Sponsor

Novartis

Generic Drug Name

Aliskiren

Therapeutic Area of Trial

Essential Hypertension

Approved Indication

Hypertension

Study Number

CSPP100A2351

Title

A nine-week, randomized, double-blind, parallel group study to evaluate the efficacy and safety of aliskiren 300 mg compared to irbesartan 300 mg and ramipril 10 mg in the setting of a missed dose in patients with essential hypertension.

Phase of Development

Phase III

Study Start/End Dates

31-May-2006 to 03-May-2007

Study Design/Methodology

This was a 9-week, randomized, double-blind, parallel group study in patients with essential hypertension, with four periods: a 2 to 3 week washout period, a 2 week single-blind run-in period, and a 7 week active treatment period, including a 2 week simulated non-adherence period. Patients started double-blind therapy with either aliskiren 150 mg, irbesartan 150 mg, or ramipril 5 mg. After two weeks patients were up-titrated to either aliskiren 300 mg, irbesartan 300 mg, or ramipril 10 mg. Patients received the higher dose for the rest of the study, except when they were randomized to miss doses (Day 42 or Day 49; Days 54 – 55 and Days 61 – 62).

Centers

97 centers in 10 countries: Brazil (6 centers), Canada (6 centers), Germany (16 centers), Hungary (6 centers), Italy (19 centers), Netherlands (9 centers), Norway (7 centers), Russia (6 centers), Slovakia (6 centers), Spain (16 centers).

Objectives

Primary objective(s)

- To evaluate the efficacy of aliskiren 300 mg following a missed dose on mean 24 hour ambulatory diastolic blood pressure (MADBP) change from baseline (1) compared to irbesartan 300 mg and (2) compared to ramipril 10 mg.

Secondary objective(s)

- Evaluate the efficacy of aliskiren 300 mg following a missed dose on mean 24 hour ambulatory systolic blood pressure (MASBP) change from baseline compared to ramipril 10 mg as well as irbesartan 300 mg.
- Compare the efficacy of aliskiren 300 mg to ramipril 10 mg as well as irbesartan 300 mg on the MASBP and MADBP change from baseline following the last active dose prior to introducing a missed dose in any treatment group.
- Evaluate the efficacy of aliskiren 300 mg following a missed dose on daytime and nighttime MASBP and MADBP change from baseline compared to rampril 10 mg as well as irbesartan 300 mg.
- Compare the effect of aliskiren 300 mg to ramipril 10 mg as well as irbesartan 300 mg on the smoothness index, trough to peak ratio, and morning surge of ambulatory systolic blood pressure and ambulatory diastolic blood pressure following a missed dose.
- Evaluate the safety and tolerability of aliskiren 300 mg, ramipril 10 mg and irbesartan 300 mg.

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

Aliskiren 150 mg film-coated tablets, taken orally, once daily

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

Capsules of Irbesartan (150 mg) and Ramipril (5 & 10 mg).

Matching Placebo of:

- Aliskiren 150 mg film-coated tablets
- Irbesartan 150 mg capsules
- Ramipril 5 mg capsules and ramipril 10 mg capsules (one placebo matching both study drugs)

In order to adequately blind the study, patients took total of 2 tablets and 3 capsules of study medication orally, once daily throughout the study

Criteria for Evaluation

Primary variables

Change from baseline in 24-hour ambulatory diastolic blood pressure (MADBP) after a missed dose in the aliskiren group; (1) compared to irbesartan 300 mg and (2) compared to ramipril 10 mg.

Secondary variables

- Change from baseline in 24-hour MASBP after a missed dose in the aliskiren 300 mg compared to ramipril 10 mg as well as irbesartan 300 mg.
- Change from baseline in 24-hour MADBP and MASBP after an active dose in the aliskiren 300 mg compared to ramipril 10 mg as well as irbesartan 300 mg.
- Change from baseline on the daytime and night time MADBP and MASBP after a missed dose in the aliskiren 300 mg compared to ramipril 10 mg as well as irbesartan 300 mg.
- Compare diastolic smoothness index, trough to peak ratio and morning surge of ambulatory systolic blood pressure and ambulatory diastolic blood pressure following a miss dose of the aliskiren 300 mg to ramipril 10 mg as well as irbesartan 300 mg.

Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events (AE) and serious adverse events (SAE), the regular monitoring of hematology and blood chemistry, regular measurement of vital signs, weight and the performance of physical examinations, pregnancy testing and Electrocardiogram (ECG).

Other

None

Statistical Methods

Baseline was defined as Day -1/1 for the ABPM analyses, with Week 6/7 as the endpoint. Day -1 was the baseline for sitting and standing blood pressure. Primary efficacy analysis: Two separate null and alternative hypotheses were tested for the variable change from baseline to Week 6/7 in mean 24-hour ambulatory diastolic BP, after a missed dose. No statistical adjustment for the sig-

nificance level was made as the two primary tests assessed the differences between aliskiren and each comparative drug belonging to a different mode of action class (ACE inhibitor (ramipril) and ARB (irbesartan)). This analysis was performed using a two-way repeated measures analysis of covariance (ANCOVA) model, with treatment, country, visit of missed dose and post-dosing hours as factors, and baseline mean 24-hour ambulatory DBP as covariate. Treatment-by-post-dosing hour interaction was included in the model. ABPM analyses were analyzed for the ABPM completer population (the per-protocol (PP) population was used in addition only for the primary efficacy analysis), while mean sitting office BP and mean self-measured BP were analyzed for the intent-to-treat (ITT) population.

Data were listed and also summarized with respect to background and demographic characteristics, efficacy measurements, and safety observations and measurements. Descriptive statistics (mean, standard deviation (SD), median, minimum and maximum) are explored for continuous variables. Categorical variables were summarized with frequency and percentage. Biomarkers were analyzed using log-transformed data.

No interim analyses were performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Male and female patients, aged 18 years of age and older with essential hypertension, and who met the following blood pressure criteria: office msDBP >=90 mmHg and < 110 mmHg at Visit 2, office msDBP >= 95 mmHg and < 110 mmHg before application of ABPM at Visit 3 (Day -1), and 24-hr MADBP >= 85 mmHg at Visit 3. Also, patients must have had an absolute difference of <= 10 mmHg in their office msDBP between Visits 2 and 3.

Exclusion criteria

- Patients with severe hypertension (office msDBP >= 110 mmHg and/or office mean sitting systolic blood pressure (msSBP) >= 180 mmHg) or any history or evidence of a secondary form of hypertension.
- Known Keith-Wagener grade III or IV hypertensive retinopathy.
- History of hypertensive encephalopathy or cerebrovascular accident.
- Transient ischemic cerebral attack during the 12 months prior to Visit 1.
- Current diagnosis of heart failure (NYHA Class II-IV).
- History of myocardial infarction, coronary bypass surgery, or any percutaneous coronary-intervention (PCI) during the 12 months prior to Visit 1.
- Current angina pectoris requiring pharmacological therapy.
- Second or third degree heart block without a pacemaker.
- Concurrent potentially life threatening arrhythmia or symptomatic arrhythmia.
- Clinically significant valvular heart disease.
- History of Type 1 diabetes or history of Type 2 diabetes and glycosylatedhemoglobin (HbA1c) > 8% at Visit 1.
- Serum sodium less than the lower limit of normal, serum potassium < 3.5 or >= 5.5 mEq/L, at

Visit 1.

- Known or suspected contraindications to the study medications, including history of allergy to ACE-Inhibitors or ARBs.
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs
- Upper arm circumference > 42 cm.
- Third shift or night workers.
- History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the past five years.
- History or evidence of drug or alcohol abuse within the last 12 months.
- Pregnant or nursing (lactating) women
- Any surgical or medical condition, which in the opinion of the investigator, may have placed the patient at higher risk from his/her participation in the study, or was likely to prevent the patient from complying with the requirements of the study or completing the study.
- History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
- Any condition that in the opinion of the investigator or the Novartis medical monitor would jeopardize the evaluation of efficacy or safety.
- Participation in any investigational drug trial within one month of Visit 1.
- Persons directly involved in the execution of this protocol.

Number of Subjects

	Aliskiren	**Irbesartan**	**Ramipril**	**Total**
Planned N	218	218	218	654
Randomized n	218	222	214	654
Intent-to-treat population (ITT) n (%)	217 (99.5)	221 (99.5)	213 (99.5)	651 (99.5)
ABPM Completer population n **(%)**	155 (71.1)	171 (77.0)	152 (71.0)	478 (73.1)
Completed n (%)	202 (92.7)	208 (93.7)	190 (88.8)	600 (91.7)
Withdrawn n (%)	16 (7.3)	14 (6.3)	24 (11.2)	54 (8.3)
Withdrawn due to adverse events n (%)	2 (0.9)	4 (1.8)	5 (2.3)	11 (1.7)
Withdrawn due to lack of efficacy n (%)	4 (1.8)	2 (0.9))	5 (2.3)	11 (1.7)
Withdrawn for other reasons n (%)	10 (4.6)	7 (3.2)	13 (6.1)	30 (4.6)

Demographic and Background Characteristics

Demographic Characteristic Category/statistic	Aliskiren N=218	Irbesartan N=222	Ramipril N=214	Total N=654
Sex n (%)				
Female	81 (37.2)	80 (36.0)	93 (43.5)	254 (38.8)
Male	137 (62.8)	142 (64.0)	121 (56.5)	400 (61.2)
Race n (%)				
Asian	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.3)
Black	5 (2.3)	3 (1.4)	3 (1.4)	11 (1.7)
Caucasian	209 (95.9)	217 (97.7)	210 (98.1)	636 (97.2)
Other	2 (0.9)	2 (0.9)	1 (0.5)	5 (0.8)
Ethnicity n (%)				
Chinese	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Hispanic/Latino	33 (15.1)	33 (14.9)	30 (14.0)	96 (14.7)
Indian (Indian subcontinent)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Mixed Ethnicity	4 (1.8)	3 (1.4)	2 (0.9)	9 (1.4)
Other	179 (82.1)	186 (83.8)	182 (85.0)	547 (83.6)
Age (yrs)				
n	218	222	214	654
Mean	53.5	53.4	53.9	53.6
SD	10.71	9.69	9.91	10.10
Age Group n (%)				
<65	186 (85.3)	192 (86.5)	185 (86.4)	563 (86.1)
>=65	32 (14.7)	30 (13.5)	29 (13.6)	91 (13.9)
>=75	3 (1.4)	2 (0.9)	4 (1.9)	9 (1.4)
Duration of Hypertension (yrs)				
n	205	216	204	625
Mean	6.7	7.6	6.9	7.1
SD	5.68	8.11	6.60	6.89
naïve patients* n (%)	13 (6.0)	6 (2.7)	10 (4.7)	29 (4.4)
Body Mass Index (kg/m^2)				
n	218	222	214	654
Mean	28.9	29.0	28.9	28.9
SD	4.40	4.56	4.39	4.44
Obesity n (%)				
BMI >=30 (kg/m^2)	74 (33.9)	84 (37.8)	79 (36.9)	237 (36.2)
BMI <30 (kg/m^2)	144 (66.1)	138 (62.2)	135 (63.1)	417 (63.8)

*Naïve patient: A patient who has not previously been treated for the indication of essential hypertension.

Primary Objective Result(s)

Change in mean 24-hour ambulatory diastolic blood pressure (MADBP) (mmHg) from baseline after a missed dose: ABPM completer population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	155	-6.98 (0.40)
Irbesartan	171	-7.32 (0.38)
Ramipril	152	-5.02 (0.40)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	0.34 (0.52)	(-0.68, 1.36)	0.5138
Aliskiren vs. Ramipril	-1.95 (0.54)	(-3.02, -0.89)	0.0004*

SE=Standard Error; LSM=Least Square Mean; CI=Confidence Interval
LS means were evaluated at the average baseline MADBP.
*Indicates statistical significance at the 0.05 level.

Secondary Objective Result(s)

Change in mean 24-hour ambulatory systolic blood pressure (MASBP) (mmHg) from baseline after a missed dose: ABPM completer population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	155	-9.25 (0.60)
Irbesartan	171	-9.48 (0.57)
Ramipril	152	-7.09 (0.60)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	0.23 (0.78)	(-1.30, 1.76)	0.7678
Aliskiren vs. Ramipril	-2.16 (0.81)	(-3.75, -0.57)	0.0080*

SE=Standard Error; LSM=Least Square Mean; CI=Confidence Interval
LS means were evaluated at the average baseline MASBP
*Indicates statistical significance at the 0.05 level.

Change in mean 24-hour ambulatory diastolic blood pressure (MADBP) (mmHg) from baseline after an active dose: ABPM completer population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	155	-7.70 (0.42)
Irbesartan	171	-9.46 (0.40)
Ramipril	152	-7.64 (0.42)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	1.76 (0.54)	(0.70, 2.82)	0.0012*
Aliskiren vs. Ramipril	-0.06 (0.56)	(-1.17, 1.05)	0.9160

Change in mean 24-hour ambulatory systolic blood pressure (MASBP) (mmHg) from baseline after an active dose: ABPM completer population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	155	-10.22 (0.63)
Irbesartan	171	-13.11 (0.60)
Ramipril	152	-11.08 (0.64)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	2.89 (0.82)	(1.27, 4.51)	0.0005*
Aliskiren vs. Ramipril	0.86 (0.86)	(-0.83, 2.55)	0.3186

Change in mean daytime ambulatory diastolic blood pressure (MADBP) (mmHg) from baseline after a missed dose: ABPM completer population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	155	-7.19 (0.64)
Irbesartan	171	-7.54 (0.61)
Ramipril	152	-5.53 (0.65)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	0.35 (0.84)	(-1.30, 2.00)	0.6783
Aliskiren vs. Ramipril	-1.66 (0.86)	(-3.36, 0.04)	0.0555

SE=Standard Error; LSM=Least Square Mean; CI=Confidence Interval
LS means were evaluated at the average baseline MADBP.
*Indicates statistical significance at the 0.05 level.

Change in mean daytime ambulatory systolic blood pressure (MASBP) (mmHg) from baseline after a missed dose: ABPM completer population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	155	-9.42 (0.94)
Irbesartan	171	-9.94 (0.90)
Ramipril	152	-7.43 (0.95)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	0.52 (1.24)	(-1.92, 2.95)	0.6773
Aliskiren vs. Ramipril	-1.99 (1.27)	(-4.49, 0.51)	0.1190

Change in mean nighttime ambulatory diastolic blood pressure (MADBP) (mmHg) from baseline after a missed dose: ABPM completer population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	155	-6.26 (0.72)
Irbesartan	171	-6.53 (0.69)
Ramipril	152	-4.36 (0.73)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	0.27 (0.95)	(-1.60, 2.14)	0.7770
Aliskiren vs. Ramipril	-1.91 (0.98)	(-3.83, 0.02)	0.0519

SE=Standard Error; LSM=Least Square Mean; CI=Confidence Interval
LS means were evaluated at the average baseline MADBP.
*Indicates statistical significance at the 0.05 level.

Change in mean nighttime ambulatory systolic blood pressure (MASBP) (mmHg) from baseline after a missed dose: ABPM completer population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	155	-9.01 (1.12)
Irbesartan	171	-8.55 (1.08)
Ramipril	152	-6.31 (1.14)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	-0.45 (1.48)	(-3.36, 2.45)	0.7587
Aliskiren vs. Ramipril	-2.69 (1.52)	(-5.68, 0.29)	0.0765

Between treatment analysis of diastolic smoothness index after a missed dose: ABPM completer population

Treatment Group	N	LS Mean (SE)
Aliskiren	155	-0.68 (0.06)
Irbesartan	171	-0.72 (0.06)
Ramipril	152	-0.50 (0.06)

Pairwise Comparison	LS Mean difference (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	0.04 (0.08)	(-0.11, 0.20)	0.5808
Aliskiren vs. Ramipril	-0.18 (0.08)	(-0.34, -0.02)	0.0258*

Between treatment analysis of systolic smoothness index after a missed dose: ABPM completer population

Treatment Group	N	LS Mean (SE)
Aliskiren	155	-0.77 (0.08)
Irbesartan	171	-0.84 (0.08)
Ramipril	152	-0.58 (0.08)

Pairwise Comparison	LS Mean difference (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	0.07 (0.10)	(-0.14, 0.27)	0.5179
Aliskiren vs. Ramipril	-0.19 (0.11)	(-0.40, 0.02)	0.0707

Statistics summary of diastolic trough to peak ratio after a missed dose: ABPM completer population

	Aliskiren	Irbesartan	Ramipril
Trough to peak ratio	0.86	0.87	0.87

Statistics summary of systolic trough to peak ratio after a missed dose: ABPM completer population

	Aliskiren	Irbesartan	Ramipril
Trough to peak ratio	0.80	0.90	0.86

Between treatment analysis for change from baseline in ambulatory diastolic morning surge, after a missed dose: ABPM completer population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	155	-6.83 (0.80)
Irbesartan	171	-8.07 (0.77)
Ramipril	152	-5.18 (0.81)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	1.25 (1.05)	(-0.81, 3.30)	0.2328
Aliskiren vs. Ramipril	-1.65 (1.09)	(-3.79, 0.49)	0.1314

Between treatment analysis for change from baseline in ambulatory systolic morning surge, after a missed dose: ABPM completer population

Treatment Group	N	LSM change from baseline (SE)
Aliskiren	155	-8.86 (1.15)
Irbesartan	171	-10.03 (1.11)
Ramipril	152	-6.93 (1.17)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-value*
Aliskiren vs. Irbesartan	1.17 (1.50)	(-1.79, 4.13)	0.4374
Aliskiren vs. Ramipril	-1.93 (1.57)	(-5.01, 1.14)	0.2176

Safety Results

Number (%) of patients with (overall) AEs in double-blind period, by treatment group and system organ class (Safety population)

Primary system organ class	Aliskiren N=218 n (%)	Irbesartan N=222 n (%)	Ramipril N=214 n (%)	Total N=654 n (%)
-Any primary system organ class	77 (35.3)	73 (32.9)	77 (36.0)	227 (34.7)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Cardiac disorders	6 (2.8)	10 (4.5)	9 (4.2)	25(3.8)
Ear and labyrinth disorders	2 (0.9)	2 (0.9)	0 (0.0)	4 (0.6)
Endocrine disorders	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)
Eye disorders	1 (0.5)	0 (0.0)	3 (1.4)	4 (0.6)
Gastrointestinal disorders	12 (5.5)	14 (6.3)	15 (7.0)	41 (6.3)
General disorders and administration site conditions	9 (4.1)	10 (4.5)	10 (4.7)	29 (4.4)
Hepatobiliary disorders	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)

Immune system disorders	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Infections and infestations	26 (11.9)	23 (10.4)	28 (13.1)	77 (11.8)
Injury, poisoning and procedural complications	3 (1.4)	4 (1.8)	4 (1.9)	11 (1.7)
Investigations	4 (1.8)	2 (0.9)	1 (0.5)	7 (1.1)
Metabolism and nutrition disorders	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.3)
Musculoskeletal and connective tissue disorders	16 (7.3)	5 (2.3)	7(3.3)	28 (4.3)
Nervous system disorders	17 (7.8)	21 (9.5)	22 (10.3)	60 (9.2)
Psychiatric disorders	4 (1.8)	3 (1.4)	1 (0.5)	8 (1.2)
Renal and urinary disorders	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.3)
Reproductive system and breast disorders	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	7 (3.2)	9 (4.1)	16 (7.5)	32 (4.9)
Skin and subcutaneous tissue disorders	5 (2.3)	3 (1.4)	2 (0.9)	10 (1.5)
Vascular disorders	1 (0.5)	2 (0.9)	1 (0.5)	4 (0.6)

Number (%) of patients with common adverse events (>= 2.0%) in double-blind period in any treatment group, by the order of the frequency (Safety population)

Preferred term	Aliskiren N=218 n (%)	Irbesartan N=222 n (%)	Ramipril N=214 n (%)	Total N=654 n (%)
Headache	12 (5.5)	13 (5.9)	15 (7.0)	40 (6.1)
Influenza	8 (3.7)	6 (2.7)	5 (2.3)	19 (2.9)
Cough	1 (0.5)	4 (1.8)	13 (6.1)	18 (2.8)
Dizziness	4 (1.8)	6 (2.7)	8 (3.7)	18 (2.8)
Nasopharyngitis	5 (2.3)	4 (1.8)	4 (1.9)	13 (2.0)
Asthenia	2 (0.9)	5 (2.3)	4 (1.9)	11 (1.7)
Diarrhoea	3 (1.4)	1 (0.5)	6 (2.8)	10 (1.5)
Dyspepsia	1 (0.5)	5 (2.3)	3 (1.4)	9 (1.4)

Serious Adverse Events and Deaths

Number (%) of patients with deaths, serious adverse events and adverse events and abnormal laboratory values leading to permanent discontinuation, during the double-blind treatment period (Safety population)

	Aliskiren N=218		Irbesartan N=222		Ramipril N=214		Total N=654	
	n	(%)	n	(%)	n	(%)	n	(%)
Deaths	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
SAEs	1	(0.5)	4	(1.8)	1	(0.5)	6	(0.9)
AE discontinuations	2	(0.9)	3	(1.4)	4	(1.9)	9	(1.4)
Drug related AE discontinuations	0	(0.0)	1	(0.5)	3	(1.4)	4	(0.6)

There were no deaths during the study in any treatment group. A similar, low proportion of patients in all three treatment groups had SAEs and discontinuations due to AEs.

None of the SAEs occurred in more than one patient. Six patients had one SAE each. None of the SAEs were considered possibly related to study drug by the investigators.

The study drug was permanently discontinued for three of the SAE cases. One patient had acute asthmatic crisis; another patient had acute alcoholic hepatitis; and the final patient had angina pectoris.

Other Relevant Findings

None

Date of Clinical Trial Report

5 November 2007

Date Inclusion on Novartis Clinical Trial Results Database

29 May 2008

Date of Latest Update

28 October 2009