Sponsor

Novartis

Generic Drug Name

Aliskiren + Amlodipine + Hydrochlorothiazide

Therapeutic Area of Trial

Essential Hypertension

Approved Indication

Investigational

Study Number

CSAH100A2301

Title

A 28 to 54-week, open-label, multicenter study to assess the long-term safety and tolerability of the combination of aliskiren/amlodipine/hydrochlorothiazide in patients with essential hypertension

Phase of Development

Phase III

Study Start/End Dates

05 Jun 2008 to 05 Oct 2009

Study Design/Methodology

This was a 28 week to 54 week, open-label, multi-center study evaluating the safety and tolerability of the combination of aliskiren/amlodipine/HCTZ in patients with essential hypertension. The blood pressure (BP) requirement for the study was as follows:

- For newly diagnosed or untreated patients (for at least 4 weeks prior to Visit 1), mean sitting diastolic blood pressure (msDBP) ≥ 100 and < 120 mmHg, and/or mean sitting systolic blood pressure (msSBP) ≥ 160 and < 200 mmHg at Visit 1 and Visit 2.
- For previously treated patients, msDBP ≥ 100 and < 120 mmHg, and/or msSBP ≥ 160 and < 200 mmHg at Visit 2 or Visit 3, or Visit 4.

This study was comprised of two periods and twelve visits.

At Visit 1, patients were screened. If eligible, they discontinued their current anti-hypertensive medication(s) and entered a washout period. For patients with previous antihypertensive medication that required a gradual downward titration, the tapering down was done according to manufacturers instructions and last dose was taken prior to entering treatment phase.
All patients that met study entry criteria at Visit 4 entered period 2 and began the initial treatment of aliskiren 300 mg/HCTZ 12.5 mg for one week. At Visit 5, all patients had amlodipine 5 mg

added for one week. At Visit 6, the dose of the study drugs was force titrated to aliskiren/amlodipine/HCTZ 300/10/25 mg for 26 weeks. Approximately 200 patients entered a 26 week extension with the treatment of aliskiren/amlodipine/HCTZ 300/10/25 mg.

Centres

82 centers in 8 countries: Belgium (14), Egypt (1), Germany (21), Poland (6), Slovakia (Slovak Republic) (9), Spain (7), Turkey (4), United States (20).

Publication

Ongoing

Objectives

Primary objective(s)

To assess the long term safety of the combination of aliskiren/amlodipine/hydrochlorothiazide in patients with essential hypertension over 28 weeks to 54 weeks of treatment.

Secondary objective(s)

- To assess the long-term blood pressure lowering (msDBP and msSBP) efficacy of the combination of aliskiren/amlodipine/hydrochlorothiazide in patients with essential hypertension.
- To evaluate the proportion of patients achieving the blood pressure control target of < 140/90 mmHg at the end of the study.

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

Study medications: Aliskiren 300 mg, amolodipine 5 mg, and HCTZ 12.5 and 25 mg.
Aliskiren 300 mg, HCTZ 12.5 mg and HCTZ 25 mg were provided in bottles and amolodipine 5 mg was provided in blisters. The study treatment was aliskiren/HCTZ 300/12.5 mg for one week followed by aliskiren/amolodipine/HCTZ 300/5/12.5 mg for one week and then aliskiren/amolodipine/HCTZ 300/10/25 mg for 26 to 52 weeks. All study medications were taken orally with water, once daily in the morning.

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

None.

Criteria for Evaluation

Primary variables

The primary assessment was safety as reported adverse events (AEs) and serious adverse events (SAEs) including death. Adverse events were assessed overall, by primary system organ class, by preferred term, by maximum severity, by relationship to the trial treatment, and by discontinuation due to adverse events.

Secondary variables

Blood pressure:

Summary statistics for the post-baseline and the changes-from-baseline measurements were assessed by timepoint (ie. at baseline and all post-baseline visits and at 26 week endpoint and at 54 week endpoint) for mean sitting diastolic blood pressure, mean sitting systolic blood pressure, standing diastolic blood pressure, and standing systolic blood pressure for the primary population.

Control rate:

Summary statistics for the proportion of patients achieving blood pressure control (msSBP/msDBP < 140/90 mmHg) were presented by timepoint for the primary population.

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious AEs (SAEs), all pregnancies, the regular monitoring of hematology and blood chemistry, regular measurement of vital signs and the performance of physical examinations.

Pharmacology

None

Other

None

Statistical Methods

The primary assessment for safety was the reporting of any AEs and SAEs including death, discontinuations due to AEs, and abnormal laboratory data.

Occurrence and frequency of AEs and SAEs were summarized by dose combinations, primary system organ class, preferred term, maximum severity and relationship to trial treatment. SAEs were narrated.
Summary statistics at baseline, at last visit, and of changes from baseline at last visit for laboratory values were provided. Occurrence of significant abnormalities in laboratory values from baseline were summarized.

Blood pressure:

Changes from baseline measurements were presented in msDBP and msSBP for the primary population by timepoint including at week 28 and at week 54 endpoints.

Control rate:

Summary statistics for the proportion of patients achieving blood pressure control (msSBP/msDBP < 140/90 mmHg) were presented by timepoint for the primary population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Outpatients 18 years of age or older
2. Male or female patients
3. msDBP & msSBP Requirements:
   - For newly diagnosed/untreated patients, msDBP ≥ 100 and < 120 mmHg, and/or msSBP ≥ 160 and < 200 mmHg at Visit 1 and Visit 2.
   - For previously treated patients, msDBP ≥ 100 and < 120 mmHg, and/or msSBP ≥ 160 and < 200 mmHg at Visit 2, Visit 3, or Visit 4.
     - Patients requiring tapering off previous antihypertensive medication, had to meet the above criteria and completely discontinue all antihypertensive treatment prior to entering the treatment phase of the study.
4. Patients who were eligible and were able to participate in the study, and who consented to do so after the purpose and nature of the investigation had been clearly explained to them (written informed consent).

Exclusion criteria

1. Inability to discontinue all prior antihypertensive medications safely for a period of 1 to 4 weeks as required by the protocol.
2. Patients on three antihypertensive drugs with msDBP ≥ 110 mmHg and/or msSBP ≥ 180 mmHg at Visit 1.
3. Patients on four or more antihypertensive drugs at Visit 1.
4. Patients with an msSBP ≥ 200 and msDBP ≥ 120 mmHg anytime during the washout period of the study Visit 1-4 must be discontinued from the study.
5. Pregnant or nursing (lactating) women, where pregnancy is 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).
6. Women of child-bearing potential, unless they met definition of post-menopausal or were using acceptable methods of contraception.
7. History or evidence of a secondary form of hypertension.

8. Any history of hypertensive encephalopathy, cerebrovascular accident, heart failure, transient ischemic cerebral attack (TIA), angina pectoris, myocardial infarction (MI), coronary bypass surgery, or any percutaneous coronary intervention (PCI).
9. Serum potassium <3.5 mEq/L (mmol/L) or ≥ 5.5 mEq/L at Visit 1.
10. Patients Type 2 diabetes mellitus (DM) who are not well controlled based on the investigator's clinical judgment. Patients with Type 2 DM enrolled in this study should be well controlled. Type 1 DM patients are excluded.
11. Second or third degree heart block with or without a pacemaker, or other potentially life-threatening or symptomatic arrhythmia current or by history.
12. Atrial fibrillation or atrial flutter during the screening period.
13. Clinically significant valvular heart disease.
14. Any medication, surgical, or medical condition, which might significantly alter the absorption, distribution, metabolism, or excretion of medications.
15. Evidence of hepatic disease as determined by any one of the following: ALT or AST values exceeding 3 x ULN at Visit 1, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt.
16. Evidence of renal impairment as determined by any one of the following: serum creatinine > 1.5 x ULN at Visit 1, a history of dialysis, or a history of nephrotic syndrome.
17. History of hypersensitivity to any of the medications or to drugs belonging to the similar therapeutic class as the study drugs (renin inhibitor, CCBs of dihydropyridine class, thiazide diuretics or other sulfonamide derived drugs).
18. History of angioedema due to usage of an ACE-I or ARB.
19. 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.
20. Gouty arthritis
21. History or evidence of drug or alcohol abuse within the last 12 months.
22. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
23. History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
24. Anyone, who entered the treatment phase of a study where the combination of aliskiren/ amlodipine / HCTZ was used, regardless of what treatment they received during the study.
25. If the patient was expected to continue or start any excluded concomitant medication.

Number of Subjects

Disposition	Total (Aliskiren/amolodipine/HCTZ)
Washout phase	635
Study treatment phase	**564 (100.0)**
Completed	493 (87.4)
Discontinued	71 (12.6)
Reason for discontinuation	
Adverse Events	39 (6.9)
Abnormal test procedure results	1 (0.2)
Unsatisfactory therapeutic effect	3 (0.5)
Protocol deviation	3 (0.5)
Patient withdrew consent	17 (3.0)
Lost to follow-up	8 (1.4)

Percentage (%) is calculated using the study treatment phase enrolled population as the denominator.

Demographic and Background Characteristics

Demographic variable	Total N=564
Age (years)	
n	564
Mean	55.9
SD	11.34
Median	56.0
Minimum	20.0
Maximum	81.0
Age group (years) n (%)	
< 65	429 (76.1)
≥ 65	135 (23.9)
< 75	537 (95.2)
≥75	27 (4.8)
Sex n (%)	
Male	326 (57.8)
Female	238 (42.2)
Race n (%)	
Caucasian	507 (89.9)
Black	42 (7.4)
Asian	10 (1.8)
Native American	1 (0.2)
Other	4 (0.7)

Ethnicity n (%)	
Hispanic/Latino	38 (6.7)
Chinese	1 (0.2)
Mixed ethnicity	3 (0.5)
Other	522 (92.6)
Body Mass Index (kg/m2)	
N	564
Mean	31.2
SD	6.09
Median	30.1
Minimum	13.4
Maximum	68.1
Duration of hypertension # (years)	
N	549
Mean	8.9
SD	7.45
Median	7.0
Minimum	1.0
Maximum	43.0
Number of naive patients n (%)	15 (2.7)
Metabolic Syndrome* n (%)	
Yes	294 (52.1)
No	270 (47.9)
BMI Status n (%)	
BMI < 20 (kg/m2)	8 (1.4)
20 (kg/m2) ≤ BMI < 25 (kg/m2)	50 (8.9)
25 (kg/m2) ≤ BMI < 30 (kg/m2)	214 (37.9)
BMI ≥30 (kg/m2)	292 (51.8)
Diabetes Status n (%)	
Yes	122 (21.6)
No	442 (78.4)

SD = standard deviation

Diabetes status is based on medical history

Note: * Metabolic Syndrome=Yes, if any 3 of the following are true:
1. Waist circumference >102 cm (40 in) for men, or > 88 cm (35 in) for women;
2. Triglycerides ≥150 mg/dL (1.69 mmol/L);
3. HDL cholesterol <40 mg/dL (1.04 mmol/L) for men, or <50 mg/dL (1.29 mmol/L) for women;
4. msSBP≥130 / or msDBP≥85 mmHg; 5. Fasting glucose ≥110 mg/dL (6.1 mmol/L).

Primary Objective Result(s)

The primary objective was to assess the long term safety of the combination of aliskiren/amlodipine/hydrochlorothiazide in this study and the results are summarized in the section "safety results".

Secondary Objective Result(s)

Long-term blood pressure lowering efficacy is summarized in two tables below one for msDBP and other for msSBP.

Summary statistics for change from baseline in mean sitting diastolic blood pressure (msDBP) by visit (Treated population)

	Total N=564	
Week (Visit)	**n***	**Mean (SD)**
Week 1 (Visit 5)	564	-9.6 (8.11)
Week 2 (Visit 6)	559	-14.4 (8.02)
Week 4 (Visit 7)	552	-18.9 (8.31)
Week 6 (Visit 8)	544	-20.1 (8.39)
Week 16 (Visit 9)	531	-20.8 (8.61)
Week 28 (Visit 10)	508	-20.6 (8.61)
Week 28 Endpoint**	**564**	**-20.3 (8.92)**
Week 41 (Visit 11)	205***	-21.7 (8.30)
Week 54 (Visit 12)	199	-21.8 (8.60)
Week 54 Endpoint**	**205**	**-21.8 (8.66)**

SD = standard deviation.

* n is the number of patients with msDBP measurements at both baseline and post-baseline visits.

** Week 28 Endpoint is the last non-missing post-baseline measurement value on or before Week 28, and Week 54 Endpoint is the last non-missing measurement value after Week 28.

*** Of the 564 treated patients, only the first 206 patients who completed the first 6-month period entered the second 6-month period.
The number of patients who had any post-baseline measurements during the second six month treatment was 205, instead of 206. This was because one patient had Visit 10 and entered the second six month period but withdrew consent before Visit 11 without completing final visit procedures

Summary statistics for change from baseline in mean sitting systolic blood pressure (msSBP) by visit (Treated population)

	Total N=564	
Week (Visit)	**n***	**Mean (SD)**
Week 1 (Visit 5)	564	-17.5 (12.87)
Week 2 (Visit 6)	559	-25.4 (13.41)
Week 4 (Visit 7)	552	-32.2 (13.52)
Week 6 (Visit 8)	544	-33.8 (13.61)
Week 16 (Visit 9)	531	-35.0 (13.73)
Week 28 (Visit 10)	508	-34.9 (13.61)
Week 28 Endpoint**	**564**	**-34.2 (14.16)**
Week 41 (Visit 11)	205***	-37.8 (13.34)
Week 54 (Visit 12)	199	-37.4 (14.67)

Week 54 Endpoint**	**205**	**-37.3 (14.63)**

SD = standard deviation.

* n is the number of patients with msSBP measurements at both baseline and post-baseline visits.

** Week 28 Endpoint is the last non-missing post-baseline measurement value on or before Week 28, and Week 54 Endpoint is the last non-missing measurement value after Week 28.

*** Of the 564 treated patients, only the first 206 patients who completed the first 6-month period entered the second 6-month period.
The number of patients who had any post-baseline measurements during the second six month treatment was 205, instead of 206. This was because one patient had Visit 10 and entered the second six month period but withdrew consent before Visit 11 without completing final visit procedures

Blood pressure control

Frequency of patients with blood pressure controlled by visits (Treated population)

	Total N=564	
Week (Visit)	**N***	**n (%)**
Week 1 (Visit 5)	564	107 (19.0)
Week 2 (Visit 6)	559	215 (38.5)
Week 4 (Visit 7)	552	345 (62.5)
Week 6 (Visit 8)	544	355 (65.3)
Week 16 (Visit 9)	531	374 (70.4)
Week 28 (Visit 10)	508	364 (71.7)
Week 28 Endpoint**	**564**	**390 (69.1)**
Week 41 (Visit 11)	205***	155 (75.6)
Week 54 (Visit 12)	199	154 (77.4)
Week 54 Endpoint**	**205**	**158 (77.1)**

* N is the number of patients with both msDBP and msSBP measurement values at post-baseline visits.

** Week 28 Endpoint is the last non-missing post-baseline measurement value on or before Week 28 and Week 54 Endpoint is the last non-missing measurement value after Week 28. Blood pressure control is defined as having a mean sitting diastolic blood pressure <90 mmHg and a mean sitting systolic blood pressure <140 mmHg.

*** Of the 564 treated patients, only the first 206 patients who completed the first 6-month period entered the second 6-month period.
The number of patients who had any post-baseline measurements during the second six month treatment was 205, instead of 206. This was because one patient had Visit 10 and entered the second six month period but withdrew consent before Visit 11 without completing final visit procedures

Safety Results

Adverse Events by System Organ Class

Number (percent) of patients with AEs by system organ class (Treated Population)

Primary system organ class	Ali/HCTZ 300/12.5 mg alone N=564 n (%)	Ali / Aml /HCTZ 300/5/12.5 mg N=561 n (%)	Ali / Aml /HCTZ 300/10/25 mg N=556 n (%)	All* Ali/Aml/ HCTZ N=561 n (%)	Total N=564 n (%)
Any system organ class	**57 (10.1)**	**54 (9.6)**	**255 (45.9)**	**275 (49.0)**	**291 (51.6)**
Infections and infestations	10 (1.8)	8 (1.4)	97 (17.4)	103 (18.4)	111 (19.7)
General disorders and administration site conditions	5 (0.9)	6 (1.1)	62 (11.2)	68 (12.1)	73 (12.9)
Nervous system disorders	18 (3.2)	10 (1.8)	50 (9.0)	59 (10.5)	72 (12.8)
Gastrointestinal disorders	11 (2.0)	6 (1.1)	50 (9.0)	56 (10.0)	66 (11.7)
Musculoskeletal and connective tissue disorders	10 (1.8)	5 (0.9)	52 (9.4)	56 (10.0)	63 (11.2)
Metabolism and nutrition disorders	4 (0.7)	3 (0.5)	27 (4.9)	29 (5.2)	32 (5.7)
Respiratory, thoracic and mediastinal disorders	2 (0.4)	8 (1.4)	23 (4.1)	31 (5.5)	32 (5.7)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.2)	21 (3.8)	22 (3.9)	22 (3.9)
Skin and subcutaneous tissue disorders	0 (0.0)	5 (0.9)	18 (3.2)	21 (3.7)	21 (3.7)
Psychiatric disorders	3 (0.5)	5 (0.9)	11 (2.0)	16 (2.9)	19 (3.4)
Vascular disorders	1 (0.2)	1 (0.2)	16 (2.9)	17 (3.0)	18 (3.2)
Cardiac disorders	1 (0.2)	2 (0.4)	13 (2.3)	15 (2.7)	16 (2.8)
Ear and labyrinth disorders	7 (1.2)	2 (0.4)	6 (1.1)	8 (1.4)	15 (2.7)
Eye disorders	3 (0.5)	1(0.2)	10 (1.8)	11 (2.0)	14 (2.5)
Investigations	1 (0.2)	3 (0.5)	9 (1.6)	12 (2.1)	13 (2.3)
Renal and urinary disorders	3 (0.5)	1 (0.2)	9 (1.6)	10 (1.8)	12 (2.1)
Reproductive system and breast disorders	3 (0.5)	1 (0.2)	8 (1.4)	9 (1.6)	12 (2.1)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	4 (0.7)	4 (0.7)	4 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.5)	3 (0.5)
Endocrine disorders	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Immune system disorders	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Surgical and medical procedures	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)

*Includes aliskiren/amlodipine/ HCTZ 300/5/12.5 mg and aliskiren/amlodipine/ HCTZ 300/10/25 mg

System organ classes are sorted in descending frequency, as reported in the Total column.
A patient is counted only once in each cell.
Planned exposure to aliskiren/HCTZ 300/12.5 mg was 7 days
Planned exposure to aliskiren/amlodipine/HCTZ 300/5/12.5 mg was 7 days

Number (percent) of patients with common adverse events (equal or more than 2.0 percent in any group) (Treated population)

Preferred term	Ali/HCTZ 300/12.5 mg alone N=564 n (%)	Ali / Aml /HCTZ 300/5/12.5 mg N=561 n (%)	Ali / Aml /HCTZ 300/10/25 mg N=556 n (%)	All* Ali/Aml/ HCTZ N=561 n (%)	Total N=564 n (%)
Any Adverse events	**57 (10.1)**	**54 (9.6)**	**255 (45.9)**	**275 (49.0)**	**291 (51.6)**
Edema peripheral	1 (0.2)	0 (0.0)	52 (9.4)	52 (9.3)	53 (9.4)
Headache	10 (1.8)	6 (1.1)	16 (2.9)	22 (3.9)	32 (5.7)
Nasopharyngitis	3 (0.5)	2 (0.4)	20 (3.6)	21 (3.7)	23 (4.1)
Bronchitis	2 (0.4)	3 (0.5)	17 (3.1)	20 (3.6)	21 (3.7)
Diarrhea	5 (0.9)	1 (0.2)	11 (2.0)	12 (2.1)	16 (2.8)
Dizziness	5 (0.9)	3 (0.5)	7 (1.3)	10 (1.8)	15 (2.7)
Influenza	0 (0.0)	0 (0.0)	15 (2.7)	15 (2.7)	15 (2.7)
Back pain	0 (0.0)	2 (0.4)	12 (2.2)	13 (2.3)	13 (2.3)
Vertigo	7 (1.2)	2 (0.4)	4 (0.7)	6 (1.1)	13 (2.3)
Upper respiratory tract infection	2 (0.4)	1 (0.2)	9 (1.6)	10 (1.8)	12 (2.1)

*Includes aliskiren/amlodipine/HCTZ 300/5/12.5 mg and aliskiren/amlodipine/HCTZ 300/10/25 mg

Preferred terms are sorted in descending frequency, as reported in the Total column.
A patient is counted only once in each cell.
Planned exposure to aliskiren/HCTZ 300/12.5 mg was 7 days
Planned exposure to aliskiren/amlodipine/HCTZ 300/5/12.5 mg was 7 days

Serious Adverse Events and Deaths

Number (percent) of patients with deaths, SAEs, and AEs and abnormal laboratory values leading to permanent discontinuation of study drugs (Treated population)

	Ali/HCTZ 300/12.5 mg alone N=564 n (%)	Ali / Aml /HCTZ 300/5/12.5 mg N=561 n (%)	Ali / Aml /HCTZ 300/10/25 mg N=556 n (%)	All* Ali/Aml/ HCTZ HCTZ N=561 n (%)	Total N=564 n (%)
Deaths	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
SAEs	**0 (0.0)**	**1 (0.2)**	**14 (2.5)**	**15 (2.7)**	**15 (2.7)**
AE discontinuations**	**3 (0.5)**	**5 (0.9)**	**32 (5.8)**	**36 (6.4)**	**39 (6.9)**
drug-related AE discontinuations	2 (0.4)	4 (0.7)	25 (4.5)	28 (5.0)	30 (5.3)
SAE discontinuations	0 (0.0)	0 (0.0)	6 (1.1)	6 (1.1)	6 (1.1)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Includes aliskiren/amlodipine/ HCTZ 300/5/12.5 mg and aliskiren/amlodipine/ HCTZ 300/10/25 mg

** AE discontinuations come from AE dataset.

Number (percent) of patients with any SAEs by preferred term (Treated population)

Preferred Term	Ali/Aml/HCTZ 300/5/12.5 mg N=561 n (%)	Ali/Aml/HCTZ 300/10/25 mg N=556 n (%)	All# Ali/Aml/ HCTZ N=561 n (%)	Total N=564 n (%)
Any SAEs	**1 (0.2)**	**14 (2.5)**	**15 (2.7)**	**15 (2.7)**
Palpitations*	0 (0.0)	2 (0.4)	2 (0.4)	2 (0.4)
Arthritis	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Atrial fibrillation	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Bronchitis	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Carotid artery stenosis	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Cerebrovascular accident	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Cervical myelopathy	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Cervical spinal stenosis	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Drug dependence	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Headache*	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Inguinal hernia, obstructive	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Interstitial lung disease	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Intervertebral disc protrusion	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Non-cardiac chest pain*	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Osteoarthritis	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)

Pain in extremity	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Peripheral ischaemia	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Presyncope*	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Renal failure*	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Sinusitis*	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Thrombocytopenia*	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Venous thrombosis	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)

Includes aliskiren/amlodipine/ HCTZ 300/5/12.5 mg and aliskiren/amlodipine/ HCTZ 300/10/25 mg SAEs are sorted in descending frequency, as reported in the Total column.

A patient is counted only once in each cell.

* All of these SAEs occurred in one patient.
Planned exposure to aliskiren/HCTZ 300/12.5 mg was 7 days – no SAEs were noted
Planned exposure to aliskiren/amlodipine/HCTZ 300/5/12.5 mg was 7 days

Other Relevant Findings

None

Date of Clinical Trial Report

17-Dec-2009

Date Inclusion on Novartis Clinical Trial Results Database

01-Oct-2010

Date of Latest Update

08-Jun-2010