Sponsor

Novartis

Generic Drug Name

Valsartan and Simvastatin

Therapeutic Area of Trial

Hypertension, Hypercholesterolemia

Approved Indication

In the US:
Valsartan is indicated for the treatment of hypertension, heart failure and post-myocardial infarction

Simvastatin is indicated in the treatment of hypercholesterolemia. It is also indicated in patients with coronary heart disease (CHD) or at high risk of CHD to reduce risk of CHD mortality and cardiovascular events.

Study Number

CVAS489A2316

Title

A 10-12 week multicenter, randomized, double blind, parallel group study to evaluate the efficacy and safety of the combination of valsartan (320 mg) and simvastatin (80 mg) compared to valsartan (320 mg) and simvastatin (80 mg) monotherapies in essential hypertension and hypercholesterolemia

Phase of Development

Phase III

Study Start/End Dates

17 Sep 2004 to 6 Jan 2006

Study Design/Methodology

This was a double-blind, multicenter, randomized, parallel-group study of valsartan (Val) 320 mg

and simvastatin (Simva) 80 mg given alone and in combination in patients with essential hypertension and primary hypercholesterolemia or mixed dyslipidemia (Frederickson Types IIa or IIb). The study was comprised of three periods. During Period 1 (2-week washout), patients discontinued all statin use and any antihypertensive therapy. Period 2, starting at Visit 2, was a 2-4 week single-blind run-in period during which blood pressure and lipid eligibility were determined. Qualified patients were randomized at Visit 4 in a double-blind fashion to one of three treatment arms for six weeks (ending at Visit 7): valsartan 320 mg, simvastatin 80 mg, or valsartan/simvastatin 320/80 mg, all administered once daily in the evening (Period 3). Monotherapy treatment arms for comparison consisted of either 2 capsules of valsartan 160 mg plus 1 capsule of placebo or 2 capsules of placebo plus 1 capsule of simvastatin 80 mg.

Centres

71 centers in the United States

Publication

Ongoing

Objectives

Primary objective(s)

The primary objectives were to evaluate the combination of valsartan and simvastatin 320/80 mg in reducing mean ambulatory systolic blood pressure (ASBP) over 24 hours compared to simvastatin 80 mg alone and in reducing low-density lipoprotein-C (LDL-C) compared to valsartan 320 mg alone.

Secondary objective(s)

To evaluate the following:

- the safety and tolerability of valsartan 320 mg and simvastatin 80 mg, given alone and in combination
- the efficacy of valsartan/simvastatin 320/80 mg in reducing mean ASBP over 24 hours compared to valsartan 320 mg alone
- the efficacy of valsartan/simvastatin 320/80 mg in reducing LDL-C compared to simvastatin 80 mg alone
- the efficacy of valsartan/simvastatin 320/80 mg compared to valsartan 320 mg alone and simvastatin 80 mg alone in reducing the following:
    1. mean ambulatory diastolic blood pressure (ADBP) over 24 hours
    2. mean ASBP and ADBP for daytime (>6 a.m. to ≤ 10 p.m.) and nighttime (>10 p.m. to ≤ 6 a.m.)
    3. mean trough (post-dose hours 21-24) ASBP and ADBP
    4. mean sitting systolic blood pressure (MSSBP) (standard cuff measurement)
    5. mean sitting diastolic blood pressure (MSDBP) (standard cuff measurement)

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

Valsartan capsules (160 mg) and/or simvastatin capsules (80 mg); treatment administered orally once a day (o.d.)

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

None

Criteria for Evaluation

Primary variables

- Mean change from baseline (Visit 4, randomization) in ASBP for 24 hours at study endpoint (Visit 7, day 43)
- Mean percent change from baseline in LDL-C at study endpoint

Secondary variables

- Mean change from baseline in ADBP for 24 hours at study endpoint
- Mean change in from baseline ASBP and ADBP for daytime (>6 a.m. to ≤ 10 p.m.) and night-time (>10 p.m. to ≤ 6 a.m.) at study endpoint
- Mean change from baseline in ASBP and ADBP at trough (post-dose hours 21-24) at study end-point
- Mean change from baseline in MSSBP at study endpoint
- Mean change from baseline in MSDBP at study endpoint

Safety and tolerability

The assessment of safety was based mainly on the frequency of AEs, SAEs, vital signs, and the number of post-baseline laboratory values outside pre-determined ranges during the double-blind, randomized treatment phase.

Pharmacology

None

Other

- Mean percent change from baseline in total cholesterol (TC) at study endpoint
- Mean percent change from baseline in triglycerides (TG) at study endpoint
- Mean percent change from baseline in high density lipoprotein-C (HDL-C) at study endpoint

Statistical Methods

Demographic and baseline characteristics, exposure to study medication and concomitant medications were summarized for all randomized patients.

The efficacy analyses were based on the intent-to-treat (ITT) population. Per-protocol analyses were also provided for the primary analyses. The ABPM variables were analyzed by ANCOVA models for repeated measures, sitting blood pressures by ANCOVA models, and lipids by ANOVA models.

The combination was compared to simvastatin alone and to valsartan alone for each efficacy variable. The primary analyses were the comparisons of the combination to simvastatin alone in reduction of post-dosing 24-hour mean ASBP and to valsartan alone in percent reduction of LDL-C. All treatment comparisons were made at the two-sided significance level of 0.05. Confidence intervals for treatment differences were provided. Descriptive summaries of efficacy variables were also provided.

Safety data were summarized including adverse events and laboratory data using descriptive statistics for the safety population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

1. Outpatients 18 to 75 years of age, inclusive
2. Males or post-menopausal (for at least 1 year) females or pre-menopausal non-pregnant, non-lactating females who were surgically sterile or using effective contraceptive methods such as barrier method with spermicide or an intrauterine device. Hormonal contraceptive use was disallowed starting 4 weeks prior to Visit 2 (start of placebo run in)
3. Patients with essential hypertension. Patients had to have a MSSBP <180 mmHg at Visit 2 and MSSBP ≥ 140 mmHg and <180 mmHg at Visit 3 (placebo run-in) and at Visit 4 (randomization).
4. Elevated serum LDL-C level ≥ 100 mg/dL and <190 mg/dL and TG ≤ 350 mg/dL despite dietary therapy and off medication. If levels were not within these ranges at Visit 3 (placebo run-in), one retest was permitted prior to Visit 4 for the patient to qualify to be randomized, provided all other criteria were fulfilled. The LDL-C and TG values collected at Visit 4 (randomization) did not serve as inclusion criteria. LDL-C was directly measured if TG levels were >350 mg/dL during the run-in period..
5. Patients had to be on an approved HMG Co-A reductase inhibitor for at least 3 months prior to enrollment. Patients who had taken higher than the minimum required dose and required down-titration due to intolerability could not be included.
6. Patients who were eligible and able to participate in the study, and who consented to do so after the purpose and nature of the investigation had been clearly explained to them (written informed consent)

Exclusion criteria:

Patients with any of the following physiological states or concomitant medical conditions prior to randomization were excluded from participation in the study.

1. Severe hypertension (MSSBP ≥ 180 mmHg and/or MSDBP ≥ 110 mmHg), history of hypertensive encephalopathy within 12 months prior to Visit 1, known Keith-Wagener grade III or IV hypertensive retinopathy
2. Evidence of a secondary form of hypertension, such as coarctation of the aorta, hyperaldosteronism, Cushing's disease, unilateral or bilateral renal artery stenosis, pheochromocytoma, polycystic kidney disease (PKD), etc.
3. History of myocardial infarction or concomitant refractory angina pectoris

4. History of cerebrovascular accident or transient ischemic cerebral attack
5. Coronary artery bypass graft, angioplasty and/or coronary or peripheral revascularization procedures including stent placement within 12 months prior to Visit 1
6. Second or third degree heart block without a pacemaker, concurrent potentially life threatening arrhythmia or symptomatic arrhythmia, clinically significant valvular heart disease
7. Heart failure requiring treatment
8. Evidence of dyslipidemia secondary to other causes. This included, but was not restricted to alcoholism, auto-immune disease, nephrotic syndrome, any viral or non-viral hepatitis clinically active within 12 months prior to Visit 1, obstructive hepatic or biliary disease, dys- or macroglobulinemia, multiple myeloma, glycogen storage disease, uncontrolled hypothyroidism or hyperthyroidism, chronic pancreatitis and porphyria
9. Inability to discontinue all prior anti-hypertensive and anti-hyperlipidemic medications safely for a period of 12 weeks, as required by the protocol
10. Administration of agents specifically intended to reduce serum lipid levels after Visit 1
11. Administration of agents indicated for the treatment of hypertension after Visit 1, with the permitted exception of those antihypertensive medications requiring tapering down commencing at Visit 1
12. Administration of agents that may interfere with the evaluation of safety, tolerability and/or efficacy after Visit 1
13. Known or suspected contraindications, including history of allergy to angiotensin receptor blockers or HMG-CoA reductase inhibitors (statins), (i.e., elevated transaminases (SGOT, SGPT), myositis, myalgia)
14. Diabetic patients requiring insulin treatment
15. Uncontrolled diabetes mellitus type II as defined by glycosylated hemoglobin (HbA1C) level > 7.5% at Visit 2 (start of placebo run-in).
16. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug including but not limited to any of the following:
    - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection, gastric bypass, gastric stapling, or gastric banding
    - Currently active or active inflammatory bowel disease during the 12 months prior to Visit 1
    - Currently active gastritis, ulcers, or gastrointestinal/rectal bleeding or urinary tract obstruction regarded as clinically meaningful by the investigator
17. Pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury within 12 months prior to Visit 1
18. Evidence of hepatic disease as determined by any one of the following: SGOT or SGPT values >1.5 x ULN at Visit 2 (start of placebo run-in), a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt. If SGOT and/or SGPT were between 1.5 and 2 x ULN, one retest was permitted prior to Visit 4 (randomization) for the patient to qualify to be randomized, provided all other entry criteria were fulfilled. SGOT and SGPT values had to be $\leq$ 1.5 x ULN at the retest for the patient to be eligible for further study participation. If SGOT and/or SGPT was > 2 x ULN at any time before Visit 4 (randomization), the patient was to be excluded from further study participation.

19. Evidence of renal impairment as determined by any one of the following: serum creatinine > 1.5 x ULN at Visit 2 or a history of dialysis. If Visit 2 (start of placebo run-in) serum creatinine was between 1.5 and 2 x ULN, one retest was permitted prior to Visit 4 (randomization) for the patient to qualify to be randomized, provided all other entry criteria were fulfilled. Serum creatinine values had to be ≤ 1.5 x ULN at the retest for the patient to be eligible for further study participation. If serum creatinine was > 2 x ULN at any time before Visit 4 (randomization), the patient was to be excluded from further study participation.
20. Serum creatine kinase (CK) levels > 2 x ULN at Visit 2 (start of placebo run-in). If Visit 2 serum CK was between 2 and 5 x ULN, or > 5 x ULN if explained by non-pathophysiological causes (e.g., intensive physical activity), one retest was permitted prior to Visit 4 (randomization) for the patient to qualify to be randomized, provided all other entry criteria were fulfilled. Serum CK values had to be ≤ 2 x ULN at the retest for the patient to be eligible for further study participation. If serum CK was > 5 x ULN at any time before Visit 4, the patient was to be excluded from further study participation.
21. Sodium depletion
22. Prior or known muscular or neuromuscular disease of any type
23. History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the past five years
24. History of any severe, life-threatening disease
25. Within the last two years, a history of drug abuse or continuous consumption of more than 65 mL pure alcohol per day (e.g., more than four 125-mL glasses of wine or three glasses of spirits per day)
26. Any condition not identified in the protocol that, in the opinion of the investigator or the medical monitor, would jeopardize the evaluation of efficacy or safety
27. Any surgical or medical conditions which, in the opinion of the investigator, place the patient at higher risk from his/her participation in the study, or were likely to prevent the patient from complying with the requirements of the study or completing the study
28. History of noncompliance to medical regimens or unwillingness to comply with the study protocol
29. Participation in any investigational drug trial within one month prior to Visit 1 or in a previous investigational drug trial on the combination valsartan and simvastatin
30. Unwillingness or inability to give informed consent
31. Persons directly involved in the execution of this protocol

Number of Subjects

	Valsartan 320 mg	Simvastatin 80 mg	Valsartan/Simvastatin 320/80 mg
Planned N	123	123	123
Randomized n	137 (100.0)	134 (100.0)	137 (100.0)
Intent-to-treat population (ITT) n (%)	137 (100.0)	134 (100.0)	137 (100.0)
Completed n (%)	132 (96.4)	119 (88.8)	132 (96.4)
Withdrawn n (%)	5 (3.6)	15 (11.2)	5 (3.6)
Withdrawn due to adverse events n (%)	2 (1.5)	3 (2.2)	2 (1.5)
Withdrawn due to lack of efficacy n (%)	0 (0.0)	4 (3.0)	1 (0.7)
Withdrawn for other reasons n (%)	3 (2.2)	8 (6.0)	2 (1.5)

Demographic and Background Characteristics

	Valsartan 320 mg	**Simvastatin 80 mg**	**Valsartan/Simvastatin 320/80 mg**
N (ITT)	137	134	137
Females : males	75 (54.7) : 62 (45.3):	68 (50.7) : 66 (49.3)	65 (47.4) : 72 (52.6)
Mean age, years (SD)	59.5 (9.2)	59.3 (8.7)	59.9 (9.1)
Mean weight, kg (SD)	88.6 (18.7)	88.2 (18.6)	90.7 (18.4)
Race n (%) Caucasian Black Hispanic Oriental Other	 100 (73.0) 19 (13.9) 13 (9.5) 1 (0.7) 4 (2.9)	 99 (73.9) 22 (16.4) 11 (8.2) 2 (1.5) 0 (0.0)	 100 (73.0) 17 (12.4) 13 (9.5) 6 (4.4) 1 (0.7)
Mean ASBP, mmHg (SD) Mean ADBP, mmHg (SD) Mean seated SBP, mmHg (SD) Mean seated DBP, mmHg (SD) Mean LDL-C, mg/dL (SD) Mean TG, mg/dL (SD)	139.8 (12.2) 83.7 (10.2) 151.6 (8.5) 90.2 (9.0) 154.1 (28.8) 183.1 (98.9)	140.9 (12.2) 84.2 (9.2) 152.1 (9.6) 91.5 (8.8) 153.9 (25.9) 179.4 (87.6)	139.7 (12.2) 83.3 (8.5) 151.9 (10.6) 89.3 (8.5) 152.3 (28.6) 183.7 (88.5)

Primary Objective Result(s)

Mean ambulatory systolic blood pressure

Within-treatment changes from baseline in mean 24 hr ambulatory systolic blood pressure (mm Hg) at endpoint (ITT population)

Treatment Group	N	Baseline mean (mm Hg)	LS mean change from baseline (mm Hg) (SE)	95% CI for LSM	p-value
Val 320 mg	114	139.4	-10.02 (0.70)	(-11.39, -8.65)	<.0001*
Simva 80 mg	109	140.1	-0.74 (0.71)	(-2.14, 0.65)	0.2949
Val/Simva 320/80 mg	119	140.0	-9.67 (0.68)	(-11.01, -8.33)	<.0001*

* Indicates a statistical significance at the level of 0.05 (p<0.05).
N is the number of patients with ambulatory blood pressure values obtained over 24 hours post-dose at both baseline and endpoint.
- Least square means, confidence intervals, and p values were from an ANCOVA model for repeated measures containing treatment, center (pooled if necessary), centered baseline, post-dosing hour and treatment by post-dosing hour interaction.

Between-treatment comparison for changes from baseline in mean 24 hr ambulatory systolic blood pressure (mm Hg) at endpoint (ITT population)

Treatment Comparison (A versus B)	LSM change from baseline		LSM difference in change from baseline (SE)	95% CI for LSM	p-value
	A	B			
Val/Simva 320/80 mg vs. Val 320 mg	-9.67	-10.02	0.35 (0.96)	(-1.54, 2.24)	0.7168
Val/Simva 320/80 mg vs. Simva 80 mg	-9.67	-0.74	-8.93 (0.97)	(-10.83, -7.02)	<.0001*

* Indicates a statistical significance at the level of 0.05 (p<0.05).
Note: Results were from an ANCOVA model containing center, treatment, centered baseline and post-dosing hour and treatment by post-dosing hour interaction.

LDL-C

Within-treatment % changes from baseline in LDL-C (mg/dl) at endpoint (ITT population)

Treatment Group	N	Baseline mean (mg/dL)	LS mean % change from baseline (SE)	95% CI for LSM	p-value
Val 320 mg	129	154.3	1.76 (1.29)	(-0.79, 4.30)	0.1749
Simva 80 mg	128	154.0	-42.54 (1.31)	(-45.10, -39.97)	<.0001*
Val/Simva 320/80 mg	135	152.5	-41.64 (1.27)	(-44.14, -39.14)	<.0001*

* Indicates a statistical significance at the level of 0.05 (p<0.05).

Between-treatment comparisons for % change from baseline in LDL-C (mg/dl) at endpoint (ITT population)

Treatment Comparison (A versus B)	LSM % change from baseline		LSM difference in % change from baseline (SE)	95% CI for LSM	p-value
	A	B			
Val/Simva 320/80 mg vs. Val 320 mg	-41.64	1.76	-43.40 (1.79)	(-46.91, -39.88)	<.0001*
Val/Simva 320/80 mg vs. Simva 80 mg	-41.64	-42.54	0.90 (1.79)	(-2.62, 4.41)	0.6160

* Indicates a statistical significance at the level of 0.05 (p<0.05).
Note: Results were from an ANCOVA model containing center, treatment, centered baseline and treatment by baseline.

Secondary Objective Result(s)

Mean ambulatory diastolic blood pressure

Within-treatment changes from baseline in mean ambulatory diastolic blood pressure (mm Hg) over 24 hours at endpoint (ITT population)

Treatment Group	N	Baseline mean (mm Hg)	LS mean change from baseline (mm Hg) (SE)	95% CI for LSM	p-value
Val 320 mg	114	83.1	-5.72 (0.47)	(-6.64, -4.79)	<.0001*
Simva 80 mg	109	83.4	-0.49 (0.48)	(-1.43, 0.45)	0.3015
Val/Simva 320/80 mg	119	83.0	-6.31 (0.46)	(-7.21, -5.41)	<.0001*

* Indicates a statistical significance at the level of 0.05 (p<0.05).
N is the number of patients with ambulatory blood pressure values obtained over 24 hours post-dose at both baseline and endpoint.

Between-treatment comparison for changes from baseline in mean ambulatory diastolic blood pressure (mm Hg) over 24 hours at endpoint (ITT population)

Treatment Comparison (A versus B)	LSM change from baseline		LSM difference in change from baseline (SE)	95% CI for LSM	p-value
	A	B			
Val/Simva 320/80 mg vs. Val 320 mg	-6.31	-5.72	-0.60 (0.65)	(-1.87, 0.68)	0.3585
Val/Simva 320/80 mg vs. Simva 80 mg	-6.31	-0.49	-5.82 (0.65)	(-7.10, -4.5)	<.0001*

* Indicates a statistical significance at the level of 0.05 (p<0.05).
Note: Results were from an ANCOVA model containing center, treatment, centered baseline and post-dosing hour and treatment by post-dosing hour interaction.

Post-dosing trough mean ambulatory blood pressure

Within-treatment analysis for change from baseline at endpoint in post-dosing trough mean ambulatory systolic and diastolic blood pressure (ASBP/ADBP, mmHg) (ITT population)

Treatment Group	N	Baseline mean (mm Hg)	LS mean change from baseline (mm Hg) (SE)	95% CI for LSM	p-value
ASBP					
Val 320 mg	114	144.6	-10.37 (1.19)	(-12.71, -8.04)	<.0001*
Simva 80 mg	109	144.4	-0.86 (1.21)	(-3.23, 1.52)	0.4786
Val/Simva 320/80 mg	119	146.7	-8.53 (1.16)	(-10.81, -6.25)	<.0001*
ADBP					
Val 320 mg	114	87.7	-5.48 (0.87)	(-7.19, -3.77)	<.0001*
Simva 80 mg	109	87.7	-0.03 (0.88)	(-1.76, 1.70)	0.9726
Val/Simva 320/80 mg	119	88.2	-5.68 (0.85)	(-7.34, -4.02)	<.0001*

- Baseline is the Week 0 value, and Endpoint is the value at Week 6 or LOCF value.
- Only patients with a value at both Baseline and Endpoint are included.
* Indicates a statistical significance at the level of 0.05 (p<0.05).
- Least square means, confidence intervals, and p values were from an ANCOVA model for repeated measures containing treatment, center (pooled if necessary), centered baseline, post-dosing hour and treatment by post-dosing hour interaction.
- The mean of post-dosing hour 21 to hour 24 is defined as trough mean.

Between-treatment comparison for change from baseline at endpoint in post-dosing trough mean ambulatory systolic and diastolic blood pressure (ASBP/ADBP, mmHg) (ITT population)

Treatment Comparison (A versus B)	LSM change from baseline		LSM difference in change from baseline (SE)	95% CI for LSM	p-value
	A	B			
ASBP					
Val/Simva 320/80 mg vs. Val 320 mg	-8.53	-10.37	1.85 (1.66)	(-1.41, 5.10)	0.2661
Val/Simva 320/80 mg vs. Simva 80 mg	-8.53	-0.86	-7.67 (1.67)	(-10.95, -4.39)	<.0001*
ADBP					
Val/Simva 320/80 mg vs. Val 320 mg	-5.68	-5.48	-0.20 (1.21)	(-2.57, 2.18)	0.8699
Val/Simva 320/80 mg vs. Simva 80 mg	-5.68	-0.03	-5.65 (1.22)	(-8.04, -3.26)	<.0001*

- Baseline is the Week 0 value, and Endpoint is the value at Week 6 or LOCF value.
- Only patients with a value at both Baseline and Endpoint are included.
* Indicates a statistical significance at the level of 0.05 (p<0.05).
- Least square means, confidence intervals, and p values were from an ANCOVA model for repeated measures containing treatment, center (pooled if necessary), centered baseline, post-dosing hour and treatment by post-dosing hour interaction.
- The mean of post-dosing hour 21 to hour 24 is defined as trough mean.

Mean sitting systolic blood pressure

Within-treatment changes from baseline in mean sitting systolic blood pressure (mm Hg) at end-

point (ITT population)

Treatment Group	N	Baseline mean (mm Hg)	LS mean change from baseline (mm Hg) (SE)	95% CI for LSM	p-value
Val 320 mg	137	151.6	-14.70 (1.08)	(-16.83, -12.57)	<.0001*
Simva 80 mg	134	152.1	-6.15 (1.10)	(-8.31, -4.00)	<.0001*
Val/Simva 320/80 mg	137	151.9	-15.70 (1.08)	(-17.83, -13.57)	<.0001*

* Indicates a statistical significance at the level of 0.05 (p<0.05).

Between-treatment comparison for changes from baseline in mean sitting systolic blood pressure (mm Hg) at endpoint (ITT population)

Treatment Comparison (A versus B)	LSM change from baseline		LSM difference in change from baseline (SE)	95% CI for LSM	p-value
	A	B			
[Val/Simva 320/80 mg] vs. [Val 320 mg]	-15.70	-14.70	-1.01 (1.51)	(-3.97, 1.96)	0.5050
[Val/Simva 320/80 mg] vs. [Simva 80 mg]	-15.70	-6.15	-9.55 (1.51)	(-12.52, -6.58)	<.0001*

* Indicates a statistical significance at the level of 0.05 (p<0.05).
Note: Results were from an ANCOVA model containing center, treatment, centered baseline and treatment by centered baseline interaction.

Mean sitting diastolic blood pressure

Within-treatment changes from baseline in mean sitting diastolic blood pressure (mm Hg) at endpoint (ITT population)

Treatment Group	N	Baseline mean (mm Hg)	LS mean change from baseline (mm Hg) (SE)	95% CI for LSM	p-value
Val 320 mg	137	90.2	-6.91 (0.69)	(-8.27, -5.55)	<.0001*
Simva 80 mg	134	91.5	-1.90 (0.71)	(-3.29, -0.52)	0.0073*
Val/Simva 320/80 mg	137	89.3	-6.99 (0.70)	(-8.36, -5.61)	<.0001*

* Indicates a statistical significance at the level of 0.05 (p<0.05).

Between-treatment comparison for changes from baseline in mean sitting diastolic blood pressure (mm Hg) at endpoint (ITT population)

Treatment Comparison (A versus B)	LSM change from baseline A	LSM change from baseline B	LSM difference in change from baseline (SE)	95% CI for LSM	p-value
[Val/Simva 320/80 mg] vs. [Val 320 mg]	-6.99	-6.91	-0.08 (0.97)	(-1.98, 1.82)	0.9369
[Val/Simva 320/80 mg] vs. [Simva 80 mg]	-6.99	-1.90	-5.08 (0.97)	(-7.00, -3.17)	<.0001*

* Indicates a statistical significance at the level of 0.05 (p<0.05).
Note: Results were from an ANCOVA model containing center, treatment, centered baseline and treatment by centered baseline interaction.

Daytime and nighttime ambulatory blood pressure

Within-treatment comparisons for changes from baseline in mean daytime and nighttime ambulatory blood pressures (mm Hg) at endpoint (ITT population)

Daytime or Nighttime Ambulatory BP/ Treatment Group	N	Baseline mean (mm Hg)	LS mean change from baseline (mm Hg) (SE)	95% CI for LSM	p-value
Daytime ASBP					
Val 320 mg	118	143.3	-9.78 (0.87)	(-11.49, -8.07)	<.0001*
Simva 80 mg	112	144.8	-1.23 (0.89)	(-2.98, 0.52)	0.1680
Val/Simva 320/80 mg	121	144.8	-9.73 (0.85)	(-11.41, -8.05)	<.0001*
Nighttime ASBP					
Val 320 mg	118	131.1	-9.53 (0.87)	(-11.24, -7.83)	<.0001*
Simva 80 mg	112	132.3	-1.39 (0.89)	(-3.14, 0.37)	0.1203
Val/Simva 320/80 mg	121	130.2	-10.17 (0.85)	(-11.85, -8.49)	<.0001*
Daytime ADBP					
Val 320 mg	118	87.0	-5.70 (0.60)	(-6.88, -4.52)	<.0001*
Simva 80 mg	112	87.5	-1.04 (0.62)	(-2.25, 0.17)	0.0927
Val/Simva 320/80 mg	121	87.5	-6.41 (0.59)	(-7.58, -5.25)	<.0001*
Nighttime ADBP					
Val 320 mg	118	75.5	-5.90 (0.60)	(-7.08, -4.72)	<.0001*
Simva 80 mg	112	75.3	-1.14 (0.62)	(-2.36, 0.07)	0.0639
Val/Simva 320/80 mg	121	74.3	-5.97 (0.59)	(-7.14, -4.81)	<.0001*

* Indicates a statistical significance at the level of 0.05 (p<0.05).

Between-treatment comparison for changes from baseline in mean daytime and nighttime ambulatory blood pressures (mm Hg) at endpoint (ITT population)

Treatment Comparison (A versus B)	LSM change from baseline		LSM difference in change from baseline (SE)	95% CI for LSM	p-value
	A	B			
Daytime ASBP					
Val/Simva 320/80 mg vs. Val 320 mg	-9.73	-9.78	0.047 (1.21)	(-2.33, 2.42)	0.9689
Val/Simva 320/80 mg vs. Simva 80 mg	-9.73	-1.23	-8.50 (1.22)	(-10.89, -6.11)	<.0001*
Nighttime ASBP					
Val/Simva 320/80 mg vs. Val 320 mg	-10.17	-9.53	-0.63 (1.21)	(-3.01, 1.74)	0.5992
Val/Simva 320/80 mg vs. Simva 80 mg	-10.17	-1.39	-8.78 (1.22)	(-11.17, -6.38)	<.0001*
Daytime ADBP					
Val/Simva 320/80 mg vs. Val 320 mg	-6.41	-5.70	-0.71 (0.83)	(-2.36, 0.93)	0.3924
Val/Simva 320/80 mg vs. Simva 80 mg	-6.41	-1.04	-5.38 (0.84)	(-7.03, -3.72)	<.0001*
Nighttime ADBP					
Val/Simva 320/80 mg vs. Val 320 mg	-5.97	-5.90	-0.077 (0.835)	(-1.72, 1.57)	0.9268
Val/Simva 320/80 mg vs. Simva 80 mg	-5.97	-1.14	-4.83 (0.843)	(-6.49, -3.17)	<.0001*

* Indicates a statistical significance at the level of 0.05 ($p<0.05$).
Note: Results were from an ANCOVA model containing center, treatment, centered baseline, time period (daytime, nighttime), and treatment by time period interaction.

Safety Results

Adverse Events by System Organ Class

Primary system organ class	Val 320 mg N = 137 n (%)	Simva 80 mg N = 134 n (%)	Val/Simva 320/80 mg N = 137 n (%)
Any primary system organ class	32 (23.4)	44 (32.8)	46 (33.6)
Musculoskeletal and connective tissue disorders	10 (7.3)	11 (8.2)	12 (8.8)
Nervous system disorders	5 (3.6)	10 (7.5)	12 (8.8)
Gastrointestinal disorders	5 (3.6)	5 (3.7)	12 (8.8)
Infections and infestations	12 (8.8)	12 (9.0)	10 (7.3)
General disorders and administration site conditions	4 (2.9)	6 (4.5)	5 (3.6)
Respiratory, thoracic and mediastinal disorders	5 (3.6)	3 (2.2)	4 (2.9)
Skin and subcutaneous tissue disorders	1 (0.7)	1 (0.7)	4 (2.9)
Investigations	3 (2.2)	9 (6.7)	3 (2.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.0)	1 (0.7)	2 (1.5)
Renal and urinary disorders	0 (0.0)	1 (0.7)	2 (1.5)
Cardiac disorders	2 (1.5)	0 (0.0)	1 (0.7)
Ear and labyrinth disorders	1 (0.7)	1 (0.7)	1 (0.7)
Eye disorders	0 (0.0)	1 (0.7)	1 (0.7)
Psychiatric disorders	1 (0.7)	3 (2.2)	1 (0.7)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (0.7)
Vascular disorders	2 (1.5)	0 (0.0)	1 (0.7)
Endocrine disorders	0 (0.0)	1 (0.7)	0 (0.0)
Immune system disorders	0 (0.0)	1 (0.7)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	2 (1.5)	0 (0.0)
Metabolism and nutrition disorders	1 (0.7)	3 (2.2)	0 (0.0)
Blood and lymphatic system disorders	2 (1.5)	0 (0.0)	0 (0.0)

* AEs are listed by primary system organ class in descending frequency in valsartan/simvastatin 320/80 mg group.

10 Most Frequently Reported AEs

	Valsartan 320 mg	Simvastatin 80 mg	Val/Simva 320/80 mg
Headache	2 (1.5)	7 (5.2)	7 (5.1)
Upper respiratory tract infection	2 (1.5)	4 (3.0)	4 (2.9)
Back pain	1 (0.7)	3 (2.2)	3 (2.2)
Nausea	2 (1.5)	1 (0.7)	3 (2.2)
Asthenia	0 (0.0)	0 (0.0)	2 (1.5)
Constipation	0 (0.0)	1 (0.7)	2 (1.5)
Dizziness	3 (2.2)	1 (0.7)	2 (1.5)
Dyspepsia	0 (0.0)	1 (0.7)	2 (1.5)
Myalgia	0 (0.0)	1 (0.7)	2 (1.5)
Edema peripheral	0 (0.0)	5 (3.7)	2 (1.5)

*AEs listed by preferred term n (%) in descending frequency in valsartan/simvastatin 320/80 mg group

Serious Adverse Events and Deaths

	Valsartan 320 mg	Simvastatin 80 mg	Val/Simva 320/80 mg
No. (%) of subjects studied	137	134	137
No. (%) of subjects with AE(s)	32 (23.4)	44 (32.8)	46 (33.6)
Number (%) of subjects with serious or other significant events	n (%)	n (%)	n (%)
Death	0 (0.0)	0 (0.0)	0 (0.0)
SAE(s)*	0 (0.0)	0 (0.0)	1 (0.7)
Discontinued due to SAE(s)	0 (0.0)	0 (0.0)	0 (0.0)

*One patient developed stage I breast cancer which was reported as an SAE.

Other Relevant Findings

Lipids

Within-treatment comparisons for percent changes from baseline in mean Total Cholesterol, Triglyceride and High Density Lipoprotein Cholesterol (mg/dL) at endpoint (ITT population)

Treatment	n	LS Mean %Change from Baseline (SE)	95% CI for LSM	P-Value
TC (mg/dL)				
Val 320 mg	135	1.187 (1.0127)	(-0.804, 3.178)	0.2419

Simva 80 mg	132	-31.343 (1.0276)	(-33.363, -29.322)	<.0001*
Val/Simva 320/80 mg	136	-30.853 (1.0095)	(-32.838, -28.868)	<.0001*
TG (mg/dL)				
Val 320 mg	135	8.029 (2.7942)	(2.534, 13.523)	0.0043*
Simva 80 mg	132	-21.949 (2.8353)	(-27.524, -16.374)	<.0001*
Val/Simva 320/80 mg	136	-18.896 (2.7854)	(-24.373, -13.419)	<.0001*
HDL-C (mg/dL)				
Val 320 mg	135	-1.602 (1.2408)	(-4.041, 0.838)	0.1975
Simva 80 mg	132	-2.345 (1.2590)	(-4.820, 0.131)	0.0633
Val/Simva 320/80 mg	136	-1.979 (1.2368)	(-4.411, 0.453)	0.1104

- Baseline is the Week 0 value, and Endpoint is the value at Week 6 or LOCF value.
- Only patients with a value at both baseline and Endpoint are included.
- If the p-value is less than 0.05 then * will appear with the value.
- Least square means, confidence intervals, and p-values were from an ANOVA model containing treatment, center (pooled if necessary).

Between-treatment comparison for changes from baseline in mean Total Cholesterol, Triglyceride and High Density Lipoprotein Cholesterol (mg/dL) at endpoint (ITT population)

	LSM %Change from Baseline		LSM Difference in %Change from		
A versus B	A	B	Baseline (SE)	95% CI for LSM	P-Value
TC (mg/dL)					
[Val/Simva 320/80 mg] vs. [Val 320 mg]	-30.853	1.187	-32.040 (1.4074)	(-34.807, -29.272)	<.0001*
[Val/Simva 320/80 mg] vs. [Simva 80 mg]	-30.853	-31.343	0.490 (1.4142)	(-2.291, 3.270)	0.7293
TG (mg/dL)					
[Val/Simva 320/80 mg] vs. [Val 320 mg]	-18.896	8.029	-26.925 (3.8833)	(-34.560, -19.289)	<.0001*
[Val/Simva 320/80 mg] vs. [Simva 80 mg]	-18.896	-21.949	3.053 (3.9018)	(-4.619, 10.725)	0.4344
HDL-C (mg/dL)					
[Val/Simva 320/80 mg] vs. [Val 320 mg]	-1.979	-1.602	-0.377 (1.7243)	(-3.768, 3.013)	0.8270
[Val/Simva 320/80 mg] vs. [Simva 80 mg]	-1.979	-2.345	0.366 (1.7326)	(-3.041, 3.773)	0.8328

- Baseline is the Week 0 value, and Endpoint is the value at Week 6 or LOCF value.
- Only patients with a value at both baseline and Endpoint are included.
- If the p-value is less than 0.05 then * will appear with the value.

- Least square means, confidence intervals, and p values were from an ANOVA model containing treatment, center (pooled if necessary).

Number (%) of patients with hematology values exceeding specified percentage changes from baseline (Safety population)

Parameter	% Change criterion	Val 320 mg N=137 N	n	(%)	Simva 80 mg N=134 N	n	(%)	Val/Simva 320/80 mg N=137 N	n	(%)
Platelet count (direct)	>75% increase	133	0	0	125	0	0	133	2	(1.5)
	>50% decrease	133	0	0	125	1	(0.7)	133	0	0
Hemoglobin	>20% decrease	135	1	(0.7)	127	0	0	135	1	(0.7)
Hematocrit	>20% decrease	133	1	(0.7)	125	0	0	133	1	(0.7)
RBC	>20% decrease	133	1	(0.7)	125	0	0	133	2	(1.5)
WBC (total)	>50% increase	133	1	(0.7)	125	4	(3.0)	133	7	(5.1)
	>50% decrease	133	0	0	125	1	(0.7)	133	0	0

Number (%) of patients with biochemistry values exceeding specified percentage changes from baseline (Safety population)

Parameter	Criterion	Val 320 mg N=137 Total	n (%)	Simva 80 mg N=134 Total	n (%)	Val/Simva 320/80 mg N=137 Total	n (%)
Albumin (g/L)	> 50% increase	137	0 (0.0)	133	0 (0.0)	136	0 (0.0)
	> 25% decrease	137	0 (0.0)	133	0 (0.0)	136	0 (0.0)
Alkaline Phosphatase (U/L)	> 100% increase	137	0 (0.0)	133	0 (0.0)	136	0 (0.0)
BUN (mmol/L)	> 50% increase	137	7 (5.1)	133	9 (6.7)	136	7 (5.1)
Calcium (mmol/L)	> 10% increase	137	7 (5.1)	133	5 (3.7)	136	3 (2.2)
	> 10% decrease	137	5 (3.6)	133	5 (3.7)	136	6 (4.4)
Chloride (mmol/L)	> 10% increase	137	0 (0.0)	133	0 (0.0)	136	0 (0.0)
	> 10% decrease	137	0 (0.0)	133	0 (0.0)	136	1 (0.7)
Creatine Kinase (U/L)	> 300% increase	137	0 (0.0)	134	2 (1.5)	137	3 (2.2)
Creatinine (umol/L)	> 50% increase	137	1 (0.7)	133	1 (0.7)	136	0 (0.0)
Glucose (mmol/L)	> 50% increase	137	0 (0.0)	133	0 (0.0)	136	0 (0.0)
	> 50% decrease	137	0 (0.0)	133	0 (0.0)	136	0 (0.0)
SGPT (U/L)	> 150% increase	137	0 (0.0)	134	3 (2.2)	137	5 (3.6)
SGOT (U/L)	> 150% increase	137	0 (0.0)	134	2 (1.5)	137	2 (1.5)
Potassium (mmol/L)	> 20% increase	137	8 (5.8)	133	9 (6.7)	136	5 (3.6)
	> 20% decrease	137	1 (0.7)	133	1 (0.7)	136	3 (2.2)
Sodium (mmol/L)	> 5% decrease	137	0 (0.0)	133	0 (0.0)	136	1 (0.7)
Total Bilirubin (umol/L)	> 100% increase	137	1 (0.7)	133	1 (0.7)	136	4 (2.9)
Uric Acid (umol/L)	> 50% increase	137	1 (0.7)	133	0 (0.0)	136	0 (0.0)

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