Sponsor– Novartis	
Generic Drug Name–Valsartan 160 mg/Hydrochlorothiazide 25 mg	
Therapeutic Area of Trial– Cardiovascular	
Approved Indication–Essential Hypertension	
Study Number–CVAH631BDE10	
Title–An open-label, multicenter study to evaluate the efficacy and safety of a 4-week therapy with valsartan /hydrochlorothiazide (HCTZ) 160/25 (fixed dose combination of valsartan 160 mg plus HCTZ 25 mg) in patients not adequately responding to a 4-week monotherapy with olmesartan medoxomil 40 mg or combination therapy with olmesartan medoxomil 20 mg plus HCTZ 12.5 mg- VALORY	
Phase of Development–III	
Study Start/End dates– 30-Nov-2004 / 18-Apr-2005	
Study Design/Methodology– This was a multicenter, open-label trial with two sequential treatment periods. Following a wash-out period of 1-2 weeks, patients with moderate hypertension (WHO grade II) were included in treatment period 1 and were treated with either olmesartan medoxomil 40 mg or combination therapy with olmesartan medoxomil 20 mg plus HCTZ 12.5 mg for 4 weeks. Patients who did not achieve a mean sitting diastolic blood pressure < 90 mmHg after treatment period 1 were included in treatment period 2 and received valsartan 160 mg/HCTZ 25 mg for 4 weeks.	
Centres– 30 centers in Germany	
Publication– ongoing	

Objectives–

Primary outcome/efficacy objective(s)–

- To evaluate the efficacy of valsartan 160 mg/HCTZ 25 mg in patients not adequately responding to monotherapy with olmesartan medoxomil 40 mg or combination therapy with olmesartan medoxomil 20 mg plus HCTZ 12.5 mg in reducing the trough mean sitting diastolic blood pressure (MSDBP)

Secondary outcome/efficacy objective(s)–

- To explore the efficacy of valsartan 160 mg/HCTZ 25 mg in patients not adequately responding to monotherapy with olmesartan medoxomil 40 mg or combination therapy with olmesartan medoxomil 20 mg plus HCTZ 12.5 mg in:
    - reducing the trough mean sitting systolic blood pressure (MSSBP)
    - leading to higher normalization rate (defined as a MSDBP < 90 mmHg) and responder rate (defined as a MSDBP < 90 mmHg or $\geq$ 10 mmHg decrease after treatment 2 relative to treatment period 1)
    - having no affect on sitting pulse rate
- To evaluate the safety of valsartan 160 mg/HCTZ 25 mg

Test Product, Dose, and Mode of Administration– Valsartan 160mg/HCTZ 25 mg once daily fixed dose combination, tablets, oral
Reference Product(s), Dose(s), and Mode(s) of Administration–olmesartan medoxomil 40 mg or olmesartan medoxomil 20 mg + HCTZ 12.5 mg once daily, tablets, oral

Criteria for Evaluation–

Primary efficacy:
Change in trough MSDBP

Secondary efficacy:
Changes in trough MSSBP, changes in pulse rate, normalization and responder rate

Safety/tolerability: Adverse events and changes in laboratory parameters.

Other: N.A.

Pharmacology: N.A.

Statistical Methods–
The primary efficacy parameter of this trial was the change in trough MSDBP between treatment period 1 (olmesartan medoxomil 40 mg or olmesartan medoxomil 20 mg plus HCTZ 12.5 mg) and treatment period 2 (valsartan 160 mg/HCTZ 25 mg). The mean change was calculated and tested against the null hypothesis of no change using a one-sample t-test. Point estimates, p-values and (95%) confidence intervals were reported for the pooled sample as well as within the two phase 1 treatment groups. The two-sided significance level was set to 5%. The primary analysis was performed using the intention-to-treat population.

The secondary efficacy parameters, changes in trough MSSBP as well as changes in pulse rate were analyzed analogously. The responder rate and normalization rate were calculated with the 95% confidence intervals.

Study Population: Inclusion/Exclusion Criteria and Demographics–

This study recruited male and female patients, aged 18 years and older with essential hypertension (for first treatment period: MSDBP $\geq$100 mmHg and < 110 mmHg; for second treatment period: MSDBP $\geq$90 mmHg). Patients with MSDBP $\geq$110 mmHg or MSSBP $\geq$180 mmHg controlled hypertension under current therapy (MSDBP < 90 mmHg and MSSBP < 140 mmHg), unable to discontinue all antihypertensive medications safely for a period of up to 2 weeks, as required by the protocol, known Keith-Wagener grade III or IV hypertensive retinopathy, history of hypertensive encephalopathy or cerebrovascular accident within the preceding 12 months, evidence of a secondary form of hypertension, such as coarctation of the aorta, hyperaldosteronism, unilateral renal artery stenosis or pheochromocytoma, known or suspected contraindications including history of allergy to angiotensin II receptor blockers or to diuretics as described in the basic product information (particularly olmesartan medoxomil 20 mg or 40 mg, valsartan 160 mg), heart failure NYHA II-IV, second or third degree heart block without pacemaker, concomitant refractory angina pectoris, concomitant potentially life-threatening arrhythmia or symptomatic arrhythmia, clinically significant valvular heart disease, transient ischemic cerebral attack, stroke or myocardial infarction during the last 12 months prior to Visit 1, and additional co-morbid conditions were excluded.

Number of Subjects	
Planned N Period I/Period II	220 / 120
Enrolled n for Period I/Period II	204 / 158
Completed n (%) for Period I/Period II	199 (97.5) / 157 (99.4)
Withdrawn n (%) for Period I/Period II	5 (2.5) / 1 (0.6)
Included in the primary analysis n (%)	158 (77.5)
Withdrawn due to adverse events n (%) for Period I/Period II	2 (1.0) / 1 (0.6)
Withdrawn due to lack of efficacy n (%)	0 (0) / 0 (0)
Withdrawn for other reasons n (%) for Period I/Period II	3 (1.5) / 0 (0)

Demographic and Background Characteristics	
N (ITT)	158
Females : Males	65 (41.1) : 93 (58.9)
Mean age, years (SD)	59.1 (11.1)
Mean weight, kg (SD)	84.4 (15.85)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 158 (100) 0 0 0

Primary Efficacy Result(s)–intent to treat population

Reduction of mean sitting diastolic blood pressure in patients treated with olmesartan medoxomil (Olm) 40 mg in treatment period 1 by treatment with the fixed dose combination of valsartan 160 mg/ HCTZ 25 mg	
Mean sitting DBP at trough: treatment period 1	93.0 mmHg
Mean sitting DBP at trough: treatment period 2	84.7 mmHg
Mean reduction of mean sitting DBP ± SD	8.3 ± 6.5 mmHg
95% confidence interval limits	6.8 – 9.8
p-value	p <0.0001
Reduction of mean sitting diastolic blood pressure in patients treated with Olm 20 mg/HCTZ 12.5 mg in treatment period 1 by treatment with the fixed dose combination of valsartan 160 mg/HCTZ 25 mg	
Mean sitting DBP at trough: treatment period 1	93.8 mmHg
Mean sitting DBP at trough: treatment period 2	84.0 mmHg
Mean reduction of mean sitting DBP ± SD	9.8 ± 7.9 mmHg
95% confidence interval limits	8.1 – 11.5
p-value	p <0.0001

Secondary efficacy result(s)–intent to treat population

Reduction of mean sitting systolic blood pressure in patients treated with Olm 40 mg in treatment period 1 by treatment with the fixed dose combination of valsartan 160 mg/HCTZ 25 mg	
Mean reduction of mean sitting SBP ± SD 95% confidence interval limits	14.2 ± 13.4 mmHg 11.1 – 17.3
p-value	p <0.0001
Reduction of mean sitting systolic blood pressure in patients treated with Olm 20 mg/HCTZ 12.5 mg in treatment period 1 by treatment with the fixed dose combination of valsartan 160 mg/HCTZ 25 mg	
Mean reduction of mean sitting SBP ± SD	12.2 ± 13.2 mmHg
95% confidence interval limits	9.3 – 15.0
p-value	p <0.0001

Normalization and responder rates at study end

Normalization and responder rates after treatment period 2 in patients treated with Olm 40 mg during treatment period 1	
Normalization rate	74 %
Responder rate	77 %
Normalization and responder rates after treatment period 2 in patients treated with Olm 20 mg/HCTZ 12.5 mg during treatment period 1	
Normalization rate	77 %
Responder rate	79 %

Change in sitting heart rate after treatment with valsartan 160mg/HCTZ 25 mg

	Treatment during Period I: Olmesartan 40mg mono	Treatment during Period I: Olmesartan 20mg +HCTZ
n	74	84
Mean decrease	0.39	1.81
95% confidence interval	1.88 – 2.68	0.08 – 3.54
p-value	0.7319	0.0406

Safety Results

Adverse Events by System Organ Class

No of patients with AEs*	Treatment period 1*	Treatment period 1*	Treatment period 2
	Olmesartan 40mg n (%) 93 (100.0)	Olmesartan 20mg /HCTZ 12.5mg n (%) 111 (100.0)	Valsartan 160mg /HCTZ 25 mg n (%) 158 (100.0)
Total no. of patients with AEs	10 (10.8)	13 (11.7)	26 (16.5)
Blood and lymphatic system disorders	0 (0.0)	1 (0.9)	1 (0.6)
Cardiac Disorders	1 (1.1)	1 (0.9)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	4 (2.5)
General disorders and administration site conditions	1 (1.1)	0 (0.0)	0 (0.0)
Immune System Disorders	0 (0.0)	0 (0.0)	1 (0.6)
Infections and infestations	5 (5.4)	5 (4.5)	7 (4.4)
Injury, poisoning and procedural complications	1 (1.1)	1 (0.9)	1 (0.6)
Investigations	0 (0)	1 (0.9)	1 (0.6)
Metabolism and nutrition disorders	2 (2.2)	1 (0.9)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (2.2)	1 (0.9)	3 (1.9)
Nervous system disorders	1 (1.1)	1 (0.9)	2 (1.3)

Psychiatric Disorders	0 (0.0)	0 (0.0)	2 (1.3)
Reproductive System and Breast Disorders	0 (0.0)	0 (0.0)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (0.9)	1 (0.6)
Skin and subcutaneous tissue disorders	0 (0)	2 (1.8)	6 (3.8)

Patients are counted only once in each body system regardless of the number of AEs experienced in that body system

* Includes follow up for patients who did not enter phase 2

10 Most Frequently Reported AEs by Preferred Term

	Treatment period I Olmesartan 40 mg and Olmesartan 20mg/HCTZ 12.5mg N =204 n (%)	Treatment period 2 Valsartan 160mg/HCTZ 25mg N =158 n (%)
Bronchitis/Bronchitis acute	4 (2.0)	5 (3.2)
Back pain	2 (1.0)	0 (0.0)
Hypertriglyceridaemia	2 (1.0)	0 (0.0)
Dizziness	1 (0.5)	2 (1.3)
Hepatic enzyme increased	1 (0.5)	1 (0.6)
Atopic dermatitis	1 (0.5)	1 (0.6)
Arthralgia	1 (0.5)	1 (0.6)
Wound	1 (0.5)	1 (0.6)
Diarrhoea	0 (0.0)	1 (0.6)
Nausea	0 (0.0)	1 (0.6)

Serious Adverse Events and Deaths

	Treatment period I Olmesartan 40mg n (%) N = 93 (100.0)	Treatment period I Olmesartan 20mg / HCTZ 12.5mg n (%) N = 111 (100.0)	Treatment period 2 Valsartan 160mg/HCTZ 25mg n (%) N =158 (100.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
SAE	1 (1.1) [1]	0 (0.0)	1 (0.6%) [2]
SAEs causing discontinuation	1 (1.1)	0 (0.0)	0 (0.0)

[1] Includes 1 patient in Olm 40mg group with pneumonia who discontinued
[2] Includes 1 patient with chronic bronchitis

Other Relevant Findings–

Date of Clinical Trial Report–	31-Jan-2006	
Date Inclusion on Registry–	02-Aug-2006	
Date of Latest Update–	26-Apr-2006	