Sponsor
Novartis

Generic Drug Name
Valsartan + hydrochlorothiazide (HCTZ)

Therapeutic Area of Trial
Hypertension

Approved Indication
Hypertension

Study Number
CVAH631C2302

Title
A double-blind, randomized, multi-center, active-controlled, parallel-group study comparing the combination of valsartan 320mg/hydrochlorothiazide 12.5 mg and valsartan 320 mg/hydrochlorothiazide 25 mg to valsartan 320 mg in mild to moderate hypertensive patients not adequately controlled with valsartan 320 mg

Phase of Development
Phase III

Study Start/End Dates
10-Sep-2004 to 04-Jul-2005

Study Design/Methodology
This was a double-blind, randomized, multi-center, active-controlled, parallel-group study designed to provide efficacy and safety data for the combination of valsartan 320 mg/HCTZ 12.5 mg and valsartan 320 mg/HCTZ 25 mg in patients with mild to moderate hypertension not adequately controlled by valsartan 320 mg alone. The study included a 1-4 week washout phase, 4 week single-blind valsartan 320 mg run-in phase. Patients with an inadequate response (defined as MSDBP = 90 mmHg and < 110 mmHg) during the run-in phase, entered the double-blind treatment phase and were received either valsartan 320 mg, valsartan 320 mg /HCTZ 12.5 mg or valsartan 320 mg/HCTZ 25 mg for 8 weeks.

Centres
237 study centers in 17 countries: Argentina (16), Austria (3), Brazil (19), Canada (11), Ecuador (3), Egypt (5), Finland (10), France (17), Germany (80), Greece (1), Hungary (4), Peru (10), Poland (8), Russia (12), South Africa (6), Spain (18), Sweden (14).

Publication
Ongoing

Objectives

Primary outcome/efficacy objective(s)

To evaluate the reduction from baseline in mean sitting diastolic blood pressure (MSDBP) with valsartan 320 mg/HCTZ 25 mg and valsartan 320 mg/HCTZ 12.5 mg compared to valsartan 320 mg

Secondary outcome/efficacy objective(s)

- To explore the reduction from baseline in MSDBP with valsartan 320 mg/HCTZ 25 mg compared to valsartan 320 mg/HCTZ 12.5 mg
- To explore the reduction of mean sitting systolic blood pressure (MSSBP) with valsartan 320 mg/HCTZ 25 mg or valsartan 320 mg/HCTZ 12.5 mg compared to valsartan 320 mg alone
- To explore the reduction of MSSBP with valsartan 320 mg/HCTZ 25 mg compared to valsartan 320 mg/HCTZ 12.5 mg
- To explore responder rates at the end of the study of these three treatments (a responder is defined as MSDBP <90 mmHg or >=10 mmHg decrease from baseline in MSDBP)
- To explore the safety of the three treatments

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

Valsartan 320 mg, Valsartan 320 mg + HCTZ 12.5 mg, Valsartan 320 mg + HCTZ 25 mg oral administration, once daily (o.d.)

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

None

Criteria for Evaluation

Primary efficacy:

The primary efficacy variable was change from baseline in MSDBP at trough, measured using a calibrated oscillometric electronic blood pressure measuring device and appropriately sized cuff.

Secondary efficacy:

The secondary efficacy variable was change in MSSBP at trough. Other efficacy variables included change from baseline in standing systolic and diastolic blood pressures, responder rate (defined as MSDBP < 90 mmHg or a = 10 mmHg decrease compared to baseline).

Safety/tolerability:

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious AEs (SAEs), pregnancies, the regular monitoring of hematology and blood chemistry (performed at the central laboratory) and regular assessments of physical condition, pulse, and weight.

Pharmacology:

Not assessed.

Other:

N/A.

Statistical Methods

The primary efficacy variable was analyzed using analysis of covariance model (ANCOVA) with treatment and center (pooled) as fixed factors, centered baseline MSDBP as a covariate, and

treatment-by-centered baseline MSDBP as an interaction. This was considered as the primary analysis for the treatment comparison. For the comparison of the two combination therapies to the monotherapy, the Dunnett multiple comparison adjustment was used in order to maintain a global significance level 0.05 in the ANCOVA model. All other tests were made at a two-sided significance level of 0.05.

The primary and secondary analysis were performed using the intent-to-treat (ITT) population. Only patients with a baseline and endpoint value were included. Baseline was defined as Visit 3 in all cases and Endpoint was defined in each case as the last non-missing post baseline assessment. Change from baseline was calculated as: Endpoint – Baseline. A positive treatment difference indicates a greater BP reduction in the second treatment group compared to the first.

The proportion of responder patients were summarized at each visit and compared across treatment groups at endpoint using a logistic model with treatment and center (pooled) as factors.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion/exclusion criteria:

Male or female outpatients between the ages of 18 and 80 years (inclusive), with mild to moderate hypertension (grades 1 or 2 World Health Organization [WHO] classification) were eligible for participation. At visit 1 (washout phase), all previously non-treated patients were required to have an MSDBP of ≥ 95 to < 110 mmHg, and previously treated patients were required to have an MSDBP of < 110 mmHg. At visit 2 (start of single blind phase), MSDBP was to be between ≥ 95 and < 110 mmHg, and at visit 3 (start of double-blind phase), MSDBP was to be between ≥ 90 mmHg and < 110 mmHg. Patients with severe hypertension (= 110 mmHg diastolic and/or = 180 mmHg systolic) or malignant hypertension were excluded.

Number of Subjects

	Val 320 mg	**Val/HCTZ 320/12.5 mg**	**Val/HCTZ 320/25 mg**
Planned N	890	890	890
Randomized n	899 (100)	903 (100)	900 (100)
Completed n (%)	843 (93.8)	872 (96.6)	864 (96.0)
Withdrawn n (%)	56 (6.2)	31 (3.4)	36 (4.0)
Included in the primary analysis n (%)	891 (99.1)	895 (99.1)	889 (98.8)
Withdrawn due to adverse events n (%)	18 (2.0)	11 (1.2)	17 (1.9)
Withdrawn due to lack of efficacy n (%)	9 (1.0)	3 (0.3)	2 (0.2)
Withdrawn for other reasons n (%)	29 (3.3)	17 (1.9)	17 (1.9)

Demographic and Background Characteristics

	Val 320 mg	**Val/HCTZ 320/12.5 mg**	**Val/HCTZ 320/25 mg**
Randomized population	899 (100)	903 (100)	900 (100)
Females n (%)	387 (43.0)	388 (43.0)	387 (43.0)

Males n (%)	512 (57.0)	515 (57.0)	513 (57.0)
Mean age, years (SD)	54.2 (10.42)	53.9 (10.03)	54.4 (10.06)
Mean weight, kg (SD)	84.2 (16.21)	84.0 (16.42)	84.0 (16.3)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 801 (89.1) 23 (2.6) 6 (0.7) 69 (7.7)	 815 (90.3) 24 (2.7) 2 (0.2) 62 (6.9)	 800 (88.9) 17 (1.9) 2 (0.2) 81 (9.0)
Mean sitting diastolic blood pressure (mmHg) (SD)	96.65 (4.9)	96.63 (4.8)	96.47 (4.9)
Mean sitting systolic blood pressure (mmHg), (SD)	152.86 (12.5)	153.28 (12.5)	153.61 (12.4)

Primary Efficacy Result(s)

Primary analysis for change from baseline in mean sitting diastolic blood pressure (MSDBP) at endpoint (ITT population)

Treatment group	N	n	Baseline Mean (SE)	Least Square (LS) Mean Change (SE)
Val 320mg	891	891	96.6 (0.16)	-5.8 (0.28)
Val 320mg/HCTZ 12.5mg	895	895	96.6 (0.16)	-9.7 (0.29)
Val 320 mg/HCTZ 25mg	889	889	96.5 (0.17)	-10.4 (0.29)

Comparison	-Difference in LS Mean Change- Mean (SE)	95%CI	p-value
Val 320mg vs Val 320 mg/HCTZ 12.5mg	3.9 (0.39)	(3.0, 4.7)	<0.0001*
Val 320mg vs Val 320 mg/HCTZ 25mg	4.6 (0.39)	(3.7, 5.4)	<0.0001*

Secondary efficacy result(s)

Secondary analysis for change from baseline in mean sitting systolic blood pressure (MSSBP) at endpoint (ITT population)

Treatment group	N	n	Baseline Mean (SE)	LS Mean Change (SE)
Val 320 mg	891	891	152.8 (0.42)	-6.1 (0.48)
Val 320mg/HCTZ 12.5 mg	895	895	153.3 (0.42)	-13.6 (0.48)
Val 320 mg/HCTZ 25 mg	889	889	153.6 (0.42)	-15.4 (0.48)

Comparison	-Difference in LS Mean Change- Mean (SE)	95% CI	p-value
Val 320 mg versus Val 320 mg/HCTZ 12.5 mg	7.5 (0.64)	(6.3, 8.8)	<0.0001*

Val 320 mg versus Val 320 mg/HCTZ 25 mg	9.4 (0.65)	(8.1, 10.7)	<0.0001*

N = ITT population; n = number with both baseline and endpoint.
* Signifies a p-value of < 0.05.

Secondary analysis for change from baseline in mean sitting diastolic and systolic blood pressure at endpoint (ITT population)

	Difference in LS Mean Change		
	Mean (SE)	95% CI	p-value
Comparison MSDBP Val/HCTZ 320/12.5 mg vs Val/HCTZ 320/25 mg	0.7 (0.39)	(-0.1,1.4)	0.0741
Comparison MSSBP Val/HCTZ 320/12.5 mg vs Val/HCTZ 320/25 mg	1.9 (0.65)	(0.6, 3.1)	0.0042*

* Signifies a p-value of < 0.05.

Responder rate for MSDBP at endpoint (ITT population)

Variable	Val 320mg N=891 n (%)	Val/HCTZ 320/12.5mg N=895 n (%)	Val/HCTZ 320/25mg N=889 n (%)
Responder rate	470 (52.7)	616 (68.8)	666 (74.9)

N = ITT population

Safety Results

Adverse Events by System Organ Class during the double-blind period

Primary system organ class	Val 320mg N=899 n (%)	Val/HCTZ 320/12.5 mg N=903 n (%)	Val/HCTZ 320/25 mg N=900 n (%)	Total N=2702 n (%)
Any primary system organ class	213 (23.7)	225 (24.9)	215 (23.9)	653 (24.2)
Infections & infestations	58 (6.5)	72 (8.0)	50 (5.6)	180 (6.7)
Nervous system disorders	44 (4.9)	48 (5.3)	34 (3.8)	126 (4.7)
Gastrointestinal disorders	28 (3.1)	29 (3.2)	31 (3.4)	88 (3.3)
Musculoskel. & connective tissue disorders	26 (2.9)	28 (3.1)	28 (3.1)	82 (3.0)
Ear and labyrinth disorders	6 (0.7)	8 (0.9)	17 (1.9)	31 (1.1)
General dis. & admin. site conditions	17 (1.9)	17 (1.9)	17 (1.9)	51 (1.9)
Respiratory, thoracic & mediastinal disorders	13 (1.4)	15 (1.7)	16 (1.8)	44 (1.6)
Investigations	5 (0.6)	9 (1.0)	14 (1.6)	28 (1.0)

Metabolism & nutrition disorders	14 (1.6)	10 (1.1)	14 (1.6)	38 (1.4)
Skin & subcutaneous tissue disorders	9 (1.0)	6 (0.7)	14 (1.6)	29 (1.1)
Vascular disorders	6 (0.7)	6 (0.7)	14 (1.6)	26 (1.0)
Psychiatric disorders	7 (0.8)	7 (0.8)	10 (1.1)	24 (0.9)
Cardiac disorders	8 (0.9)	13 (1.4)	7 (0.8)	28 (1.0)
Injury, poisoning & procedural complictions	7 (0.8)	7 (0.8)	7 (0.8)	21 (0.8)
Renal and urinary disorders	5 (0.6)	5 (0.6)	6 (0.7)	16 (0.6)
Reproductive system & breast disorders	6 (0.7)	5 (0.6)	6 (0.7)	17 (0.6)
Eye disorders	6 (0.7)	5 (0.6)	3 (0.3)	14 (0.5)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)
Neoplasms benign, malignant & unspecified (incl cysts and polyps)	0 (0.0)	2 (0.2)	1 (0.1)	3 (0.1)
Blood & lymphatic system disorders	3 (0.3)	1 (0.1)	0 (0.0)	4 (0.1)
Immune system disorders	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.1)
Pregnancy, puerperium & perinatal conditions	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)

A patient with multiple AEs within a primary system organ class is counted only once in the total
N = double-blind safety population

10 Most Frequently Reported AEs by Preferred Term during the double-blind period

Preferred term	Val 320 mg N=899 n (%)	Val/HCTZ 320/12.5 mg N=903 n (%)	Val/HCTZ 320/25 mg N=900 n (%)	Total N=2702 n (%)
Total	213 (23.7)	225 (24.9)	215 (23.9)	653 (24.2)
Nasopharyngitis	25 (2.8)	21 (2.3)	20 (2.2)	66 (2.4)
Dizziness	11 (1.2)	25 (2.8)	14 (1.6)	50 (1.9)
Vertigo	4 (0.4)	4 (0.4)	13 (1.4)	21 (0.8)
Headache	24 (2.7)	18 (2.0)	12 (1.3)	54 (2.0)
Back pain	6 (0.7)	9 (1.0)	10 (1.1)	25 (0.9)
Diarrhoea	11 (1.2)	4 (0.4)	8 (0.9)	23 (0.9)
Arthralgia	3 (0.3)	4 (0.4)	6 (0.7)	13 (0.5)
Bronchitis	4 (0.4)	5 (0.6)	5 (0.6)	14 (0.5)
Influenza	4 (0.4)	9 (1.0)	5 (0.6)	18 (0.7)
Asthenia	5 (0.6)	6 (0.7)	4 (0.4)	15 (0.6)

A patient with multiple AEs within a primary system organ class is counted only once in the total
N = double-blind safety population

Serious Adverse Events and Deaths (Single-blind and double-blind period)

	Single-blind phase	Double-blind phase			
	Val 320 mg N=3803 n (%)	Val 320 mg N=899 n (%)	Val/HCTZ 320/12.5 mg N=903 n (%)	Val/HCTZ 320/25 mg N=900 n (%)	Total N=2702 n (%)
Total number of patients	83 (2.2)	21 (2.3)	15 (1.7)	16 (1.8)	52 (1.9)
Deaths	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	21 (0.6)	7 (0.8)	7 (0.8)	2 (0.2)	16 (0.6)
Discontinuation due to SAEs	15 (0.4)	2 (0.2)	2 (0.2)	1 (0.1)	5 (0.2)
Discontinuation due to AEs	78 (2.1)	16 (1.8)	10 (1.1)	15 (1.7)	41 (1.5)

Other Relevant Findings

None

Date of Clinical Trial Report

23-Sep-2005

Date Inclusion on Novartis Clinical Trial Results Database

22-Aug-2006

Date of Latest Update

16-Aug-2006