## 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 orallywith 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 (i.e., 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.
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**

- Outpatients 18 years of age or older
- Male or female participants are eligible.
- Mean sitting diastolic blood pressure (msDBP) and mean sitting systolic blood pressure (msSBP) Requirements:
  - For newly diagnosed/untreated participants, msDBP ≥ 100 and < 120 millimeters of mercury (mmHg), and/or msSBP ≥ 160 and < 200 mmHg at Visit 1 and Visit 2.
  - For previously treated participants, msDBP ≥ 100 and < 120 mmHg, and/or msSBP ≥ 160 and < 200 mmHg at Visit 2, Visit 3, or Visit 4.
- For participants requiring tapering off their previous antihypertensive medication, they must meet the above criteria and completely discontinue all antihypertensive treatment prior to entering the treatment phase of the study.
- Participants who are eligible and able to participate in the study, and who consent to do so after the purpose and nature of the investigation has been clearly explained to them (written informed consent).

**Exclusion Criteria:**

- Inability to discontinue all prior antihypertensive medications safely for a period of 1 week to 4 weeks as required by the protocol.
- Participants on three antihypertensive drugs with msDBP ≥ 110 mmHg and/or msSBP ≥ 180 mmHg at Visit 1.
- Participants on four or more antihypertensive drugs at Visit 1.
- Participants 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.
- 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 human chorionic gonadotropin (hCG) laboratory test (≥ 5 milliinternational units per milliliter mIU/mL).

## Number of Subjects

| Disposition, n(%) | 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) |
| **BMI (kg/m$^2$)** | |
| 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/m$^2$) | 8 (1.4) |
| 20 (kg/m2) ≤ BMI < 25 (kg/m$^2$) | 50 (8.9) |
| 25 (kg/m2) ≤ BMI < 30 (kg/m$^2$) | 214 (37.9) |
| BMI ≥30 (kg/m$^2$) | 292 (51.8) |
| **Diabetes Status n (%)** | |
| Yes | 122 (21.6) |
| No | 442 (78.4) |

BMI = body mass index; 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)

### Number of Participants With Any Adverse Events (AEs), Serious Adverse Events (SAEs) and Death

| | Aliskiren/Hydrochlorothiazide 300/12.5 mg | Aliskiren/Amlodipine/Hydrochlorothiazide 300/5/12.5 mg | Aliskiren/Amlodipine/Hydrochlorothiazide 300/10/25 mg |
|---|---|---|---|
| Overall Number of Participants Analyzed | 564 | 561 | 556 |
| Any Adverse Events | **57** | **54** | **255** |

| | | | |
|---|---|---|---|
| Serious Adverse Events | **0** | **1** | **14** |
| Death | **0** | **0** | **0** |

## Secondary Objective Result(s)

**Summary of baseline (Visit 4) values for mean sitting systolic and diastolic blood pressure (Treated population)**

| | Total N=564 | |
|---|---|---|
| **Baseline variable** | **msSBP (mmHg)** | **msDBP (mmHg)** |
| n | 564 | 564 |
| Mean | 166.1 | 101.8 |
| SD | 11.59 | 7.74 |
| Median | 165.3 | 102.7 |
| Minimum | 130.3 | 67.0 |
| Maximum | 198.7 | 120.0 |

SD = standard deviation

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

| Week (Visit) | Total N =564 | |
|---|---|---|
| | **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 patient SAH100A2301-0515-00006 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 patient SAH100A2301-0515-00006 had Visit 10 and entered the second six month period but withdrew consent before Visit 11 without completing final visit procedures.

**Percentage of Participants Achieving the Blood Pressure Control Target of <140/90 mmHg**

| | | |
|---|---|---|
| Percentage of Participants Achieving the Blood Pressure Control Target of <140/90 mmHg<br>Measure Type: Number<br>Unit of measure: percentage of participants | | Aliskiren/Amlodipine/Hydrochlorothiazide |
| Week 28 Endpoint | Number Analyzed | 564 |
| | | 69.1 |
| Week 54 Endpoint | Number Analyzed | 205 |
| | | 77.1 |

**Percentage of Participants Who Achieved a Blood Pressure Response in Mean Sitting Diastolic Blood Pressure**

| | | |
|---|---|---|
| Percentage of Participants Who Achieved a Blood Pressure Response in Mean Sitting Diastolic Blood Pressure<br>Measure Type: Number<br>Unit of measure: percentage of participants | | Aliskiren/Amlodipine/Hydrochlorothiazide |
| Week 28 Endpoint | Number Analyzed | 564 |
| | | 91.8 |
| Week 54 Endpoint | Number Analyzed | 205 |
| | | 96.6 |

**Percentage of Participants Who Achieved a Blood Pressure Response in Mean Sitting Systolic Blood Pressure**

| | | |
|---|---|---|
| Percentage of Participants Who Achieved a Blood Pressure Response in Mean Sitting Systolic Blood Pressure<br>Measure Type: Number<br>Unit of measure: percentage of participants | | Aliskiren/Amlodipine/Hydrochlorothiazide |
| Week 28 Endpoint | Number Analyzed | 564 |
| | | 90.2 |
| Week 54 Endpoint | Number Analyzed | 205 |
| | | 93.7 |

## 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 an 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 m N=561 n (%) | Ali / Aml /HCTZ 300/10/25 mg N=556 n (%) | All* Ali/Aml/ HCTZ HCTZ N=561n (%) | 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 pop ulation)**

| 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

**Conclusion:**

• This study included an adequate number of patients required for the evaluation of the long term safety (>300 patients for 6-month exposure and >100 with 12-month exposure) of aliskiren/amlodipine/HCTZ combination.
• This study showed a good tolerability even when the maximum dose of the triple combination of aliskiren/amlodipine/HCTZ 300/10/25 mg was used for up to 1 year.
• The safety profile seen in this long term study is similar to that seen in the short term study (CSAH100A2302) and consistent with the known safety profile of the three component drugs when used alone or in combinations.
• The study demonstrated the superior blood pressure lowering effects of aliskiren/amlodipine/HCTZ combination when used in long term treatment of patients with moderate to severe hypertension.

**Date of Clinical Trial Report**

3-Dec-2009