Sponsor

Novartis

Generic Drug Name

Valsartan, Amlodipine, & Hydrochlorothiazide

Therapeutic Area of Trial

Hypertension

Approved Indication

Investigational

Study Number

CVEA489A2302

Title

An 8-week, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of the combination of valsartan/HCTZ/amlodipine compared to valsartan/HCTZ, valsartan/amlodipine, and HCTZ/amlodipine in patients with moderate to severe hypertension

Phase of Development

Phase III

Study Start/End Dates

15 May 2006 to 02 Aug 2007

Study Design/Methodology

Multicenter, double-blind, randomized, parallel group trial, designed to evaluate the efficacy and safety of once-daily treatment with the combination of valsartan/HCTZ/amlodipine 320/25/10 mg compared to 3 dual therapies: valsartan/HCTZ 320/25 mg, valsartan/amlodipine 320/10 mg, and HCTZ/amlodipine 25/10 mg.

Patients meeting the eligibility criteria had their antihypertensive therapy withdrawn and entered the single-blind placebo run-in period for a duration of 4 days to 4 weeks. After 1 week of placebo run-in, patients returned to the study site for a blood pressure measurement to determine eligibility for randomization into the trial. Patients with severe hypertension were randomized immediately. Patients who did not meet these criteria were randomized after 2 to 3 weeks of placebo, if they achieved entry criteria.

At Visit 3 (Week 1), patients were randomized in a double-blind fashion to one of four treatment groups. At Visit 3, patients received lower doses of the study drugs (valsartan/HCTZ/amlodipine 160/12.5/0 mg o.d., valsartan/HCTZ 160/12.5 mg o.d., valsartan/amlodipine 160/5 mg o.d., and

HCTZ/amlodipine 12.5/5 o.d.) and were force-titrated over a two-week period to the maximum doses of valsartan/HCTZ/amlodipine 320/25/10 mg o.d., valsartan/HCTZ 320/25 mg o.d., valsartan/amlodipine 320/10 mg o.d., and HCTZ/amlodipine 25/10 o.d. Treatment at these maximum doses continued for 6 weeks until the end of the study (Visit 5 to Visit 8). Downward dose adjustment of the study drugs was not permitted.

Centres

273 study centers in 15 countries: Argentina (20), Canada (7), Denmark (16), Ecuador (4), Greece (3), Hong Kong (3), Norway (9), Peru (5), Portugal (3), Russia (15), Sweden (5), Turkey (4), UK (28), USA (147), Venezuela (4).

Publication

None

Objectives

Primary objective(s)

The primary objective of the study was to demonstrate that at least one of the following two efficacy criteria was met in the study population of patients with moderate to severe hypertension:

- Superiority of a once daily dosing regimen of the triple combination of valsartan/HCTZ/amlodipine compared to the dual combinations of valsartan/HCTZ, valsartan/amlodipine, and HCTZ/amlodipine in lowering mean sitting diastolic blood pressure (MSDBP)
- Superiority of a once daily dosing regimen of the triple combination of valsartan/HCTZ/amlodipine compared to the dual combinations of valsartan/HCTZ, valsartan/amlodipine, and HCTZ/amlodipine in lowering mean sitting systolic blood pressure (MSSBP)

Secondary objective(s)

- To evaluate overall blood pressure control rates (MSSBP/MSDBP <140/90 mmHg)
- To evaluate MSSBP control rates (MSSBP <140 mmHg) and MSDBP control rates (MSDBP <90 mmHg)
- To evaluate MSSBP responder rates (MSSBP <140 mmHg and/or >= 15 mmHg reduction from baseline) and MSDBP responder rates (MSDBP <90 mmHg and/or >= 10 mmHg reduction from baseline)
- To evaluate the decrease in 24-hour mean ambulatory systolic and diastolic blood pressures

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

Oral tablets of valsartan/HCTZ/amlodipine 160/12.5/0 mg, valsartan/HCTZ 160/12.5 mg, valsartan/amlodipine 160/5 mg, HCTZ/amlodipine 12.5/5, valsartan/HCTZ/amlodipine 320/25/10 mg, valsartan/HCTZ 320/25 mg, valsartan/amlodipine 320/10 mg once daily, and HCTZ/amlodipine

25/10, once daily.

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

Not applicable

Criteria for Evaluation

Primary variables

The primary efficacy variables were change from baseline in MSDBP and MSSBP at endpoint.

Secondary variables

- MSSBP/MSDBP control rate (MSSBP/MSDBP < 140/90 mmHg) at endpoint
- MSDBP control rate (MSDBP < 90 mmHg) at endpoint
- MSSBP control rate (MSSBP < 140 mmHg) at endpoint
- Change from baseline to Endpoint (Week 9) in post-dosing 24-hour mean ambulatory diastolic blood pressure (ADBP)
- Change from baseline to Endpoint (Week 9) in post-dosing 24-hour mean ambulatory systolic blood pressure (ASBP)

Safety and tolerability

The assessment of safety was based primarily on the frequency of adverse events, serious adverse events, and notable laboratory abnormalities. Other safety data were summarized as appropriate.

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

The change from baseline to endpoint in blood pressures were analyzed as primary efficacy variables using two sets of three hypothesis tests comparing the triple versus the three dual therapies. To control the overall type I error rate at 0.05, Hochberg's multiple-testing step-up procedure was used for the adjustment of assessing the two blood pressure endpoints. Within the analysis of each endpoint (MSDBP or MSSBP), the three individual comparisons were assessed at the common significance level (0.05 or 0.025) as called for by Hochberg's procedure, since all three individual comparisons had to be significant to conclude superiority of the triple for the respective blood pressure type.
An analysis of covariance (ANCOVA) model was used to analyze the change from baseline to endpoint in MSDBP or MSSBP with treatment and region as factors, and baseline MSDBP or MSSBP as a covariate in the model. The 95% and 97.5% confidence intervals were provided for the differences between the triple and each of the dual therapies.

Among the secondary analyses, the blood pressure control rates and responder rates were analyzed using logistic regression models. The subgroup of patients taking part in the ABPM substudy had their ambulatory blood pressure data analyzed using analysis of covariance (ANCOVA) models for repeated measures to assess treatment effects on lowering ambulatory blood pressures.
For patients who discontinued the study prematurely, the LOCF approach was used to obtain their endpoint values. The blood pressure control rates and responder rates were evaluated based on the patients with fulfilled observations (including LOCF values if the assessment was for endpoint) at the assessed time point.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Male or female patients >= 18 years and <86 years of age
2. Diastolic and systolic blood pressure requirements:
   - Diagnosis of moderate to severe hypertension (MSDBP >= 100 mmHg and <120 mmHg, and MSSBP >= 145 mmHg and <200 mmHg) at Visit 3
   - Patients also had to meet the blood pressure requirements (MSDBP >= 95 mmHg and <110 mmHg, and MSSBP <180 mmHg) at Visit 2
     or
   - MSDBP >= 110 mmHg and <120 mmHg, and MSSBP >= 145 mmHg and <200 mmHg, or MSDBP >= 100 mmHg and <110 mmHg and MSSBP >= 180 mmHg and <200 mmHg after one week of treatment with placebo (blood pressure check) or at any subsequent scheduled study visit or blood pressure evaluation during the single-blind run-in period (designated Visit 3)
3. Written informed consent to participate in the study prior to any study procedures.

Ability to communicate and comply with all study requirements.

Exclusion criteria

1. Inability to discontinue all prior antihypertensive medications safely for a period of 1 to 5 weeks as required by the protocol.
2. Patients with an MSDBP >= 120 mmHg or an MSSBP >= 200 mmHg at screening or any time during the single-blind run-in period.
3. Patients with an MSSBP >= 180 mmHg and MSDBP <100 mmHg at any time between one week (7 ± 3 days) and four weeks of treatment with placebo had to be discontinued from the study.
4. Patients on two or more antihypertensive drugs with MSSBP >= 180 mmHg and/or MSDBP >= 110 mmHg at Visit 1.
5. Patients on three or more antihypertensive drugs with MSDBP >= 90 mmHg and <110 mmHg, and/or MSSBP >= 140 mmHg and <180 mmHg at Visit 1.
6. Patients on four or more antihypertensive drugs at Visit 1.
7. Pregnant or nursing (lactating) women, where pregnancy was 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).
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and woman whose partners have been sterilized by vasectomy or other means, UNLESS they met the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels

>40 mIU/ml or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy OR were using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation, hysterectomy), double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap). Acceptable methods of contraception included total abstinence at the discretion of the investigator in cases where the age, career, lifestyle, or sexual orientation of the patient ensured compliance. Reliable contraception had to be maintained throughout the study and for 7 days after study drug discontinuation. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal were not acceptable methods of contraception. Hormonal contraceptive use was disallowed.

9. Known moderate or malignant retinopathy. Defined as: moderate (retinal signs of hemorrhage, microaneurysm, cotton-wool spot, hard exudates, or a combination thereof) or malignant (signs of moderate retinopathy plus swelling of the optic disk).
10. Any history of hypertensive encephalopathy, cerebrovascular accident or transient ischemic attack.
11. Any history of myocardial infarction or all types of revascularization procedures.
12. Heart failure requiring treatment.
13. Second or third degree heart block with or without a pacemaker.
14. Angina pectoris of any type.
15. Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.
16. Clinically significant valvular heart disease.
17. Evidence of a secondary form of hypertension, including but not limited to any of the following: coarctation of the aorta, hyperaldosteronism, unilateral or bilateral renal artery stenosis, Cushing disease, pheochromocytoma, polycystic kidney disease.
18. All patients with Type 1 diabetes mellitus and those patients with Type 2 diabetes mellitus who were not well controlled based on the Investigator's clinical judgement. It was recommended that Type 2 diabetic patients be adequately controlled and, if treated with medication, be on a stable dose of oral anti-diabetic medication for at least 4 weeks prior to Visit 1.
19. Any condition, not identified in the protocol, that in the opinion of the Investigator or the Novartis monitor, placed the patient at higher risk from his/her participation in the study, or was likely to prevent the patient from complying with the requirements of the study or completing the trial period.
20. Administration of any agent indicated for the treatment of hypertension after Visit 1, with the permitted exception of those antihypertensive medications requiring tapering down (e.g. beta-blocker and/or clonidine) commencing with the washout period that preceded Visit 1 and continued at Visit 1.
21. Known or suspected contraindications, including a history of hypersensitivity to angiotensin receptor blockers, thiazide diuretics, dihydropyridine calcium antagonists, or drugs with similar chemical structures.
22. Any surgical or medical conditions with the potential to 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, bowel resection, gastric bypass, gastric stapling, or gastric banding, currently active or active inflammatory bowel syndrome within 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.
23. Any history of pancreatic injury, pancreatitis or evidence of impaired pancreatic func-

tion/injury within 1 year of Visit 1.

24. Evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values >2 x ULN at Visit 1, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt.
25. Evidence of renal impairment as determined by any one of the following: serum creatinine >= 1.5 x ULN, a history of dialysis, or a history of nephrotic syndrome.
26. History of clinically significant allergies including asthma, multiple drug allergies.
27. History of gouty arthritis or autoimmune diseases including systemic lupus erythematosus.
28. Serum sodium and/or serum potassium less than 132 mEq/L and 3.2 mEq/L, respectively, at Visit 1.
29. Volume depletion based on the Investigator's clinical judgement using vital signs, skin turgor, moistness of mucous membranes, and laboratory values.
30. Currently taking concomitant medication(s) with the potential to interfere with the evaluation of efficacy, safety, and tolerability.
31. Any chronic inflammatory condition needing chronic anti-inflammatory therapy.
32. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there was evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
33. History of drug or alcohol abuse within the last 2 years.
34. History of non-compliance to medical regimens, or patients unwilling to comply with the study protocol.
35. Use of other investigational drugs within 30 days of enrollment.
36. Unwillingness or inability to give informed consent.
37. Persons directly involved in the execution of this protocol.
38. Arm circumference > 42 cm for patients participating in ABPM.

Number of Subjects

	Val/HCTZ/Aml	Val/HCTZ	Val/Aml	HCTZ/Aml
Planned N	506	506	506	506
Randomised n	583	559	568	561
Intent-to-treat population (ITT) n (%)	571 (97.9)	553 (98.9)	558 (98.2)	554 (98.8)
Completed n (%)	522 (89.5)	506 (90.5)	526 (92.6)	506 (90.2)
Withdrawn n (%)	61 (10.5)	53 (9.5)	42 (7.4)	55 (9.8)
Withdrawn due to adverse events n (%)	24 (4.1)	17 (3.0)	10 (1.8)	20 (3.6)
Withdrawn due to unsatisfactory therapeutic effect n (%)	4 (0.7)	6 (1.1)	0 (0.0)	7 (1.2)
Withdrawn for other reasons n (%)	32 (5.5)	30 (5.4)	32 (5.6)	28 (5.0)

Demographic and Background Characteristics

	Val/HCTZ/Aml	Val/HCTZ	Val/Aml	HCTZ/Aml
N (ITT)	571	553	558	554
Females : males	267: 316	256: 303	249:319	244: 317
Mean age, years (SD)	53.3 (10.28)	53.1 (10.36)	52.8 (10.29)	53.6 (10.13)
Mean BMI, kg (SD)	32.2 (6.91)	32.3 (6.95)	31.8 (6.41)	31.5 (6.07)
Race White n (%)	420 (72.0%) 98 (16.8%)	412 (73.7%) 93 (16.6%)	403 (71.0%) 91 (16.0%)	392 (69.9%) 107 (19.1%)

Black n (%) Asian n (%) Other n (%)	4 (0.7%) 49 (8.5%)	6 (1.1% 42 (7.6%)	10 (1.8%) 54 (9.7%)	7 (1.2%) 48 (8.7%)

Primary Objective Result(s)

Between-treatment comparisons for change from baseline to endpoint in mean sitting BP (mmHg) (Intent-to-Treat population)

Treatment (mg)	LSM change from baseline	LSM difference in change from baseline (SE)	p-value	Hochberg adjusted p-value
Diastolic BP				
Val/HCTZ/Aml 320/25/10	-24.74			<0.0001*
Val/HCTZ 320/25	-19.69	-5.05 (0.539)	<0.0001	
Val/Aml 320/10	-21.49	-3.25 (0.537)	<0.0001+	
HCTZ/Aml 25/10	-19.46	-5.28 (0.539)	<0.0001	
Systolic BP				
Val/HCTZ/Aml 320/25/10	-39.68			<0.0001*
Val/HCTZ 320/25	-32.04	-7.64 (0.848)	<0.0001	
Val/Aml 320/10	-33.50	-6.18 (0.846)	<0.0001+	
HCTZ/Aml 25/10	-31.48	-8.20 (0.848)	<0.0001	

Least square means and standard errors, confidence intervals, and p-values were provided by the ANCOVA model containing treatment and region as factors and centered baseline value as covariate.
The Hochberg adjusted p-values are based on the maximum p-value for the three comparisons in MSDBP and the maximum p-value for the three comparisons in MSSBP.
+ Maximum p-values of the three comparisons.
* Indicates statistical significance at 0.05 level.

Secondary Objective Result(s)

Overall BP control rate at endpoint (Intent to treat population)

Treatment comparison (A vs. B)	Treatment A n/N (%)	Treatment B n/N (%)	p-value
Val/HCTZ/Aml 320/25/10 vs. Val/HCTZ 320/25	404/571 (70.8)	267/553 (48.3)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. Val/Aml 320/10	404/571 (70.8)	302/558 (54.1)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. HCTZ/Aml 25/10	404/571 (70.8)	248/554 (44.8)	<0.0001 *

Overall BP control is defined as MSSBP/MSDBP < 140/90 mmHg
P-values were from a logistic model with treatment and region as factors.
*Indicates statistical significance at 0.05 level.

Diastolic control rate at endpoint (Intent-to-treat population)

Treatment comparison (A vs. B)	Treatment A n/N (%)	Treatment B n/N (%)	p-value
Val/HCTZ/Aml 320/25/10 vs. Val/HCTZ 320/25	463/571 (81.1)	362/553 (65.5)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. Val/Aml 320/10	463/571 (81.1)	397/558 (71.1)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. HCTZ/Aml 25/10	463/571 (81.1)	346/554 (62.5)	<0.0001 *

Diastolic control is defined as a MSDBP < 90 mmHg
P-values were from a logistic model with treatment and region as factors.
* Indicates statistical significance at 0.05 level.

Systolic control rate at endpoint (Intent-to-treat population)

Treatment comparison (A vs. B)	Treatment A n/N (%)	Treatment B n/N (%)	p-value
Val/HCTZ/Aml 320/25/10 vs. Val/HCTZ 320/25	442/571 (77.4)	317/553 (57.3)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. Val/Aml 320/10	442/571 (77.4)	340/558 (60.9)	<0.0001 *
Val/HCTZ/Aml 320/25/10 vs. HCTZ/Aml 25/10	442/571 (77.4)	308/554 (55.6)	<0.0001 *

Systolic control is defined as a MSSBP < 140 mmHg
P-values were from a logistic model with treatment and region as factors.
* Indicates statistical significance at 0.05 level.

Change from baseline in post-dosing 24-hour mean diastolic ABP (mmHg) (ABPM population)

	Val/HCTZ/Aml 320/25/10 mg N=67	Val/HCTZ 320/25 mg N=69	Val/Aml 320/10 mg N=71	HCTZ/Aml 25/10 mg N=76
Baseline				
Mean (SD)	94.4 (10.03)	92.8 (9.06)	93.1 (8.14)	93.4 (9.41)
Range	70.3-124.3	74.2-113.2	78.6-115.7	73.8-124.2
Endpoint				
Mean (SD)	74.5 (6.90)	77.9 (7.62)	78.7 (7.68)	81.9 (8.15)
Range	58.3-90.0	60.0-98.4	63.4-101.5	66.4-105.9
Change from baseline to Endpoint				
LS Mean (SE)	-19.7 (0.52)	-15.5 (0.50)	-14.9 (0.51)	-11.7 (0.47)
95% CI	(-20.72,-18.69)	(-16.46,-14.47)	(-15.87,-13.88)	(-12.59,-10.73)
p-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Treatment comparisons				
Triple combination versus		Val/HCTZ	Val/Aml	HCTZ/Aml
LS Mean (SE)		-4.2 (0.70)	-4.8 (0.69)	-8.0 (0.68)
95% CI		(-5.61,-2.87)	(-6.19,-3.47)	(-9.38,-6.71)
p-value		<0.0001*	<0.0001*	<0.0001*

* Indicates statistical significance at 0.05 level.

Change from baseline in post-dosing 24-hour mean systolic ABP (mmHg) (ABPM population)

	Val/HCTZ/Aml 320/25/10 mg N=67	Val/HCTZ 320/25 mg N=69	Val/Aml 320/10 mg N=71	HCTZ/Aml 25/10 mg N=76
Baseline				
Mean (SD)	149.6 (13.38)	146.4 (13.51)	149.7 (14.15)	147.3 (13.09)
Range	117.6-191.5	120.2-186.0	121.6-176.3	117.6-191.2
Endpoint				
Mean (SD)	119.1 (10.25)	123.8 (12.05)	125.1 (12.03)	129.1 (10.92)
Range	99.1-161.1	96.6-165.4	100.2-156.7	107.5-163.5
Change from baseline to Endpoint				
LS Mean (SE)	-30.3 (0.75)	-23.9 (0.73)	-24.1 (0.73)	-18.8 (0.69)
95% CI	(-31.74,-28.79)	(-25.30,-22.42)	(-25.55,-22.66)	(-20.11,-17.41)
p-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Treatment comparison				
Triple combination versus		Val/HCTZ	Val/Aml	HCTZ/Aml
LS Mean (SE)		-6.4 (1.01)	-6.2 (1.00)	-11.5 (0.99)
95% CI		(-8.40,-4.41)	(-8.13,-4.19)	(-13.45,-9.56)
p-value		<0.0001*	<0.0001*	<0.0001*

* Indicates statistical significance at 0.05 level.

Safety Results

Number (percent) of patients with AEs*, by primary system organ class and treatment (Safety population)

Primary system organ class	Val/HCTZ/Aml 320/25/10 mg N=582 n (%)	Val/HCTZ 320/25 mg N=559 n (%)	Val/Aml 320/10 mg N=566 n (%)	HCTZ/Aml 25/10 mg N=561 n (%)	Total N=2268 n (%)
Any primary system organ class	263 (45.2)	253 (45.3)	254 (44.9)	271 (48.3)	1041 (45.9)
Nervous system disorders	93 (16.0)	81 (14.5)	57 (10.1)	68 (12.1)	299 (13.2)
General disorders and administration site conditions	72 (12.4)	35 (6.3)	86 (15.2)	80 (14.3)	273 (12.0)
Gastrointestinal disorders	55 (9.5)	55 (9.8)	57 (10.1)	45 (8.0)	212 (9.3)
Infections and infestations	53 (9.1)	66 (11.8)	55 (9.7)	55 (9.8)	229 (10.1)
Musculoskeletal and connective tissue disorders	49 (8.4)	44 (7.9)	37 (6.5)	44 (7.8)	174 (7.7)
Respiratory, thoracic and mediastinal disorders	23 (4.0)	36 (6.4)	24 (4.2)	35 (6.2)	118 (5.2)
Metabolism and nutrition disorders	21 (3.6)	14 (2.5)	12 (2.1)	15 (2.7)	62 (2.7)
Injury, poisoning and procedural complications	19 (3.3)	14 (2.5)	17 (3.0)	14 (2.5)	64 (2.8)
Skin and subcutaneous tissue disorders	14 (2.4)	21 (3.8)	13 (2.3)	17 (3.0)	65 (2.9)
Investigations	12 (2.1)	15 (2.7)	8 (1.4)	11 (2.0)	46 (2.0)
Psychiatric disorders	12 (2.1)	8 (1.4)	7 (1.2)	11 (2.0)	38 (1.7)
Vascular disorders	12 (2.1)	10 (1.8)	8 (1.4)	6 (1.1)	36 (1.6)
Renal and urinary disorders	12 (2.1)	5 (0.9)	4 (0.7)	8 (1.4)	29 (1.3)
Ear and labyrinth disorders	7 (1.2)	6 (1.1)	7 (1.2)	2 (0.4)	22 (1.0)
Cardiac disorders	5 (0.9)	13 (2.3)	11 (1.9)	12 (2.1)	41 (1.8)
Eye disorders	5 (0.9)	6 (1.1)	9 (1.6)	4 (0.7)	24 (1.1)
Reproductive system and breast disorders	5 (0.9)	9 (1.6)	4 (0.7)	4 (0.7)	22 (1.0)
Immune system disorders	2 (0.3)	2 (0.4)	2 (0.4)	5 (0.9)	11 (0.5)
Blood and lymphatic system disorders	2 (0.3)	0 (0.0)	5 (0.9)	0 (0.0)	7 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)	4 (0.2)
Hepatobiliary disorders	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.1)
Surgical and medical procedures	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)

* Primary system organ classes were sorted by total incidences (descending) of adverse events in the Val/HCTZ/Aml treatment group.

9 Most Frequently Reported AEs in Val/HCTZ/Aml group (=2% of patients) Overall by Preferred Term n (%)

Preferred term	Val/HCTZ/Aml 320/25/10 mg N=582 n (%)	Val/HCTZ 320/25 mg N=559 n (%)	Val/Aml 320/10 mg N=566 n (%)	HCTZ/Aml 25/10 mg N=561 n (%)	Total N=2268 n (%)
Any preferred term	263 (45.2)	253 (45.3)	254 (44.9)	271 (48.3)	1041 (45.9)
Dizziness	45 (7.7)	39 (7.0)	13 (2.3)	22 (3.9)	119 (5.2)
Edema peripheral	26 (4.5)	5 (0.9)	48 (8.5)	50 (8.9)	129 (5.7)
Headache	25 (4.3)	30 (5.4)	28 (4.9)	39 (7.0)	122 (5.4)
Dyspepsia	13 (2.2)	5 (0.9)	6 (1.1)	2 (0.4)	26 (1.1)
Fatigue	13 (2.2)	15 (2.7)	12 (2.1)	8 (1.4)	48 (2.1)
Muscle spasms	13 (2.2)	7 (1.3)	7 (1.2)	5 (0.9)	32 (1.4)
Back pain	12 (2.1)	13 (2.3)	5 (0.9)	12 (2.1)	42 (1.9)
Nasopharyngitis	12 (2.1)	13 (2.3)	13 (2.3)	12 (2.1)	50 (2.2)
Nausea	12 (2.1)	7 (1.3)	10 (1.8)	12 (2.1)	41 (1.8)

Serious Adverse Events and Deaths

	Val/HCTZ/Aml 320/25/10 mg N=582 n (%)	Val/HCTZ 320/25 mg N=559 n (%)	Val/Aml 320/10 mg N=566 n (%)	HCTZ/Aml 25/10 mg N=561 n (%)	Total N=2268 N(%)
Deaths	0	0	0	0	0
SAEs	5 (0.9)	7 (1.3)	4 (0.7)	5 (0.9)	21 (0.9)
AEs leading to discontinuation	23 (4.0)	16 (2.9)	9 (1.6)	19 (3.4)	67 (3.0)
SAEs leading to discon-tinuation	5 (0.9)	3 (0.5)	0 (0.0)	3 (0.5)	11 (0.5)
Lab abnormalities leading to discontinuation	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)

SAEs = serious adverse events; AEs = adverse events.

Five patients in the triple therapy group val/HCTZ/aml 320/25/10 experienced SAEs:

1 patient experienced hypokalemia.
1 patient experienced several SAEs (abasia, neuropathy, abnormal coordination, asthenia and acute renal failure; hyponatremia, urinary tract infection, rhabdomyolysis, fungal rash, chronic obstructive pulmonary disease and hypomagnesaemia
1 patient experienced a myocardial infarction, coronary artery disease and angina pectoris
1 patient experienced pancreatitis, nausea and abdominal pain
1 patient experienced cerebrovascular accident and muscular weakness, neither of which were suspected to be study drug related.

Seven patients in the val/HCTZ 320/25 group experienced SAEs:

1 patient experienced appendicitis, 1 patient experienced chest pain and angina pectoris, 1 patient experienced non-cardiac chest pain, 1 patient experienced orthostatic hypotension and syncope, 1 patient experienced acute cholecystitis, abdominal pain, and a left bundle branch block, 1 patient experienced hypotension, 1 patient experienced erysipelas

Four patients in the val/aml 320/10 group experienced SAEs:

1 patient experienced a gastrointestinal hemorrhage, 1 patient experienced gastroenteritis, syncope, respiratory, hypotension, and vomiting, 1 patient had elevated CPK, 1 patient experienced thyroid cancer

Five patients in the HCTZ/aml 25/10 experienced SAEs:

1 patient experienced hemiparesis and brain stem infarction, 1 patient experienced dyspnea and non-cardiac chest pain, 1 patient experienced coronary artery disease and angina pectoris, 1 patient experienced an acute myocardial infarction, 1 patient experienced squamous cell carcinoma

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

1 May 2008

Date Inclusion on Novartis Clinical Trial Results Database

18 August 2008

Date of Latest Update

11 August 2008