Sponsor

Novartis

Generic Drug Name

Valsartan + Simvastatin

Therapeutic Area of Trial

Hypertension and hypercholesterolemia

Approved Indication

Valsartan: Is indicated for the treatment of hypertension, post myocardial infarction, congestive heart failure.

Simvastatin: Is indicated for reductions in risk of coronary heart disease (CHD) mortality and cardiovascular events and in patients with hypercholesterolemia requiring modifications of lipid profiles

Study Number

CVAS489A2403

Title

A 12-week treatment, randomized, double-blind, parallel group, multicenter study to evaluate the efficacy of the valsartan/simvastatin combinations 160/20mg up titrated to 320/20mg versus 160/40mg up titrated to 320/40mg in patients with both essential hypertension and hypercholesterolemia

Phase of Development

Phase III

Study Start/End Dates

04-Nov-2005 to 07-Sep-2006

Study Design/Methodology

This study used a randomized, double-blind, double-dummy, parallel-group, multicenter, active-controlled, 2-treatment-arm, forced-titrated design. A screening/wash-out period of 2-4 weeks, depending on patient's lipid lowering and/or antihypertensive pre-treatment, was used to assess eligibility and to taper patients off disallowed medications. Upon confirmation of eligibility patients started the single-blind placebo run-in period at week -2.

At the baseline visit, patients fulfilling all criteria, entered the study and were randomized to take either valsartan 160mg/simvastatin 20mg or valsartan 160mg/simvastatin 40mg. Six weeks following randomization patients taking valsartan 160mg/simvastatin 20mg were forced-titrated to valsartan 320mg/simvastatin 20mg and patients taking valsartan 160mg/simvastatin 40mg were forced-titrated to valsartan 320mg/simvastatin 40mg for a duration of 6 additional weeks.

Centres

92 centers in 7 countries: Belgium (6), Canada (3), Germany (52), Norway (7), Poland (6), Russia (10), Sweden (8)

Publication

Ongoing

Objectives

Primary objective

To investigate if the combination of valsartan 160mg/simvastatin 40mg has superior efficacy compared to the combination of valsartan 160mg/simvastatin 20mg in the percentage change from baseline to week 6 in low density lipoprotein cholesterol (LDL-C)

Secondary objectives

To compare the effects of valsartan 160mg/simvastatin 20mg versus valsartan 160mg/simvastatin 40mg in reducing total cholesterol (TC), triglycerides (TG), non-high density lipoprotein cholesterol (non-HDL-C) and in increasing high density lipoprotein cholesterol (HDL-C) from baseline to week 6

To compare the effects of valsartan 320mg/simvastatin 20mg titrated treatment versus valsartan 320mg/simvastatin 40mg titrated treatment in reducing LDL-C, TC, TG, non-HDL-C and in increasing HDL-C from baseline to week 12

To estimate the percentage of patients who reach blood pressure (BP) and/or LDL-C control at week 6 and 12 in each treatment group

To estimate the BP responder rate at week 6 and 12 in each treatment group

To evaluate the safety and tolerability of the combination of valsartan 160mg/simvastatin 20mg titrated to valsartan 320mg/simvastatin 20mg, and valsartan 160mg/simvastatin 40mg titrated to valsartan 320mg/simvastatin 40mg.

Test Products, Doses, and Mode of Administration

Valsartan 160 mg capsules, and simvastatin 20 mg capsules, for oral administration (4 capsules a day, taken in the evening, approximately between 7:00 and 10:00 pm.).

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

None

Criteria for Evaluation

Primary variables

Change in LDL-C level from baseline to Week 6

Secondary variables

Change in LDL-C, TC, TG, non-HDLC and HDL-C

BP control, LDL-C control and combined BP and LDL-C control

BP responder rate

Safety and tolerability

Frequency of adverse events, incidence of clinically notable laboratory abnormalities, particularly involving vital signs.

Statistical Methods

The primary efficacy variable was percentage change from baseline in LDL-C to Week 6 Endpoint.

The percentage change in LDL-C was analyzed using analysis of variance. Treatment, country, previous treatment group (lipid lowering medication and antihypertensive medication, lipid lowering medication, antihypertensive medication, naïve for both) and diabetes (yes/no) were added as fixed factors. The least square means, treatment difference with 95% confidence interval, and p-value were presented.

The primary analysis was performed using the intent-to-treat (ITT) population. All patients from Center 59 (n = 27) were excluded from all analysis populations (ITT, per-protocol [PP] and safety) due to GCP violations with severe quality issues. The same analysis was performed for ITT including center 59 population and Per-protocol population also.

Summary statistics of LDL-C (mean, standard deviation, median, minimum and maximum) were presented for the ITT population at baseline, Week 6 and Week 12 for percentage change from baseline.

For the secondary variables the same statistical model was used as for the primary variable.

The least square means, treatment difference with 95% confidence interval, and p-value were presented.

For BP control and/or LDL-C control 95% confidence interval for each treatment group were presented at Baseline (for LDL-C and combined), Week 6 and Week 12. The control rates were defined as follows:

BP control: the proportion of patients who reach BP control (BP<140/90 mmHg non-diabetic patients and < 130/80 mmHg diabetic patients)

LDL-C control: patients who had no or 1 risk factor and the value of LDL-C < 4.1 mmol/l (160 mg/dl) or patients who had 2 or more risk factors and the value of LDL-C < 3.4 mmol/l (130 mg/dl) or patients with CHD and CHD risk equivalents and the value of LDL-C < 2.6 mmol/l (100 mg/dl)

Diabetes was regarded as a CHD risk equivalent. HDL ≥ 1.6 mmol/l (60mg/dL) counts as a 'negative' risk factor, i.e. its presence remove 1 risk factor from the total count.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

1. Male or female outpatients ≥ 18 years of age, at the first visit
2. Elevated LDL-C ≥ 3.4mmol/l (130mg/dl) [or ≥ 2.6mmol/l (100mg/dl) for diabetic patients] and < 4.9mmol/l (190mg/dl) and TG ≤ 4mmol/l (350mg/dl) based on lab results of lipid profile drawn at Visit 3 for previously treated patients and at the first visit and at week -2 for previously untreated patients.
3. MSSBP ≥ 140 mmHg (or ≥ 130 mmHg for diabetic patients) and < 180 and/or MSDBP ≥ 90 mmHg (or ≥ 80 mmHg for diabetic patients) and < 110 mmHg at the randomization visit for previously treated patients and at all visits prior randomization for previously untreated patients.
4. Written informed consent to participate in this study prior to any study procedures

Exclusion criteria

Patients with any of the following exclusion criteria could not be randomized in the study:

1. MSSBP ≥ 180 mmHg and/or MSDBP ≥ 110 mmHg at any time between the first visit and randomization
2. Inability to discontinue all prior lipid lowering and antihypertensive medications safely for a period of six and four weeks respectively prior to randomization
3. History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures
4. Prior or known muscular or neuromuscular disease of any type
5. A history of cardiovascular disease, including angina, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, transient ischemic attack, stroke, and peripheral artery disease
6. Known Keith-Wagener grade III or IV hypertensive retinopathy
7. Second or third degree heart block without a pacemaker, concurrent potentially life threatening arrhythmia or symptomatic arrhythmia, clinically significant valvular heart disease
8. Heart failure requiring treatment
9. Evidence of a secondary form of hypertension, to include coarctation of the aorta, hyperaldosteronism, Cushing's disease, unilateral or bilateral renal artery stenosis, pheochromocytoma, polycystic kidney disease
10. Evidence of hypercholesterolemia secondary to other causes.
11. Uncontrolled diabetes mellitus type 2, as defined by glycosylated hemoglobin HbA1c > 8% at the first visit
12. Diabetic patients requiring insulin treatment
13. Evidence of hepatic disease as determined by aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values > 2 x upper limit of normal (ULN) at the first visit
14. A history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt
15. Evidence of renal impairment as determined by one of the followings: serum creatinine > 1.5 x ULN at Visit 1, a history of dialysis, or a history of nephrotic syndrome. If creatinine is found to be between 1.5 and 2 x UNL, a retest can be performed prior to randomization
16. Serum creatine kinase (CK) levels > 2 x ULN at the first visit. In case of doubt the test should be redone at the discretion of the investigator
17. 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.
18. Any severe, life-threatening disease within the past five years
19. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug
20. Women of child-bearing potential unless using acceptable methods of contraception
21. Pregnant or nursing (lactating) women

22. Any surgical or medical condition which, at the discretion of the investigator, place the patient at higher risk from his/her participation in the study, or are 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. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer
25. History of noncompliance to medical regimens, or patients unwilling to comply with the study protocol
26. Persons directly involved in the execution of this protocol/study
27. Inability to communicate and comply with all study requirements

Number of Subjects

Patient disposition by treatment group (Randomized population)

Disposition/Reason	Val 160-320/ Simva 20 mg n (%)	Val 160-320/ Simva 40 mg n (%)	Total n (%)
Planned N	398	398	796
Randomized n	437 (100.0)	435 (100.0)	872 (100.0)
Intent-to-treat population (ITT) n (%)*	421 (96.3)	417 (95.9)	838 (96.1)
Completed n(%)	412 (94.3)	415 (95.4)	827 (94.8)
Withdrawn n (%)	25 (5.7)	20 (4.6)	45 (5.2)
Withdrawn due to adverse events n (%)	13 (3.0)	7 (1.6)	20 (2.3)
Withdrawn due to unsatisfactory therapeutic effect n (%)	1 (0.2)	2 (0.5)	3 (0.3)
Withdrawn for other reasons n (%)	11 (2.5)	11 (2.5)	22 (2.5)

*There were 14 patients excluded from Val 160-320/ Simva 20 mg and 13 patients excluded from Val 160-320/ Simva 40 mg at Center 59 (due to GCP violations with severe quality issues).

Demographic and Baseline Background Characteristics

Demographics by treatment group (ITT population)

Demographic Variable	Val 160-320/ Simva 20 mg N=421	Val 160-320/ Simva 40 mg N=417	Total N=838
Mean Age (year) (SD)	59.5 (10.29)	60.1 (9.70)	59.8 (9.99)
Gender n (%)			
Male	203 (48.2%)	198 (47.5%)	401 (47.9%)
Female	218 (51.8%)	219 (52.5%)	437 (52.1%)
Race n (%)			
Caucasian	420 (99.8%)	415 (99.5%)	835 (99.6%)
Asian	1 (0.2%)	0 (0.0%)	1 (0.1%)
Other	0 (0.0%)	2 (0.5%)	2 (0.2%)
LDL-C (mmol/L)			
Mean (SD)	4.050 (0.6231)	4.019 (0.6490)	4.035 (0.6359)
TC (mmol/L)			
Mean (SD)	6.234 (0.7273)	6.224 (0.7503)	6.229 (0.7384)
TG (mmol/L)			
Mean (SD)	1.707 (0.7463)	1.838 (0.9226)	1.772 (0.8408)
Non HDL-C (mmol/L)			
Mean (SD)	4.833 (0.6969)	4.851 (0.7410)	4.842 (0.7188)
HDL-C (mmol/L)			
Mean (SD)	1.401 (0.3670)	1.373 (0.3458)	1.387 (0.3567)
MSSBP (mmHg)			
Mean (SD)	153.639 (9.6751)	153.938 (9.4569)	153.788 (9.5626)
MSDBP (mmHg)			
Mean (SD)	93.641 (6.2272)	93.460 (6.0981)	93.551 (6.1603)

Baseline disease characteristics by treatment group (ITT population)

Baseline Variable	Val 160-320/ Simva 20 mg N=421	Val 160-320/ Simva 40 mg N=417	Total N=838
Diabetes status			
No	350 (83.1%)	341 (81.8%)	691 (82.5%)
Yes	71 (16.9%)	76 (18.2%)	147 (17.5%)
Smoking status			
No	371 (88.1%)	355 (85.1%)	726 (86.6%)
Yes	50 (11.9%)	62 (14.9%)	112 (13.4%)
CHD History in first degree relative*			
No	338 (80.3%)	339 (81.3%)	677 (80.8%)
Yes	82 (19.5%)	78 (18.7%)	160 (19.1%)
Missing	1 (0.2%)	0 (0.0%)	1 (0.1%)
Previous treatment			
Lipid lowering without antihypertensive	10 (2.4%)	12 (2.9%)	22 (2.6%)
Antihypertensive without lipid lowering	234 (55.6%)	234 (56.1%)	468 (55.8%)
Lipid lowering and antihypertensive	82 (19.5%)	79 (18.9%)	161 (19.2%)
Naïve to both	95 (22.6%)	92 (22.1%)	187 (22.3%)
Risk category			
CHD and CHD risk equivalents	75 (17.8%)	79 (18.9%)	154 (18.4%)
Multiple (2+) risk factors	235 (55.8%)	255 (61.2%)	490 (58.5%)
0-1 risk factor	111 (26.4%)	83 (19.9%)	194 (23.2%)

*CHD History in first degree relatives: Yes=> either female < 65 yrs; male < 55 yrs or both have CHD history; No=> Neither female < 65 yrs nor male < 55 years had CHD history

Primary Objective Result(s)

Primary efficacy analysis: Percent change from baseline to Week 6 in LDL-C (ITT population)

Treatment	n	LSM change in % (SEM)	Contrast	Difference	95% CI	p-value
Val 160-320/ Simva 20 mg (N=421)	415	-33.6 (1.55)	Val 160-320/Simva 40 mg vs Val 160-320/Simva 20 mg	-4.94	-7.52, -2.36	0.0002*
Val 160-320/ Simva 40 mg (N=417)	412	-38.5 (1.53)				

N is the number in ITT population; n is the number of ITT patients with both baseline and Week 6 or end-point measurements.
Negative values for estimated difference favor Val 160-320/Simva 40 mg
* Significant at 5% level
LSM change = least squares mean percent change from baseline, SEM = standard error of the mean.

Secondary Objective Result(s)

Percent change from baseline to Week 6 in other lipids (ITT population)

Parameter Treatment	n	LSM change in % (SEM)	Contrast	Difference	95% CI	p-value
Total Cholesterol						
Val 160-320/Simva 20 mg (N=421)	415	-23.5 (1.05)	Val 160-320/Simva 40 mg vs Val 160-320/Simva 20 mg	-3.67	-5.41, -1.93	<.0001*
Val 160-320/Simva 40 mg (N=417)	414	-27.2 (1.03)				
Triglycerides						
Val 160-320/Simva 20 mg (N=421)	415	-8.9 (2.91)	Val 160-320/Simva 40 mg vs Val 160-320/Simva 20 mg	-9.33	-14.18, -4.48	0.0002*
Val 160-320/Simva 40 mg (N=417)	414	-18.3 (2.88)				
non-HDL-C						
Val 160-320/Simva 20 mg (N=421)	415	-30.1 (1.37)	Val 160-320/Simva 40 mg vs Val 160-320/Simva 20 mg	-5.66	-7.94, -3.38	<.0001*
Val 160-320/Simva 40 mg (N=417)	414	-35.8 (1.36)				
HDL-C						
Val 160-320/Simva 20 mg (N=421)	415	2.5 (1.21)	Val 160-320/Simva 40 mg vs Val 160-320/Simva 20 mg	3.56	1.54, 5.57	0.0005*
Val 160-320/Simva 40 mg (N=417)	414	6.0 (1.19)				

N is the number in ITT population; n is the number of ITT patients with both baseline and Week 6 or endpoint measurements.
Negative values for estimated difference favor Val 160-320/ Simva 40 mg for all the parameters except HDL-C.
* Significant at 5% level

Percent change from baseline to Week 12 in lipids (ITT population)

Parameter Treatment	n	LSM change in % (SEM)	Contrast	Difference	95% CI	p-value
LDL-C						
Val 160-320/Simva 20 mg (N=421)	417	-32.7 (1.54)	Val 160-320/Simva 40 mg vs Val 160-320/Simva 20 mg	-4.04	-6.63, -1.46	0.0022*
Val 160-320/Simva 40 mg (N=417)	414	-36.8 (1.52)				
Total Cholesterol						
Val 160-320/Simva 20 mg (N=421)	417	-23.4 (1.08)	Val 160-320/Simva 40 mg vs Val 160-320/Simva 20 mg	-3.61	-5.42, -1.79	0.0001*
Val 160-320/Simva 40 mg (N=417)	414	-27.0 (1.07)				
Triglycerides						
Val 160-320/Simva 20 mg (N=421)	417	-5.0 (2.90)	Val 160-320/Simva 40 mg vs Val 160-320/Simva 20 mg	-11.5	-16.36, -6.62	<.0001*
Val 160-320/Simva 40 mg (N=417)	414	-16.5 (2.87)				
non-HDL-C						
Val 160-320/Simva 20 mg (N=421)	417	-29.1 (1.40)	Val 160-320/Simva 40 mg vs Val 160-320/Simva 20 mg	-5.08	-7.43, -2.73	<.0001*
Val 160-320/Simva 40 mg (N=417)	414	-34.2 (1.39)				
HDL-C						
Val 160-320/Simva 20 mg (N=421)	417	-0.3 (1.32)	Val 160-320/Simva 40 mg vs Val 160-320/Simva 20 mg	2.26	0.03, 4.48	0.0470*
Val 160-320/Simva 40 mg (N=417)	414	2.0 (1.31)				

N is the number in ITT population; n is the number of ITT patients with both baseline and Week 12 or endpoint measurements.
Negative values for estimated difference favor Val 160-320/ Simva 40 mg for all the parameters except HDL-C.
* Significant at 5% level

BP control and/or LDL-C control by timepoint (ITT population)

Parameter Timepoint	Treatment	n	Number controlled	Proportion	95% CI*
BP control at					
Week 6	Val 160-320/Simva 20 mg (N=421)	421	161	0.38	0.336, 0.431
	Val 160-320/Simva 40 mg (N=417)	417	172	0.41	0.365, 0.461
Week 12	Val 160-320/Simva 20 mg (N=421)	421	238	0.57	0.517, 0.613
	Val 160-320/Simva 40 mg (N=417)	417	230	0.55	0.502, 0.600
LDL-C control at					
Baseline	Val 160-320/Simva 20 mg (N=421)	421	84	0.20	0.162, 0.241
	Val 160-320/Simva 40 mg (N=417)	417	76	0.18	0.146, 0.223
Week 6	Val 160-320/Simva 20 mg (N=421)	416	347	0.83	0.795, 0.869
	Val 160-320/Simva 40 mg (N=417)	412	362	0.88	0.843, 0.909
Week 12	Val 160-320/Simva 20 mg (N=421)	418	352	0.84	0.804, 0.876
	Val 160-320/Simva 40 mg (N=417)	412	357	0.87	0.825, 0.894
BP and LDL-C control at					
Week 6	Val 160-320/Simva 20 mg (N=421)	416	146	0.35	0.305, 0.399
	Val 160-320/Simva 40 mg (N=417)	412	154	0.37	0.327, 0.423
Week 12	Val 160-320/Simva 20 mg (N=421)	418	212	0.51	0.458, 0.556
	Val 160-320/Simva 40 mg (N=417)	412	206	0.50	0.448, 0.547

BP control: The proportion of patients with BP <140/90 mmHg (non-diabetics) or <130/80 mmHg (diabetics)
N is the number in ITT population; n is the number of ITT patients with a non-missing measurement at timepoint or LOCF.
*The exact confidence intervals are presented.

Secondary efficacy analysis: Responder rate by timepoint (ITT population)

Parameter	Timepoint	n	No. responders	Proportion	95% CI*
Systolic responder rate					
Val 160-320/ Simva 20 mg (N=421)	Week 6 Endpoint	421	238	0.57	0.517, 0.613
Val 160-320/ Simva 40 mg (N=417)		417	229	0.55	0.500, 0.598
Val 160-320/ Simva 20 mg (N=421)	Week 12 Endpoint	421	299	0.71	0.664, 0.753
Val 160-320/ Simva 40 mg (N=417)		417	291	0.70	0.651, 0.742
Diastolic responder rate					
Val 160-320/ Simva 20 mg (N=421)	Week 6 Endpoint	421	278	0.66	0.613, 0.706
Val 160-320/ Simva 40 mg (N=417)		417	283	0.68	0.632, 0.723
Val 160-320/ Simva 20 mg (N=421)	Week 12 Endpoint	421	332	0.79	0.746, 0.827
Val 160-320/ Simva 40 mg (N=417)		417	317	0.76	0.716, 0.800
BP responder rate					
Val 160-320/ Simva 20 mg (N=421)	Week 6 Endpoint	421	190	0.45	0.403, 0.500
Val 160-320/ Simva 40 mg (N=417)		417	198	0.47	0.426, 0.524
Val 160-320/ Simva 20 mg (N=421)	Week 12 Endpoint	421	271	0.64	0.596, 0.690
Val 160-320/ Simva 40 mg (N=417)		417	260	0.62	0.575, 0.670

BP Responder rate: MSSBP<140 mmHg (or <130 mmHg for diabetic patients) or at least 20 mmHg reduction from baseline in MSSBP and MSDBP<90 mmHg (or <80 mmHg for diabetic patients) or at least 10 mmHg reduction from baseline MSDBP.
N is the number in ITT population; n is the number of ITT patients with both baseline and post baseline measurement at each timepoint or LOCF
*The exact confidence intervals are presented.

Safety Results

Adverse Events by System Organ Class

Primary System Organ Class	Val 160-320/ Simva 20 mg (N=420) n (%)	Val 160-320/ Simva 40 mg (N=419) n (%)
Total no. (%) with AEs	102 (24.3)	93 (22.2)
Infections and infestations	28 (6.7)	33 (7.9)
Nervous system disorders	25 (6.0)	20 (4.8)
Gastrointestinal disorders	18 (4.3)	16 (3.8)
Musculoskeletal and connective tissue disorders	14 (3.3)	12 (2.9)
Gen'l disorders and administration site conditions	14 (3.3)	7 (1.7)
Investigations	6 (1.4)	7 (1.7)
Ear and labyrinth disorders	3 (0.7)	5 (1.2)
Cardiac disorders	2 (0.5)	4 (1.0)
Injury, poisoning and procedural complications	3 (0.7)	4 (1.0)
Respiratory, thoracic and mediastinal disorders	10 (2.4)	4 (1.0)
Skin and subcutaneous tissue disorders	4 (1.0)	3 (0.7)
Eye disorders	1 (0.2)	2 (0.5)
Renal and urinary disorders	4 (1.0)	2 (0.5)
Reproductive system and breast disorders	1 (0.2)	2 (0.5)
Vascular disorders	9 (2.1)	2 (0.5)
Psychiatric disorders	3 (0.7)	1 (0.2)
Surgical and medical procedures	1 (0.2)	1 (0.2)
Metabolism and nutrition disorders	2 (0.5)	0 (0.0)

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

Number (%) of patients with most frequent AEs during the double blind period by preferred term (>= 1.0% for either group) (Safety population)

Adverse Events	Val 160-320/ Simva 20 mg (N=420) n (%)	Val 160-320/ Simva 40 mg (N=419) n (%)
Total no. (%) with AEs	102 (24.3)	93 (22.2)
Nasopharyngitis	10 (2.4)	15 (3.6)
Headache	10 (2.4)	14 (3.3)
Diarrhea	7 (1.7)	5 (1.2)
Back pain	1 (0.2)	4 (1.0)
Blood creatine phosphokinase increased	1 (0.2)	4 (1.0)
Influenza	1 (0.2)	4 (1.0)
Dizziness	9 (2.1)	2 (0.5)
Bronchitis	4 (1.0)	2 (0.5)
Edema peripheral	4 (1.0)	2 (0.5)
Fatigue	4 (1.0)	1 (0.2)
Pain in extremity	4 (1.0)	1 (0.2)
Nausea	7 (1.7)	0 (0.0)

Serious Adverse Events and Deaths

Incidence rate of deaths, serious adverse events and discontinuations due to adverse events

Event	Val 160-320/ Simva 20 mg N= 420 n(%)	Val 160-320/ Simva 40 mg N= 419 n(%)
Deaths	0 (0.0)	0 (0.0)
Patients with non-fatal SAEs	3 (0.7)	2 (0.5)
Patients with other significant AEs:		
AEs leading to study drug dose adjustment/interruption	3 (0.7)	2 (0.5)
Discontinuations due to:		
Any AEs including SAEs	12 (2.9)	6 (1.4)
AEs (non-serious)	11 (2.6)	5 (1.2)
SAEs	1 (0.2)	1 (0.2)

SAEs:

Val 160-320/ Simva 20 mg: 1 angina pectoris, 1 peripheral arterial occlusive disease,1 urinary tract disorder

Val 160-320/ Simva 40 mg: 1renal colic, 1 third degree atrioventricular block with increase BP

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

23 March 2007

Date Inclusion on Novartis Clinical Trial Results Database

7 September 2007

Date of Latest Update

19 July 2007