=4909)		
	No. of deaths (%)[1] valsartan/captopril	Hazard ratio CI [2]	p-value	No. of deaths (%)[1] comb/captopril	Hazard ratio CI [2]	p-value
All-cause mortality	979 (19.9) /958 (19.5)	1.001 (0.902, 1.111) (0, 1.094)[4]	0.9824[3] 0.0038[4]	941 (19.3) /958 (19.5)	0.984 (0.886, 1.093)	0.7260[3]

1. Percent = raw estimate of the mortality rate: (number of deaths / number of patients in each group)*100%.
2. Hazard ratio = valsartan or valsartan + captopril / captopril. A value less than 1.0 is in favor of valsartan or valsartan + captopril. The two-sided CI (97.82%) has been adjusted for all interim analyses.
3. P-value is from Cox regression model with factor of treatment group and covariates of age (continuous) and previous MI (yes/no) for a two-sided null hypothesis with no treatment difference.
4. One-sided 97.47% CI for non-inferiority analysis of valsartan vs. captopril. The p-value is one-sided and is based on a pre-defined non-inferiority threshold of 1.13 for hazard ratio from a meta-analysis.

Sensitivity analyses for all-cause mortality

	Valsartan vs. Captopril			Valsartan + Captopril vs. Captopril		
All-cause mortality	No. of deaths (%)[1] valsartan/captopril	Hazard ratio CI [2]	p-value	No. of deaths (%)[1] comb/captopril	Hazard ratio CI [2]	p-value
Per-protocol[5]	786 (16.5) /779 (16.3)	0.979 (0.872, 1.099) (0, 1.081)[4]	0.6735[3] 0.0023[4]	757 (15.9) /779 (16.3)	0.992 (0.883, 1.116)	0.8816[3]
Safety[6]	969 (19.8) /946 (19.4)	1.003 (0.903, 1.114) (0, 1.097)[4]	0.9430[3] 0.0046[4]	928 (19.1) /946 (19.4)	0.982 (0.883, 1.091)	0.6870[3]

1. Percent = raw estimate of the mortality rate: (number of deaths / number of patients in each group)*100%; total number of patients in the valsartan, valsartan + captopril, and captopril groups is 4764, 4751, and 4770,respectively, for the per-protocol population and 4885, 4862, and 4879, respectively, for the safety population.
2. Hazard ratio = valsartan or valsartan + captopril / captopril. A value less than 1.0 is in favor of valsartan or valsartan + captopril. The two-sided CI (97.82%) has been adjusted for all interim analyses.
3. P-value is from Cox regression model with factor of treatment group and covariates of age (continuous) and previous MI (yes/no) for a two-sided null hypothesis with no treatment difference.
4. One-sided 97.47% CI for non-inferiority analysis of valsartan vs. captopril. The p-value is one-sided and is based on a pre-defined non-inferiority threshold of 1.13 for hazard ratio from a meta-analysis.

5. Per-protocol population includes all patients who met criteria for acute MI and received at least one dose of study drug. Differences in mortality in the per-protocol vs. primary analysis populations were due to censoring procedures for the per-protocol population and patients who were randomized but did not receive study drug.
6. Safety population includes all patients who received at least one dose of study drug.

Secondary Outcome Result(s)

Number (%) of secondary endpoint events (primary analysis population)

Endpoint	Valsartan N = 4909 n (%)	Valsartan + Captopril N = 4885 n (%)	Captopril N = 4909 n (%)	Overall N = 14703 n (%)
Cardiovascular mortality	827 (16.8)	827 (16.9)	830 (16.9)	2484 (16.9)
Three-event composite[1]	1529 (31.1)	1518 (31.1)	1567 (31.9)	4614 (31.4)
Cardiovascular mortality	827 (16.8)	827 (16.9)	830 (16.9)	2484 (16.9)
Hospitalization for heart failure	813 (16.6)	774 (15.8)	801 (16.3)	2388 (16.2)
Recurrent non-fatal MI[2]	397 (8.1)	365 (7.5)	402 (8.2)	1164 (7.9)
Five-event composite[1]	1612 (32.8)	1580 (32.3)	1641 (33.4)	4833 (32.9)
Additional variables:				
Non-fatal stroke[3]	131 (2.7)	119 (2.4)	123 (2.5)	373 (2.5)
Cardiac arrest with resuscitation	56 (1.1)	52 (1.1)	59 (1.2)	167 (1.1)

1. Only the first event was counted toward the composite endpoints if a patient experienced two or more events.
2. Only MI occurring ≥ 15 days before death is included.

3. Only stroke occurring ≥ 15 days before death is included.

Analysis results for the secondary endpoint, comparing valsartan vs. captopril and valsartan + captopril vs. captopril (primary analysis population)

Secondary efficacy endpoints	Valsartan vs. Captopril (N=4909) No. of events (%)[1] valsartan/captopril	Valsartan vs. Captopril (N=4909) Hazard ratio[2] 97.47% CI	Valsartan vs. Captopril (N=4909) p-value	Valsartan + Captopril vs. Captopril (N=4885) No. of events (%)[1] comb/captopril	Valsartan + Captopril vs. Captopril (N=4909) Hazard ratio[2] 97.47% CI	Valsartan + Captopril vs. Captopril (N=4909) p-value
CV mortality	827 (16.8) /830 (16.9)	0.976 (0.875, 1.090) (0, 1.075)[4]	0.6225[3] 0.0014[4]	827 (16.9) /830 (16.9)	0.997 (0.893, 1.113)	0.9523[3]
CV mortality, hospitalization for HF, and recurrent non-fatal MI	1529 (31.1) /1567 (31.9)	0.955 (0.881, 1.035) (0, 1.024)[4]	0.1983[3] <0.0001[4]	1518 (31.1) /1567 (31.9)	0.968 (0.893, 1.049)	0.3690[3]
CV mortality, hospitalization for HF, recurrent non-fatal MI, non-fatal stroke, and sudden cardiac arrest with resuscitation	1612 (32.8) /1641 (33.4)	0.961 (0.888, 1.039) (0, 1.029)[4]	0.2501[3] <0.0001[4]	1580 (32.3) /1641 (33.4)	0.961 (0.888, 1.040)	0.2607[3]

1. Percent = raw estimate of the event rate: (number of events / number of patients in each group)*100%.
2. Hazard ratio = valsartan or valsartan + captopril / captopril. A value less than 1.0 is in favor of valsartan or valsartan + captopril.
3. P-values are from Cox regression model with factor of treatment group and covariates of age (continuous) and previous MI (yes/no) for a two-sided null hypothesis with no treatment difference.
4. One-sided 97.47% CI for non-inferiority analysis of valsartan vs. captopril. The p-value is one-sided and is based on the same non-inferiority threshold defined for the primary endpoint..

Analysis results for cardiovascular (CV) mortality (per-protocol population[5])

Endpoint	Valsartan vs. Captopril (N=4764) (N=4770)			Valsartan + Captopril vs. Captopril (N=4751) (N=4770)		
	No. of CV deaths (%)[1] val/cap	Hazard ratio[2] 95% CI	p-value	No. of CV deaths (%)[1] comb/cap	Hazard ratio[2] 95% CI	p-value
CV mortality	681 (14.3) /688 (14.4)	0.962 (0.852, 1.085) (0, 1.069)	0.4676[3] 0.0014[4]	679 (14.3) / 688 (14.4)	1.006 (0.891, 1.135)	0.9144[3]

1. Percent = raw estimate of the mortality rate: (number of CV deaths / number of patients in each group)*100%.
2. Hazard ratio = valsartan or valsartan + captopril / captopril. A value less than 1.0 is in favor of valsartan or valsartan + captopril.
3. P-value is from Cox regression model with factor of treatment group and covariates of age (continuous) and previous MI (yes/no) for a two-sided null hypothesis with no treatment difference.
4. One-sided 97.47% CI for non-inferiority analysis of valsartan vs. captopril. The p-value is one-sided and is based on the same non-inferiority threshold defined for the primary endpoint.
5. Per-protocol population includes all patients who met criteria for acute MI and received at least one dose of study drug. Differences in mortality in the per-protocol vs. primary analysis populations were due to censoring procedures for the per-protocol population and patients who were randomized but did not receive study drug.

Summary of Safety

Safety Results

Number (%) of patients with serious adverse events by primary system organ class (safety population)

	Valsartan	Valsartan + Captopril	Captopril
	n (%)	n (%)	n (%)
Patients studied			
total no. of patients	4885 (100)	4862 (100)	4879 (100)
no. with at least one SAE [1]	2358 (48.3)	2290 (47.1)	2310 (47.3)
Primary system organ class [2]			
Blood and lymphatic system disorders	45 (0.9)	50 (1.0)	45 (0.9)
Cardiac disorders	1917 (39.2)	1838 (37.8)	1910 (39.1)
Congenital, familial and genetic disorders	1 (0.0)	3 (0.1)	0 (0.0)
Ear and labyrinth disorders	4 (0.1)	4 (0.1)	9 (0.2)
Endocrine disorders	3 (0.1)	1 (0.0)	0 (0.0)
Eye disorders	10 (0.2)	20 (0.4)	13 (0.3)
Gastrointestinal disorders	151 (3.1)	124 (2.6)	114 (2.3)
General disorders and administration site conditions	71 (1.5)	91 (1.9)	79 (1.6)
Hepatobiliary	31 (0.6)	27 (0.6)	16 (0.3)
Immune system disorders	5 (0.1)	4 (0.1)	9 (0.2)
Infections and infestations	145 (3.0)	128 (2.6)	134 (2.7)
Injury, poisoning, and procedural complications	65 (1.3)	62 (1.3)	56 (1.1)
Investigations	52 (1.1)	64 (1.3)	43 (0.9)
Metabolism and nutrition disorders	75 (1.5)	73 (1.5)	68 (1.4)
Musculoskeletal and nutrition disorders	44 (0.9)	37 (0.8)	43 (0.9)
Neoplasms benign, malignant and unspecified	91 (1.9)	64 (1.3)	86 (1.8)
Nervous system disorders	300 (6.1)	303 (6.2)	322 (6.6)
Psychiatric disorders	28 (0.6)	16 (0.3)	15 (0.3)
Renal and urinary disorders	154 (3.2)	153 (3.1)	108 (2.2)
Reproductive system and breast disorders	9 (0.2)	13 (0.3)	12 (0.2)
Respiratory, thoracic and mediastinal disorders	128 (2.6)	117 (2.4)	113 (2.3)
Skin and subcutaneous tissue disorders	39 (0.8)	48 (1.0)	47 (1.0)
Social circumstances	1 (0.0)	1 (0.0)	0 (0.0)
Surgical and medical procedures	9 (0.2)	10 (0.2)	9 (0.2)
Vascular disorders	218 (4.5)	220 (4.5)	158 (3.2)

[1] Excludes causes of death and reasons for hospitalization.
[2] A patient can have more than one event or type of event; each patient is counted once in each category.

Number (%) of patients with most frequent serious adverse events (≥0.5% in any treatment group) by treatment (safety population)

	Valsartan	Valsartan + Captopril	Captopril
	n (%)	n (%)	n (%)
Patients studied			
total no. of patients	4885 (100)	4862 (100)	4879 (100)
no. with at least one SAE [1]	2358 (48.3)	2290 (47.1)	2310 (47.3)
Preferred term [2]			
Cardiac failure NOS	1095 (22.4)	1014 (20.9)	1038 (21.3)
Angina unstable	812 (16.6)	796 (16.4)	787 (16.1)
Myocardial infarction	677 (13.9)	626 (12.9)	680 (13.9)
Cardiac arrest	200 (4.1)	205 (4.2)	207 (4.2)
Cerebrovascular accident	156 (3.2)	145 (3.0)	159 (3.3)
Hypotension NOS	128 (2.6)	155 (3.2)	96 (2.0)
Cerebral infarction	108 (2.2)	106 (2.2)	112 (2.3)
Transient ischaemic attack	60 (1.2)	62 (1.3)	80 (1.6)
Renal impairment NOS	55 (1.1)	57 (1.2)	34 (0.7)
Pneumonia NOS	54 (1.1)	46 (0.9)	49 (1.0)
Atrial fibrillation	47 (1.0)	34 (0.7)	37 (0.8)
Renal failure acute	41 (0.8)	36 (0.7)	24 (0.5)
Chest pain	34 (0.7)	60 (1.2)	46 (0.9)
Ventricular tachycardia	35 (0.7)	33 (0.7)	24 (0.5)
Renal failure NOS	32 (0.7)	29 (0.6)	20 (0.4)
Syncope	32 (0.7)	28 (0.6)	30 (0.6)
Anaemia NOS	29 (0.6)	31 (0.6)	32 (0.7)
Angina pectoris	30 (0.6)	40 (0.8)	27 (0.6)
Cardiac failure congestive	28 (0.6)	22 (0.5)	25 (0.5)
Gastrointestinal haemorrhage NOS	23 (0.5)	14 (0.3)	24 (0.5)
Hyperkalaemia	19 (0.4)	27 (0.6)	18 (0.4)
Blood creatinine increased	19 (0.4)	23 (0.5)	13 (0.3)
Cough	13 (0.3)	22 (0.5)	19 (0.4)

[1] Excludes causes of death and reasons for hospitalization.
[2] Listed in decreasing order of frequency in the valsartan group. A patient can have more than one event or type of event; each patient is counted once in each category.

Number (%) of patients who died (investigator assessment), had other serious or clinically significant adverse events or discontinued study drug due to adverse events (safety population)

	Valsartan n (%)	Valsartan + Captopril n (%)	Captopril n (%)
Patients studied			
total no. of patients [1]	4885 (100)	4862 (100)	4879 (100)
Serious or significant adverse events			
Deaths total (investigator assessment)	970 (19.9)	928 (19.1)	946 (19.4)
Suspected	5 (0.1)	2 (0.0)	3 (0.1)
Not related	927 (19.0)	901 (18.5)	919 (18.8)
Not specified [2]	38 (0.8)	25 (0.5)	24 (0.5)
SAEs total	2358 (48.3)	2290 (47.1)	2310 (47.3)
Suspected	123 (2.5)	200 (4.1)	114 (2.3)
SAEs during the first month of study treatment	949 (19.4)	1003 (20.6)	918 (18.8)
Hospitalizations	2709 (55.5)	2622 (53.9)	2709 (55.5)
Changes in study drug			
Permanent discontinuation due to any reason [4]	1001 (20.5)	1139 (23.4)	1055 (21.6)
Permanent discontinuation due to adverse events	282 (5.8)	438 (9.0)	375 (7.7)
Down-titration [3]	1443 (29.5)	1641 (33.8)	1379 (28.3)
Temporary discontinuation [3], [4]	809 (16.6)	865 (17.8)	787 (16.1)

[1] A patient can have more than one event or type of event; each patient is counted once in each category.
[2] No relationship to study drug was specified by the investigator.
[3] Includes patients with non-safety reasons for down-titration and temporary discontinuation.
[4] Frequencies of patients with all permanent discontinuations and temporary discontinuations derived from source table using number of patients in the safety population as the denominator.

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

17-Oct-2003