Sponsor

Novartis

Generic Drug Name

Fixed combination aliskiren + amlodipine

Therapeutic Area of Trial

Essential hypertension

Approved Indication

Hypertension

Study Number

CSPA100ADE01

Title

An open-label, multicenter study to evaluate the efficacy and safety of a 4 week therapy with the single pill combination (SPC) of Aliskiren 300 mg / Amlodipine 10 mg in hypertensive patients not adequately responding to an uptitrated 4 week therapy with the SPC of Olmesartan 40 mg / Amlodipine 10 mg, with a potential extension if patients still not adequately respond with a 4 week therapy with the SPC Aliskiren 300 mg / Amlodipine 10 mg / HCTZ 12.5 mg

Phase of Development

Phase III

Study Start/End Dates

18-May-2010 to 26-Oct-2010

Study Design/Methodology

This was a multicenter, open-label, non-randomized, single-arm study. After a screening period of up to 2 weeks to assess patients' eligibility and to taper off disallowed medications (wash-out phase: Visit 1 – Visit 2 or Visit 3) and if all inclusion criteria had been met and none of the exclusion criteria applied, patients were included into the study depending on the blood pressure values at Visit 2 or Visit 3. If patients had been naïve to anti-hypertensive therapy for more than 4 weeks and fulfilled all inclusion and none of the exclusion criteria, they could directly proceed to Visit 3 as soon as safety laboratory parameters were available but not on the same day as Visit 1. At the baseline phase 1 visit (Visit 3), eligible patients were started on study treatment with olmesartan 10 mg plus amlodipine 5 mg free combination for 4 days. Patients with msDBP ≥ 85 mmHg (self measurement at home) after 4 days of treatment were treated with olmesartan 20 mg plus amlodipine 10 mg in free combination for 4 days. Patients with msDBP < 85 mmHg (home BP) were discontinued from the study once blood pressure values had been confirmed at the office. At Visit 4, patients with msDBP ≥ 90 mmHg (home BP) were force titrated to olmesartan 40 mg / amlodipine 10 mg in SPC for additional 20 days. Patients with msDBP < 90 mmHg were discontinued from the study. Patients who did not achieve controlled blood pressure level at Visit 5 (msDBP ≥ 90 mmHg) were included in the second treatment phase of aliskiren 300 mg / amlodipine 10 mg in SPC for additional 4 weeks. Patients with msDBP < 90 mmHg were discontinued from the study. Safety and efficacy were regularly assessed. The assessment to address the primary objective was performed after the 4 additional weeks of treatment. In selected centers the first 60 patients not controlled at Visit 6 (i.e., msDBP ≥ 90 mmHg and/or msSBP ≥ 140 mmHg) were offered a 4 week extension trial with SPC aliskiren 300 mg / amlodipine 10 mg / HCTZ 12.5 mg. Patients with msDBP < 90 mmHg and msSBP < 140 mmHg were not allowed to participate in the extension.

Centres

A total of 38 centers in Germany enrolled and treated patients.

Publication

Ongoing

Objectives

Primary objective(s)

Core study:

- To demonstrate that 4 weeks of treatment with SPC aliskiren 300 mg / amlodipine 10 mg at Visit 6 provide additional mean sitting diastolic blood pressure reduction in hypertensive patients not adequately responding (i.e., msDBP ≥ 90 mmHg) to 4 weeks of treatment with an angiotensin receptor blocker plus amlodipine 10 mg in SPC (olmesartan 40 mg / amlodipine 10 mg) at Visit 5.

Extension study:

- To demonstrate that 4 weeks of treatment with SPC aliskiren 300 mg / amlodipine 10 mg / HCTZ 12.5 mg (Visit 7) provide an additional mean sitting diastolic blood pressure reduction at trough in patients not adequately responding (i.e., msDBP ≥ 90 mmHg and/or msSBP ≥ 140 mmHg) to 4 weeks of treatment with SPC olmesartan 40 mg / amlodipine 10 mg (Visit 5) followed by 4 weeks of SPC aliskiren 300 mg / amlodipine 10 mg (Visit 6).

Secondary objective(s)

Core study:

- To evaluate the effects of 4 weeks of treatment with SPC aliskiren 300 mg / amlodipine 10 mg at Visit 6 in patients not adequately responding /i.e., msDBP ≥ 90 mmHg) to 4 weeks of treatment with an ARB plus amlodipine 10 mg in SPC (olmesartan 40 mg / amlodipine 10 mg) on the difference in mean sitting systolic blood pressure, pulse pressure, heart rate, normalization, control and responder rate at Visit 5.
- To assess the safety and tolerability of aliskiren 300 mg / amlodipine 10 mg.

Extension study:

- To evaluate the effects of HCTZ 12.5 mg in addition to aliskiren 300 mg plus amlodipine 10 mg on mean sitting systolic blood pressure at trough, pulse pressure, heart rate, normalization, control and responder rate.
- To assess the safety and tolerability of the SPC aliskiren 300 mg / amlodipine 10 mg / HCTZ 12.5 mg.

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

The study drug was manufactured by Novartis Pharma AG Stein (SPA100 with Batch No. H651BF) and Novartis Pharmaceuticals East Hanover, New Jersey (SAH100 with Batch No. AEUS/2009-0072).

SPA100 formulation is SPC tablets Aliskiren 300 mg/Amlodipine 10 mg.

SAH100 formulation is SPC tablets Aliskiren 300 mg/Amlodipine 10 mg/HCTZ 12.5 mg (extension study).

At Visit 5 study drugs were provided as an investigational drug (one tablet of aliskiren 300 mg / amlodipine 10 mg, in SPC) to be dispensed to the patient in bottles of 35 tablets. At Visit 6 60 eligible patients in selected centers could participate in the extension of the study. For the extension study they received investigational drug containing 35 tablets of SPC aliskiren 300 mg / amlodipine 10 mg / HCTZ 12.5 mg.

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

As the control drugs were commodities the manufacturing state is unknown.

Olmetec® - Olmesartan 10 mg film tablets

Amlobesilat Sandoz® - Amlodipine 5 mg tablets

Sevikar® - Olmesartan 40 mg/Amlodipine 10 mg SPC film tablets.

At Visit 2 or 3 patients received packs containing 28 tablets of olmesartan 10 mg and 50 tablets of amlodipine 5 mg to be dispensed to the patient. Patients had to be instructed to take one tablet of olmesartan 10 mg and one tablet of amlodipine 5 mg p.o. (i.e., two tablets per day) for a total of four days. The first drug was to be taken at the end of the Visit 2 or 3. From day 5 to day 8 (Visit 4) patients were instructed by the investigator to take two tablets of olmesartan 10 mg

and two tablets of amlodipine 5 mg p.o. (i.e., four tablets per day) after the telephone visit (day 4) had demonstrated that the patient did not suffer from signs and symptoms of hypotension and sitting diastolic BP at home was ≥ 85 mmHg or office BP had been reconfirmed to be ≥ 90 mmHg msDBP. At Visit 4 patients with msDBP ≥ 90 mmHg took olmesartan 40 mg / amlodipine 10 mg as SPC for three weeks. Patients received a commercial preparation containing 28 tablets.

Criteria for Evaluation

Primary variables

The primary efficacy parameter of the core trial was the change in trough msDBP between Visit 5 (SPC olmesartan 40 mg / amlodipine 10 mg baseline phase 2) and Visit 6 (SPC aliskiren 300 mg / amlodipine 10 mg in SPC).

The primary efficacy parameter of the extension trial was the change in trough msDBP between Visit 6 and Visit 7.

Secondary variables

The secondary efficacy parameters of the core and the extension study were changes in trough msSBP, changes in pulse pressure as well as changes in pulse rate as well as responder rate and normalization rate.

Safety and tolerability

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug and pregnancies. They included the regular monitoring of hematology and blood chemistry performed at a central laboratory and regular assessments of vital signs, physical condition and body weight. A pregnancy test and EEG were performed at Visit 1.

Pharmacology

None

Other

None

Statistical Methods

Efficacy: For the primary efficacy parameter, the mean change was calculated and tested against the null hypothesis of no change using a one-sample t-test. Point estimate, p-value and (95%) confidence interval were reported. The two-sided significance level was set to 5%. The primary analysis (core study) was performed using the ITT-population. A secondary PP-analysis was conducted as a confirmation of the results from the core study obtained from the ITT-analyses.

For the extension, the analyses were performed in the safety population. Patients who dropped out after Visit 5 were included in the ITT-population, if there was any blood pressure measurement available after Visit 5; their last available blood pressure measurement was used for the analysis. Missing values of secondary parameters were not replaced. Missing values of any data of the extension phase were not replaced.

The secondary efficacy parameters, changes in trough msSBP, changes in pulse pressure as well as changes in pulse rate were analyzed analogously to the primary efficacy parameter. The responder rate and normalization rate were calculated with its 95% confidence interval. The interpretation of all secondary parameters from both the core and the extension study was only explorative.

Safety: Adverse events were coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). In the data listings of adverse events, the severity of an AE, whether or not an AE is study drug related, and whether or not it is a serious AE, was indicated. An adverse event related to study drug was defined as one considered by the investigator to have a suspected relationship with the study drug. The adverse events were summarized by the number and percentage of patients in each primary system organ class and preferred term. For summaries by severity of event, the most severe occurrence for a particular preferred term was used for a given patient. Summary tables of adverse events by severity were provided.

Laboratory values were summarized using descriptive statistics for the raw values as well as for the changes. For all patients having values outside normal ranges all individual values of the respective parameter were listed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients eligible for inclusion in the core study were required to fulfill all of the following criteria:

1. Male or female patients ≥ 18 years.
2. Patients with essential hypertension:
   - At Visit 1, untreated (never been treated with antihypertensives or in the last 4 weeks not been treated with antihypertensives) patients must have an msDBP ≥ 100 and < 110 mmHg and msSBP ≥ 160 and < 180 mmHg and treated patients needed to have an msDBP < 110 mmHg and msSBP < 180 mmHg. Untreated patients could be included as soon as the safety laboratory parameters were available, but not at the day of Visit 1. This inclusion visit was recorded as Visit 3 in the CRF.
   - At Visit 2, patients previously treated for hypertension needed to have an msDBP ≥ 100 and < 110 and msSBP ≥ 160 and < 180 mmHg for entry into the first treatment phase. Patients previously treated for hypertension who had an msDBP < 100 mmHg and/or msSBP < 160 mmHg at Visit 2 continued the wash-out phase and were again evaluated with regard to BP criteria at Visit 3. Untreated patients did not perform Visit 2.
   - At Visit 3, which was not performed for patients who entered the first treatment phase already at Visit 2, patients needed to have an msDBP ≥ 100 and < 110 mmHg and msSBP ≥ 160 and < 180 mmHg for entry into the first treatment phase.
   - At Visit 5, all patients needed to have an msDBP ≥ 90 mmHg for entry into the second treatment phase.
3. Written informed consent to participate in the study prior to any study procedures

Patients eligible for inclusion in the extension study were required to fulfill all of the following criteria:

1. msSBP ≥ 140 mmHg and/or msDBP ≥ 90 mmHg at Visit 6 of the core study
2. Written informed consent to participate in the extension study

Exclusion criteria

Patients who met the following criteria were excluded from the core study:

1. Patients with controlled blood pressure levels (msSBP < 140 mmHg and msDBP < 90 mmHg) under current antihypertensive therapy at Visit 1.
2. msDBP ≥ 110 mmHg or msSBP ≥ 180 mmHg at any time between Visit 1 and baseline
3. Inability to completely discontinue all antihypertensive medication safely for a period of up to 2 weeks, as required by the protocol
4. Known Keith-Wagener grade III or IV hypertensive retinopathy
5. Evidence of a secondary form of hypertension, such as coarctation of the aorta, hyperaldosteronism, unilateral renal artery stenosis or pheochromocytoma
6. History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures, known or suspected contraindications to angiotensin II receptor blockers, direct renin inhibitors or to calcium channel blockers as described in the SmPC (particularly olmesartan 10-40 mg, amlodipine 5-10 mg, aliskiren 300 mg)
7. Concurrent treatment with cyclosporine or quinidine or verapamile at Visit 1 or during the trial
8. History of angiooedema due to aliskiren treatment
9. Bilateral renal artery stenosis
10. Heart failure NYHA II-IV
11. Second or third degree heart block without pacemaker
12. Current angina pectoris requiring pharmacological therapy
13. Concomitant potentially life-threatening arrhythmia or symptomatic arrhythmia
14. Clinically significant valvular heart disease
15. Transient ischemic cerebral attack, stroke, hypertensive encephalopathy or myocardial infarction prior to Visit 1
16. Type 1 diabetes mellitus
17. Type 2 diabetes mellitus with poor glucose control as defined by persistent fasting blood glucose > 11 mmol/l or > 200 mg/dl at Visit 1
18. Advanced aortic stenosis
19. Shock and cardiogenic shock
20. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of any drug including but not limited to any of the following:
    - History of major gastrointestinal surgery such as gastrectomy, gastroenterostomy, or bowel resection
    - Currently active inflammatory bowel syndrome within 12 months prior to Visit 1
    - Currently active gastritis, ulcers or gastrointestinal / rectal bleeding (hemorrhoids not included)
    - Any history of pancreatic injury, pancreatitis or evidence of impaired pancreatic function / injury
    - Evidence of hepatic disease or cholestasis as determined by any one of the following: ALT or AST values > 2 x ULN at Visit 1, a history of hepatic encephalopathy, a history of esophageal varices, or a history of a portocaval shunt, obstruction of the biliary tract
    - Evidence of renal impairment as determined by any one of the following: serum creatinine > 1.5 x ULN or active acute glomerulonephritis at Visit 1, a history of dialysis, or a history of nephrotic syndrome
    - Current obstruction of the urinary tract or difficulty in voiding due to mechanical as well as inflammatory conditions which is likely to require intervention during the course of the study or is regarded as clinically meaningful by the investigator
21. Therapy resistant hypokalemia, hypercalcemia, symptomatic hyperuricemia or sodium depletion (< 134 mmol/l), patients with volume depletion
22. History of any severe, life-threatening disease
23. History of drug or alcohol abuse within the last 2 years
24. History of non-compliance to medical regimens or those patients unwilling to comply with the trial protocol
25. Any condition, which in the judgment of the investigator or medical monitor, would jeopardize the evaluation of efficacy or safety
26. Any surgical or medical conditions which, at the discretion of the investigator, place the patient at higher risk for his/her participation in the study, or are likely to prevent the patient from complying with the requirements of the study or completing it

27. Unwillingness or inability to give informed consent
28. Study personnel or first degree relatives of the investigator(s) must not be included in the study
29. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer
30. 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
31. Women
    - who were pregnant or breast feeding (pregnancy 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))
    - who were menstruating and capable of becoming pregnant* and did not practice a medically approved method of contraception (Pearl Index < 1**) during and up to at least 4 weeks after the end of treatment. A negative pregnancy test (serum) for all women and for girls entering menarche is required with sufficient lead time before inclusion
      *definition of postmenopausal: 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

      **examples of particularly reliable methods with Pearl Index (PI) < 1, according to guidelines of Deutsche Gesellschaft for Gynäkologie und Geburtshilfe:

      a. Combination pill with estrogen and gestagen (no mini-pill, PI=0.1-0.9)
      b. Vaginal ring (NuvaRing®, PI=0.65 uncorr.; 0.4 corr.)
      c. Contraceptive patch (EVRA®, PI=0.72 uncorr.; 0.9 corr.)
      d. Estrogen-free ovulation inhibitors (Cerazette®, PI=0.14)
      e. Progestin-containing contraceptives (Implanon®, PI=0-0.88)
      f. Injectable 3-month depot progestins (PI=0.3-1.4; 0.88 corr.)
      g. Intra-uterine progestine device (Mirena®, PI=0.16)

Patients who met the following criteria were excluded from the extension study:

1. Premature discontinuation in the core study or failure to comply with the core study protocol
2. History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures, known or suspected contraindications to diuretics as described in the SmPC (particularly HCTZ 12.5 mg), e.g., therapy resistant hyperkalemia, severe hyponatraemia, hypercelcaemia, hypovolaemia
3. Any patient that should not participate in the extension study for medical reasons according to the decision of the investigator
4. Severe renal dysfunction (with oliguria, anuria, creatinine clearance < 30 ml/min and/or serum creatinine > 1.8 ml/100 ml
5. Acute glomerulonephritis
6. Coma and precoma hepaticum
7. Gouty arthritis
8. All patients that fulfilled one of the exclusion criteria of the core study were **not** to be included in the extension study

Number of Subjects

Patient disposition for the core study

	Treatment phase 1 olmesartan / amlodipine	Treatment phase 2 aliskiren / amlodipine
Total no. of patients – n(%)		
Screened	439	
Treated	342 (100)	188 (100)
Discontinued	14 (4.1)	4 (2.1)
Completed	328 (95.9)	184 (97.9)
Main cause of study discontinuation		
Adverse event(s)	9 (2.6)	4 (2.1)
Protocol violation(s)	1 (0.3)	0 (0.0)
Subject withdrew consent	3 (0.9)	0 (0.0)
Lost to follow-up	1 (0.3)	0 (0.0)

Patient disposition for the extension study

	Treatment phase 3 aliskiren / amlodipine / HCTZ
Total no. of patients – n(%)	
Treated	65 (100)
Discontinued	1 (1.5)
Completed	64 (98.5)
Main cause of study discontinuation	
Administrative problems	1 (1.5)

Demographic and Background Characteristics

Demographic summary by treatment group in the core study

Variable		Safety population 1 olmesartan + amlodipine N = 342	Safety population 2 aliskiren + amlodipine N = 188	ITT aliskiren + amlodipine N = 187	PP aliskiren + amlodipine N = 149
Age (years)					
Mean (SD)		60.4 (10.86)	60.4 (10.73)	60.5 (10.69)	60.8 (10.88)
Range		25 – 87	28 – 83	28 – 83	28 – 81
< 65 years	n (%)	210 (61.4)	119 (63.3)	118 (63.1)	92 (61.7)
≥ 65 years	n (%)	132 (38.6)	69 (36.7)	69 (36.9)	57 (38.3)
Sex – n (%)					
male		182 (53.2)	109 (58.0)	109 (58.3)	84 (56.4)
female		160 (46.8)	79 (42.0)	78 (41.7)	65 (43.6)
Race – n (%)					
Caucasian		340 (99.4)	186 (98.9)	185 (98.9)	148 (99.3)

Black		2 (0.6)	2 (1.1)	2 (1.1)	1 (0.7)
Weight (kg)					
Mean (SD)		88.5 (19.25)	90.6 (20.06)	90.6 (20.10)	90.8 (20.99)
Range		51 – 183	57.0 – 183.0	57.0 – 183.0	57.0 – 183.0
Body mass index (kg/m²)					
Mean (SD)		30.4 (5.72)	30.9 (5.95)	30.8 (5.94)	31.0 (6.27)
Range		19.0 – 61.9	21.0 – 61.9	21.0 – 61.9	21.0 – 61.9
msSBP (mmHg)					
Mean (SD)		166.6 (6.15)	167.9 (5.33)	167.9 (5.33)	167.9 (5.35)
Range		112.0 – 179.7	158.3 – 179.3	158.3 – 179.3	158.7 – 179.3
msDBP (mmHg)					
Mean (SD)		103.1 (2.95)	103.6 (2.58)	103.6 (2.59)	103.7 (2.32)
Range		73.3 – 109.0	90.3 – 109.0	90.3 – 109.0	99.7 – 109.0
Duration of hypertension at study start (years)					
Mean (SD)		8.5 (7.54)	9.9 (8.00)	n.a.	n.a.
Range		0.0 – 40.0	0.0 – 40.0		
< 1 year	n (%)	43 (12.6)	19 (10.1)		
1 to < 2 years	n (%)	17 (5.0)	7 (3.7)		
2 to < 5 years	n (%)	67 (19.6)	26 (13.8)		
5 to < 10 years	n (%)	89 (26.0)	52 (27.7)		
≥ 10 years	n (%)	126 (36.8)	84 (44.7)		

Demographic summary of the extension group

Variable		**Safety population 3 aliskiren + amlodipine + HCTZ N = 65**
Age (years)		
Mean (SD)		60.8 (10.77)
Range		28 – 83
< 65 years	n (%)	41 (63.1)
≥ 65 years	n (%)	24 (36.9)
Sex – n (%)		
male		46 (70.8)
female		19 (29.2)
Race – n (%)		
Caucasian		64 (98.5)
Black		1 (1.5)
Weight (kg)		
Mean (SD)		91.1 (18.98)
Range		57 – 183
Body mass index (kg/m²)		
Mean (SD)		30.7 (6.09)
Range		21.3 – 61.9
msSBP (mmHg)		

Mean (SD)	168.3 (5.23)
Range	158.3 – 179.3
msDBP (mmHg)	
Mean (SD)	103.3 (2.33)
Range	96.0 – 108.7

Primary Objective Result(s)

Core study:
Decrease of sitting diastolic blood pressure between week 4 (Visit 5) and week 8 (Visit 6)

	ITT population aliskiren + amlodipine N = 187	**PP population aliskiren + amlodipine N = 149**
Sitting diastolic blood pressure (primary efficacy parameter)		
mean decrease during phase 2 (mmHg)	4.81	4.87
95% confidence interval [a]	3.83 – 5.79	3.83 – 5.91
p value [a]	< 0.0001	< 0.0001

[a] resulting from a two-sided, one-sample t-test

Extension study:
Decrease of sitting diastolic blood pressure between week 8 (Visit 6) and week 12 (Visit 7)

	Treatment phase 3 aliskiren + amlodipine + HCTZ N = 65
Sitting diastolic blood pressure (primary efficacy parameter)	
mean decrease during phase 3 (mmHg)	6.65
95% confidence interval [a]	5.11 – 8.20
p value [a]	< 0.0001

[a] resulting from a two-sided, one-sample t-test

Secondary Objective Result(s)

Core study:

Decrease of sitting systolic blood pressure between week 4 (Visit 5) and week 8 (Visit 6)

	ITT population aliskiren + amlodipine N = 187	PP population aliskiren + amlodipine N = 149
Sitting systolic blood pressure (secondary efficacy parameter)		
mean decrease during phase 2 (mmHg)	5.11	5.43
95% confidence interval [a]	3.72 – 6.50	3.89 – 6.96
p value [a]	< 0.0001	< 0.0001

[a] resulting from a two-sided, one-sample t-test

Core study:

Decrease of other secondary efficacy parameters between week 4 (Visit 5) and week 8 (Visit 6) and normalization / responder rates

	ITT population aliskiren + amlodipine N = 187	PP population aliskiren + amlodipine N = 149
Sitting pulse rate (bpm)		
mean decrease during phase 2 [b]	-0.88	-0.97
95% confidence interval [a]	-2.59 – 0.82	-2.50 – 0.57
p value [a]	0.3090	0.2159
Sitting pulse pressure (mmHg)		
mean decrease during phase 2 [b]	0.30	0.56
95% confidence interval [a]	-0.80 – 1.40	-0.70 – 1.82
p value [a]	0.5889	0.3835
Syst. normalization rate n (%) (msSBP < 140 mmHg)	81 (43.3)	67 (45.0)
Syst. responder rate n (%) (msSBP < 140 mmHg or decrease ≥ 20 mmHg vs. Visit 5)	83 (44.4)	68 (45.6)
Diast. normalization rate n (%) (msDBP < 90 mmHg)	9 (50.3)	76 (51.0)
Diast. responder rate n (%) (msDBP < 90 mmHg or decrease ≥ 10 mmHg vs. Visit 5)	96 (51.3)	78 (52.3)
Treated to target n (%) (msSBP < 140 mmHg and msDBP < 90 mmHg)	68 (36.4)	54 (36.2)

[a] resulting from a two-sided, one-sample t-test
[b] decrease between week 4 and week 8

Extension study:

Decrease of sitting systolic blood pressure between week 8 (Visit 6) and week 12 (Visit 7)

	Treatment phase 3 aliskiren + amlodipine + HCTZ N = 65
Sitting systolic blood pressure (secondary efficacy parameter)	
mean decrease during phase 2 (mmHg)	8.07
95% confidence interval [a]	5.68 – 10.46
p value [a]	< 0.0001

[a] resulting from a two-sided, one-sample t-test

Extension study:

Decrease of other secondary efficacy parameters between week 8 (Visit 6) and week 12 (Visit 7) and normalization / responder rates

	Treatment phase 3 aliskiren + amlodipine + HCTZ N = 65
Sitting pulse rate (bpm)	
mean decrease during phase 3 [b]	2.29
95% confidence interval [a]	0.36 – 4.22
p value [a]	0.0207
Sitting pulse pressure (mmHg)	
mean decrease during phase 3 [b]	1.42
95% confidence interval [a]	-0.35 – 3.19
p value [a]	0.1136
Syst. normalization rate n (%) (msSBP < 140 mmHg)	34 (52.3)
Syst. responder rate n (%) (msSBP < 140 mmHg or decrease ≥ 20 mmHg vs. Visit 5)	35 (53.8)
Diast. normalization rate n (%) (msDBP < 90 mmHg)	49 (75.4)
Diast. responder rate n (%) (msDBP < 90 mmHg or decrease ≥ 10 mmHg vs. Visit 5)	50 (76.9)
Treated to target n (%) (msSBP < 140 mmHg and msDBP < 90 mmHg)	30 (46.2)

[a] resulting from a two-sided, one-sample t-test
[b] decrease between week 4 and week 8

Safety Results

Adverse Events by System Organ Class

Core study:

Number (%) of patients with Adverse Events overall and by system organ class

	Treatment phase 1 olmesartan + amlodipine	Treatment phase 2 aliskiren + amlodipine
Patients studied		
Total no. of patients	342	188
Total no. (%) of patients with AE(s)	44 (12.9)	19 (10.1)
Total no. of AEs	52	22
System organ class	**n (%) of patients**	**n (%) of patients**
Ear and labyrinth disorders	2 (0.6)	0 (0.0)
Eye disorders	1 (0.3)	0 (0.0)
Gastrointestinal disorders	1 (0.3)	2 (1.1)
General disorders and admin. site disord.	11 (3.2)	11 (5.9)
Infections and infestations	11 (3.2)	3 (1.6)
Injury, poisoning and proc. complications	5 (1.5)	0 (0.0)
Metabolism and nutrition disorders	1 (0.3)	0 (0.0)
Musculoskeletal and conn. tissue disord.	4 (1.2)	1 (0.5)
Nervous system disorders	3 (0.9)	2 (1.1)
Renal and urinary disorders	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediast. dis.	2 (0.6)	0 (0.0)
Skin and subcutaneous tissue disorders	5 (1.5)	2 (1.1)
Vascular disorders	1 (0.3)	1 (0.5)

Patients are counted only once in each body system regardless of the number of AEs experienced in that body system.
AEs are allocated to treatment phase of onset.

Extension study:

Number (%) of patients with Adverse Events overall and by system organ class

	Treatment phase 3 aliskiren + amlodipine + HCTZ
Patients studied	
Total no. of patients	65
Total no. (%) of patients with AE(s)	7 (10.8)
Total no. of AEs	8
System organ class	**n (%) of patients**
Gastrointestinal disorders	1 (1.5)
Infections and infestations	5 (7.7)
Injury, poisoning and proc. complications	1 (1.5)
Nervous system disorders	1 (1.5)

Patients are counted only once in each body system regardless of the number of AEs experienced in that body system.
AEs are allocated to treatment phase of onset.

Most Frequently Reported AEs Overall by Preferred Term

Core study:

Number (%) of patients with Adverse Events overall and by MedDRA preferred term (only those that occurred in more than one patient during phase 1 and 2)

	Treatment phase 1 olmesartan + amlodipine	Treatment phase 2 aliskiren + amlodipine
Patients studied		
Total no. of patients	342	188
Total no. (%) of patients with AE(s)	44 (12.9)	19 (10.1)
Total no. of AEs	52	22
Adverse event preferred term	**n (%) of patients**	**n (%) of patients**
Arthralgia	1 (0.3)	1 (0.5)
Contusion	2 (0.6)	0 (0.0)
Dizziness	2 (0.6)	0 (0.0)
Eczema	3 (0.9)	1 (0.5)
Headache	1 (0.3)	1 (0.5)
Nasopharyngitis	1 (0.3)	1 (0.5)
Oedema	1 (0.3)	3 (1.6)
Oedema peripheral	9 (2.6)	7 (3.7)
Rash	2 (0.6)	0 (0.0)
Skin laceration	2 (0.6)	0 (0.0)
Vertigo	2 (0.6)	0 (0.0)

AEs are allocated to treatment phase of onset.

Extension study:

Number (%) of patients with Adverse Events overall and by MedDRA preferred term

	Treatment phase 3 aliskiren + amlodipine + HCTZ
Patients studied	
Total no. of patients	65
Total no. (%) of patients with AE(s)	7 (10.8)
Total no. of AEs	8
Adverse event preferred term	**n (%) of patients**
Dizziness	1 (1.5)
Gastritis	1 (1.5)
Gastroenteritis	1 (1.5)
Nasopharyngitis	1 (1.5)
Rib fracture	1 (1.5)
Sinusitis	1 (1.5)
Tinea pedis	1 (1.5)
Wound infection	1 (1.5)

AEs are allocated to treatment phase of onset.

Serious Adverse Events and Deaths

Core study: Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them

	Treatment phase 1 olmesartan + amlodipine	Treatment phase 2 aliskiren + amlodipine
Patients studied		
Total no. of patients	342	188
Total no. (%) of patients with AE(s)	44 (12.9)	19 (10.1)
Serious of significant adverse events	**n (%) of patients**	**n (%) of patients**
Deaths	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	0 (0.0)
Significant events		
SAEs leading to discontinuation	0 (0.0)	0 (0.0)
Non-serious AEs leading to discontinuation	9 (2.6)	5 (2.7)
AEs leading to temporary dose interruption	1 (0.3)	0 (0.0)

AEs are allocated to treatment phase of onset.

Extension Study:

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them

	Treatment phase 3 aliskiren + amlodipine + HCTZ
Patients studied	
Total no. of patients	65
Total no. (%) of patients with AE(s)	7 (10.8)
Serious of significant adverse events	**n (%) of patients**
Deaths	0 (0.0)
SAEs	0 (0.0)
Significant events	
SAEs leading to discontinuation	0 (0.0)
Non-serious AEs leading to discontinuation	0 (0.0)
AEs leading to temporary dose interruption	0 (0.0)

No patients died or experienced other SAEs during both the core and the extension study.

The relative number of patients with drug-related oedema / peripheral oedema that led to discontinuation of study drug (less than 3%) did not increase with aliskiren plus amlodipine as compared to olmesartan plus amlodipine. For both therapies this type of AEs is well known and expected.

However, during the extension study with aliskiren, amlodipine and HCTZ neither drug-related AEs nor discontinuations due to AEs occurred.

Other Relevant Findings

None

Date of Clinical Trial Report

18-May-2011

Date Inclusion on Novartis Clinical Trial Results Database

22-September-2011

Date of Latest Update

13-September-2011