Journal of Human Hypertension (2013) **27,** 321–327

www.nature.com/jhh

ORIGINAL ARTICLE

Efficacy and safety of aliskiren and amlodipine combination therapy in patients with hypertension: a randomized, double-blind, multifactorial study

TW Littlejohn III[1,*], SW Jones[2], J Zhang[3], H Hsu[3] and DL Keefe[3]

Most patients with hypertension need more than one drug to achieve blood pressure (BP) control. This randomized, double-blind, multifactorial study evaluated whether combinations of aliskiren and amlodipine provided superior BP reductions to component monotherapies in patients with hypertension (mean sitting diastolic BP (msDBP) 95–<110 mm Hg). Overall, 1688 patients were randomized to once-daily monotherapy with aliskiren 150 or 300 mg or amlodipine 5 or 10 mg, combination therapy with one of four corresponding aliskiren/amlodipine doses, or placebo for 8 weeks. At week 8 end point, aliskiren/amlodipine combinations provided significant msDBP reductions from baseline of 14.0–16.5 mm Hg, compared with reductions of 8.0 and 10.2 mm Hg for aliskiren 150 and 300 mg, respectively ($P<0.001$), and 11.0 and 13.8 mm Hg for amlodipine 5 and 10 mg, respectively ($P<0.05$). Aliskiren/amlodipine combinations provided reductions in mean sitting systolic BP 20.6–23.9 mm Hg, compared with decreases of 10.7 and 15.4 mm Hg for aliskiren 150 and 300 mg, respectively ($P<0.001$), and 15.8 and 21.0 mm Hg for amlodipine 5 ($P\leqslant0.001$) and 10 mg ($P=$NS), respectively. Aliskiren/amlodipine combination therapy provides greater BP lowering than either agent alone, hence offering an effective treatment option for patients with hypertension.

Journal of Human Hypertension (2013) **27,** 321–327; doi:10.1038/jhh.2012.42; published online 18 October 2012

Keywords: aliskiren; amlodipine; calcium channel blocker; combination therapy; direct renin inhibitor; hypertension

INTRODUCTION

Patients with hypertension are at increased risk of cardiovascular events compared with healthy individuals. Most patients are likely to need more than one agent to achieve blood pressure (BP) target. Current United States and European treatment guidelines for patients with BP > 20/10 mm Hg above goal, or those at high risk of developing cardiovascular events recommend that therapy is initiated with two agents from different therapeutic classes.[1,2]

The direct renin inhibitor aliskiren offers a different option for inhibiting the renin–angiotensin–aldosterone system (RAAS) to angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Aliskiren targets the rate-limiting step of the RAAS by directly inhibiting the enzyme renin, thereby reducing the plasma renin activity (PRA) and all other downstream components of the system (angiotensin I, angiotensin II and aldosterone).[3] Hence, aliskiren may provide more effective RAAS suppression than that produced by ACE inhibitors or ARBs, which both increase PRA. The BP-lowering effects of aliskiren/amlodipine combination therapy were demonstrated in 1254 patients with hypertension in the ACCELERATE study (aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control). Patients who received initial combination therapy with aliskiren/amlodipine achieved a significant additional reduction from baseline in systolic BP of 6.5 mm Hg ($P<0.0001$) over 8–24 weeks of treatment compared with those who received first-line treatment with either agent as monotherapy (with subsequent addition of the other drug).[4]

The aim of this randomized, double-blind, multifactorial study was to assess the efficacy, safety and tolerability of four aliskiren/amlodipine dose combinations (150/5, 150/10, 300/5 and 300/10 mg) administered as single-pill combinations compared with those of the component monotherapies in patients with hypertension. Aliskiren/amlodipine combinations have been approved in the United States for the treatment of hypertension as initial therapy in patients likely to need multiple drugs to control BP, as a replacement in patients whose BP is not controlled with either monotherapy or as a substitute for its components given in combination.

MATERIALS AND METHODS

Patients

Men and women aged ⩾18 years with primary hypertension were eligible for inclusion in the study. All patients had to have mean sitting diastolic BP (msDBP) ⩾95 mm Hg and <110 mm Hg at randomization. The main exclusion criteria were grade III hypertension (msDBP ⩾110 mm Hg or mean sitting systolic BP (msSBP) ⩾180 mm Hg), secondary hypertension, a history of severe cardiovascular or cerebrovascular disease, type 1 or type 2 diabetes mellitus that was not well controlled (glycosylated hemoglobin [HbA1c] >8.0%), and severe renal impairment (glomerular filtration rate <30 ml min^{-1} at visit 1, a history of dialysis, or a history of nephrotic syndrome) or hepatic disease (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values exceeding 3× upper limit of normal (ULN) at visit 1, a history of hepatic encephalopathy, a history of esophageal varices or a history of portocaval shunt). Women of childbearing potential had to be using effective contraceptive methods for inclusion in the study; pregnant or lactating women were excluded.

[1]Piedmont Medical Research Group, Winston-Salem, NC, USA; [2]Jones Family Practice, Shelby, NC, USA and [3]Clinical Development and Medical Affairs, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. Correspondence: Dr SW Jones, Jones Family Practice, 113 East Grover Street, Shelby, NC 28150, USA.
E-mail: swjskidoc@yahoo.com
*Before submission of this manuscript, Dr TW Littlejohn III passed away.
Received 12 March 2012; revised 14 September 2012; accepted 19 September 2012; published online 18 October 2012

All patients submitted written informed consent before participating in any study procedure. The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. This study and any amendments were reviewed by the Independent Ethics Committee or the Institutional Review Board for each center. The trial was conducted according to the ethical principles of the Declaration of Helsinki and is registered with clinicaltrials.gov (identifier: NCT00739973).

Study design

The present double-blind, multicenter, randomized, placebo-controlled, multifactorial study was conducted at 208 centers across 18 countries (Argentina, Australia, Canada, Colombia, Denmark, Finland, Greece, Italy, Mexico, Panama, Peru, Romania, Russia, South Africa, Spain, Sweden, Taiwan and the United States).

Following a 3-day washout and a 2- or 4-week placebo run-in period, eligible patients with msDBP $\geqslant$95 mm Hg and $<$110 mm Hg who met other inclusion criteria were randomly assigned in an equal ratio, using a validated interactive voice response system, to one of the following once-daily treatment groups: aliskiren 150 mg, aliskiren 300 mg, amlodipine 5 mg, amlodipine 10 mg, or the single-pill combination of aliskiren/amlodipine 150/5 mg, aliskiren/amlodipine 150/10 mg, aliskiren/amlodipine 300/5 mg, aliskiren/amlodipine 300/10 mg or placebo. Patients assigned to amlodipine 10 mg, or aliskiren/amlodipine 150/10 or 300/10 mg began treatment with amlodipine 5 mg, or aliskiren/amlodipine 150/5 or 300/5 mg, respectively, and were force-titrated to the higher amlodipine doses after 1 week of treatment. Treatment was administered once daily at $\sim$0800 hours, except on clinic visit days, when patients were instructed to delay the treatment until all assessments had been completed.

Study assessments

The primary objective of the study was to assess whether antihypertensive efficacy of the combination of aliskiren/amlodipine was superior to each of the component monotherapies, as assessed by change in msDBP from baseline to week 8 end point across doses. Secondary efficacy variables included change in msSBP from baseline to week 8 end point and the proportion of patients achieving BP control ($<$140/90 mm Hg) at week 8 in each treatment group. The effect of study treatments on mean 24 h ambulatory BP was assessed as change from baseline to week 8 end point in a subgroup of patients. Changes in PRA from baseline to week 8 end point were also measured in a subset of patients.

BP measurements

Clinic (office) BP was measured using an OMRON (models HEM 705CP or HEM 705IT) BP monitor with an appropriate cuff size, in accordance with the British Hypertension Society Guidelines.[5] The sitting BP was measured after the patient had been sitting for at least 5 min; three measurements were made at each study visit and the mean of these was used as the value for that visit. BP was measured at trough (24 $\pm$ 3 h after the previous dose).

Ambulatory BP monitoring

Ambulatory BP monitoring was conducted at baseline and week 8 in a subset of patients ($n = 819$). Measurements were made using a SpaceLabs 90207 ambulatory BP monitoring device (Spacelabs, Redmond, WA, USA). The device was attached to the non-dominant arm of the patient between 0700 and 1000 hours; BP was automatically measured every 15 min between 0600 and 2159 hours, and every 20 min between 2200 and 0559 hours. The patient wore the device for a minimum of 24 h.

RAAS biomarker analyses

The effect of study treatments on PRA was evaluated in a predefined subset of patients ($n = 608$; approximately one third of patients) at baseline and at week 8 end point. Blood was collected from patients in the sitting position who were calm, and had been seated for at least 10 min. PRA was measured at a central laboratory by radioimmunoassay of generated angiotensin I (DiaSorin kit; DiaSorin, Stillwater, MN, USA).

Safety, tolerability and laboratory evaluations

All adverse events (AEs) and serious AEs were recorded throughout the study and assessed by the investigator for their relationship to study medication. Hematology, blood chemistry, urine values and vital signs were monitored regularly.

Statistical analyses

The primary efficacy variable (change in msDBP from baseline to week 8 end point) was assessed by Hung's AVE test.[6] If this test was statistically significant, the contribution of the individual monotherapies to the BP reduction with each combination was assessed using a two-way analysis of covariance model with treatment and region as factors, and baseline msDBP as a covariate. Pairwise comparisons were performed at a two-sided significance level of 0.05. Changes in msSBP from baseline to week 8 were assessed in the same way as for the primary efficacy variable, except that the analysis of covariance model included baseline msSBP as a covariate.

The proportion of patients in each treatment group achieving BP control ($<$140/90 mm Hg) at week 8 end point were compared using a logistic regression model with treatment and region as factors, and baseline msDBP as a covariate. Changes in hourly mean ambulatory diastolic BP were assessed using a two-way repeated-measures analysis of covariance model with treatment and region as factors, and baseline 24 h mean ambulatory diastolic BP as a covariate. Mean ambulatory systolic BP was assessed using the same model, except that baseline 24 h mean ambulatory systolic BP was used as a covariate. PRA measurements were calculated as geometric means; changes from baseline to week 8 were calculated as the ratio of geometric means at week 8 end point to baseline.

A sample size of 1449 patients completing the study (161 per arm) was targeted to provide 90% power to detect that combination therapy was different from both monotherapies at a two-sided significance level of 0.05 (assuming a treatment difference in msDBP of 3.2 mm Hg and a s.d. of 8 mm Hg). The study investigators therefore aimed to randomize 1611 patients (179 per arm), assuming a withdrawal rate of 10%.

The full analysis set, used for all efficacy analyses, excluded patients randomized incorrectly, those who did not receive study drug and those who did not have a post-baseline efficacy measurement. For end point analyses, the last observation was carried forward for patients who did not have a measurement at week 8. Analyses of ambulatory BP and PRA were performed in subsets of patients from the full analysis set. The safety set consisted of all randomized patients who received double-blind trial medication. All statistical analyses were performed using SAS software version 8.2 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient disposition and baseline characteristics

A total of 1688 patients were randomized and 1539 patients (91%) completed the study (Figure 1). Overall, the most common reason for discontinuation during the double-blind period was unsatisfactory therapeutic effect. The incidence of unsatisfactory therapeutic effect was lower in the combination groups (0.5–1.1%) than in the placebo (8.6%) and monotherapy (1.1–4.1%) groups. Other common reasons for discontinuation included AEs and withdrawal of consent, with the incidence generally similar across treatment groups (Figure 1).

Demographics and baseline characteristics were broadly similar across treatment groups (Table 1). The randomized population consisted mainly of Caucasian (62.1%) and Black (19.9%) patients; the mean patient age was 54.1 years, with 17.2% of participants aged 65 years or older. Almost half (46.0%) of the patients were obese (body mass index $\geqslant$30 kg m^{-2}), and 11.0% of participants had diabetes. The overall msSBP/diastolic BP at baseline was 157.3/99.7 mm Hg, and mean BP values were similar across the treatment groups.

Sitting BP

All active treatments significantly lowered msDBP from baseline to week 8 end point compared with placebo (Figure 2a). All four aliskiren/amlodipine combination doses (150/5, 150/10, 300/5 and 300/10 mg) provided significantly greater msDBP reductions than the respective monotherapies ($P<0.05$). The magnitude of additional msDBP reductions with aliskiren/amlodipine ranged from 2.3–4.0 mm Hg over the respective amlodipine doses and from 4.8–8.2 mm Hg over the respective aliskiren doses.

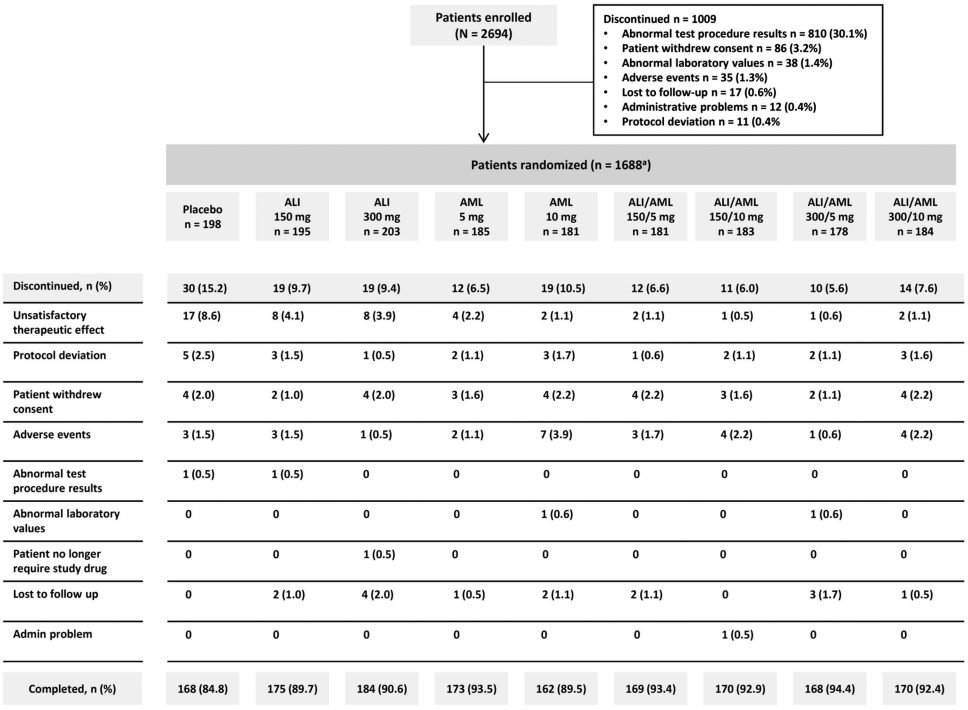

Figure 1. Patient flow diagram. Data are shown as number of patients (%). [a]Three patients who were ineligible for entry into the double-blind period of the study were mistakenly randomized (one in the ALI 150-mg group and two in the ALI/AML 150/10-mg group); they did not receive medication and took no further part in the study. ALI, aliskiren; AML, amlodipine.

Table 1. Patient demographics and baseline characteristics (randomized set)

	Placebo (n = *198*)	*ALI, 150 mg* (n = *195*)	*ALI, 300 mg* (n = *203*)	*AML, 5 mg* (n = *185*)	*AML, 10 mg* (n = *181*)	*ALI/AML, 150/5 mg* (n = *181*)	*ALI/AML, 150/10 mg* (n = *183*)	*ALI/AML, 300/5 mg* (n = *178*)	*ALI/AML, 300/10 mg* (n = *184*)
Age, years	53.7 ± 10.3	54.3 ± 11.1	54.0 ± 10.0	54.2 ± 11.6	55.0 ± 10.3	53.9 ± 10.8	53.0 ± 10.6	54.8 ± 10.3	54.4 ± 10.9
⩾ 65, *n* (%)	34 (17.2)	39 (20.0)	31 (15.3)	40 (21.6)	31 (17.1)	26 (14.4)	26 (14.2)	34 (19.1)	30 (16.3)
Sex, n (%)									
Male	90 (45.5)	119 (61.0)	95 (46.8)	99 (53.5)	87 (48.1)	97 (53.6)	87 (47.5)	78 (43.8)	106 (57.6)
Female	108 (54.5)	76 (39.0)	108 (53.2)	86 (46.5)	94 (51.9)	84 (46.4)	96 (52.5)	100 (56.2)	78 (42.4)
Race, n (%)									
Caucasian	119 (60.1)	123 (63.1)	127 (62.6)	121 (65.4)	113 (62.4)	112 (61.9)	108 (59.0)	110 (61.8)	116 (63.0)
Black	39 (19.7)	36 (18.5)	39 (19.2)	36 (19.5)	34 (18.8)	38 (21.0)	41 (22.4)	38 (21.3)	35 (19.0)
Asian	14 (7.1)	14 (7.2)	10 (4.9)	10 (5.4)	12 (6.6)	13 (7.2)	13 (7.1)	11 (6.2)	15 (8.2)
Other	26 (13.1)	22 (11.3)	27 (13.3)	18 (9.7)	22 (12.2)	18 (9.9)	21 (11.5)	19 (10.7)	18 (9.8)
BMI, kg m^{-2}	30.1 ± 5.4[b]	30.4 ± 5.1	30.4 ± 5.2	30.5 ± 5.7	29.9 ± 5.5[c]	29.9 ± 5.0	30.7 ± 6.3[d]	30.0 ± 5.4[e]	30.3 ± 5.3
Obese[a]	93 (47.0)[b]	91 (46.7)	95 (46.8)	86 (46.5)	74 (40.9)[c]	79 (43.6)	86 (47.0)[d]	78 (43.8)[e]	94 (51.1)
Diabetes mellitus, *n* (%)	15 (7.6)	25 (12.8)	24 (11.8)	17 (9.2)	11 (6.1)	21 (11.6)	30 (16.4)	17 (9.6)	25 (13.6)
Duration of hypertension, years	7.1 ± 6.8	7.2 ± 6.5	8.2 ± 7.2	7.4 ± 6.6	8.2 ± 7.2	8.9 ± 7.9	7.8 ± 7.2	7.4 ± 6.3	8.0 ± 8.0
Naive patients, *n* (%)	16 (8.1)	19 (9.7)	14 (6.9)	14 (7.6)	11 (6.1)	14 (7.7)	11 (6.0)	13 (7.3)	12 (6.5)
msSBP, mm Hg	157.2 ± 12.1	156.5 ± 12.5	158.9 ± 11.1	157.2 ± 10.9	157.6 ± 11.9	158.1 ± 11.2	156.5 ± 11.8	156.8 ± 11.4	157.0 ± 11.7
msDBP, mm Hg	99.6 ± 3.9	99.7 ± 3.6	100.1 ± 3.7	99.7 ± 3.6	100.1 ± 4.1	99.9 ± 3.6	99.4 ± 4.2	99.6 ± 3.7	99.5 ± 3.8

Abbreviations: ALI, aliskiren; AML, amlodipine; BMI, body mass index; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure. Data are shown as mean ± s.d., unless otherwise stated. [a]Defined as BMI ⩾30 kg m^{-2}. [b]*n* = 197. [c]*n* = 180. [d]*n* = 182. [e]*n* = 176.

Aliskiren and amlodipine, alone and in combination, provided greater msSBP reductions than placebo (Figure 2b). The four aliskiren/amlodipine combinations also produced additional msSBP reductions over the component monotherapies. For aliskiren/amlodipine 150/5 and 300/5 mg, additional reductions of 10.0 and 6.5 mm Hg were obtained over aliskiren 150 and 300 mg monotherapies, respectively ($P < 0.001$), and additional reductions of 4.8 and 6.0 mm Hg, respectively, were obtained over amlodipine 5 mg alone ($P \leqslant 0.001$). Aliskiren/amlodipine 150/10 and 300/10 mg provided additional reductions of 13.2 and 7.8 mm Hg, respectively, over aliskiren 150 and 300 mg monotherapies ($P < 0.001$), and nonsignificant additional reductions of 2.8 and 2.2 mm Hg, respectively, over amlodipine 10 mg (aliskiren/amlodipine 150/10 mg, $P = 0.056$; aliskiren/amlodipine 300/10 mg, $P = 0.143$).

BP control

At week 8 end point, all aliskiren/amlodipine combination therapies provided significantly greater rates of BP control (< 140/90 mm Hg) than placebo ($P < 0.001$) and the corresponding

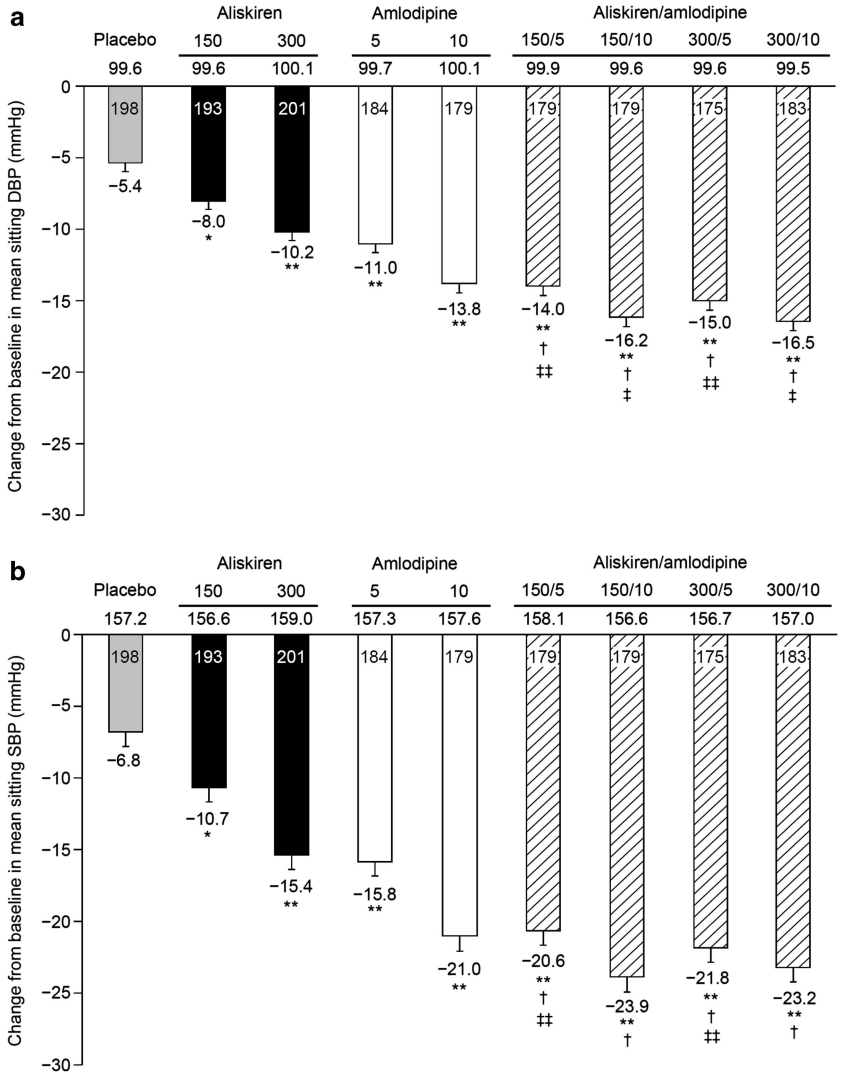

Figure 2. Change from baseline to week 8 end point in mean sitting (**a**) diastolic BP (DBP) and (**b**) systolic BP (SBP). *$P<0.01$, **$P<0.001$ vs placebo; †$P<0.001$ vs aliskiren; ‡$P<0.05$, ‡‡$P\leqslant0.001$ vs amlodipine. Doses of aliskiren and amlodipine are shown in milligrams. Data are shown as least-squares means ± s.e. of the mean for the full analysis set. Values inside bars are the number of patients; baseline blood pressure values are shown on the x axes. DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2. Proportion of patients achieving BP control with aliskiren and amlodipine alone and in combination

	Placebo (n = *198*)	*ALI 150 mg,* (n = *193*)	*ALI 300 mg,* (n = *201*)	*AML 5 mg,* (n = *184*)	*AML 10 mg,* (n = *179*)	*ALI/AML 150/5 mg,* (n = *179*)	*ALI/AML 150/10 mg,* (n = *175*)	*ALI/AML 300/5 mg,* (n = *175*)	*ALI/AML 300/10 mg,* (n = *183*)
BP control, %	19.2	26.9	36.3*	35.9*	50.3*	49.2*,†,‡	65.4*,†,‡	56.6*,†,‡‡	68.3*,†,‡‡

Abbreviations: ALI, aliskiren; AML, amlodipine; BP, blood pressure. *$P<0.001$ vs placebo; †$P<0.001$ vs aliskiren; ‡$P<0.01$, ‡‡$P<0.001$ vs amlodipine. The *P* value indicates the significance of combination therapy vs the component dose of the amlodipine monotherapy. Data shown are for the full analysis set at week 8 end point. BP control was defined as BP < 140/90 mm Hg.

monotherapy doses ($P<0.01$; Table 2). Aliskiren/amlodipine 300/10 mg combination therapy enabled 68.3% of patients to achieve BP control at week 8 end point.

Ambulatory BP

In the subgroup of 819 patients who underwent 24 h ambulatory BP monitoring, all active treatments provided greater reductions from baseline in 24 h mean ambulatory diastolic BP than placebo (4.3–13.0 mm Hg vs an increase of 0.7 mm Hg; $P<0.001$; Table 3). The four aliskiren/amlodipine dose combinations provided significantly greater reductions than the corresponding monotherapies ($P<0.001$). Reductions in 24 h mean ambulatory systolic BP were also larger with all active treatments than with placebo ($P<0.001$), and all aliskiren/amlodipine combinations provided significantly greater reductions than the respective monotherapies

Table 3. Change from baseline in mean 24-h ambulatory SBP and DBP at week 8 end point for all treatment groups

	Placebo (n = *83*)	*ALI 150 mg* (n = *99*)	*ALI 300 mg* (n = *94*)	*AML 5 mg* (n = *100*)	*AML 10 mg* (n = *91*)	*ALI/AML 150/ 5 mg* (n = *89*)	*ALI/AML 150/ 10 mg* (n = *84*)	*ALI/AML 300/ 5 mg* (n = *94*)	*ALI/AML 300/ 10 mg* (n = *85*)
Baseline ambulatory SBP/DBP, mm Hg	141.8/90.1	139.6/89.5	142.4/90.1	139.0/88.6	141.3/90.8	140.2/89.8	141.6/91.0	142.2/90.2	141.3/91.2
Mean change from baseline, mm Hg									
DBP	0.7 ± 0.5	− 4.3 ± 0.4*	− 6.3 ± 0.4*	− 5.0 ± 0.4*	− 7.9 ± 0.4*	− 8.9 ± 0.5*,†	− 11.5 ± 0.5*,†	− 10.0 ± 0.4*,†	− 13.0 ± 0.5*,†
SBP	0.0 ± 0.6	− 6.7 ± 0.6*	− 9.1 ± 0.6*	− 8.9 ± 0.6*	− 12.6 ± 0.6*	− 14.2 ± 0.6*,†	− 17.3 ± 0.6*,†	− 16.0 ± 0.6*,†	− 19.8 ± 0.6*,†

Abbreviations: ALI, aliskiren; AML, amlodipine; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure. *$P<0.001$ vs placebo; †$P<0.001$ vs each component monotherapy. Baseline data are shown as mean ± s.d. for the ambulatory subset of the full analysis set; changes in BP are shown as least-squares means ± s.e. of the mean.

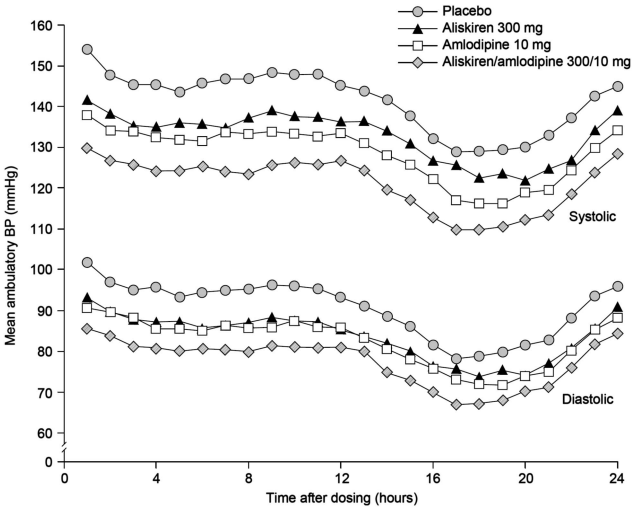

Figure 3. Mean hourly ambulatory BP throughout the 24 h dosing interval. Data are shown as mean values for the ambulatory subset of the full analysis set. BP, blood pressure.

($P<0.001$; Table 3). Greater reductions in ambulatory BP with aliskiren/amlodipine 300/10 mg, compared with those achieved with either monotherapy, were seen at each hour throughout the 24 h dosing period (Figure 3). Similar trends were seen for the other doses (data not shown).

RAAS activity

PRA was measured in a subgroup of 608 patients at baseline and at week 8 end point. Aliskiren 150 and 300 mg monotherapy reduced PRA by up to 68.3%, whereas amlodipine 5 and 10 mg monotherapy increased it by up to 72.9% (Figure 4). All aliskiren/amlodipine dose combinations neutralized amlodipine-induced increases in PRA, and reduced PRA by 54.9–68.1%.

Safety and tolerability

Aliskiren, alone and in combination with amlodipine, was generally well tolerated (Table 4). The incidence of total AEs ranged from 31.4 to 44.6% in all active treatment groups, and was 37.4% in the placebo group. The incidence of serious AEs was low (0.5% overall), and there were no deaths or discontinuations from the study owing to serious AEs. A total of nine patients (two in the placebo group and seven patients in treatment groups) experienced serious AEs, such as retinal detachment, abdominal mass, bronchitis, calculus ureteric, cerebrovascular accident, gastroenteritis, hand fracture, hydronephrosis and pneumonia. None of the serious AEs were suspected to be related to the drug being studied. The overall incidence of discontinuations owing to AEs was low (1.7%), but was higher in the amlodipine 10-mg group ($n=7$; 3.9%) than in the other groups ($n=1$–4; 0.5–2.2%). Most AEs were mild or moderate in severity.

Headache occurred most frequently in the placebo group (10.1%). As expected, rates of peripheral edema were greater in treatment groups containing amlodipine 10 mg (amlodipine 10 mg monotherapy, 13.8%; aliskiren/amlodipine 150/10 mg combination, 7.7%; aliskiren/amlodipine 300/10 mg combination, 13.6%) than in other treatment groups (1.0–4.3%).

Few patients had abnormal laboratory test values (Table 4). The incidence of serum potassium levels >5.5 mmol l^{-1} was low (0–1.2%). Serum creatinine levels >176.8 μmol l^{-1} were observed in one patient in the aliskiren/amlodipine 300/5-mg group (0.6%), and blood urea nitrogen levels >14.28 mmol l^{-1} were reported in three patients (one each in the placebo, aliskiren/amlodipine 150/5 mg and aliskiren/amlodipine 300/5-mg groups).

DISCUSSION

The present study showed that initial combination therapy with aliskiren and amlodipine provided significant additional BP reductions over those achieved with the respective monotherapies and was generally well tolerated in patients with mild-to-moderate hypertension.

Previous clinical trials have demonstrated that aliskiren/amlodipine combination therapy provides significant additional BP reductions over those obtained with amlodipine monotherapy in patients with hypertension.[7] Aliskiren/amlodipine combination therapy has also demonstrated BP-lowering efficacy during long-term treatment.[8]

This study demonstrated the greater BP-lowering effect of aliskiren/amlodipine single-pill combination compared with each mono-component, indicating the contribution from each mono-component toward combination. Treatments that combine two antihypertensive agents in a single pill may offer patients a more convenient option than the free combination because they reduce the pill burden and thus simplify the dosing regimen. A meta-analysis has shown that combination therapy was associated with improved compliance compared with use of the free combinations.[9] Moreover, an increase in the number of prescribed medications has been associated with a reduction in treatment adherence.[10] Patient adherence to a prescribed treatment regimen is a key factor in managing hypertension, and is associated with better cardiovascular outcomes compared with suboptimal adherence.[11–13] Low-dose combination therapy may also confer advantages in terms of safety over higher dose of monotherapy. In the present study, aliskiren/amlodipine combination at low dose of 150/5 mg produced similar BP

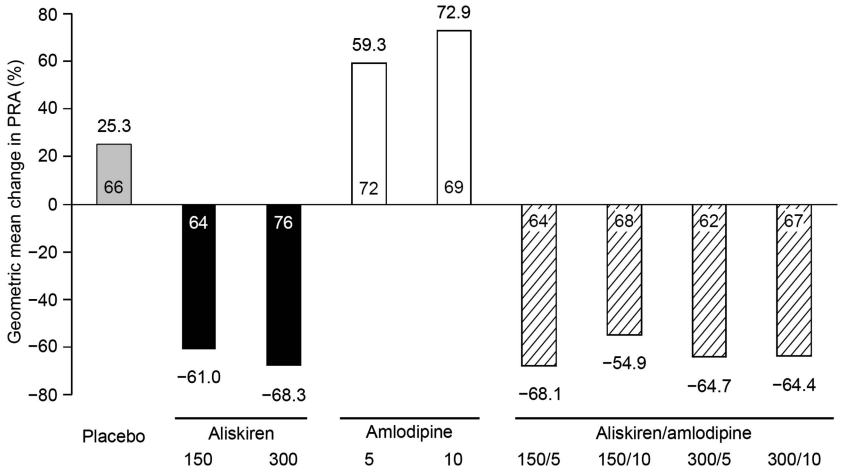

Figure 4. Change from baseline in plasma renin activity (PRA). Data are shown as geometric mean (%) for the biomarker subset of the full analysis set. Doses of aliskiren and amlodipine are shown in milligrams. Values inside bars are the number of patients. PRA, plasma renin activity.

Table 4. Safety and tolerability of study treatments (safety set)

	Placebo (n = *198*)	*ALI 150 mg,* (n = *194*)	*ALI 300 mg,* (n = *203*)	*AML 5 mg,* (n = *185*)	*AML 10 mg,* (n = *181*)	*ALI/AML 150/5 mg,* (n = *181*)	*ALI/AML 150/10 mg,* (n = *181*)	*ALI/AML 300/5 mg,* (n = *178*)	*ALI/AML 300/10 mg,* (n = *184*)
Any AE	74 (37.4)	65 (33.5)	65 (32.0)	58 (31.4)	67 (37.0)	60 (33.1)	59 (32.6)	57 (32.0)	82 (44.6)
Serious AEs	2 (1.0)	0	0	1 (0.5)	1 (0.6)	1 (0.6)	2 (1.1)	1 (0.6)	1 (0.5)
Discontinuation due to AE	3 (1.5)	3 (1.6)	1 (0.5)	2 (1.1)	7 (3.9)	3 (1.7)	4 (2.2)	1 (0.6)	4 (2.2)
Most frequent AEs (⩾3% in any group)									
Headache	20 (10.1)	13 (6.7)	15 (7.4)	11 (5.9)	8 (4.4)	11 (6.1)	8 (4.4)	6 (3.4)	5 (2.7)
Nasopharyngitis	6 (3.0)	3 (1.5)	9 (4.4)	7 (3.8)	2 (1.1)	3 (1.7)	4 (2.2)	1 (0.6)	3 (1.6)
Upper respiratory tract infection	5 (2.5)	6 (3.1)	2 (1.0)	0	2 (1.1)	7 (3.9)	5 (2.8)	5 (2.8)	4 (2.2)
Dizziness	3 (1.5)	5 (2.6)	6 (3.0)	4 (2.2)	1 (0.6)	2 (1.1)	2 (1.1)	5 (2.8)	3 (1.6)
Peripheral edema	2 (1.0)	2 (1.0)	3 (1.5)	8 (4.3)	25 (13.8)	4 (2.2)	14 (7.7)	2 (1.1)	25 (13.6)
Diarrhea	1 (0.5)	7 (3.6)	2 (1.0)	2 (1.1)	2 (1.1)	1 (0.6)	0	4 (2.2)	2 (1.1)
Laboratory test abnormalities	*n* = 191	*n* = 187	*n* = 195	*n* = 179	*n* = 176	*n* = 173	*n* = 176	*n* = 173	*n* = 176
Serum potassium									
$<3.5\ mmol\ l^{-1}$	4 (2.1)	2 (1.1)	0	7 (3.9)	6 (3.4)	3 (1.7)	1 (0.6)	1 (0.6)	0
$>5.5\ mmol\ l^{-1}$	1 (0.5)	1 (0.5)	2 (1.0)	0	0	1 (0.6)	1 (0.6)	2 (1.2)	1 (0.6)
$\geqslant 6.0\ mmol\ l^{-1}$	0	0	0	0	0	1 (0.6)	0	1 (0.6)	0
Serum creatinine									
$>176.8\ \mu mol\ l^{-1}$	0	0	0	0[a]	0[b]	0[c]	0[e]	1 (0.6)	0[f]
Blood urea nitrogen									
$>14.28\ mmol\ l^{-1}$	1 (0.5)	0	0	0[a]	0[b]	1 (0.6)[d]	0[e]	1 (0.6)	0[f]

Abbreviations: AE, adverse event; ALI, aliskiren; AML, amlodipine. Data are shown as number of patients (%). [a]*n* = 181. [b]*n* = 177. [c]*n* = 174. [d]*n* = 175. [e]*n* = 178. [f]*n* = 177.

lowering, but significantly lower rate of peripheral edema as compared with amlodipine monotherapy at high dose of 10 mg. This is consistent with the previous findings.[14]

In our study, aliskiren monotherapy reduced PRA by 61–68% from baseline at week 8 end point, whereas amlodipine monotherapy increased PRA by 59–73%. The combination of aliskiren and amlodipine reduced PRA to a similar extent as aliskiren monotherapy; thus, aliskiren neutralized the increase in PRA observed with amlodipine alone.

Combination therapy with aliskiren and amlodipine was generally well tolerated during the trial. This is consistent with the findings of previous studies.[4,7,15] Most AEs reported during the present study were mild or moderate in severity, and few patients experienced serious AEs or discontinued participation because of AEs. Overall, aliskiren/amlodipine combination therapy had a similar safety and tolerability profile to that of the individual monotherapies, with no evidence of new treatment-emergent AEs.

In summary, the present study shows that aliskiren/amlodipine combination therapy provides significantly greater BP reductions and improved rates of BP control than the respective monotherapies in patients with hypertension after 8 weeks of treatment. Combination therapy was well tolerated, with a similar safety and tolerability profile to those of the individual monotherapies.

Aliskiren/amlodipine combination offers a convenient and effective option for the treatment of patients with hypertension.

What is known about this topic

- Most patients are likely to need two or more agents to achieve BP control.
- A well-established combination therapy regimen involves use of the complementary mechanisms of action of an inhibitor of the renin–angiotensin–aldosterone system, in conjunction with a calcium channel blocker.
- The direct renin inhibitor aliskiren, in combination with the calcium channel blocker amlodipine, has been approved in the United States as an initial treatment for hypertension in patients likely to need multiple drugs to control BP, as replacement therapy for patients not achieving BP control with either monotherapy or as a substitute for the individual components given in combination.

What this study adds

- Aliskiren/amlodipine combination therapy at doses of 150/5, 150/10, 300/5 mg and 300/10 mg for 8 weeks provided clinically relevant BP reductions of 20.6–23.9/14.0–16.5 mm Hg, with additional least-squares mean reductions over all respective monotherapies. Combination therapy resulted in BP control rates of 49–68%.
- Aliskiren/amlodipine combination therapy provides an effective treatment option for patients with hypertension.

CONFLICT OF INTEREST

J Zhang, H Hsu and DL Keefe are employees of Novartis Pharmaceuticals Corporation and are therefore eligible for Novartis stock and stock options. The remaining authors declare no conflict of interest.

ACKNOWLEDGEMENTS

All authors participated in the development and writing of the paper, and approved the final paper for publication. The authors take full responsibility for the content of the paper and thank Dr Steven Inglis (Oxford PharmaGenesis Ltd, UK) and Dr Adam Tearle (Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) for medical writing support, editorial assistance, and collation, and incorporation of comments from all authors. This work was funded by Novartis Pharmaceuticals Corporation.

REFERENCES

1 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**: 1206–1252.
2 Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ *et al.* Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009; **27**: 2121–2158.
3 Azizi M, Webb R, Nussberger J, Hollenberg NK. Renin inhibition with aliskiren: where are we now, and where are we going? *J Hypertens* 2006; **24**: 243–256.
4 Brown MJ, McInnes GT, Cherif PC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. *Lancet* 2011; **377**: 312–320.
5 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF *et al.* Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; **18**: 139–185.
6 Hung HM. Evaluation of a combination drug with multiple doses in unbalanced factorial design clinical trials. *Stat Med* 2000; **19**: 2079–2087.
7 Braun-Dullaeus RC, Zhang J, Hristoskova S, Haring DA, Liao W. First-line therapy with aliskiren/amlodipine combination provides robust blood pressure reductions in patients with moderate to severe hypertension. *J Clin Hypertens* 2010; **12**(Suppl 1): abstract 27 PO-22.
8 Littlejohn III TW, Trenkwalder P, Hollanders G, Zhao Y, Liao W. Long-term safety, tolerability and efficacy of combination therapy with aliskiren and amlodipine in patients with hypertension. *Curr Med Res Opin* 2009; **25**: 951–959.
9 Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension* 2010; **55**: 399–407.
10 Shah NR, Hirsch AG, Zacker C, Wood GC, Schoenthaler A, Ogedegbe G *et al.* Predictors of first-fill adherence for patients with hypertension. *Am J Hypertens* 2009; **22**: 392–396.
11 Kettani FZ, Dragomir A, Cote R, Roy L, Berard A, Blais L *et al.* Impact of a better adherence to antihypertensive agents on cerebrovascular disease for primary prevention. *Stroke* 2009; **40**: 213–220.
12 Perreault S, Dragomir A, White M, Lalonde L, Blais L, Berard A. Better adherence to antihypertensive agents and risk reduction of chronic heart failure. *J Intern Med* 2009; **266**: 207–218.
13 Wu PH, Yang CY, Yao ZL, Lin WZ, Wu LW, Chang CC. Relationship of blood pressure control and hospitalization risk to medication adherence among patients with hypertension in Taiwan. *Am J Hypertens* 2010; **23**: 155–160.
14 Drummond W, Munger MA, Rafique EM, Maboudian M, Khan M, Keefe DL. Antihypertensive efficacy of the oral direct renin inhibitor aliskiren as add-on therapy in patients not responding to amlodipine monotherapy. *J Clin Hypertens* 2007; **9**: 742–750.
15 Black HR, Weinberger MH, Purkayastha D, Lee J, Israel M, Hilkert R *et al.* Combination aliskiren/amlodipine is more effective than amlodipine monotherapy in male and female African American subjects with stage 2 hypertension. *J Clin Hypertens* 2010; **12**(Suppl 1): abstract 26 PO-20.