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Web Page/Link to Prescribing/Label Information

http://www.pharma.us.novartis.com/product/pi.jsp

Generic Drug Name
Valsartan; Valsartan/Hydrochlorothiazide combination tablets

Therapeutic Area of Trial
Hypertension

Approved Indication
Valsartan: Hypertension, Post Myocardial Infarction, Heart Failure
Valsartan/Hydrochlorothiazide: Hypertension

Study Number
CVAH631DUS02

Title
Effects of blood pressure reduction on high sensitivity C-reactive protein (hsCRP): a multicenter, randomized, open-label, 2-arm parallel group study to evaluate the efficacy of moderate vs. aggressive antihypertensive therapy with Valsartan and Valsartan and Hydrochlorothiazide to reduce blood pressure and plasma hsCRP levels in patients with stage 2 hypertension

Phase of Development - IV

Study Start/End Dates
04-Jan-2004 to 16-Jun-2005

Study Design/Methodology
This was a multicenter, randomized, open-label study with 2 parallel treatment groups. After a 1 to 7 day screening period, eligible patients were randomly assigned to receive either Valsartan 160 mg or Valsartan plus Hydrochlorothiazide (HCTZ) 160/12.5 mg once daily for 2 weeks. At Visit 2 (Week 2), treatment was up-titrated to either Valsartan 320 mg or Valsartan HCTZ 320/12.5 mg once daily for 4 weeks. At Visit 3 (Week 6), patients whose blood pressure was controlled (systolic blood pressure [SBP] <140 mm Hg, diastolic blood pressure [DBP] <90 mm Hg) remained at their current dosage level. Patients whose blood pressure was not controlled (SBP = 140 mm Hg or DBP = 90 mm Hg) at Visit 3 could have their dosage increased, at the investigator's discretion, from Valsartan 320 mg to Valsartan HCTZ 320/12.5 mg once daily for 6 weeks, or from Valsartan HCTZ 320/12.5 mg to Valsartan HCTZ 320/25 mg once daily for 6 weeks. The final study visit (Visit 4) occurred at Week 12. In this study, moderate therapy was defined as treatment with Valsartan alone, and aggressive therapy was defined as treatment with Valsartan in combination with Hydrochlorothiazide, a thiazide diuretic.

Centres

384 sites in the United States

Publication

Ridker PM, Danielson E, Rifai N, Glynn RJ; Val-MARC Investigators. Valsartan, blood pressure reduction, and C-reactive protein: primary report of the Val-MARC trial. Hypertension. 2006 Jul;48(1):73-9.

http://www.ncbi.nlm.nih.gov/pubmed/16714425?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Objectives

Primary outcome/efficacy objective(s)

To compare a moderate (Valsartan alone) versus an aggressive (Valsartan HCTZ) antihypertensive regimen with respect to:

(1) reduction in mean SBP

(2) change in plasma high sensitivity C-reactive protein (hsCRP)

Secondary outcome/efficacy objective(s)

To compare the reduction in mean DBP of a moderate versus an aggressive initial antihypertensive regimen

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

Valsartan tablets for oral administration, 160 mg once daily

Valsartan tablets for oral administration, 320 mg once daily

Valsartan/Hydrochlorothiazide 160 mg/12.5 mg combination tablets for oral administration, once daily

Valsartan/Hydrochlorothiazide 160 mg/25 mg combination tablets for oral administration, once daily

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

N/A

Criteria for Evaluation

Primary efficacy:

The 3 primary efficacy variables were:

- Change in mean sitting SBP from baseline to Week 6
- Change in plasma hsCRP level from baseline to Week 12
- Change in plasma hsCRP level from baseline to Week 6

Secondary efficacy:

Five protocol-defined secondary efficacy variables were as follows:

- Proportion of responders (mean reduction from baseline in SBP = 15 mm Hg) by Week 6
- Proportion of patients achieving SBP control (SBP < 140 mm Hg) by Week 6
- Change in mean sitting DBP from baseline to Week 6
- Proportion of patients achieving DBP <90 mm Hg by Week 6
- Change in plasma hsCRP from baseline to Week 6 for patients with baseline hsCRP =3.0 mg/L

Safety/tolerability:

Safety assessments included the incidence of adverse events and serious adverse events

Pharmacology:
No pharmacokinetic analyses were planned or performed

Other*:* N/A

Statistical Methods

Unless otherwise specified, all statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 0.05. Data from all centers were pooled to ensure that adequate patient numbers were available for subgroup analyses.

Background and relevant baseline information were summarized with appropriate descriptive statistics. Chi-square tests for categorical variables and two-sample t-tests for continuous variables were used to test for homogeneity between the treatment groups. Baseline p-values obtained from these comparisons were provided for descriptive purposes, and were not to be considered to define any formal basis for determining factors which should be included in statistical analysis models.

Three primary efficacy hypotheses were evaluated for this study. A stepwise multiple test procedure controlling for the overall type I error rate of 0.05 was used.

The primary time point for testing primary efficacy hypotheses 1 and 3 was Week 6. Analysis of Covariance (ANCOVA) models with baseline measurement and treatment as covariate/factors were used to analyze and estimate treatment effects for testing primary efficacy hypotheses 1 and 3. Also, a two-sided 95% confidence interval for the difference between the two treatment groups was reported. These analyses were performed at Week 12 also. A paired-t test was used to test for the hypothesis of no mean change within each treatment group.

Normality assumptions were not satisfied for change in hsCRP. A nonparametric test (i.e.

Wilcoxon rank-sum test) was used to make comparisons between the treatment groups. Also, the Wilcoxon sign-rank test was used to test for the change from baseline in hsCRP within each treatment group.

As appropriate, subgroup analyses by age, race, gender and strata by baseline hsCRP and blood pressure level were also performed.

Adverse events were summarized by the number and percentage of patients 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

Eligible patients were men and women, aged 18 to 75 years, inclusive, with stage 2 hypertension (defined as SBP = 160 mm Hg and = 185 mm Hg and/or DBP = 100 mm Hg and = 109 mm Hg). Patients also had documented serum creatinine = 2.0 mg/dL, serum potassium = 3.5 mmol/L and = 5.5 mmol/L, serum AST or ALT less than 2 times the upper limit of normal (all within 3 months of study entry), and documented HbA_{1c} = 11.0% (within 1 month of study entry).

A patient with any of the following exclusion criteria could not be enrolled in the study: secondary hypertension; antihypertensive therapy with ACE inhibitors, angiotensin receptor blockers, or aldosterone blockers within 3 months prior to Visit 1 or with thiazide diuretics within 1 month prior to Visit 1; initiation of lipid-lowering drugs or any change in lipid-lowering dose less than 6 weeks prior to Visit 1; and serious, concomitant cardiovascular, hepatic or renal disease or uncontrolled diabetes mellitus.

Number of Patients

	Valsartan (Moderate regimen)	**Valsartan HCTZ (Aggressive regimen)**
Planned N	1264	1264
Randomized n	839	834
Completed n (%)	661 (78.8)	652 (78.2)
Withdrawn n (%)	178 (21.2)	182 (21.8)
Included in the primary analysis n (%)	807 (96.5)	808 (97.1)
Withdrawn due to adverse events n (%)	42 (5.0)	63 (7.6)
Withdrawn due to lack of efficacy n (%)	17 (2.0)	7 (0.8)
Withdrawn for other reasons n (%)	119 (14.2)	112 (13.4)

Demographic and Background Characteristics

	Valsartan (Moderate regimen)	**Valsartan HCTZ (Aggressive regimen)**
N (Safety)	836	832
Females:males	1:1.24	1:1.17
Mean age, years (SD)	50.6 (11.55)	51.0 (11.81)
Mean weight, kg (SD)	94.3 (23.22)	93.5 (23.97)
Race		
White n (%)	567 (67.8)	562 (67.5)
Black n (%)	190 (22.7)	202 (24.3)
Asian n (%)	9 (1.1)	10 (1.2)
Hispanic n (%)	58 (6.9)	51 (6.1)
Other n (%)	12 (1.4)	7 (0.8)
Mean sitting SBP (SD) (mm Hg)	164.4 (12.71)	165.0 (13.33)
Mean sitting DBP (SD) (mm Hg)	99.9 (8.94)	99.6 (8.73)

Primary Efficacy Result(s)		
	Valsartan (Moderate regimen) (n=781)	**Valsartan HCTZ (Aggressive regimen)** (n=770)
Change from baseline to Week 6 in mean sitting SBP, mean (SD) (mm Hg)	-17.6 (17.13) p-Value for within group comparison < 0.0001	-24.8 (17.66) p-Value for within group comparison <0.0001
	p-Value between-group comparison < 0.0001	
	Overall study population (Valsartan and Valsartan HCTZ [Moderate and Aggressive regimens], pooled) (n=1436)	
Change from baseline to Week 12 in plasma hsCRP, median (mg/L)	0.03 p-Value 0.1824	
	Valsartan (Moderate regimen) (n=649)	**Valsartan HCTZ (Aggressive regimen)** (n=619)
Change from baseline to Week 6 in plasma hsCRP, median (mg/L)	-0.12 p-Value for within treatment 0.0023	0.05 p-Value for within treatment 0.3246
	p-Value between treatment groups 0.0068	
Secondary efficacy result(s)		
	Valsartan (Moderate regimen)	**Valsartan HCTZ (Aggressive regimen)**
Proportion of responders (mean reduction from baseline in SBP of = 15 mm Hg) by Week 6 [n]	65.1% [525]	76.0% [614]
Proportion of patients achieving SBP control (SBP <140 mm Hg) by Week 6 [n]	44.9% [362]	60.8% [491]
Change in sitting DBP from baseline to Week 6, mean (SD) (mm Hg) [n]	-9.6 (10.45) [781]	-13.4 (10.33) [770]
Proportion of patients achieving DBP <90 mm Hg by Week 6 [n]	59.4 [479]	72.5 [586]
Change in hsCRP at Week 6 for patients with baseline hsCRP = 3.0 mg/L, median (mg/L) [n]	-1.11 [257]	-0.60 [216]

Safety Results

Adverse Events by System Organ Class

	Valsartan (Moderate regimen)	Valsartan HCTZ (Aggressive regimen)
No. (%) of patients studied	836	832
No. (%) of patients with AE(s)	337 (40.3)	356 (42.8)
System organ class affected [1] [2]	n (%)	n (%)
Blood and lymphatic system disorders	0 (0.0)	2 (0.2)
Cardiac disorders	12 (1.4)	17 (2.0)
Congenital, familiar, and genetic disorders	0 (0.0)	1 (0.1)
Ear and labyrinth disorders	11 (1.3)	7 (0.8)
Endocrine disorders	2 (0.2)	2 (0.2)
Eye disorders	7 (0.8)	11 (1.3)
Gastrointestinal disorders	68 (8.1)	68 (8.2)
General disorders and administration site disorders	49 (5.9)	64 (7.7)
Hepatobiliary disorders	1 (0.1)	1 (0.1)
Immune system disorders	4 (0.5)	5 (0.6)
Infections and infestations	105 (12.6)	92 (11.1)
Injury, poisoning and procedural complications	14 (1.7)	22 (2.6)
Investigations	6 (0.7)	8 (1.0)
Metabolism and nutrition disorders	10 (1.2)	11 (1.3)
Musculoskeletal and connective tissue disorders	66 (7.9)	74 (8.9)
Neoplasms benign, malignant and unspecified	4 (0.5)	1 (0.1)
Nervous system disorders	84 (10.0)	121 (14.5)
Psychiatric disorders	23 (2.8)	27 (3.2)
Renal and urinary disorders	14 (1.7)	13 (1.6)
Reproductive system and breast disorders	11 (1.3)	12 (1.4)
Respiratory, thoracic and mediastinal disorders	40 (4.8)	34 (4.1)
Skin and subcutaneous tissue disorders	19 (2.3)	20 (2.4)
Surgical and medical procedures	1 (0.1)	0 (0.0)
Vascular disorders	16 (1.9)	21 (2.5)

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

	Valsartan (Moderate regimen)	**Valsartan HCTZ** (Aggressive regimen)
Dizziness	39 (4.7)	71 (8.5)
Headache	32 (3.8)	38 (4.6)
Fatigue	27 (3.2)	38 (4.6)
Sinusitis	16 (1.9)	18 (2.2)
Upper respiratory tract infection	20 (2.4)	14 (1.7)
Arthralgia	17 (2.0)	16 (1.9)
Nausea	13 (1.6)	20 (2.4)
Diarrhea	20 (2.4)	12 (1.4)
Back pain	12 (1.4)	17 (2.0)
Nasopharyngitis	16 (1.9)	11 (1.3)

Serious Adverse Events and Deaths

	Valsartan (Moderate regimen)	Valsartan HCTZ (Aggressive regimen)
Number (%) of patients with serious (SAE) or other significant events	n (%)	n (%)
Death	1 (0.1)†	0 (0.0)
SAE(s)	14 (1.7)	21 (2.5)
Clinically significant AE(s)	40 (4.8)	55 (6.6)
Discontinued due to SAE(s)	2 (0.2)	8 (1.0)
Discontinued due to clinically significant AE(s)	40 (4.8)	55 (6.6)

†One patient died as a result of a motor vehicle accident; this event was not suspected to be related to study medication.

Note: Patients randomized to Valsartan were allowed to take Valsartan HCTZ after Week 6 if necessary.

Other Relevant Findings

None

Date of Clinical Trial Report

9-June-2006

Date Inclusion on Novartis Clinical Trial Results Database

9-October-2006

Date of Latest Update

13-February-2008