Sponsor

Novartis

Generic Drug Name

Valsartan

Therapeutic Area of Trial

Hypertension

Approved Indication

Indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Study Number

CVAL489ADE25

Title

A 12 week treatment, open-label, multicenter study to investigate the efficacy and safety of valsartan 160-320 mg with regard to effects on lipid subfractions in hypertensive patients with metabolic syndrome

Phase of Development

Phase III

Study Start/End Dates

24 Nov 2005 to 18 Jun 2007

Study Design/Methodology

This study was an open-label pilot trial. A screening period of 3 weeks was used to assess eligibility and to taper patients off disallowed medications. Patients who were naïve to treatment with antihypertensive drugs (never treated or no treatment in the last 2 months prior to Visit 1) could be included one week after Visit 1 / as soon as safety laboratory results of Visit 1 were available. At the baseline visit, patients whose eligibility was confirmed started on study treatment. Patients were treated with valsartan 160 mg for 4 weeks. Then forced titration to valsartan 320 mg was performed and patients were treated for another 8 weeks.

Centres

15 centers in Germany

Publication

None

Objectives

Primary objective(s)

To investigate if valsartan 320 mg has a positive effect on small, dense low density lipoprotein (LDL) subfractions (LDL 5+6) in hypertensive patients with metabolic syndrome after 12 weeks of treatment.

Secondary objective(s)

- To evaluate whether valsartan 320 mg has positive effects on further lipid parameters, e.g.: LDL, total cholesterol, triglycerides.
- To evaluate the effect of valsartan 160-320 mg on blood pressure and pulse rate.
- To assess the safety and tolerability of valsartan 160-320mg.

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

One oral tablet of valsartan 160 mg each morning (day 1 to day 28), 160 mg twice each morning (day 29 to day 84)

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

N/A

Criteria for Evaluation

Primary variables

The primary efficacy parameter was Apolipoprotein B (ApoB) in low density lipoprotein subfractions 5+6 (LDL 5+6) determined from a 12-hour fasting blood sample. Blood samples were drawn at screening, baseline, and at end of study (EoS).

The primary efficacy variable was analyzed as reduction from baseline at study finalization.

Secondary variables

- Effect of valsartan 320 mg has positive effects on further lipid subfractions and enzymes related to the lipoprotein metabolism (e.g. LDL, total cholesterol, triglycerides)
- Effect of valsartan 320 mg on blood pressure and pulse rate.

The secondary efficacy parameters were analyzed similar to the methods described for the primary variable.

Safety and tolerability

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

Statistical Methods

Descriptive statistics were provided for the primary endpoint, ApoB in small, dense LDL subfractions 5 + 6, at baseline, at end of treatment and for change between both visits. The change from baseline was tested against the null-hypothesis of no change in the primary endpoint, using a t-test for paired observations. The two-sided p-value and its corresponding confidence interval were provided.

The secondary efficacy parameters were analyzed similar to the methods described for the primary variable. Tolerability (adverse events) and safety (laboratory values) information was evaluated descriptively.

Safety and tolerability analyses were performed on the safety sample which comprises all patients who received at least one dose of study medication.

For efficacy analysis, the intent-to-treat sample (ITT) was established which contains all patients of the safety sample for whom at least one assessment of post-baseline efficacy parameters was available.

A per-protocol sample (PP) was defined by using all intent-to-treat patients who did not show major deviations from the protocol procedures that may have an impact on the study outcome. Criteria that are assumed to have such an impact were defined in a Review Meeting before analysis and documented in the corresponding protocol.

The efficacy analyses were primarily conducted in the PP sample.

Adverse events were summarized by the number and percentage of subjects who had any adverse event (AE), who had an AE in each body system, and who had each individual AE.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients were eligible for inclusion if they met all of the following criteria:

1. Male or female outpatients >= 18 years of age at Visit 1
2. Mean sitting systolic blood pressure (MSSBP) >= 140 mmHg and < 170 and/or mean sitting diastolic blood pressure (MSDBP) >= 90 mmHg and < 105 mmHg at Visit 2 for previously treated patients and at Visit 1 and 2 for previously untreated patients.
3. Fasting triglycerides greater than or equal to 150 mg/dL (1.69 mmol/L) at V1
4. Metabolic syndrome as defined by ATP III (involving one or more of the following) at Visit 1 (high triglycerides and elevated BP were mandatory in this trial):
   - Central/abdominal obesity as measured by waist circumference (Men > 102 cm; Women > 88 cm)
   - HDL cholesterol [Men < 40 mg/dL (1.04 mmol/L); Women < 50 mg/ dL (1.29 mmol/L)]
   - Fasting glucose greater than or equal to 110 mg/dL (6.1 mmol/L)
5. Written informed consent to participate in this study prior to any study procedures

Patients were to be excluded from participation if they met any of the following criteria:

1. MSSBP >= 170 mmHg and/or MSDBP >= 105 mmHg at any time between Visit 1 and Visit 2
2. Fasting plasma glucose >= 126 mg/dl at Visit 1
3. Fasting LDL cholesterol >= 160 mg/dl, fasting triglycerides >= 600 mg/dl at Visit 1
4. Inability to discontinue all antihypertensive medications safely for a period of three weeks prior to initiation of treatment
5. Patients treated with lipid lowering drugs in the last 6 weeks prior to Visit 1, use of probucol in the last 6 months prior to V1
6. History of hypersensitivity to valsartan, inactive ingredients of valsartan capsules or to drugs with similar chemical structures
7. A history of cardiovascular disease, including angina pectoris, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, transient ischemic attack, stroke, and peripheral artery disease
8. Known Keith-Wagener grade III or IV hypertensive retinopathy
9. Second or third degree heart block without a pacemaker, concurrent potentially life threatening arrhythmia or symptomatic arrhythmia, clinically significant valvular heart disease
10. Heart failure NYHA II -IV
11. Evidence of a secondary form of hypertension, to include coarctation of the aorta, hyper-

aldosteronism, Cushing's disease, unilateral or bilateral renal artery stenosis, pheochromocytoma, polycystic kidney disease

12. Evidence of hypercholesterolemia secondary to other causes. This includes, but is 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
13. Diabetes mellitus type I or II
14. Major depression requiring pharmacolgical treatment
15. Evidence of hepatic disease as determined by AST (SGOT) or ALT (SGPT) values > 3 x ULN at Visit 1
16. A history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt
17. 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 initiation of treatment
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 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
20. Any surgical or medical condition which, at the discretion of the investigator, places 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
21. History of drug or alcohol abuse within the last 2 years
22. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 halflives before enrollment, whichever is longer
23. History of noncompliance with medical regimens, or patients unwilling to comply with the study protocol
24. Persons directly involved in the execution of this protocol/study
25. Inability to communicate and comply with all study requirements
26. 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.
27. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ml).

28. Women UNLESS they meet the following definition of post-menopausal: 24 months of natural (spontaneous) amenorrhea or 3 months post surgical bilateral oophorectomy with or without hysterectomy.

Number of Subjects

	Valsartan 160-320mg/day	
Planned N	50	
Treated n	45	
Intent-to-treat population (ITT) n (%)	43 (95.6%)	
Completed n (%)	44 (97.8%)	
Withdrawn n (%)	1 (2.2%)	
Withdrawn due to adverse events n (%)	1 (2.2%)	
Withdrawn due to lack of efficacy n (%)	0	
Withdrawn for other reasons n (%)	0	

Demographic and Background Characteristics

	Valsartan 160-320mg/day	
N (safety population)	45	
Females : males	18:27	
Mean age, years (SD)	54.3 (11.8)	
Mean weight, kg (SD)	87.9 (14.0)	
Race White n (%) Black n (%) Asian n (%) Other n (%)	 44 (97.8) 0 1 (2.2) 0	
Systolic blood pressure, mmHg (SD)	154.5 (8.66)	
Diastolic blood pressure, mmHg (SD)	96.8 (4.03)	

Primary Objective Result(s)

Change in Apolipoprotein B in Low Density Lipoprotein subfractions 5+6 determined from a 12-hour fasting blood sample between the baseline Visit 2 and the end-of-study Visit 5 (per-protocol (PP) population)

		PP
	Statistics	(N = 42)
Baseline	Mean ± SD	33.3 ± 13.2
	Median	30.9
	Range	9.4 – 59.5
EoS	Mean ± SD	34.3 ± 12.2
	Median	32.5

	Range	14.3 – 64.1
Change from BL	Mean ± SD	0.75 ± 11.3
	Median	0.15
	Range	-31.3 – +28.3
	CI	[-2.76; +4.27]
	p-value	0.6678

Note: Confidence interval (CI) is the two-sided 95% interval
p-value is associated with two-sided t-test comparing baseline values and EoS values for dependent samples

Secondary Objective Result(s)

Change in triglycerides and total cholesterol determined from a 12-hour fasting blood sample between the baseline Visit 2 and the end-of-study Visit 5 (per-protocol (PP) population)

		Baseline	**EoS**	**Change**
	Statistics	(N = 42)	(N = 42)	(N = 42)
Triglycerides	Mean ± SD	230 ± 106	248 ± 105	18.6 ± 92.4
[mg/dl]	Median	200	237	18.5
	Range	105 – 539	68 – 614	-196 – 185
	CI	n.a.	n.a.	[-10.2; +47.4]
	p-value	n.a.	n.a.	0.1993
Total cholesterol	Mean ± SD	213 ± 31	222 ± 30	8.6 ± 30.3
[mg/dl]	Median	210	220	5.0
	Range	160 – 326	168 – 310	-46 – 90
	CI	n.a.	n.a.	[-0.79; +18.07]
	p-value	n.a.	n.a.	0.0714
	p-value	n.a.	n.a.	0.4633
LDL-Cholesterol	Mean ± SD	110.5 ± 25.4	118.7 ± 23.1	8.20 ± 25.7
[mg/dl]	Median	109.8	119.3	3.85
	Range	66.0 – 169.4	66.1 – 174.5	-42.8 – 68.2
	CI	n.a.	n.a.	[+0.19;+16.21]
	p-value	n.a.	n.a.	0.0451

Note: p-value is associated with two-sided t-test comparing baseline values and EoS values for dependent samples

Change in sitting blood pressure and pulse rate between the baseline Visit 2 and the end-of-study Visit 5 (per-protocol (PP) population)

		Baseline	**EoS**	**Change**
	Statistics	(N = 42)	(N = 42)	(N = 42)
Systolic BP	Mean ± SD	154.8 ± 8.8	136.9 ± 12.6	-17.9 ± 13.0
[mmHg]	Median	153.5	135.0	-18.2
	Range	136.7 – 175.7	110.7 – 164.7	-51.3 – +16.0
	CI	n.a.	n.a.	[-21.9;-13.8]
	p-value	n.a.	n.a.	<0.0001
Diastolic BP	Mean ± SD	97.1 ± 4.1	87.1 ± 7.6	-10.0 ± 8.2
[mmHg]	Median	96.7	85.3	-11.8
	Range	88.0 – 107.0	70.7 – 107.0	-21.3 – +13.3
	CI	n.a.	n.a.	[-12.5;-7.4]
	p-value	n.a.	n.a.	<0.0001
Pulse rate	Mean ± SD	74.8 ± 8.7	75.2 ± 10.0	0.0 ± 8.4
[bpm]	Median	76.0	74.5	0

	Range	58.0 – 98.0	52.0 – 96.0	-16.0 – +18.0
	CI	n.a.	n.a.	[-2.6;+2.7]
	p-value	n.a.	n.a.	0.9707
	n	41	42	41

Note: BP: blood pressure

Safety Results

Adverse Events by System Organ Class

	Valsartan 160-320mg/day
	N (%)
Patients studied	
Treated patients	45
Patients with drug-related AE	1 (2.2)
Drug-related AEs by primary system organ class	
Vascular disorders	1 (2.2)

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

	Valsartan 160-320mg/day
Nasopharyngitis	3 (6.7)
Sinobronchitis	2 (4.4)
Arthralgia	2 (4.4)
Intervertrebal disc degeneration	2 (4.4)
Osteoarthritis	2 (4.4)
Orthostatic hypotension	1 (2.2)
Pharyngitis	1 (2.2)
Respiratory tract infection	1 (2.2)
Skin infection	1 (2.2)
Vomiting	1 (2.2)

Serious Adverse Events and Deaths

	Valsartan 160-320mg/day
No. (%) of subjects studied	45 (100)
No. (%) of subjects with AE(s)	17 (37.8)
Number (%) of subjects with serious or other significant events	n (%)
Death	0
SAE(s)	0
Discontinued due to SAE(s)	0

Other Relevant Findings

N/A

Date of Clinical Trial Report

24 April 2008

Date Inclusion on Novartis Clinical Trial Results Database

09 July 2008

Date of Latest Update

09 July 2008