Sponsor Novartis Pharmaceuticals
Generic Drug Name Valsartan, valsartan + hydrochlorothiazide (HCTZ) in fixed-dose combination
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.
Protocol Number CVAL489ADE24
Title A randomized, open-label, multicenter, parallel group study to assess the impact of supportive measures on the drug adherence of patients with essential hypertension treated with valsartan or valsartan plus HCTZ for 34 weeks with or without respective measures
Phase of Development Phase III

Study Start/End Dates

29 November 2005 to 01 June 2007

Study Design/Methodology

This trial was a cluster-randomized (by center), open-label, multicenter, parallel-group study. Two arms were defined: the first one provided standard care whereas patients included in the second one received a supportive intervention. To avoid any investigator bias in treating one patient with and another patient without supportive measures, investigators were randomized to provide only treatment with or without supportive measures for all their patients. Consequently, centers were randomized to use of supportive measures or standard care. According to the randomization of the recruiting center, patients were assigned to the respective treatment arm in a ratio of 1:1. A screening period of 3 days was used to assess eligibility (safety lab). At the baseline visit, patients whose eligibility was confirmed started on study treatment with valsartan 160 mg for 4 weeks. Patients not achieving controlled blood pressure levels (BP < 140/90 mmHg) were then up-titrated to valsartan 160 mg plus HCTZ 12.5 mg. Patients with controlled BP continued the treatment with valsartan 160 mg. Visits were planned after 2, 4, 8, 14, 24, and 34 weeks. Safety and efficacy were regularly assessed. The primary objective was assessed by the MEMS monitor (Medication Event Monitoring System) which compiles date and time of drug intake through the opening of the medication container.

Centres

30 centers in Germany

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Outcome measures

Primary outcome measures(s)

- Weekly mean adherence to medication

Secondary outcome measures(s)

- Persistence over time
- Weekly mean compliance
- MEMS vs. other measurements (pill counts, Morisky questionnaire)
- Relationship between drug exposure and BP reduction
- Likelihood to switch to valsartan 160 mg plus HCTZ 12.5 mg
- Safety and tolerability of valsartan 160 mg and valsartan 160 mg plus HCTZ 12.5 mg
- BP normalization and BP response

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

Valsartan 160 mg tablets or valsartan 160 mg plus HCTZ 12.5 mg tablets were taken orally once daily.

Statistical Methods

Primary outcome measure (adherence pattern) is summarized in a sequence of binary data Z_{it} defined as follows:
For visit days:

- Z_{it} = 1 if patient i has opened the MEMS monitor at least once
- Z_{it} = 0 otherwise

For other days:

- Z_{it} = 1 if patient i has opened the MEMS monitor exactly once between 07:00 and 11:00 AM on day t
- Z_{it} = 0 otherwise

Additional openings of the monitors due to refills or pill count are expected at visit days. The timing of those extra openings is unknown.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Male or female patients >= 18 years
- Patients with mild essential hypertension (msDBP >= 90 mmHg and < 100 mmHg and/or msSBP >=140 mmHg and < 160 mmHg) at visits 1 and 2 not having been treated with antihypertensive drugs before or not having been treated with antihypertensive drugs for at least one year prior to visit 1
- Written informed consent to participate in the study prior to any study procedures

Exclusion criteria:

- msSBP >= 160 mmHg and/or msDBP >= 100 mmHg at any time between visit 1 and 2
- Patients currently requiring/likely to require any regular long-term drug treatment, i.e. for more than 28 days
- History of: hypersensitivity to valsartan or HCTZ or their inactive ingredients or drugs with similar chemical structures; cardiovascular disease; hepatic encephalopathy, esophageal varices, or portocaval shunt
- Known Keith-Wagener grade III or IV hypertensive retinopathy
- Second or third degree heart block without a pacemaker, concurrent potentially life threatening arrhythmia or symptomatic arrhythmia, clinically significant valvular heart disease
- Heart failure NYHA II – IV
- Evidence of a secondary form of hypertension
- Diabetes mellitus type I or type II requiring drug treatment
- Evidence of hepatic disease
- Evidence of renal impairment
- Therapy resistant hypokalemia, hyponatremia, hypercalcemia, or symptomatic hyperuricemia
- Any severe, life-threatening disease within the past 5 years
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug (i.e. History of major gastrointestinal tract surgery; currently active or inactive inflammatory bowel disease during the 12 months prior to visit 1; currently active gastritis, ulcers, or gastrointestinal/rectal bleeding or urinary tract obstruction)
- Any surgical or medical condition which, at the discretion of the investigator, places the patient at high 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.
- History of drug or alcohol abuse within the last 2 years
- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives before enrollment, whichever is longer
- History of noncompliance with medical regimens
- Persons directly involved in the execution of this protocol/study
- Inability to communicate and comply with all study requirements
- 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
- Pregnant or nursing women
- Women of child-bearing potential

Participant Flow

Patient disposition for each group

	Standard Care n(%)	Intervention n(%)	Total n(%)
Enrolled	110	105	215
Screening failure	5	4	9
Safety Population	105	101	206
Fire at investigator's site	0	2	2
Monitor Destroyed	0	2	2
ITT Population	105	97	202
Completer	97 (92.4)	94 (96.9)	191 (94.6)
Discontinued	8 (7.6)	3 (3.1)	11 (5.4)
Adverse event(s)	2 (1.9)	0 (0.0)	2 (1.0)
Protocol violation	1 (1.0)	0 (0.0)	1 (0.5)
Subject withdrew consent	3 (2.9)	2 (2.1)	5 (2.5)
Administrative reason	2 (1.9)	1 (1.0)	3 (1.5)

Note: ITT population used as denominator

Baseline Characteristics

Demographic characteristics - ITT population

Variable		Standard Care (N=105)	Intervention (N=97)	Total (N=202)
Gender N(%)	Male	57 (54.3)	53 (54.6)	110 (54.5)
	Female	48 (45.7)	44 (45.4)	92 (45.5)
Race N(%)	Caucasian	102 (97.1)	94 (96.9)	196 (97.0)
	Black	1 (1.0)	1 (1.0)	2 (1.0)
	Oriental	1 (1.0)	2 (2.1)	3 (1.5)
	Other	1 (1.0)	0 (0.0)	1 (0.5)
Age (Years)	Mean (SD)	52.8(11.7)	49.8(12.0)	51.4(11.9)
	Median (min-max)	52.0(18.0-78.0)	49.0(22.0-78.0)	51.0(18.0-78.0)
Weight (kg)	Mean (SD)	83.9(15.4)	85.4(16.1)	84.6(15.7)
	Median (min-max)	83.0(50.0-139.0)	86.0(55.0-147.0)	84.0(50.0-147.0)
Height (cm)	Mean (SD)	169.9(8.9)	171.6(8.5)	170.7(8.8)
	Median (min-max)	170.0(150.0-189.0)	172.0(153.0-198.0)	170.0(150.0-198.0)
BMI (kg/m^2)	Mean (SD)	29.0(4.6)	29.0(4.8)	29.0(4.7)
	Median (min-max)	28.4(20.3-43.2)	28.7(20.2-43.9)	28.4(20.2-43.9)

Outcome measures

Primary Outcome Result(s)

Weekly mean adherence defined as 'Zit = 1 if patient I has opened the MEMS monitor exactly once between 07:00 and 11:00 AM on day t', by group - ITT population

Week	Adherence (%) Standard Care	Adherence (%) Intervention
1	75.0	80.7
2	74.2	77.4
3	65.5	76.2
4	68.4	75.9
5	66.0	75.3
6	66.1	69.8
7	65.0	72.5
8	68.1	73.3
9	64.4	70.4
10	63.3	69.2
11	62.0	69.8
12	60.4	70.4
13	59.7	67.3
14	60.9	70.1
15	58.5	68.6
16	57.7	66.7
17	57.7	66.3
18	58.5	62.9
19	58.0	59.1
20	59.6	63.0
21	60.3	63.6
22	59.3	62.4
23	58.0	64.1
24	62.9	67.0
25	59.4	62.2
26	58.1	61.7
27	56.6	62.7
28	55.9	60.5
29	57.8	58.8
30	60.1	62.4
31	56.2	60.4
32	56.3	60.5
33	57.0	55.9
34	56.7	57.8

Secondary Outcome Result(s)

Persistence over time (%): Kaplan-Meier estimates - ITT population

Days	Standard Care	Intervention
0	100.0	100.0
11	99.0	100.0
14	97.1	100.0
38	97.1	99.0
39	97.1	97.9
55	96.2	97.9
60	95.2	97.9
91	94.2	97.9
97	94.2	96.9
108	93.3	96.9
175	92.3	96.9
195	92.3	95.9
197	91.3	95.9
202	90.4	95.9
223	89.4	95.9
228	88.3	95.9

Weekly mean compliance defined as 'Zit = 1 if patient i has opened the MEMS monitor exactly once between 07:00 and 11:00 AM on day t', by group - ITT population

Week	Compliance (%) Standard Care	Compliance (%) Intervention
1	75.0	80.7
2	74.5	77.4
3	67.5	76.2
4	70.4	75.9
5	68.0	75.3
6	68.0	70.5
7	66.9	74.0
8	70.3	74.9
9	67.3	71.9
10	66.6	70.7
11	65.2	71.3
12	63.5	71.9
13	62.7	68.7
14	64.6	71.7
15	62.1	70.8
16	61.6	68.8
17	61.9	68.4
18	62.7	64.9
19	62.2	60.9
20	63.9	65.0

21	64.7	65.6
22	63.6	64.4
23	62.2	66.1
24	67.5	69.1
25	63.7	64.1
26	63.0	63.7
27	61.4	64.7
28	60.6	62.6
29	63.4	61.3
30	66.6	65.1
31	62.3	63.0
32	62.5	63.1
33	64.6	58.3
34	66.0	60.7

MEMS vs other measurements

Mean pill count, by group and visit - ITT population

Visit	Mean pill count (SD, n) Standard Care	Mean pill count (SD, n) Intervention
Visit 4	29.0 (4.4 , 101)	27.9 (3.6 , 97)
Visit 5	26.7 (5.8 , 100)	28.0 (3.3 , 95)
Visit 6	40.2 (5.7 , 100)	40.3 (4.2 , 94)
Visit 7	64.9 (9.6 , 97)	67.6 (4.5 , 95)
Visit 8	64.3 (13.9 , 104)	66.3 (9.3 , 96)
Overall	215.2 (48.3 , 105)	226.2 (29.0 , 97)

Mean MEMs count, by group and visit - ITT population

Visit	Mean MEMS count (SD, n) Standard Care	Mean MEMS count (SD, n) Intervention
Visit 4	28.3 (5.5 , 101)	27.5 (4.2 , 97)
Visit 5	25.9 (7.3 , 100)	27.1 (4.4 , 95)
Visit 6	37.7 (9.5 , 100)	39.9 (5.8 , 95)
Visit 7	61.7 (15.2 , 97)	66.1 (9.7 , 95)
Visit 8	59.4 (19.5 , 105)	63.1 (14.0 , 97)
Overall	204.3 (58.6 , 105)	221.0 (35.2 , 97)

Summary of reported adherence (Morisky Question 6), by group and visit - ITT population

Visit	Mean number of days without intake over the last 7 days (SD, n, missing) Standard Care	Mean number of days without intake over the last 7 days (SD, n, missing) Intervention
Visit 4	0.1 (0.4 , 95 , 7)	0.2 (0.4 , 86 , 11)
Visit 8	0.6 (1.7 , 94 , 11)	0.4 (0.9 , 90 , 7)
Overall	0.7 (1.8 , 87 , 18)	0.6 (1.1 , 81 , 16)

Drug exposure and BP reduction

Association between adherence (7 days) and change in msDBP

Effect	*Estimate*	*Pr > |t|*
Intercept	-6.1692	<.0001
DBPcenteredV2	-0.5666	<.0001
vrel	-0.01312	<.0001
adhlastweekz2	-0.02589	0.0074

Association between adherence (7 days) and change in msSBP

Effect	*Estimate*	*Pr > |t|*
Intercept	-10.3714	<.0001
SBPcenteredV2	-0.3010	0.0003
vrel	-0.01642	<.0001
adhlastweekz2	-0.03822	0.0090

Likelihood to switch to valsartan 160 mg plus HCTZ 12.5 mg

Switch to Valsartan 160 mg plus HCTZ 12.5 mg, by group - ITT population

	Standard Care n(%)	Intervention n(%)	Total n(%)
No Switch	61 (58.1)	61 (62.9)	122 (60.4)
Temporary Switch	7 (6.7)	5 (5.2)	12 (5.9)
Definitive Switch	37 (35.2)	31 (32.0)	68 (33.7)

Safety and tolerability of valsartan 160 mg and valsartan 160 mg plus HCTZ 12.5
Please see the safety section.

BP normalization and BP response

Number (%) of patients with blood pressure normalization and blood pressure response, by group - ITT population

	Standard Care n(%)	Intervention n(%)	Total n(%)
BP Normalization	69 (66.3)	82 (84.5)	151 (75.1)
No BP Normalization	35 (33.7)	15 (15.5)	50 (24.9)
BP Response	89 (85.6)	94 (96.9)	183 (91.0)
No BP Response	15 (14.4)	3 (3.1)	18 (9.0)

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with AEs by group and system organ class – safety population

Primary system organ class	Standard Care N=105 n(%)	Intervention N=101 n(%)	Total N=206 n(%)
ANY PRIMARY SYSTEM ORGAN CLASS	58 (55.2)	44 (43.6)	102 (49.5)
CARDIAC DISORDERS	1 (1.0)	2 (2.0)	3 (1.5)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (1.0)	1 (1.0)	2 (1.0)
EAR AND LABYRINTH DISORDERS	2 (1.9)	4 (4.0)	6 (2.9)
ENDOCRINE DISORDERS	1 (1.0)	1 (1.0)	2 (1.0)
EYE DISORDERS	2 (1.9)	2 (2.0)	4 (1.9)
GASTROINTESTINAL DISORDERS	15 (14.3)	5 (5.0)	20 (9.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (1.9)	3 (3.0)	5 (2.4)
IMMUNE SYSTEM DISORDERS	0 (0.0)	1 (1.0)	1 (0.5)
INFECTIONS AND INFESTATIONS	35 (33.3)	17 (16.8)	52 (25.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	8 (7.6)	3 (3.0)	11 (5.3)
METABOLISM AND NUTRITION DISORDERS	5 (4.8)	4 (4.0)	9 (4.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	15 (14.3)	10 (9.9)	25 (12.1)
NERVOUS SYSTEM DISORDERS	9 (8.6)	7 (6.9)	16 (7.8)
PSYCHIATRIC DISORDERS	0 (0.0)	3 (3.0)	3 (1.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0)	2 (2.0)	2 (1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (3.8)	4 (4.0)	8 (3.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (3.8)	2 (2.0)	6 (2.9)
SURGICAL AND MEDICAL PROCEDURES	0 (0.0)	1 (1.0)	1 (0.5)
VASCULAR DISORDERS	1 (1.0)	1 (1.0)	2 (1.0)

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

Number (%) of patients with AEs by group, order of frequency (>= 2%) - safety population

Preferred term	Standard Care N=105 n(%)	Intervention N=101 n(%)	Total N=206 n(%)
BRONCHITIS	10 (9.5)	3 (3.0)	13 (6.3)
NASOPHARYNGITIS	7 (6.7)	3 (3.0)	10 (4.9)
BACK PAIN	7 (6.7)	2 (2.0)	9 (4.4)
DIARRHOEA	5 (4.8)	1 (1.0)	6 (2.9)
TONSILLITIS	3 (2.9)	3 (3.0)	6 (2.9)
VERTIGO	2 (1.9)	4 (4.0)	6 (2.9)
CERVICOBRACHIAL SYNDROME	2 (1.9)	3 (3.0)	5 (2.4)
GASTRITIS	5 (4.8)	0 (0.0)	5 (2.4)

Serious Adverse Events and Deaths

Number (%) of patients with AEs/SAEs by group, relation to the study drug and action taken - safety population

		Standard Care N=105 n(%)	Intervention N=101 n(%)	Total N=206 n(%)
All AEs	Overall	58 (55.2)	44 (43.6)	102 (49.5)
	Suspected relation with study drug	0 (0.0)	4 (4.0)	4 (1.9)
	Study drug dose adjusted/temp interrupted	1 (1.0)	4 (4.0)	5 (2.4)
	Study drug permanently discontinued	2 (1.9)	0 (0.0)	2 (1.0)
	Requiring concomitant medication/non-drug therapy	48 (45.7)	32 (31.7)	80 (38.8)
Serious AEs	Overall	4 (3.8)	4 (4.0)	8 (3.9)
	Death	0 (0.0)	0 (0.0)	0 (0.0)
	Suspected relation with study drug	0 (0.0)	0 (0.0)	0 (0.0)
	Study drug permanently discontinued	2 (1.9)	0 (0.0)	2 (1.0)

Date of Clinical Trial Report 03 June 2008 **Date Inclusion on Novartis Clinical Trial Results Database** 26 June 2008
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