Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Prevention of left ventricular remodeling in high risk post-acute myocardial infarction (post-AMI) patients.

Approved Indication

Hypertension

Protocol Number

CSPP100A2340E1

Title

A 2 year extension to a 36-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren on the prevention of left ventricular remodeling in high risk post-acute myocardial infarction patients when added to optimized standard therapy

Phase of Development

Phase III

Study Start/End Dates

18 Apr 2008 to 05 Jul 2011

Study Design/Methodology

Patients who completed the core study CSPP100A2340 were offered continued participation in an additional 2-year safety extension to the protocol. Patients received open-label aliskiren for 24 months in addition to their standard background therapies.

Centers

154 centers in 23 countries: Argentina (7), Belgium (7), Canada (4), Colombia (3), Czech Republic (3), Denmark (12), Germany (17), Hungary (5), India (6), Israel (3), Italy (14), Netherlands (10), Norway (2), Poland (3), Russia (7), Slovakia (5), South Korea (5), Spain (16), Sweden (5), Turkey (4), UK (1), USA (12) and Venezuela (3).

Publication

None

Outcome Measures

Primary Outcome Measure(s)

- Long term safety data. (Refer to Safety Section)

Secondary Outcome Measure(s)

- Change from baseline in left ventricular end systolic volume (LVESV) (mL) at Month

12 as assessed by echocardiogram (ECHO) (Echocardiogram Analysis Set)

- Change from baseline in left ventricular end diastolic volume (LVEDV) at Month 12 as assessed by ECHO (Echocardiogram Analysis Set)
- Change from baseline in left ventricular ejection fraction (LVEF) at Month 12 as assessed by ECHO (Echocardiogram Analysis Set)

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

150 mg aliskiren tablet orally once a day for two weeks. Patients were then up-titrated to 300 mg aliskiren orally once a day at the discretion of the principal investigator based on their clinical condition for the duration of the study.

Statistical Methods

The primary objective of this extension study was to provide additional long term safety data as a post marketing commitment to the European Medicines Agency (EMA). The assessment of safety was based primarily on the frequency of adverse events (AEs), laboratory abnormalities, and serious adverse events (SAEs). SAEs suspected by the Investigator to be related to study medication and other safety data were summarized as appropriate.

Occurrence and frequency of AEs was summarized by body system and preferred term. The incidence of selected AEs (hypotension, hyperkalemia or renal dysfunction) during the extension study was summarized separately using the pre-defined MedDRA codes and terms which were also used for reporting during the core study (Study A2340). SAEs were narrated. Summary statistics at baseline, at last visit, and of changes from baseline to last visit for laboratory values were provided. Occurrence of significant abnormality in change of laboratory values from baseline was summarized.

Other safety data such as vital signs and laboratory data were summarized using descriptive statistics. The frequency of patients who experienced orthostatic blood pressure changes was summarized by visit. Orthostatic blood pressure change is defined as a decrease of at least 20 mmHg in systolic blood pressure or a decrease of at least 10 mmHg in diastolic blood pressure when a patient moves from a sitting position to a standing position.

A secondary objective was to provide additional follow-up efficacy data on the effect of aliskiren on left ventricular remodeling as measured by echocardiography in terms of:

- Change from baseline to the post-baseline measurement in left ventricular end systolic volume (LVESV)
- Change from baseline to the post-baseline measurement in left ventricular end diastolic volume (LVEDV)
- Change from baseline to the post-baseline measurement in left ventricular ejection fraction(LVEF)

The baseline measurements were defined as the echocardiogram (ECHO) measurements at Visit 1 in the extension period which were carried over from Visit 10 in the core study (Study A2340). The post-baseline measurement was defined as the ECHO measurement at Visit 17 or discontinued visit in the extension study.

Efficacy variables were summarized using n, mean, standard deviation, median, minimum, maximum, geometric mean and 95% confidence interval for geometric mean.
No interim analysis was planned or performed for this study.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Male or female patients who completed the core study (Study A2340) through Visit 10, while on double-blind study drug.
- Patients who were able to participate in the study, and who consented to do so after the purpose and nature of the study had been clearly explained to them (written informed consent).

Exclusion Criteria

- New York Heart Association (NYHA) class IV Congestive Heart Failure at Visit 1 (Core study Visit 10).
- Symptomatic hypotension, or reported systolic blood pressure (BP) <90 mmHg within 24 hours prior to Visit 1 (Core study Visit 10)
- Known Estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m2 using the Modification of Diet in Renal Disease (MDRD) formula at Visit 1 (Core study Visit 10)
- 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).
- Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precluded intercourse with a male partner and women whose partners had 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 follicle stimulating hormone (FSH) levels >40 mIU/mL or 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy OR are using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral or tubal ligation), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: intrauterine device (IUD), male or female condom with spermicidal gel, diaphragm, sponge, cervical cap) if accepted by local ethics committees. Reliable contraception was to be maintained throughout the study and for at least 7 days after study drug discontinuation.
- Any surgical or medical condition that in the opinion of the investigator may place the patient at higher risk from his/her participation in the study or was likely to prevent the patient from complying with the requirements or completing the study.

Participant Flow (Extension Population)

Disposition	Aliskiren n (%)
All extension population	422
Completed the extension period	365 (86.5)
Discontinued during the extension period	57 (13.5)
Reason for discontinuation	
Adverse events	14 (3.3)
Unsatisfactory therapeutic effect	2 (0.5)
Patient withdrew consent	13 (3.1)
Lost to follow-up	10 (2.4)
Administrative problems	1 (0.2)
Death	17 (4.0)

Percentage (%) is calculated using all extension population as the denominator

Baseline Characteristics (Extension Population)

Demographic characteristic category/statistic	Aliskiren N=422
Age (years)	
n	422
Mean	60.4
SD	11.62
Age group (years) n (%)	
<65	271 (64.2%)
≥65	151 (35.8%)
<75	372 (88.2%)
≥75	50 (11.8)
Sex n (%)	
Male	362 (85.8%)
Female	60 (14.2%)

Outcome Measure Results

Primary Outcome Measure(s)

- Long term safety data. (Refer to Safety Section)

Preferred term	Aliskiren N=422 n (%)
Deaths	17 (4.0)
SAEs	126 (29.9)
AE discontinuations	30 (7.1)
drug-related AE discontinuations	10 (2.4)
SAE discontinuations	22 (5.2)
Discontinuations for abnormal lab values	0

Secondary Outcome Measure(s)

- Change from baseline in left ventricular end systolic volume (LVESV) (mL) at Month 12 as assessed by echocardiogram (ECHO) (Echocardiogram Analysis Set)

		Aliskiren (N=400)		
Visit	Statistics	Baseline	Post baseline	Change
Baseline (Week 0)	n	400		
	Mean	77.7		
	SD	27.33		
Visit 7 (Month 12)	n	302	302	302
	Mean	76.4	70.2	-6.2
	SD	26.02	27.17	14.32

Change=Post baseline – Baseline. Baseline is Visit 10 in the core study
Only patients with a value at both Baseline and Visit 7 (extension period) are included

- Change from baseline in left ventricular end diastolic volume (LVEDV) (mL) at Month 12 as assessed by ECHO (Echocardiogram Analysis Set)

		Aliskiren (N=400)		
Visit	**Statistics**	**Baseline**	**Post baseline**	**Change**
Baseline (Week 0)	n	400		
	Mean	127.4		
	SD	33.93		
Visit 7 (Month 12)	n	302	302	302
	Mean	126.0	132.0	6.0
	SD	31.85	36.00	18.34

Change=Post baseline – Baseline. Baseline is Visit 10 in the core study
Only patients with a value at both Baseline and Visit 7 (extension period) are included

- Change from baseline in left ventricular ejection fraction (LVEF) (%) at Month 12 as assessed by ECHO (Echocardiogram Analysis Set)

		Aliskiren (N=400)		
Visit	**Statistics**	**Baseline**	**Post baseline**	**Change**
Baseline (Week 0)	n	400		
	Mean	40.2		
	SD	6.58		
Visit 7 (Month 12)	n	302	302	302
	Mean	40.5	47.9	7.4
	SD	6.56	8.66	6.46

Change=Post baseline – Baseline. Baseline is Visit 10 in the core study
Only patients with a value at both Baseline and Visit 7 (extension period) are included

Safety Results

Adverse Events by System Organ Class (Extension Population)

Primary System Organ Class	Aliskiren N=422 n (%)
Any system organ class	**312 (73.9)**
Cardiac disorders	110 (26.1)
Infections and infestations	94 (22.3)
Nervous system disorders	74 (17.5)
Vascular disorders	72 (17.1)
General disorders and administration site conditions	68 (16.1)
Gastrointestinal disorders	64 (15.2)
Musculoskeletal and connective tissue disorders	54 (12.8)
Investigations	51 (12.1)
Respiratory, thoracic and mediastinal disorders	50 (11.8)
Metabolism and nutrition disorders	45 (10.7)
Injury, poisoning and procedural complications	26 (6.2)
Skin and subcutaneous tissue disorders	22 (5.2)
Renal and urinary disorders	19 (4.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16 (3.8)
Reproductive system and breast disorders	14 (3.3)
Blood and lymphatic system disorders	11 (2.6)
Psychiatric disorders	11 (2.6)
Eye disorders	10 (2.4)
Ear and labyrinth disorders	7 (1.7)
Endocrine disorders	4 (0.9)
Hepatobiliary disorders	2 (0.5)
Immune system disorders	2 (0.5)
Congenital, familial and genetic disorders	1 (0.2)
Social circumstances	1 (0.2)
Surgical and medical procedures	1 (0.2)

Adverse Events Overall by Preferred Term reported in ≥ 2 % patients in any treatment group (Extension Population)

Preferred term	Aliskiren N=422 n (%)
Any adverse events	**312 (73.9)**
Hypotension	43 (10.2)
Angina pectoris	31 (7.3)
Nasopharyngitis	28 (6.6)
Dizziness	25 (5.9)
Non-cardiac chest pain	25 (5.9)
Dyspnoea	20 (4.7)
Oedema peripheral	16 (3.8)
Cough	15 (3.6)
Bronchitis	14 (3.3)
Cardiac failure	14 (3.3)
Diarrhoea	14 (3.3)
Influenza	14 (3.3)
Headache	12 (2.8)
Hyperkalaemia	12 (2.8)
Blood creatinine increased	11 (2.6)
Fatigue	11 (2.6)
Hypertension	11 (2.6)
Syncope	11 (2.6)
Atrial fibrillation	10 (2.4)
Pain in extremity	10 (2.4)
Anaemia	9 (2.1)
Arthralgia	9 (2.1)
Back pain	9 (2.1)
Urinary tract infection	9 (2.1)

Serious Adverse Events and Deaths (Extension Population)

Primary system organ class Preferred term	Aliskiren N=422 n (%)
Any primary system organ class -Total	126(29.9)
Blood and lymphatic system disorders -Total	1(0.2)
Haemorrhagic anaemia	1(0.2)

Cardiac disorders	
-Total	55(13.0)
Angina pectoris	15(3.6)
Cardiac failure	9(2.1)
Acute myocardial infarction	6(1.4)
Myocardial infarction	6(1.4)
Cardiac failure chronic	5(1.2)
Angina unstable	4(0.9)
Acute coronary syndrome	3(0.7)
Atrial fibrillation	3(0.7)
Cardiac arrest	2(0.5)
Coronary artery disease	2(0.5)
Coronary artery stenosis	2(0.5)
Myocardial ischaemia	2(0.5)
Arteriospasm coronary	1(0.2)
Cardiac failure congestive	1(0.2)
Cardio-respiratory arrest	1(0.2)
Cardiopulmonary failure	1(0.2)
Ischaemic cardiomyopathy	1(0.2)
Ventricular tachycardia	1(0.2)
Eye disorders	
-Total	1(0.2)
Cataract	1(0.2)
Gastrointestinal disorders	
-Total	7(1.7)
Abdominal hernia	1(0.2)
Abdominal tenderness	1(0.2)
Chronic gastrointestinal bleeding	1(0.2)
Duodenal ulcer perforation	1(0.2)
Gastrointestinal obstruction	1(0.2)
Inguinal hernia, obstructive	1(0.2)
Nausea	1(0.2)
Peritonitis	1(0.2)
Rectal haemorrhage	1(0.2)
General disorders and administration site conditions	
-Total	16(3.8)
Non-cardiac chest pain	7(1.7)
Sudden death	4(0.9)
Thrombosis in device	2(0.5)
Chest pain	1(0.2)
Device failure	1(0.2)
Multi-organ failure	1(0.2)
Pyrexia	1(0.2)

Hepatobiliary disorders	
-Total	1(0.2)
Cholangitis	1(0.2)
Infections and infestations	
-Total	8(1.9)
Pneumonia	3(0.7)
Urinary tract infection	2(0.5)
Appendicitis	1(0.2)
Gastroenteritis	1(0.2)
Peritoneal abscess	1(0.2)
Injury, poisoning and procedural complications	
-Total	10(2.4)
In-stent coronary artery restenosis	2(0.5)
Ankle fracture	1(0.2)
Face injury	1(0.2)
Graft thrombosis	1(0.2)
Hip fracture	1(0.2)
Laceration	1(0.2)
Lower limb fracture	1(0.2)
Radius fracture	1(0.2)
Tendon rupture	1(0.2)
Investigations	
-Total	3(0.7)
Blood creatinine increased	2(0.5)
Aspartate aminotransferase increased	1(0.2)
Blood potassium increased	1(0.2)
Renal function test abnormal	1(0.2)
Metabolism and nutrition disorders	
-Total	4(0.9)
Hypoglycaemia	2(0.5)
Dehydration	1(0.2)
Diabetes mellitus	1(0.2)
Musculoskeletal and connective tissue disorders	
-Total	9(2.1)
Back pain	2(0.5)
Musculoskeletal chest pain	2(0.5)
Gouty arthritis	1(0.2)
Intervertebral disc protrusion	1(0.2)
Muscular weakness	1(0.2)
Musculoskeletal pain	1(0.2)
Rhabdomyolysis	1(0.2)
Rheumatoid arthritis	1(0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
-Total	11(2.6)
Lung neoplasm	2(0.5)
Benign neoplasm of skin	1(0.2)
Brain neoplasm malignant	1(0.2)
Colon cancer	1(0.2)
Gastric cancer	1(0.2)
Leukaemia	1(0.2)
Lung neoplasm malignant	1(0.2)
Metastatic neoplasm	1(0.2)
Myeloproliferative disorder	1(0.2)
Ovarian cancer	1(0.2)
Plasmacytoma	1(0.2)

Nervous system disorders	
-Total	21(5.0)
Syncope	6(1.4)
Cerebrovascular accident	5(1.2)
Transient ischaemic attack	3(0.7)
Cerebral ischaemia	2(0.5)
Basilar artery occlusion	1(0.2)
Brain stem infarction	1(0.2)
Carotid artery stenosis	1(0.2)
Cerebral infarction	1(0.2)
Dizziness	1(0.2)
Encephalomalacia	1(0.2)
Psychiatric disorders	
-Total	1(0.2)
Confusional state	1(0.2)
Renal and urinary disorders	
-Total	3(0.7)
Haematuria	1(0.2)
Nephropathy toxic	1(0.2)
Nephrotic syndrome	1(0.2)
Renal failure	1(0.2)
Renal failure acute	1(0.2)
Reproductive system and breast disorders	
-Total	1(0.2)
Metrorrhagia	1(0.2)
Respiratory, thoracic and mediastinal disorders	
-Total	10(2.4)
Pulmonary oedema	3(0.7)
Chronic obstructive pulmonary disease	2(0.5)
Dyspnoea	2(0.5)
Pulmonary embolism	2(0.5)
Acute pulmonary oedema	1(0.2)
Pleural effusion	1(0.2)
Pneumothorax	1(0.2)
Respiratory failure	1(0.2)
Skin and subcutaneous tissue disorders	
-Total	2(0.5)
Cold sweat	1(0.2)
Psoriasis	1(0.2)
Surgical and medical procedures	
-Total	1(0.2)
Hospitalisation	1(0.2)
Vascular disorders	
-Total	7(1.7)
Hypotension	3(0.7)
Aortic aneurysm	1(0.2)
Femoral artery occlusion	1(0.2)
Intermittent claudication	1(0.2)
Peripheral vascular disorder	1(0.2)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency.
- A patient with multiple occurrences of an AE is counted only once in the AE category.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Deaths during the Extension Period by primary system organ class and preferred term (Extension Population)

Primary system organ class Preferred term	Aliskiren N=422 n (%)
Any primary system organ class -Total	17(4.0)
Cardiac disorders -Total	6(1.4)
Cardiac failure	2(0.5)
Cardiac arrest	1(0.2)
Cardiopulmonary failure	1(0.2)
Myocardial infarction	1(0.2)
Myocardial ischaemia	1(0.2)
General disorders and administration site conditions -Total	6(1.4)
Sudden death	4(0.9)
Death	1(0.2)
Multi-organ failure	1(0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) -Total	1(0.2)
Brain neoplasm malignant	1(0.2)
Nervous system disorders -Total	3(0.7)
Cerebral infarction	1(0.2)
Cerebral ischaemia	1(0.2)
Cerebrovascular accident	1(0.2)
Respiratory, thoracic and mediastinal disorders -Total	1(0.2)
Pulmonary embolism	1(0.2)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency.

Other Relevant Findings

No other important or notable findings were reported in this study.

Date of Clinical Trial Report

Nov 12, 2011

Date Inclusion on Novartis Clinical Trial Results Database

July 5th, 2012

Date of Latest Update