

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Two of the submitted controlled studies were reviewed at the request of the medical reviewer. Results in the two reviewed studies support efficacy of the aliskiren/amlodipine combination in patients with essential hypertension.

Study SPA100A2305 was a pivotal double-blind, randomized, multifactorial study to evaluate efficacy and safety of four doses of aliskiren/amlodipine combination. Relative to the primary efficacy endpoint, reduction in msDBP, all combination doses showed statistically significantly greater msDBP reduction than the respective monotherapies ($p \leq 0.004$). Relative to the secondary endpoint, msSBP, most of the pair-wise comparisons of the combination doses to their respective monotherapies were statistically significant ($p < 0.001$). However, two combination doses compared to amlodipine 10 mg showed only numerically greater reductions in msSBP: aliskiren/amlodipine 150/10 mg ($p = 0.056$) and aliskiren/amlodipine 300/10 mg ($p = 0.143$). Similar results were shown in the per protocol set.

Pivotal Study SPA100A2304 examined mostly comparisons of the two combination doses that failed in Study SPA100A2305. Study SPA100A2304 showed that the combination aliskiren/amlodipine at doses 300/10 mg and 150/10 mg was statistically significantly better than amlodipine 10 mg relative to the reduction in both msDBP ($p < 0.001$ and $p = 0.0077$, respectively) and msSBP ($p < 0.001$ and $p = 0.0033$, respectively). These results were supported by the analyses in the per protocol set ($p < 0.001$ and $p \leq 0.0042$, respectively). The SBP response rate was statistically significantly greater in aliskiren/amlodipine 300/10 mg group ($p < 0.0001$) and aliskiren/amlodipine 150/10mg group ($p < 0.0048$) compared to amlodipine 10 mg group.

Safety analyses showed no deaths or unexpected adverse events. Safety of the aliskiren/amlodipine combination is a matter of clinical judgment of the medical division.

1.2 Brief Overview of Clinical Studies

Two of the controlled studies, SPA100A2304 and SPA100A2305, are reviewed here at the request of the medical reviewer. For brevity these studies will be called Study 04 and Study 05.

Statistical Issues and Findings

There are no statistical issues in this NDA. This reviewer agrees with the statistical methods used by the sponsor. All secondary endpoints are blood pressure endpoints intended to support the primary efficacy claim. Therefore, no adjustment for multiple doses and multiple secondary endpoints is required.

The primary efficacy results in Studies 04 and 05 were verified and confirmed by this reviewer.

2. INTRODUCTION

2.1 Overview

This is a statistical review of two pivotal studies, SPA100A2304 and SPA100A2305, as was requested by the medical reviewer.

2.2 Data Sources and Data Integrity

The sponsor has submitted an electronic NDA. Electronic submission and SAS datasets can be found at the following link: <\\CDSESUB1\EVSPROD\NDA22545\0000>.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy of Study 04

Title: A randomized, 8-week, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren / amlodipine (150/10 mg and 300/10 mg) in comparison with amlodipine 10 mg in patients with essential hypertension not adequately responsive to amlodipine 10 mg monotherapy.

Design of Study 04:

This was a randomized, double-blind, parallel group study consisted of a 7-day washout period, a 4-week single-blind run-in period in which patients received amlodipine 10 mg monotherapy, and an 8-week double-blind study drug treatment period. In the double-blind period, patients were randomly assigned to one of the following 3 treatment arms in a ratio of 1:1:1: aliskiren/amlodipine 150/10 mg, aliskiren/amlodipine 300/10 mg, or amlodipine 10mg.

Number of patients: A total of 1358 patients entered the single-blind run in period and 847 patients were randomized for the double-blind period.

Efficacy:

The primary efficacy variable was the change from baseline of the double-blind period to endpoint in mean sitting diastolic blood pressure (msDBP).

Secondary efficacy variables were: mean sitting systolic blood pressure (msSBP), the proportions of patients achieving a blood pressure control target of msSBP/msDBP < 140/90 mmHg, and the proportions of patients achieving a diastolic blood pressure response (msDBP < 90 mmHg or a ≥ 10 mmHg reduction from baseline).

Statistical methods

The primary efficacy population FAS (Full Analysis Set) consisted of all randomized patients who took study drug. The Per-Protocol Set consisted of all FAS patients who completed the trial without any major deviations from the protocol.

Primary efficacy analysis

The primary efficacy analysis was a comparison of change in msDBP of aliskiren/amlodipine (150/10 mg) or aliskiren/ amlodipine (300/10 mg) compared to amlodipine 10 mg alone.

The primary efficacy analysis model was a two-way analysis of ANCOVA model with treatment and region as two factors and the baseline as a covariate.

Several centers participating in this protocol were combined into regions so that an adequate number of patients were available for analyses. The participating countries in the study were Argentina, Germany, Norway, Poland, Slovakia, Sweden and Turkey. Each of these countries was considered as individual regions except for Germany which were split into Northern Germany and Southern Germany. Argentina and Sweden were pooled in order to keep a similar number of patients in the regions. This study did not have US centers.

A hierarchical testing procedure was used to assess the effects of aliskiren 300 mg and aliskiren 150 mg combinations with amlodipine 10 mg versus amlodipine 10 mg monotherapy. First aliskiren/amlodipine (300/10 mg) was compared to amlodipine 10 mg. If aliskiren/amlodipine (300/10 mg) was statistically superior to amlodipine 10 mg at the 5% significance level, then the effectiveness of aliskiren/amlodipine (300/10 mg) was established and further assessment for efficacy of aliskiren/amlodipine (150/10 mg) compared to amlodipine 10 mg were made. Since this was a closed procedure, no multiple comparison adjustments were made and significance level was 5%.

Secondary efficacy analyses

The same analyses as for msDBP were preformed for the msSBP.

The proportion of patients achieving blood pressure control and target response during the double-blind period was compared at endpoint using a logistic regression model with treatment and region as factors and baseline msDBP value as a covariate. Pair-wise treatment comparisons were made at a two-sided significance level of 0.05.

Interim analyses: No interim analyses were planned or performed.

Results of Study 04

Study patients

A total of 1358 patients entered the 4-week single-blind run-in period, and 843 completed this period. Treatment groups were balanced with regard to the number of patients randomized to the double-blind period of the study (Table 1). Overall, 847 patients were randomized, of whom 782 patients (92.3%) completed the study and 61 patients (7.2%) discontinued. Table 1 shows that the percentage of discontinuations was higher in the amlodipine 10 mg monotherapy group (9.2%) compared to the combination groups of aliskiren/amlodipine 300/10 mg (6.5%) and aliskiren/amlodipine 150/10 mg (6.0%). The major reason for discontinuation was AEs in all treatment groups.

Table 1. Patient disposition in Study 04 by treatment group

Disposition	Ali/Aml 300/10 mg n (%)	Ali/Aml 150/10 mg n (%)	Aml 10 mg n (%)	Total n(%)
Single-blind set				1358
Completed				843
Discontinued				515
Randomized set	279	285 ¹	283 ¹	847 ¹
Completed	261 (93.6)	266 (93.3)	255 (90.1)	782 (92.3)
Discontinued	18 (6.5)	17 (6.0)	26 (9.2)	61 (7.2)
Reason for discontinuation				
Adverse Event(s)	9 (3.2)	10 (3.5)	14 (5.0)	33 (3.9)
Abnormal laboratory value(s)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.2)
Unsatisfactory therapeutic effect	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Patient's condition no longer requires study drug	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Patient withdrew consent	3 (1.1)	1 (0.4)	6 (2.1)	10 (1.2)
Lost to follow-up	0 (0.0)	2 (0.7)	1 (0.4)	3 (0.4)
Administrative problems	1 (0.4)	2 (0.7)	0 (0.0)	3 (0.4)
Protocol deviation	3 (1.1)	0 (0.0)	2 (0.7)	5 (0.6)

Percentage (%) was calculated using the randomized set as the denominator.

¹ Four patients were randomized in error and were assigned a randomization number (2 in aliskiren/amlodipine 150/10 mg group and 2 in amlodipine 10 mg group). All these patients were discontinued from the single-blind period without taking any double-blind study medication. Therefore, these patients were not counted as discontinued from the double-blind period.

Data sets analyzed

The number of patients included in each analysis population for the double-blind period is presented in Table 2. This table shows similar proportions of patients in each treatment group for each population. All randomized patients in aliskiren/amlodipine 300/10 mg group (n= 279) received the study medication and were included in the FAS. In addition, two patients each in aliskiren/amlodipine 150/10 mg group (n=285) and amlodipine 10 mg group (n=283) did not take any study medication and thus were not included in the safety set and the FAS. In all, 86.3% of the patients were included in the per protocol set.

Table 2. Analysis populations by treatment group in Study 04

Population	Ali/Aml 300/10 mg n (%)	Ali/Aml 150/10 mg n (%)	Aml 10mg n (%)	Total n (%)
Randomized (RAN)	279 (100.0)	285 (100.0)	283 (100.0)	847 (100.0)
Safety (SAF)	279 (100.0)	283 (99.3)	281 (99.3)	843 (99.5)
Full Analysis (FAS)	279 (100.0)	283 (99.3)	281 (99.3)	843 (99.5)
Per-Protocol (PPS)	241 (86.4)	252 (88.4)	238 (84.1)	731 (86.3)

Percentages in SAF, FAS and PPS were computed using the randomized number in that treatment group as the denominator.

Demographic and other baseline characteristics

The treatment groups were comparable with respect to the demographic characteristics. The study population was predominantly Caucasian (99.4%). There were more male patients (61.3%) as compared to the female patients (38.7%). The overall mean age was 54.6 years. Overall, 18.1% of the total patients were ≥ 65 years old.

Primary efficacy results

Change from baseline in msDBP

The combination of aliskiren/amlodipine 300/10 mg showed a statistically significantly greater reduction in msDBP at endpoint compared to amlodipine 10mg alone, with a LSM difference of 3.76 mmHg ($p < 0.0001$). The combination of aliskiren/amlodipine 150/10 mg produced a statistically significantly greater reduction in msDBP compared to amlodipine 10mg monotherapy with a LSM difference of 1.72 mmHg ($p = 0.0077$) at the endpoint (Table 3). Similar results were observed in the per protocol set ($p < 0.0001$ and $p = 0.0037$, respectively).

Table 3. Primary efficacy analysis for Study 04[§].

Change from baseline in msDBP to endpoint (FAS)

Treatment Group	N	LSM change from baseline (SE)		
Aliskiren/Amlodipine 300/10 mg	277	-10.99 (0.462)		
Aliskiren/Amlodipine 150/10 mg	281	-8.95 (0.460)		
Amlodipine 10mg	279	-7.23 (0.459)		
Pair wise Comparison		LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
Aliskiren/amlodipine 300/10 mg vs. Amlodipine 10mg		-3.76 (0.644)	(-5.03, -2.50)	<0.0001*
Aliskiren/amlodipine 150/10 mg vs. Amlodipine 10mg		-1.72 (0.642)	(-2.98, -0.46)	0.0077*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval

Least square means, confidence intervals and p-values were from an ANCOVA model containing treatment, region and baseline.

* Indicates statistical significance at 0.05 level

[§] Source: Sponsor's Table 11-4.

The results were verified by the statistical reviewer.

Secondary efficacy analyses

Change from baseline in msSBP

The combination of aliskiren/amlodipine 300/10 mg showed a statistically significantly greater reduction in msSBP at endpoint compared to amlodipine 10mg alone, with a LSM difference of 6.22 mmHg ($p < 0.0001$) (Table 4). The combination of aliskiren/amlodipine 150/10 mg produced a statistically significantly greater reduction in msDBP with a LSM difference of 2.81 mmHg at the endpoint compared to amlodipine 10mg monotherapy ($p = 0.0033$). Similar results were observed in the per protocol set ($p < 0.0001$ and $p = 0.0042$, respectively).

Table 4. Change from baseline in msSBP in Study 04[§].

Treatment Group	N	LSM change from baseline (SE)		
Aliskiren/Amlodipine 300/10 mg	277	-14.42 (0.684)		
Aliskiren/Amlodipine 150/10 mg	281	-11.01 (0.681)		
Amlodipine 10mg	279	-8.20 (0.680)		
Pair wise Comparison		LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
Aliskiren/amlodipine 300/10 mg vs. Amlodipine 10 mg		-6.22 (0.953)	(-8.09, -4.35)	<0.0001*
Aliskiren/amlodipine 150/10 mg vs. Amlodipine 10 mg		-2.81 (0.953)	(-4.69, -0.94)	0.0033*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval
Least square means, confidence intervals and p-values were from an ANCOVA model containing treatment, region and baseline.

* Indicates statistical significance at 0.05 level

[§] Source: Sponsor's Table 11-5.

The results were verified by the statistical reviewer.

Blood pressure response

DBP response

A statistically significantly greater number of patients reached DBP response (msDBP <90 mmHg, or a ≥ 10 mmHg reduction from baseline) at endpoint in aliskiren/amlodipine 300/10 mg group than amlodipine 10 mg group ($p < 0.0001$) (Table 5). Numerically more patients in aliskiren/amlodipine 150/10 mg group reached DBP response as compared to amlodipine 10 mg monotherapy but the difference was not statistically significant ($p = 0.096$).

Table 5. Between treatment comparisons in Study 04 for DBP response (FAS)

Pairwise Comparison A vs. B	Treatment A n/N (%)	Treatment B n/N (%)	p-value
Aliskiren/amlodipine 300/10 mg vs. Amlodipine 10 mg	226/277 (81.6)	177/279 (63.4)	<.0001*
Aliskiren/amlodipine 150/10 mg vs. Amlodipine 10 mg	195/281 (69.4)	177/279 (63.4)	0.0965

Diastolic blood pressure response is defined as having a msDBP < 90 mmHg or ≥ 10 mmHg reduction from baseline.

The percentage of patients with diastolic blood pressure response was analyzed using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.

Baseline is the Day 1 value.

SBP

A statistically significantly greater number of patients reached the SBP response (msSBP <140 mmHg or a ≥ 20 mmHg reduction from baseline) in aliskiren/amlodipine 300/10 mg group (P<0.0001) and aliskiren/amlodipine 150/10mg group (P<0.0048) compared to amlodipine 10 mg group (Table 6).

Table 6. Between treatment comparisons in Study 04 for SBP response at endpoint (FAS)

Pairwise Comparison (A vs. B)	Treatment A		Treatment B		p-value
	n/N	(%)	n/N	(%)	
Aliskiren/amlodipine 300/10 mg vs. Amlodipine 10 mg	195/277	(70.4)	136/279	(48.8)	<.0001*
Aliskiren/amlodipine 150/10 mg vs. Amlodipine 10 mg	159/281	(56.6)	136/279	(48.8)	0.0048*

Systolic blood pressure response is defined as a mean sitting systolic blood pressure <140 mmHg or a ≥ 20 mmHg reduction from baseline (Day 1 value).

The percentage of patients with systolic blood pressure response was analyzed using a logistic regression model with treatment and region as factors and baseline msSBP as a covariate.

* Indicates statistical significance at 0.05 level.

BP control

Table 7 shows the results for the blood pressure control rate at endpoint. For each patient, blood pressure control was defined as msDBP < 90 mmHg and msSBP < 140 mmHg. The aliskiren/amlodipine 300/10 mg combination group showed a statistically significantly greater blood pressure control rate compared to amlodipine 10 mg monotherapy group (p<0.0001). Aliskiren/amlodipine 150/10 mg showed numerically greater blood pressure control rate in comparison to amlodipine 10 mg monotherapy group but the difference was not statistically significant (P=0.32).

Table 7. Between treatment comparisons for BP control at endpoint in Study 04 (FAS)

Pairwise Comparison A vs. B	Treatment A		Treatment B		p-value
	n/N	(%)	n/N	(%)	
Aliskiren/amlodipine 300/10 mg vs. Amlodipine 10mg	163/277	(58.8)	107/279	(38.4)	<0.0001*
Aliskiren/amlodipine 150/10 mg vs. Amlodipine 10mg	117/281	(41.6)	107/279	(38.4)	0.3248

Blood pressure control is defined as having a mean sitting diastolic blood pressure <90 mmHg and a mean sitting systolic blood pressure <140 mmHg.

The percentage of patients with blood pressure control was analyzed using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate. Baseline is the Day 1 value.

* Indicates statistical significance at 0.05 level

Efficacy Conclusions for Study 04

Study 04 showed that the combination aliskiren/amlodipine at doses 300/10 mg and 150/10 mg was statistically significantly better than amlodipine 10 mg in reduction of both msDBP (p<0.001 and p=0.0077, respectively) and msSBP (p<0.001 and p=0.0033, respectively). These

results were supported by the analyses in the per protocol set ($p < 0.001$ and $p < 0.0037$, respectively).

3.2 Evaluation of Efficacy in Study 05

Study title: An 8-week double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with amlodipine in patients with essential hypertension.

Design: This was a double-blind, multicenter, randomized, placebo-controlled, multifactorial, parallel-group study of aliskiren and amlodipine given alone and in combination in patients with essential hypertension ($\text{msDBP} \geq 95$ mmHg and < 110 mmHg). The study had three periods: washout, single-blind placebo run-in, and 8-week double-blind treatment. Patients were randomized to one of the following 9 treatment arms in a ratio of 1:1:1:1:1:1:1:1:1:

- 4 fixed combination arms: aliskiren/amlodipine 150mg/5mg, aliskiren/amlodipine 150/10mg, aliskiren/amlodipine 300/5mg, or aliskiren/amlodipine 300/10mg
- 4 monotherapy arms: aliskiren 150mg, aliskiren 300mg, amlodipine 5mg, or amlodipine 10mg
- Placebo.

Number of patients: A total of 1688 patients were randomized into the double-blind treatment period. For the ABPM sub-study, 819 patients were analyzed.

Efficacy of Study 05

The primary efficacy variable was change from baseline of the double-blind period in msDBP at endpoint.

Secondary efficacy variables included:

- change from baseline (Visit 3) in mean sitting systolic blood pressure (msSBP)
- percent of patients achieving the diastolic blood pressure response ($\text{msDBP} < 90$ mmHg or at least 10 mmHg reduction from baseline in msDBP)
 - percent of patients achieving the systolic blood pressure response ($\text{msSBP} < 140$ mmHg or at least 20 mmHg reduction from baseline in msSBP)
 - percent of patients achieving the blood pressure control ($\text{msDBP} < 90$ mmHg and $\text{msSBP} < 140$ mmHg)
- change from baseline in 24-hour ABPM (diastolic and systolic)
- change from baseline in daytime and nighttime ABPM (diastolic and systolic).

Statistical methods in Study 05:

All centers participating in this study were combined into 8 regions according to the geographical locations, so that adequate numbers of patients for each center were available. The 8 regions included 1 region for Canada and United States, 1 region for Panama, Mexico, and Columbia, 1 region for Argentina and Peru, 1 region for Romania and Russia, 1 region for Finland, Denmark, and Sweden, 1 region for Greece, Italy, and Spain, 1 region for Australia and Taiwan, and 1 region for South Africa.

The following **population sets** were used for the analyses:

- Randomized set (RAN) – All patients who received a randomization number, regardless of receiving trial medication.
- Full analysis set (FAS) – All patients who were randomized and received the study medication.
- Per-protocol set (PPS) – All FAS patients who completed the study without any major protocol deviations that impact on efficacy assessment. The major protocol deviations were pre-specified prior to unblinding.

Data sets analyzed

The primary analysis time point was the Endpoint. For each patient, the last post-baseline measurement of a variable during the double-blind treatment period was carried forward to Week 8 as the endpoint measurement. All efficacy variables were analyzed for the FAS. In addition, the primary and some secondary efficacy variables were analyzed at endpoint for the Per-protocol set (PPS) to examine the effect due to dropouts and/or major protocol deviations.

Primary efficacy analysis

Efficacy of the combination treatment relative to change in msDBP at Endpoint

To assess whether both monotherapy treatments (aliskiren and amlodipine) contribute to the overall effect in blood pressure reduction of the combination treatment, the primary variable at endpoint was analyzed by Hung's AVE test (Hung, Evaluation of a combination drug, Statist. Med. 2000; 19:2079-2087). If the AVE test was statistically significant, it was to be concluded that the aliskiren/amlodipine combination treatment was superior in reducing the msDBP from baseline to endpoint compared to aliskiren and amlodipine monotherapies.

If the AVE test was positive, the following additional analyses were to be performed to quantify the add-on effects for a given aliskiren/amlodipine combination dose due to the respective monotherapy doses. The primary efficacy variable at endpoint was analyzed using a two-way analysis of covariance model with treatment and region as two factors, and the baseline as a covariate. The regions were pre-specified prior to unblinding treatment codes for analyses. All pair-wise treatment comparisons were made based on this model.

For a given combination dose, the null hypotheses were that the combination dose was at most as good as one of its respective monotherapy doses versus that the combination was better than each monotherapy. The statistical test for each of the pair-wise comparisons was to be made at a two-sided significance level of 0.05.

Supportive analyses

The primary efficacy variable was also analyzed using the primary model at Week 8 for FAS and at endpoint for the Per-protocol set.

Secondary analyses

For **msSBP**, the same analyses as for msDBP were performed.

Blood pressure response analysis

The proportion of patients in each treatment achieving a response in mean sitting diastolic and systolic blood pressure during the double-blind period was compared using a logistic regression model with treatment and region as the factors and baseline msDBP or msSBP value as a covariate at endpoint for FAS. Pair-wise treatment comparisons were made at a two-sided significance level of 0.05. The diastolic blood pressure response was defined as a mean sitting diastolic blood pressure < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline. The systolic blood pressure response was defined as a mean sitting systolic blood pressure < 140 mmHg or a ≥ 20 mmHg decrease compared to baseline.

Blood pressure control analysis

A patient with control in blood pressure was defined as having a mean sitting diastolic blood pressure < 90 mmHg and a mean sitting systolic blood pressure < 140 mmHg. The proportion of patients in each treatment with control in blood pressure during the double-blind treatment period was compared using a logistic regression model with treatment and region as the factors and baseline as a covariate at endpoint for the primary efficacy population. Pair-wise treatment comparisons were made at a two-sided significance level of 0.05.

Mean Ambulatory Diastolic Blood Pressure (MADBP) Over 24 Hours

The hourly mean ambulatory diastolic blood pressure post dosing was calculated for each post-dosing hour over 24 hours by taking the average of the readings taken in the corresponding post-dosing hour. A two-way repeated-measures analysis-of-covariance model with treatment, region, and post-dosing hours as factors and baseline mean 24-hour ambulatory DBP as a covariate was performed.

Interim analyses No interim analyses were planned or performed.

Disposition of patients

Double-blind treatment period

A total of 1688 patients were randomized into the double-blind treatment period. The majority of the patients in all treatment groups completed the study (91.2%). Patient disposition was generally similar in all groups and is summarized in Table 8. Slightly more patients in the placebo group discontinued from the study, primarily due to lack of efficacy. Discontinuation due to adverse events was slightly more frequent in the amlodipine 10 mg group (3.9%) than other groups (0.5% - 2.2%).

Table 8. Patient disposition in double-blind period of Study 05

Disposition	Placebo N (%)	Ali 150 mg N (%)	Ali 300 mg N (%)	Aml 5 mg N (%)	Aml 10 mg N (%)	Ali/Aml 150/5 mg N (%)	Ali/Aml 150/10 mg N (%)	Ali/Aml 300/5 mg N (%)	Ali/Aml 300/10 mg N (%)	Total N (%)
Enrolled										2694
Randomized	198 (100.0)	195 (100.0)	203 (100.0)	185 (100.0)	181 (100.0)	181 (100.0)	183 (100.0)	178 (100.0)	184 (100.0)	1688 (100.0)
Completed	168 (84.8)	175 (89.7)	184 (90.6)	173 (93.5)	162 (89.5)	169 (93.4)	170 (92.9)	168 (94.4)	170 (92.4)	1539 (91.2)
Discontinued	30 (15.2)	19 (9.7)	19 (9.4)	12 (6.5)	19 (10.5)	12 (6.6)	11 (6.0)	10 (5.6)	14 (7.6)	146 (8.6)
Reason for discontinuation (double blind)										
Adverse events	3 (1.5)	3 (1.5)	1 (0.5)	2 (1.1)	7 (3.9)	3 (1.7)	4 (2.2)	1 (0.6)	4 (2.2)	28 (1.7)
Abnormal laboratory values	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.1)
Abnormal test procedure results	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Unsatisfactory therapeutic effect	17 (8.6)	8 (4.1)	8 (3.9)	4 (2.2)	2 (1.1)	2 (1.1)	1 (0.5)	1 (0.6)	2 (1.1)	45 (2.7)
Patient's condition no longer requires study drug	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Patient withdrew consent	4 (2.0)	2 (1.0)	4 (2.0)	3 (1.6)	4 (2.2)	4 (2.2)	3 (1.6)	2 (1.1)	4 (2.2)	30 (1.8)
Lost to follow-up	0 (0.0)	2 (1.0)	4 (2.0)	1 (0.5)	2 (1.1)	2 (1.1)	0 (0.0)	3 (1.7)	1 (0.5)	15 (0.9)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Protocol deviation	5 (2.5)	3 (1.5)	1 (0.5)	2 (1.1)	3 (1.7)	1 (0.6)	2 (1.1)	2 (1.1)	3 (1.6)	22 (1.3)

Efficacy Results in Study 05**Data sets analyzed**

As shown in Table 9, all randomized patients with the exception of 3 patients (1 patient, aliskiren 150 mg group; 2 patients, aliskiren/amlodipine 150/10mg group) received the study medication and were included in the FAS. The majority of patients were included in the Per-Protocol Set (79.9%).

Table 9. Analysis sets for each treatment group (randomized set of Study 05)

Population	Placebo N (%)	Ali 150 mg N (%)	Ali 300 mg N (%)	Aml 5 mg N (%)	Aml 10 mg N (%)	Ali/Aml 150/5 mg N (%)	Ali/Aml 150/10 mg N (%)	Ali/Aml 300/5 mg N (%)	Ali/Aml 300/10 mg N (%)	Total N (%)
Randomized set (RAN)	198 (100)	195 (100)	203 (100)	185 (100)	181 (100)	181 (100)	183 (100)	178 (100)	184 (100)	1688 (100)
Full analysis set (FAS)	198 (100)	194 (99.5)	203 (100)	185 (100)	181 (100)	181 (100)	181 (98.9)	178 (100)	184 (100)	1685 (99.8)
Safety set (SAF)	198 (100)	194 (99.5)	203 (100)	185 (100)	181 (100)	181 (100)	181 (98.9)	178 (100)	184 (100)	1685 (99.8)
Per-protocol set (PPS)	154 (77.8)	156 (80.0)	165 (81.3)	149 (80.5)	142 (78.5)	146 (80.7)	144 (78.7)	147 (82.6)	145 (78.8)	1348 (79.9)

Major protocol deviations are those that lead to exclusion from the Per-protocol set.

Demographic and other baseline characteristics

The treatment groups were generally comparable with respect to the demographics and baseline characteristics. Approximately 17% (14 % to 22 %) of the patients were elderly (≥ 65 years of age). The percentage of male patients across treatment arms ranged from 43.8% to 61.0%. Caucasian patients accounted for the majority (approximately 62%) of the study population followed by Black patients (approximately 20%). The majority (83%) of the Black population were enrolled in sites in South Africa. The number of patients of other races was small.

Analysis of efficacy in Study 05

Primary efficacy results

Change from baseline in msDBP

The primary efficacy variable was the change from Baseline in msDBP. The primary efficacy analysis, Hung's AVE test at endpoint, was statistically significant with $p < 0.001$ indicating that there is at least one aliskiren/amlodipine dose with statistically significantly greater msDBP reduction than both respective monotherapy groups. Table 10 shows that in the pair-wise comparisons between a combination group and its respective monotherapy group, all aliskiren/amlodipine dose groups showed statistically significantly greater msDBP reduction than the respective monotherapies ($p \leq 0.004$).

**Table 10. Pair-wise comparisons for the primary efficacy analysis in FAS of Study 05[§].
Change from baseline in msDBP at endpoint.**

Treatment Group	N	LSM change from baseline (mmHg) (SE)	
Placebo	198	-5.35 (0.62)	
Ali 150 mg	193	-7.99 (0.63)	
Ali 300 mg	201	-10.19 (0.62)	
Aml 5 mg	184	-11.0 (0.65)	
Aml 10 mg	179	-13.82 (0.66)	
Ali/Aml 150/5 mg	179	-13.98 (0.66)	
Ali/Aml 150/10 mg	179	-16.16 (0.66)	
Ali/Aml 300/5 mg	175	-14.99 (0.66)	
Ali/Aml 300/10 mg	183	-16.45 (0.65)	

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
Ali 150 mg vs. Placebo	-2.64 (0.88)	(-4.37, -0.91)	0.003*
Ali 300 mg vs. Placebo	-4.85 (0.87)	(-6.55, -3.14)	<.001*
Aml 5 mg vs. Placebo	-5.66 (0.89)	(-7.40, -3.91)	<.001*
Aml 10 mg vs. Placebo	-8.47 (0.90)	(-10.24, -6.71)	<.001*
Ali/Aml 150/5 mg vs. Ali 150 mg	-6.00 (0.90)	(-7.77, -4.22)	<.001*
Ali/Aml 150/5 mg vs. Aml 5 mg	-2.98 (0.91)	(-4.77, -1.19)	0.001*
Ali/Aml 150/5 mg vs. Placebo	-8.63 (0.90)	(-10.39, -6.87)	<.001*
Ali/Aml 150/10 mg vs. Ali 150 mg	-8.17 (0.90)	(-9.94, -6.40)	<.001*
Ali/Aml 150/10 mg vs. Aml 10 mg	-2.33 (0.92)	(-4.14, -0.53)	0.011*
Ali/Aml 150/10 mg vs. Placebo	-10.81 (0.90)	(-12.57, -9.05)	<.001*
Ali/Aml 300/5 mg vs. Ali 300 mg	-4.79 (0.90)	(-6.56, -3.03)	<.001*
Ali/Aml 300/5 mg vs. Aml 5 mg	-3.98 (0.92)	(-5.78, -2.18)	<.001*
Ali/Aml 300/5 mg vs. Placebo	-9.64 (0.90)	(-11.41, -7.87)	<.001*
Ali/Aml 300/10 mg vs. Ali 300 mg	-6.26 (0.89)	(-8.00, -4.51)	<.001*
Ali/Aml 300/10 mg vs. Aml 10 mg	-2.63 (0.92)	(-4.42, -0.83)	0.004*
Ali/Aml 300/10 mg vs. Placebo	-11.10 (0.89)	(-12.85, -9.35)	<.001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval

Only patients with both baseline and post-baseline values are included.

Least square means, confidence intervals and p-values were from an ANCOVA model containing treatment, region and baseline.

P-values and treatment comparisons were evaluated at the average baseline level.

* Indicates statistical significance at 0.05 level

[§] Source: Sponsor's Table 11-4. The results were verified by the statistical reviewer.

Secondary efficacy results**Change from baseline in msSBP**

One of the key secondary efficacy variables was the change from baseline in msSBP. The Hung's AVE test at endpoint was statistically significant ($p < 0.001$) indicating that there is at least one aliskiren/amlodipine dose with statistically significantly greater msSBP reduction than both respective monotherapy groups.

Table 11 shows that most of the aliskiren/amlodipine doses demonstrated statistically significantly ($p < 0.001$) greater reduction in msSBP than their respective monotherapies. However, two combination doses produced only numerically greater reduction in msSBP compared to amlodipine 10mg: aliskiren/amlodipine 150/10 mg ($p = 0.056$) and aliskiren/amlodipine 300/10 mg ($p = 0.143$).

Table 11. Pair-wise comparisons for the change from baseline in msSBP at endpoint in FAS of Study 05[§].

Treatment Group	N	LSM change from baseline (mmHg) (SE)	
Placebo	198	-6.79 (1.00)	
Ali 150 mg	193	-10.67 (1.01)	
Ali 300 mg	201	-15.37 (0.99)	
Aml 5 mg	184	-15.82 (1.04)	
Aml 10 mg	179	-21.04 (1.05)	
Ali/Aml 150/5 mg	179	-20.64 (1.05)	
Ali/Aml 150/10 mg	179	-23.87 (1.05)	
Ali/Aml 300/5 mg	175	-21.82 (1.06)	
Ali/Aml 300/10 mg	183	-23.19 (1.04)	

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
Ali 150 mg vs. Placebo	-3.88 (1.41)	(-6.66, -1.11)	0.006*
Ali 300 mg vs. Placebo	-8.58 (1.40)	(-11.32, -5.83)	<.001*
Aml 5 mg vs. Placebo	-9.03 (1.43)	(-11.84, -6.22)	<.001*
Aml 10 mg vs. Placebo	-14.25 (1.44)	(-17.07, -11.4)	<.001*
Ali/Aml 150/5 mg vs. Ali 150 mg	-9.97 (1.45)	(-12.81, -7.12)	<.001*
Ali/Aml 150/5 mg vs. Aml 5 mg	-4.82 (1.47)	(-7.70, -1.94)	0.001*
Ali/Aml 150/5 mg vs. Placebo	-13.85 (1.44)	(-16.68, -11.0)	<.001*
Ali/Aml 150/10 mg vs. Ali 150 mg	-13.20 (1.45)	(-16.04, -10.4)	<.001*
Ali/Aml 150/10 mg vs. Aml 10 mg	-2.83 (1.48)	(-5.73, 0.07)	0.056
Ali/Aml 150/10 mg vs. Placebo	-17.08 (1.44)	(-19.91, -14.3)	<.001*
Ali/Aml 300/5 mg vs. Ali 300 mg	-6.45 (1.45)	(-9.29, -3.62)	<.001*
Ali/Aml 300/5 mg vs. Aml 5 mg	-6.00 (1.48)	(-8.90, -3.11)	<.001*
Ali/Aml 300/5 mg vs. Placebo	-15.03 (1.45)	(-17.88, -12.2)	<.001*
Ali/Aml 300/10 mg vs. Ali 300 mg	-7.82 (1.43)	(-10.63, -5.02)	<.001*
Ali/Aml 300/10 mg vs. Aml 10 mg	-2.16 (1.47)	(-5.04, 0.73)	0.143
Ali/Aml 300/10 mg vs. Placebo	-16.40 (1.43)	(-19.21, -13.6)	<.001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval.

Only patients with both baseline and post-baseline values are included.

Least square means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region, and baseline.

P-Values and treatment comparisons were evaluated at the average baseline level.

* Indicates statistical significance at 0.05 level.

[§] Source: Sponsor's Table 11-5.

The results were verified by the statistical reviewer.

The changes from baseline in msDBP and msSBP by week for aliskiren/amlodipine 300/10 mg and respective monotherapies and placebo are illustrated in Figure 1 (msDBP) and Figure 2 (msSBP). Greater msDBP and msSBP reductions for the aliskiren/amlodipine combination group vs. each respective monotherapy or placebo was seen at all time points beginning at Week 1, and reaching a maximum at Week 4, which was sustained throughout the study. The same trend was observed for all other doses of aliskiren/amlodipine combination.

Figure 1. Change from baseline in msDBP by week for aliskiren/amlodipine 300/10 mg vs. component monotherapies and placebo (FAS of Study 05)

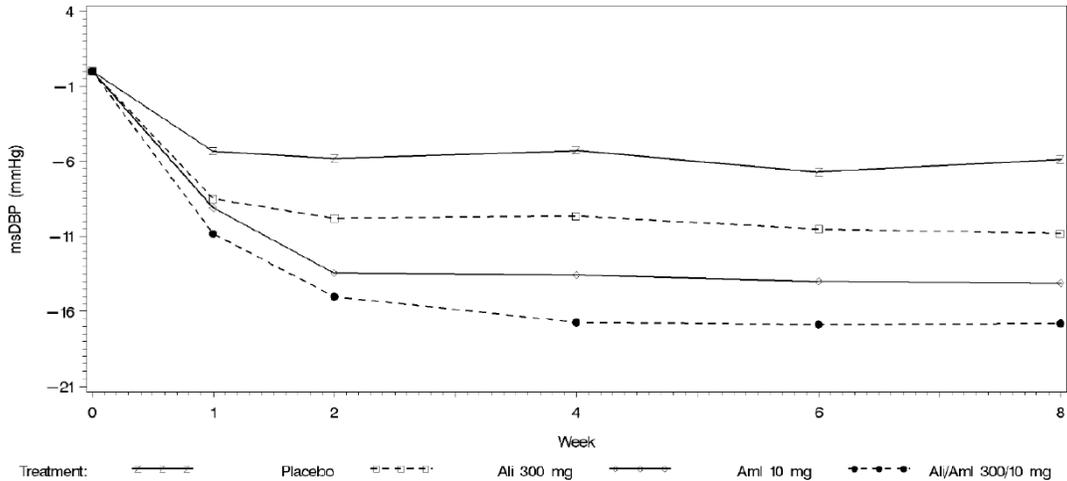
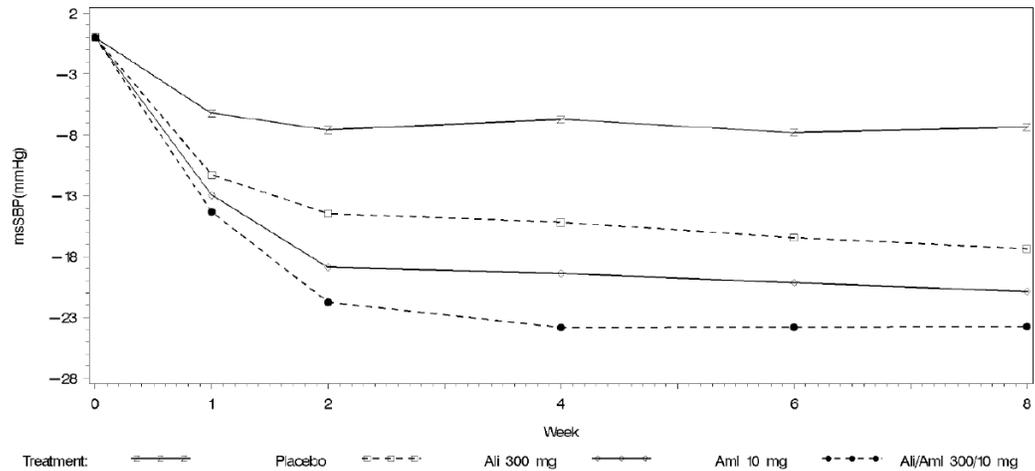


Figure 2. Change from baseline in msSBP by week for aliskiren/amlodipine 300/10 mg vs. component monotherapies and placebo (FAS of Study 05)



Blood control

The between-treatment comparisons between the combination treatment and each of the respective monotherapy treatment groups for blood pressure control (msDBP < 90 mmHg and msSBP < 140 mmHg) showed that all combination therapies of aliskiren/amlodipine were statistically superior to component monotherapies in controlling blood pressure at endpoint (Table 12). The greatest BP control rate was seen in the aliskiren/amlodipine 300/10 mg group (68.3%).

Table 12. Between treatment comparisons for blood pressure control rate at endpoint by treatment group (FAS of Study 05).

Pairwise Comparison	Treatment A n/N (%)	Treatment B n/N (%)	p-value
Ali 150 mg vs. Placebo	52/193 (26.9)	38/198 (19.2)	0.054
Ali 300 mg vs. Placebo	73/201 (36.3)	38/198 (19.2)	<.001*
Aml 5 mg vs. Placebo	66/184 (35.9)	38/198 (19.2)	<.001*
Aml 10 mg vs. Placebo	90/179 (50.3)	38/198 (19.2)	<.001*
Ali/Aml 150/5 mg vs. Ali 150 mg	88/179 (49.2)	52/193 (26.9)	<.001*
Ali/Aml 150/5 mg vs. Aml 5 mg	88/179 (49.2)	66/184 (35.9)	0.006*
Ali/Aml 150/5 mg vs. Placebo	88/179 (49.2)	38/198 (19.2)	<.001*
Ali/Aml 150/10 mg vs. Ali 150 mg	117/179 (65.4)	52/193 (26.9)	<.001*
Ali/Aml 150/10 mg vs. Aml 10 mg	117/179 (65.4)	90/179 (50.3)	0.006*
Ali/Aml 150/10 mg vs. Placebo	117/179 (65.4)	38/198 (19.2)	<.001*
Ali/Aml 300/5 mg vs. Ali 300 mg	99/175 (56.6)	73/201 (36.3)	<.001*
Ali/Aml 300/5 mg vs. Aml 5 mg	99/175 (56.6)	66/184 (35.9)	<.001*
Ali/Aml 300/5 mg vs. Placebo	99/175 (56.6)	38/198 (19.2)	<.001*
Ali/Aml 300/10 mg vs. Ali 300 mg	125/183 (68.3)	73/201 (36.3)	<.001*
Ali/Aml 300/10 mg vs. Aml 10 mg	125/183 (68.3)	90/179 (50.3)	<.001*
Ali/Aml 300/10 mg vs. Placebo	125/183 (68.3)	38/198 (19.2)	<.001*

Blood pressure control is defined as msDBP < 90 mmHg and msSBP < 140 mmHg.

Only patients with both baseline and post-baseline values are included.

P-Values were from a logistic regression model with treatment and region as factors and baseline as a covariate. Baseline is the Visit 5 value.

N = Number of patients with baseline and Endpoint msDBP values.

* indicates statistical significance at 0.05 level.

BP response

The between-treatment comparisons of DBP response (msDBP <90 mmHg or a ≥ 10 mmHg reduction from baseline) at endpoint showed that all combination therapy doses were statistically significantly superior to their respective monotherapies (Table 13). The greatest DBP response rate was seen in aliskiren/amlodipine 300/10 mg group (84.7%).

Table 13. Number (%) of DBP response at endpoint by treatment group (FAS of Study 05)

Pairwise Comparison			Treatment A	Treatment B	P-Value
A	vs.	B	n/N (%)	n/N (%)	
Ali 150 mg	vs. Placebo		97/193 (50.3)	68/198 (34.3)	0.002*
Ali 300 mg	vs. Placebo		109/201 (54.2)	68/198 (34.3)	<.001*
Aml 5 mg	vs. Placebo		114/184 (62.0)	68/198 (34.3)	<.001*
Aml 10 mg	vs. Placebo		133/179 (74.3)	68/198 (34.3)	<.001*
Ali/Aml 150/5 mg	vs. Ali 150 mg		131/179 (73.2)	97/193 (50.3)	<.001*
Ali/Aml 150/5 mg	vs. Aml 5 mg		131/179 (73.2)	114/184 (62.0)	0.016*
Ali/Aml 150/5 mg	vs. Placebo		131/179 (73.2)	68/198 (34.3)	<.001*
Ali/Aml 150/10 mg	vs. Ali 150 mg		150/179 (83.8)	97/193 (50.3)	<.001*
Ali/Aml 150/10 mg	vs. Aml 10 mg		150/179 (83.8)	133/179 (74.3)	0.030*
Ali/Aml 150/10 mg	vs. Placebo		150/179 (83.8)	68/198 (34.3)	<.001*
Ali/Aml 300/5 mg	vs. Ali 300 mg		129/175 (73.7)	109/201 (54.2)	<.001*
Ali/Aml 300/5 mg	vs. Aml 5 mg		129/175 (73.7)	114/184 (62.0)	0.015*
Ali/Aml 300/5 mg	vs. Placebo		129/175 (73.7)	68/198 (34.3)	<.001*
Ali/Aml 300/10 mg	vs. Ali 300 mg		155/183 (84.7)	109/201 (54.2)	<.001*
Ali/Aml 300/10 mg	vs. Aml 10 mg		155/183 (84.7)	133/179 (74.3)	0.013*
Ali/Aml 300/10 mg	vs. Placebo		155/183 (84.7)	68/198 (34.3)	<.001*

Diastolic blood pressure response is defined as msDBP < 90 mmHg or at least 10 mmHg reduction from baseline in msDBP.

Only patients with both baseline and post-baseline values are included.

P-Values were from a logistic regression model with treatment and region as factors and baseline as a covariate.

Baseline is the Week 0 value.

N = Number of patients with baseline and Endpoint msDBP values.

* indicates statistical significance at 0.05 level.

The comparisons of SBP response (msSBP < 140 mmHg or at least 20 mmHg reduction from baseline) at Endpoint showed that most combination aliskiren/amlodipine doses were statistically significantly superior to their respective aliskiren monotherapy or amlodipine component monotherapy, with the exceptions of aliskiren/amlodipine 150/10 mg and 300/10 mg doses vs. amlodipine 10 mg, which did not reach statistical significance (Table 14). The greatest SBP response rate was seen in the aliskiren/amlodipine 300/10 mg group (80.3%).

Table 14. Number (%) of SBP response at endpoint by treatment group (FAS of Study 05).

Pairwise Comparison			Treatment A	Treatment B	P-Value
A	vs.	B	n/N (%)	n/N (%)	
Ali 150 mg	vs.	Placebo	80/193 (41.5)	64/198 (32.3)	0.063
Ali 300 mg	vs.	Placebo	107/201 (53.2)	64/198 (32.3)	<.001*
Aml 5 mg	vs.	Placebo	101/184 (54.9)	64/198 (32.3)	<.001*
Aml 10 mg	vs.	Placebo	129/179 (72.1)	64/198 (32.3)	<.001*
Ali/Aml 150/5 mg	vs.	Ali 150 mg	121/179 (67.6)	80/193 (41.5)	<.001*
Ali/Aml 150/5 mg	vs.	Aml 5 mg	121/179 (67.6)	101/184 (54.9)	0.009*
Ali/Aml 150/5 mg	vs.	Placebo	121/179 (67.6)	64/198 (32.3)	<.001*
Ali/Aml 150/10 mg	vs.	Ali 150 mg	138/179 (77.1)	80/193 (41.5)	<.001*
Ali/Aml 150/10 mg	vs.	Aml 10 mg	138/179 (77.1)	129/179 (72.1)	0.284
Ali/Aml 150/10 mg	vs.	Placebo	138/179 (77.1)	64/198 (32.3)	<.001*
Ali/Aml 300/5 mg	vs.	Ali 300 mg	122/175 (69.7)	107/201 (53.2)	0.002*
Ali/Aml 300/5 mg	vs.	Aml 5 mg	122/175 (69.7)	101/184 (54.9)	0.004*
Ali/Aml 300/5 mg	vs.	Placebo	122/175 (69.7)	64/198 (32.3)	<.001*
Ali/Aml 300/10 mg	vs.	Ali 300 mg	147/183 (80.3)	107/201 (53.2)	<.001*
Ali/Aml 300/10 mg	vs.	Aml 10 mg	147/183 (80.3)	129/179 (72.1)	0.060
Ali/Aml 300/10 mg	vs.	Placebo	147/183 (80.3)	64/198 (32.3)	<.001*

Systolic blood pressure response is defined as msSBP < 140 mmHg or at least 20 mmHg reduction from baseline in msSBP.

Only patients with both baseline and post-baseline values are included.

P-Values were from a logistic regression model with treatment and region as factors and baseline as a covariate.

Baseline is the Week 0 value.

N = Number of patients with baseline and Endpoint msSBP values.

* indicates statistical significance at 0.05 level.

AMBP

Twenty-four hour ambulatory blood pressure measurements (ABPM) were conducted in a subset of patients. The between-treatment comparisons for mean 24-hour ambulatory DBP and SBP between the combination treatment and each of the respective component monotherapy treatment groups are presented in Table 15 and Table 16, respectively. The analyses showed that all combination therapies of aliskiren/amlodipine were statistically superior to component monotherapies in reduction of the mean 24-hour ambulatory DBP and SBP at Endpoint. There was practically no placebo effect on the mean 24-hour ambulatory DBP and SBP (LSM change from baseline of 0.73 mmHg and -0.01, respectively).

Table 15. Between treatment comparisons for change from baseline in mean 24 hour ambulatory DBP at endpoint (FAS of Study 05)

Treatment Group	N	LSM change from baseline (mmHg) (SE)	
Placebo	83	0.73 (0.46)	
Ali 150 mg	99	-4.29 (0.42)	
Ali 300 mg	94	-6.31 (0.43)	
Aml 5 mg	100	-4.96 (0.43)	
Aml 10 mg	91	-7.89 (0.44)	
Ali/Aml 150/5 mg	89	-8.86 (0.45)	
Ali/Aml 150/10 mg	84	-11.45 (0.46)	
Ali/Aml 300/5 mg	94	-10.04 (0.44)	
Ali/Aml 300/10 mg	85	-12.98 (0.46)	

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value
Ali 150 mg vs. Placebo	-5.02 (0.61)	(-6.22, -3.82)	<.001*
Ali 300 mg vs. Placebo	-7.04 (0.62)	(-8.26, -5.83)	<.001*
Aml 5 mg vs. Placebo	-5.69 (0.61)	(-6.89, -4.50)	<.001*
Aml 10 mg vs. Placebo	-8.62 (0.63)	(-9.85, -7.39)	<.001*
Ali/Aml 150/5 mg vs. Ali 150 mg	-4.57 (0.60)	(-5.75, -3.40)	<.001*
Ali/Aml 150/5 mg vs. Aml 5 mg	-3.90 (0.60)	(-5.07, -2.73)	<.001*
Ali/Aml 150/5 mg vs. Placebo	-9.59 (0.63)	(-10.82, -8.37)	<.001*
Ali/Aml 150/10 mg vs. Ali 150 mg	-7.16 (0.61)	(-8.35, -5.97)	<.001*
Ali/Aml 150/10 mg vs. Aml 10 mg	-3.56 (0.62)	(-4.79, -2.33)	<.001*
Ali/Aml 150/10 mg vs. Placebo	-12.18 (0.63)	(-13.43, -10.9)	<.001*
Ali/Aml 300/5 mg vs. Ali 300 mg	-3.73 (0.60)	(-4.90, -2.55)	<.001*
Ali/Aml 300/5 mg vs. Aml 5 mg	-5.08 (0.59)	(-6.24, -3.92)	<.001*
Ali/Aml 300/5 mg vs. Placebo	-10.77 (0.62)	(-11.99, -9.55)	<.001*
Ali/Aml 300/10 mg vs. Ali 300 mg	-6.67 (0.62)	(-7.88, -5.46)	<.001*
Ali/Aml 300/10 mg vs. Aml 10 mg	-5.09 (0.63)	(-6.33, -3.86)	<.001*
Ali/Aml 300/10 mg vs. Placebo	-13.71 (0.64)	(-14.97, -12.5)	<.001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval

P-Values and treatment comparisons were from a two-way repeated-measures analysis-of-covariance model with treatment, region, and post-dosing hours as factors and baseline mean 24-hour ambulatory DBP as a covariate with treatment by post-dosing-hour interaction and autoregressive order 1 covariance structure (AR1).

* Indicates statistical significance at 0.05 level

Table 16. Between treatment comparisons for change from baseline in mean 24 hour ambulatory SBP at endpoint (FAS of Study 05)

Treatment Group	N	LSM change from baseline (mmHg) (SE)
Placebo	83	-0.01 (0.62)
Ali 150 mg	99	-6.65 (0.57)
Ali 300 mg	94	-9.09 (0.58)
Aml 5 mg	100	-8.86 (0.58)
Aml 10 mg	91	-12.59 (0.60)
Ali/Aml 150/5 mg	89	-14.24 (0.61)
Ali/Aml 150/10 mg	84	-17.28 (0.62)
Ali/Aml 300/5 mg	94	-15.97 (0.59)
Ali/Aml 300/10 mg	85	-19.81 (0.62)

Pairwise Comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	P-Value
Ali 150 mg vs. Placebo	-6.64 (0.83)	(-8.26, -5.01)	<.001*
Ali 300 mg vs. Placebo	-9.08 (0.84)	(-10.72, -7.44)	<.001*
Aml 5 mg vs. Placebo	-8.85 (0.83)	(-10.47, -7.23)	<.001*
Aml 10 mg vs. Placebo	-12.58 (0.85)	(-14.25, -10.92)	<.001*
Ali/Aml 150/5 mg vs. Ali 150 mg	-7.59 (0.81)	(-9.18, -6.00)	<.001*
Ali/Aml 150/5 mg vs. Aml 5 mg	-5.37 (0.81)	(-6.95, -3.79)	<.001*
Ali/Aml 150/5 mg vs. Placebo	-14.23 (0.85)	(-15.89, -12.56)	<.001*
Ali/Aml 150/10 mg vs. Ali 150 mg	-10.63 (0.82)	(-12.24, -9.01)	<.001*
Ali/Aml 150/10 mg vs. Aml 10 mg	-4.68 (0.85)	(-6.34, -3.02)	<.001*
Ali/Aml 150/10 mg vs. Placebo	-17.27 (0.86)	(-18.95, -15.58)	<.001*
Ali/Aml 300/5 mg vs. Ali 300 mg	-6.88 (0.81)	(-8.47, -5.29)	<.001*
Ali/Aml 300/5 mg vs. Aml 5 mg	-7.11 (0.80)	(-8.68, -5.54)	<.001*
Ali/Aml 300/5 mg vs. Placebo	-15.96 (0.84)	(-17.61, -14.31)	<.001*
Ali/Aml 300/10 mg vs. Ali 300 mg	-10.72 (0.84)	(-12.36, -9.08)	<.001*
Ali/Aml 300/10 mg vs. Aml 10 mg	-7.21 (0.85)	(-8.88, -5.55)	<.001*
Ali/Aml 300/10 mg vs. Placebo	-19.80 (0.86)	(-21.49, -18.10)	<.001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval

P-Values and treatment comparisons were from a two-way repeated-measures analysis-of-covariance model with treatment, region, and post-dosing hours as factors and baseline mean 24-hour ambulatory DBP as a covariate with treatment by post-dosing-hour interaction and autoregressive order 1 covariance structure (AR1).

* Indicates statistical significance at 0.05 level

Per-protocol population analyses

Analyses were repeated for the Per-Protocol population to examine the effect of protocol deviations and early discontinuation from the study. Most patients (79.9%) were included in the Per-Protocol population. Efficacy results for the Per-Protocol population were consistent with those obtained for the FAS.

3.3 Evaluation of Safety

The AE profiles seen in Study 04 and Study 05 are similar to previous safety results for hypertensive patients treated with aliskiren and/or amlodipine, and no unusual or unexpected AEs were reported. There were no deaths during the studies.

Safety in Study 04

The most commonly reported AE in all three treatment groups was peripheral edema, which is a known side effect of amlodipine treatment especially at the dose of 10 mg. The incidence of peripheral edema was similar in aliskiren/amlodipine 150/10 mg and amlodipine 10 mg group while it was lower in aliskiren/amlodipine 300/10 mg group. In this study, the incidence of diarrhea was low and similar in all treatment groups. Hyperkalemia was uncommonly (<2%) in all groups. The majority of reported AEs were mild or moderate.

Safety in Study 05

Serious AEs were infrequent and reported in 9 patients (0.5%) overall. The only SAE that occurred in more than one patient was pneumonia, which occurred in one patient in the amlodipine 5 mg group, and one patient in the amlodipine 10 mg group. None of the SAEs were suspected to be related to study drug.

Safety of Tekamlo is a matter of clinical judgment of the medical division.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**4.1 Subgroup analyses in Study 04**

Mean changes from baseline in mean sitting blood pressure in Study 04 were summarized for the following subgroups: Region, Ethnicity, Race, Sex, and Age. Subgroup analyses indicated that the combinations of aliskiren/amlodipine 300/10 mg and aliskiren/amlodipine 150/10 mg showed a numerically greater reduction in msDBP and msSBP as compared to the amlodipine 10 mg monotherapy across all subgroups of age, geographical region, and sex. Since the study population was predominantly Caucasian (>99%), no conclusion can be drawn for other races.

4.2 Subgroup analyses in Study 05

Subgroup analysis by race indicated that in Caucasians (62%), all combination therapies showed a greater reduction of msDBP and msSBP than the respective monotherapies. A total of 336 (20%) randomized subjects were Blacks with 35-41 subjects in each of the 9 treatment groups. The majority (83%) of the Black subjects were enrolled in sites in South Africa. In the Black population, all combination therapies showed a numerically greater reduction of msDBP than the respective monotherapies with the exception of aliskiren/amlodipine 300/10 mg vs. amlodipine 10 mg. All combination therapies showed a numerically greater reduction of msSBP than the respective aliskiren monotherapies, but only one dose of the combination (aliskiren/amlodipine 150/5 mg) showed a numerically greater reduction of msDBP than the respective dose of amlodipine monotherapies. The small number of Black patients in this study limited the interpretation of the data in this population. An ongoing African American study is expected to be submitted to the FDA.

Subgroup analysis by sex indicated that in both males and females, all combination therapies showed a greater reduction of msDBP and msSBP than the respective monotherapies. When analyzed by age subgroup, all combination therapies showed a greater reduction of msDBP and msSBP than the respective monotherapies in both age subgroups <65 years and ≥ 65 years.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no statistical issues in this submission. This reviewer agrees with the statistical methods used by the sponsor. All secondary endpoints are BP endpoints intended to support the primary efficacy claim. Therefore, no adjustment for multiple doses and multiple secondary endpoints is required.

5.2 Conclusions and Recommendations

Two of the submitted controlled studies were reviewed at the request of the clinical reviewer. Results in the two reviewed studies support efficacy of the aliskiren/amlodipine combination in patients with essential hypertension.

Study SPA100A2305 was a pivotal double-blind, randomized, multifactorial study to evaluate efficacy and safety of four doses of aliskiren/amlodipine combination in patients with essential hypertension. Relative to the primary efficacy endpoint, reduction in msDBP, all combination doses showed statistically significantly greater msDBP reduction than the respective monotherapies ($p \leq 0.004$). Relative to the secondary endpoint, msSBP, most of the pair-wise comparisons of the combination doses to their respective monotherapies were statistically significant ($p < 0.001$). However, two combination doses compared to amlodipine 10 mg showed only numerically greater reductions in msSBP: aliskiren/amlodipine 150/10 mg ($p = 0.056$) and aliskiren/amlodipine 300/10 mg ($p = 0.143$). Similar results were shown in the per protocol set.

Pivotal Study SPA100A2304 examined mostly comparisons of the two combination doses that failed in Study SPA100A2305. Study SPA100A2304 showed that the combination aliskiren/amlodipine at doses 300/10 mg and 150/10 mg was statistically significantly better than amlodipine 10 mg relative to the reduction in both msDBP ($p < 0.001$ and $p = 0.0077$, respectively) and msSBP ($p < 0.001$ and $p = 0.0033$, respectively). These results were supported by the analyses in the per protocol set ($p < 0.001$ and $p \leq 0.0042$, respectively). The SBP response rate was statistically significantly greater in aliskiren/amlodipine 300/10 mg group ($p < 0.0001$) and aliskiren/amlodipine 150/10mg group ($p < 0.0048$) compared to amlodipine 10 mg group.

Safety analyses showed no deaths or unexpected adverse events. Safety of aliskiren/amlodipine combination is a matter of clinical judgment of the medical division.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VALERIA FREIDLIN
06/02/2010

HSIEN MING J J HUNG
06/02/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-545

Applicant: Novartis

Stamp Date: 10-29-09

Drug Name: Tekamlo

NDA/BLA Type:

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Valeria Freidlin	12/09/09
Reviewing Statistician	Date
Jim Hung	12/29/09
Supervisor/Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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/s/

VALERIA FREIDLIN
12/29/2009

HSIEN MING J J HUNG
12/29/2009