Original Article

Aliskiren, a Novel Oral Renin Inhibitor, Provides Dose-Dependent Efficacy and Placebo-Like Tolerability in Japanese Patients with Hypertension

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Aliskiren is a novel orally active renin inhibitor for the treatment of hypertension. This study evaluated the antihypertensive efficacy, safety and tolerability of aliskiren in Japanese patients with hypertension. Forty hundred and fifty-five Japanese men and women with a mean sitting diastolic blood pressure of 95–110 mmHg were randomized to receive once-daily double-blind treatment for 8 weeks with aliskiren 75, 150 or 300 mg or placebo. Aliskiren produced significant, dose-dependent reductions in mean sitting diastolic blood pressure ($p<0.0005$ *vs.* placebo for each dose) and mean sitting systolic blood pressure ($p<0.001$ *vs.* placebo for each dose). The placebo-corrected reductions in mean sitting systolic/diastolic blood pressure were 5.7/4.0, 5.9/4.5 and 11.2/7.5 mmHg in the aliskiren 75, 150 and 300 mg groups, respectively. After 8 weeks' treatment, 27.8%, 47.8%, 48.2% and 63.7% of patients in the placebo and aliskiren 75, 150 and 300 mg groups, respectively, achieved a successful treatment response (diastolic blood pressure <90 mmHg and/or reduced by ≥10 mmHg from baseline; $p<0.005$ *vs.* placebo for each dose). Aliskiren treatment was well tolerated, with the incidence of adverse events reported in the active treatment groups (53–55%) being similar to that in the placebo group (50%). This study, which is the first to assess the antihypertensive efficacy and safety of aliskiren in Japanese patients with hypertension, demonstrates that the once-daily oral renin inhibitor aliskiren provides significant, dose-dependent reductions in blood pressure with placebo-like tolerability. (*Hypertens Res* 2006; 29: 997–1005)

***Key Words*: hypertension, aliskiren, renin inhibitor, Japanese, renin-angiotensin system**

Introduction

Hypertension affects 15–37% of the global adult population (*1*), accounts for 13% of global mortality and is predicted to substantially increase over the next 20 years (*2*). Although this highly prevalent condition is treatable, in the US approximately 30% of adults with hypertension are unaware that they have a problem, more than 40% are not on treatment and only about one-third of treated patients have their high blood pressure (BP) controlled (*3*). Similarly in Japan, approximately 30% of hypertensive adults over the age of 40 years are not receiving treatment, and in about half of treated patients, BP is not controlled to the target level (*4*).

The most recent advances in antihypertensive therapies include drugs targeting the renin-angiotensin-aldosterone system (RAAS) (*5*), and antihypertensive agents that suppress RAAS have been increasingly utilized in Japan (*6*). The

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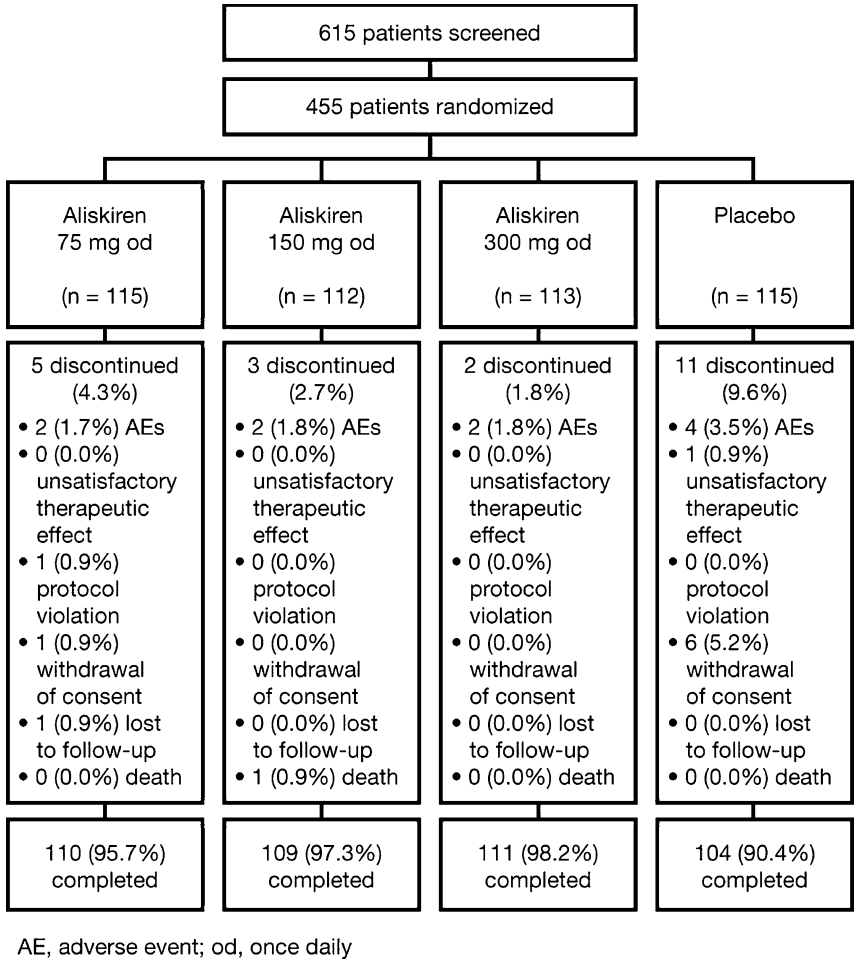

Fig. 1. *Patient flow diagram.*

RAAS, *via* angiotensin II and aldosterone, is a key regulator of BP and body fluid volume. In the RAAS, renin converts angiotensinogen to angiotensin I, which is then converted to the potent vasoconstrictor angiotensin II, primarily by angiotensin converting enzyme (ACE). The binding of angiotensin II to the angiotensin II type 1 (AT1) receptor on target cells results in increased peripheral vascular resistance and elevated BP. Increased and continued activation of the RAAS leads to chronic hypertension and is a major underlying cause of end-organ damage and cardiovascular events—which are both long term consequences of hypertension (*7*, *8*).

Suppression of RAAS with ACE inhibitors or angiotensin receptor blockers (ARBs) has proven to be clinically effective, producing a reduction in BP and evidence of end organ protection. ACE inhibitors reduce production of angiotensin II by inhibiting its conversion from angiotensin I by ACE, while ARBs suppress the action of angiotensin II by blocking binding to AT1 receptors (*9*–*11*). In addition to their antihypertensive efficacy, ACE inhibitors produce further beneficial effects, such as improved insulin sensitivity *via* the inhibition of kininase II and subsequent increase in bradykinin levels (*12*). However, elevated bradykinin levels are thought to be responsible for the dry cough that is reported by up to 20% of patients receiving treatment with this drug class (*10*, *13*). ACE inhibitors also fail to block angiotensin II production *via* ACE independent mechanisms (*14*, *15*). Meanwhile, ARBs have been shown to suppress cardiovascular remodelling *via* inhibition of AT1 receptor function (*16*, *17*). However, increased circulating levels of angiotensin II may lead to the stimulation of the angiotensin II type 2 (AT2) receptor population. The precise physiological role of AT2 receptors has yet to be determined, but they have been reported to be involved in the development of left ventricular hypertrophy (*16*, *18*). In addition to these effects, both ACE inhibitors and ARBs cause an increase in plasma renin activity (PRA) (*19*, *20*). Therefore, the optimal means of suppressing the RAAS may be to directly inhibit renin and thereby target the system at its point of activation. This would 1) reduce angiotensin II production; and 2) prevent a rise in PRA by inactivating the renin released as a result of compensatory feedback mechanisms (*21*, *22*). Through this strategy, it is unlikely that renin inhibitors would produce detrimental

Table 1. Patient Baseline and Demographic Characteristics

Baseline characteristics	Placebo ($n=115$)	Aliskiren		
		75 mg ($n=115$)	150 mg ($n=112$)	300 mg ($n=113$)
Sex (male/female)	90/25	79/36	81/31	80/33
Age (years)	52.7±9.5	52.3±10.8	53.3±10.4	51.6±9.9
Duration of hypertension (years)	4.6±4.1	5.9±5.5	5.9±6.5	6.2±6.5
BMI (kg/m^2)	25.3±3.4	25.5±3.7	25.3±3.2	25.6±4.2
Diabetes (*n* (%))	8 (7.0)	6 (5.2)	11 (9.8)	8 (7.1)
Mean sitting DBP (mmHg)	99.4±3.9	99.4±4.0	99.5±4.0	99.6±4.4
Mean sitting SBP (mmHg)	155.4±10.7	152.7±11.8	155.6±11.1	155.0±11.7
Sitting pulse (bpm)	72.0±9.8	75.0±9.7	72.0±9.7	73.8±8.9
Plasma renin activity (μg/l/h)	1.2±1.2	1.4±1.3	1.5±1.8	1.6±2.0
Plasma aldosterone (ng/dl)	10.2±3.6	10.9±4.8	10.5±4.5	10.1±4.4

Data are presented as mean±SD, unless otherwise stated. BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure.

effects analogous to those described above for ACE inhibitors and ARBs.

In the 1990s, several renin inhibitors were developed. These reduced angiotensin levels, lowered BP and had few significant adverse effects (*23–27*); however, low potency, poor bioavailability and short duration of action after oral administration prevented their practical use in hypertension (*28*). Aliskiren is the first in a new class of orally effective, nonpeptide, renin inhibitors for the treatment of hypertension (*29*, *30*). *In vitro*, aliskiren is a potent inhibitor of renin ($IC_{50}=0.6$ nmol/l) (*29*, *30*) with a plasma half-life of approximately 40 h (*31*). In non-hypertensive humans, aliskiren (40–640 mg once daily) was well tolerated and provided dose-dependent sustained inhibition of PRA and of angiotensin I and angiotensin II production (*19*, *20*). Clinical trials in patients with essential hypertension demonstrated that once-daily oral treatment with aliskiren achieved dose dependent (up to 300 mg/day) reductions in ambulatory BP, reducing both diastolic BP (DBP) and systolic BP (SBP). In these studies, aliskiren compared favorably with the ARBs irbesartan and losartan, displaying similar efficacy and tolerability after 4 and 8 weeks of treatment (*32*, *33*).

Hypertension is a global problem and racial differences in response to antihypertensive treatment and renin activity have been shown. However, many clinical trials have recruited predominantly Western populations, and thus there are few data for Asian populations (*34*). Studies of antihypertensive agents across the range of racial groups are therefore important.

The aim of this randomized, double-blind, placebo-controlled study was to assess the antihypertensive efficacy of aliskiren 75 mg, 150 mg and 300 mg once daily in Japanese patients with hypertension. This is the first placebo-controlled study to investigate the effects of a renin inhibitor in Japanese patients with hypertension.

Methods

Participants

For this study, Japanese men and women with essential hypertension between the ages of 20 and 80 years were recruited from 29 clinical centers in Japan. To be eligible for the study, patients were required to have a mean sitting DBP of ≥90 mmHg and <110 mmHg during the run-in period, and ≥95 mmHg and <110 mmHg at baseline (when patients were randomized to treatment), with a <10 mmHg difference in DBP between the two measurements. Exclusion criteria included severe hypertension (sitting DBP ≥110 mmHg and/or SBP ≥180 mmHg); suspected secondary hypertension; suspected malignant hypertension; type 1 diabetes or type 2 diabetes receiving insulin or with poor glucose control (HbA_{1C} >8%); serious cardiac, hepatic, renal or cerebrovascular disease; and clinically significant allergy. Patients were also excluded if they had a history of pancreatitis; malignant tumours in the last 5 years; autoimmune diseases; anemia, gout, or hyperthyroidism; apparent dehydration; and pregnancy. In addition, patients were not eligible if they were receiving treatment for a gastric or duodenal ulcer or had taken any other investigational product within the last 12 weeks.

Study Design

This was a 13-week, multicenter, randomized, placebo-controlled, double-blind, parallel-group study. After screening, eligible patients received placebo during a 4-week single-blind "wash out" period. Patients were then randomized to receive once-daily treatment for 8 weeks with aliskiren 75 mg, aliskiren 150 mg, aliskiren 300 mg, or placebo. Following the treatment phase the trial ended with a 1-week withdrawal period. Each dose of medication was administered

Table 2. Concomitant Medications Received by Patients during the Double-Blind Phase of the Study by ATC Class

	Placebo ($n=115$)	Aliskiren		
		75 mg ($n=115$)	150 mg ($n=112$)	300 mg ($n=113$)
Concomitant medication received in ≥ 6% of patients in any group				
HMG CoA reductase inhibitors	7 (6.1)	19 (16.5)	12 (10.7)	10 (8.8)
Propionic acid derivatives	10 (8.7)	19 (16.5)	9 (8.0)	14 (12.4)
Anilides	10 (8.7)	14 (12.2)	12 (10.7)	11 (9.7)
Drugs for peptic ulcer and GERD	9 (7.8)	11 (9.6)	6 (5.4)	8 (7.1)
Antiinflammatory agents, non steroids	4 (3.5)	6 (5.2)	5 (4.5)	10 (8.8)
Non-drug therapies and derivatives	9 (7.8)	5 (4.3)	5 (4.5)	7 (6.2)
Platelet aggregation inhibitors (excl. heparin)	5 (4.3)	9 (7.8)	4 (3.6)	1 (0.9)
Opium alkaloids and derivatives	7 (6.1)	4 (3.5)	6 (5.4)	8 (7.1)
Cephalosporins and related substances	6 (5.2)	8 (7.0)	2 (1.8)	5 (4.4)
Macrolides	2 (1.7)	3 (2.6)	7 (6.3)	4 (3.5)
Influenza vaccines	4 (3.5)	7 (6.1)	3 (2.7)	2 (1.8)
Other therapeutic products	7 (6.1)	2 (1.7)	2 (1.8)	1 (0.9)
Other antiallergics	2 (1.7)	7 (6.1)	0 (0.0)	1 (0.9)

Data are presented as number (%) of patients. ATC, anatomical therapeutic chemical; HMG CoA, 3-hydroxy-3-methyl-glutaryl-CoA; GERD, gastro-esophageal reflux disease.

between 6:00 AM and 10:00 AM every morning and had to be taken at least 30 min before a meal. The only exception was on the day of each scheduled study visit (excluding visit 1), when patients were instructed to take their medication after all examinations and observations were completed.

Aliskiren was available as film-coated tablets of 75 mg and 150 mg. Patients randomized to receive aliskiren 75 mg or 150 mg took one tablet of the relevant dose and patients randomized to receive aliskiren 300 mg took two 150 mg tablets. To maintain blinding, all patients took three tablets a day (two aliskiren tablets plus one placebo, two placebo tablets plus one aliskiren, or three placebo tablets). Drug allocation tables were prepared by computer-generated random numbers and patients were assigned to treatment groups *via* central allocation. The allocation schedule was then concealed until the key code was broken, so all patients, investigators, collaborators and the sponsor were unaware of the treatment assignments throughout the study.

The study was performed in compliance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki of the World Medical Association, and received approval by the Institutional Review Board. All patients gave written informed consent.

Assessments

Patients were screened for inclusion/exclusion criteria and given information and consent forms at the start of the study. Eligible patients were then further screened for demographic characteristics (including age, gender, height, weight, hypertension history), previous drug use, sitting BP and pulse rate, chest X-ray, laboratory tests, pregnancy test and 12-lead resting ECG. A second visit took place 2 weeks later during the wash out period to assess sitting BP and pulse, and treatment compliance to placebo. Patients were randomized at the baseline visit (4 weeks after the first assessment), at which time they were given a third assessment that included trough BP measurement (standing, sitting and supine) using the automatic Omron HEM-907, sitting pulse, laboratory and pregnancy tests, assessment of compliance to placebo and an inquiry about concomitant medication. Follow-up study visits took place at 2, 4, 6 and 8 weeks after randomization, and during the withdrawal period.

The primary efficacy assessment was mean sitting DBP at the study endpoint, calculated by the average of three measurements taken at 1- to 2-min intervals after resting for at least 5 min in the seated position. Sitting BP and pulse were measured at all intermediate visits while standing, and supine BP values were measured at the baseline visit just prior to randomization (visit 3 [week 0]) and the visit at week 8 (or at the time of discontinuation).

To assess safety, adverse events were recorded by date of onset, rated as mild, moderate or severe, and judged as being related to the study medication or not. Laboratory variables were measured at baseline, week 4 and week 8. Tests included hematology (leukocyte count, hemoglobin), blood biochemistry (liver transaminases, serum creatinine) and urinalysis (including glucose and protein). At baseline and at week 8, body weight was measured and a 12-lead ECG obtained. Treatment compliance was monitored at all visits by asking patients the dates and times that they took the study drug before the current visit. Compliance was defined as correct medication compliance on at least 70% of the days.

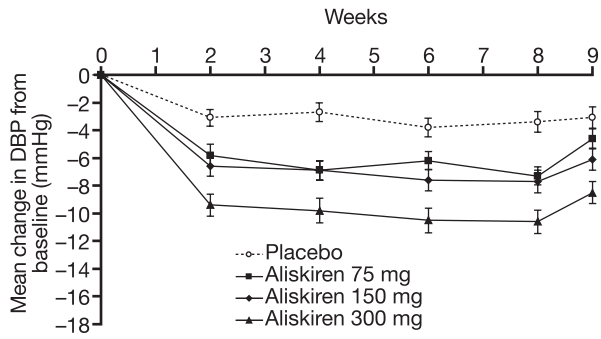

Fig. 2. *Effect of aliskiren on mean sitting diastolic blood pressure (DBP) in Japanese patients with hypertension over the course of the double-blind treatment period (week 0–8) and following the 1-week withdrawal period (week 9). Data are presented as mean changes in DBP from baseline following treatment with aliskiren 75 mg (filled squares), 150 mg (filled diamonds), 300 mg (filled triangles) or placebo (open circles). Data are presented as mean ± SEM.*

Data Analysis and Statistical Methods

The primary efficacy variable was the change in mean trough sitting DBP from baseline at endpoint. The primary efficacy analysis was a comparison of the primary efficacy variable between the aliskiren treatment groups and placebo. Secondary efficacy variables were change in mean trough sitting SBP from baseline, proportion of patients responding to treatment (those with mean sitting DBP <90 mmHg and/or with a ≥ 10 mmHg decrease in mean sitting DBP from baseline on completion of treatment) and dose-response relationship (in terms of the primary and secondary efficacy variables). Changes in mean trough sitting DBP and SBP from baseline in each treatment group were assessed by a two-way analysis of covariance, using dose of aliskiren as an explanatory variable and baseline mean trough sitting SBP and DBP as covariates. The least square mean change and its 95% confidence interval were obtained for each treatment group. The least square mean differences between changes in each of the aliskiren treatment groups and the placebo treatment group, the 95% confidence intervals and the *p*-values were also obtained. Dunnett's sequential rejection test was then used to adjust for multiple comparisons. In the case of missing data, the last measurement in the double-blind period was carried forward.

The number and proportion of patients responding to treatment in each of the active drug groups was compared with the corresponding values in the placebo group using logistic regression analysis. Odds ratios and their 95% confidence intervals were also calculated for each treatment group.

The dose-response relationship was assessed with respect to the primary and secondary variables as: linearly increased; saturated at medium dose; increased at high dose; or constant depending on the relative response to each dose.

Efficacy and safety analyses were performed on the full analysis set (FAS) of all randomized patients. Patients who discontinued the study treatment or had major protocol deviations were excluded from the per protocol set (PPS). A target sample size of 440 patients (110 in each treatment group) was selected to be able to detect a 3.5 mmHg difference in mean sitting DBP between treatment groups and the placebo group with a power of 80% as estimated using the Dunnett's sequential rejection procedure, assuming a standard deviation of 8 mmHg and a drop-out rate of 10%.

Results

Patients

A total of 615 patients with essential hypertension were screened for the study, of which 455 patients were randomized to the four treatment groups (115 patients in the placebo group, 115 in the aliskiren 75 mg group, 112 in the aliskiren 150 mg group and 113 in the aliskiren 300 mg group). Of the 455 patients randomized (FAS), 21 (4.6%) patients, mainly from the placebo group, discontinued study treatment during the double-blind phase of the trial. The main reasons for discontinuation among all patients were adverse events ($n=10$) and withdrawal of consent ($n=7$) (Fig. 1). No difference was observed between the FAS and PPS populations in terms of results for the primary endpoint.

Patient demographics and disease characteristics were similar in all treatment groups at baseline and are shown in Table 1.

During the double-blind treatment phase of the study, only one patient was non-compliant with the study medication; this patient was in the aliskiren 75 mg group. Also during this phase, more than half the patients used concomitant medications: 47.8%, 61.7%, 55.4%, and 55.8% of patients receiving placebo, aliskiren 75 mg, 150 mg, and 300 mg, respectively. The principal concomitant medications received by patients are listed in Table 2.

Efficacy

All doses of aliskiren caused significant reductions ($p<0.0005$) in mean sitting DBP compared with placebo (Fig. 2 and Table 3). The antihypertensive effect of aliskiren on mean sitting DBP became evident after 2 weeks of treatment and further BP lowering was observed until week 8. A significant reduction ($p<0.001$) was also observed in the mean sitting SBP following treatment with aliskiren (all groups) compared to placebo (Fig. 2 and Table 3). The placebo-corrected reductions in mean sitting SBP/DBP due to active treatment were 5.7/4.0, 5.9/4.5, 11.2/7.5 mmHg in the aliskiren 75 mg, 150 mg, and 300 mg groups, respectively. Similar reductions were observed for the trough standing and supine DBP and SBP following treatment with aliskiren

Table 3. Effect of Aliskiren on Mean Sitting Blood Pressure in Japanese Patients with Hypertension

	Least squares mean change from baseline (SEM)*	Placebo-corrected change	95% CI	*p*-value *vs*. placebo
Mean sitting diastolic BP (mmHg)				
Placebo	−3.26 (0.75)			
Aliskiren 75 mg	−7.22 (0.75)	−3.96	−6.03, −1.89	0.0002
Aliskiren 150 mg	−7.75 (0.76)	−4.49	−6.57, −2.41	<0.0001
Aliskiren 300 mg	−10.72 (0.75)	−7.46	−9.54, −5.38	<0.0001
Mean sitting systolic BP (mmHg)				
Placebo	−2.85 (1.17)			
Aliskiren 75 mg	−8.57 (1.17)	−5.72	−8.97, −2.47	0.0006
Aliskiren 150 mg	−8.72 (1.18)	−5.87	−9.13, −2.61	0.0009
Aliskiren 300 mg	−14.09 (1.18)	−11.24	−14.50, −7.99	<0.0001

BP, blood pressure; CI, confidence interval. *Least squares mean change obtained by ANCOVA model using baseline as a covariate.

Table 4. Proportion of Patients with Response to Treatment at End Point

Treatment group	*n*/*N*	%	Odds ratio	95% CI	*p*-value *vs*. placebo*
Placebo	32/115	27.8			
Aliskiren 75 mg	55/115	47.8	2.52	1.42, 4.46	0.0015
Aliskiren 150 mg	54/112	48.2	2.60	1.46, 4.62	0.0011
Aliskiren 300 mg	72/113	63.7	5.22	2.89, 9.42	0.0001

CI, confidence interval. Responders (*n*) were defined as patients in whom mean sitting DBP was <90 mmHg at the end of the treatment period and/or decreased by ≥10 mmHg from baseline. **p*-values were calculated using a logistic regression model using baseline blood pressures as a covariate.

(data not shown).

Dose-response analysis showed that the relationship between reductions in mean sitting DBP and SBP and aliskiren dose was almost linear. However, further contrast analysis revealed that a pattern of similar reductions with aliskiren 75 mg and 150 mg and greater reductions with aliskiren 300 mg was a better fit for both mean sitting DBP and SBP.

The "successful responder" was defined as a patient whose mean trough sitting DBP decreased to <90 mmHg or decreased by ≥10 mmHg from baseline during the double-blind period, or if both these criteria were satisfied. The proportion of patients who responded to treatment was significantly higher ($p<0.005$) in each of the aliskiren groups compared with the placebo group, and increased with dose from 47.8% in the aliskiren 75 mg group to 63.7% in the aliskiren 300 mg group (Table 4). In addition, the proportion of patients whose BP was controlled (mean sitting BP <140/90 mmHg) in the aliskiren treatment groups was significantly higher ($p<0.05$) than in the placebo group, and increased in a dose-dependent manner (from 23.5% to 41.6%).

The reductions in mean sitting DBP were sustained following withdrawal from aliskiren. At 1 week after treatment withdrawal, the mean sitting DBP was lower than at baseline in 77/110 (70.0%), 84/109 (77.1%) and 92/111 (82.9%) of patients receiving aliskiren 75 mg, 150 mg, and 300 mg, respectively, compared with 62/104 (59.6%) of patients receiving placebo.

Safety and Tolerability

Aliskiren treatment was well tolerated, displaying a placebo-like safety profile with the incidence of adverse events (AEs) reported in the active treatment groups (53–55%) being similar to that in the placebo group (50%). Furthermore, there was no evidence of any increase in the incidence of drug-related AEs with increasing dose of aliskiren (Table 5). AEs were reported in a total of 239 patients (52.5%) and led to study discontinuation for ten patients, four in the placebo group and two in each of the aliskiren groups. AEs suspected to be related to the study drug occurred in 71 (15.6%) patients, broken down as 21 (4.6%), 13 (2.9%), 19 (4.2%) and 18 (4.0%) patients in the placebo, 75 mg, 150 mg and 300 mg aliskiren groups, respectively. The most commonly reported all-causality AEs were nasopharyngitis, headache and laryngopharyngitis. Although the incidence of nasopharyngitis was numerically higher in the active treatment groups than in the placebo group, there was no evidence of any increase in the incidence of all-causality AEs with increasing dose (Table 5).

Clinical laboratory values were unaltered in the majority of

Table 5. Adverse Events Newly Observed during the Treatment Period (at a ≥1.5% Incidence in Any of the Groups)

	Placebo ($n=115$)	Aliskiren		
		75 mg ($n=115$)	150 mg ($n=112$)	300 mg ($n=113$)
Total	58 (50.4)	61 (53.0)	58 (51.8)	62 (54.9)
Nasopharyngitis	16 (13.9)	24 (20.9)	20 (17.9)	20 (17.7)
Headache	4 (3.5)	3 (2.6)	3 (2.7)	6 (5.3)
Laryngopharyngitis	3 (2.6)	2 (1.7)	1 (0.9)	1 (0.9)
Blood pressure increased	3 (2.6)	1 (0.9)	1 (0.9)	0 (0.0)
Diarrhea	1 (0.9)	1 (0.9)	1 (0.9)	4 (3.5)
Vertigo	2 (1.7)	0 (0.0)	0 (0.0)	1 (0.9)
Abdominal pain	0 (0.0)	2 (1.7)	0 (0.0)	1 (0.9)
Gastritis	2 (1.7)	0 (0.0)	0 (0.0)	1 (0.9)
Joint sprain	0 (0.0)	1 (0.9)	2 (1.8)	0 (0.0)
Arthralgia	3 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)
Herpes zoster	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Back pain	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
Eczema	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)

Conversion of adverse event names is based on MedDRA ver 8.0. Data are presented as the number (%) of patients reporting adverse events.

Table 6. Clinically Significant Changes in Laboratory Values Observed during the Double-Blind Period of the Study

Laboratory value	Placebo ($n=115$)	Aliskiren		
		75 mg ($n=115$)	150 mg ($n=112$)	300 mg ($n=113$)
Increase in WBC (>50% from baseline)	2 (1.7)	2 (1.7)	1 (0.9)	1 (0.9)
Increase in ALT (GPT) (≥150% increase from baseline)	3 (2.6)	5 (4.3)	4 (3.6)	2 (1.8)
Hyperkalemia	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)

Data are presented as the number (%) of patients reporting adverse events. ALT, alanine aminotransferase; GPT, glutamic pyruvic transaminase.

patients, with no evidence of a clinically significant change from baseline in any of the treatment groups. The most frequent abnormality was elevated alanine aminotransferase (Table 6), but its incidence was similar across the active treatment (1.8–4.3%) and placebo (2.6%) groups. Only two patients, both receiving aliskiren 75 mg, had hyperkalemia (≥20% increase in potassium levels from baseline).

During the treatment period, serious AEs, including one death, were observed in five patients. Three serious AEs were reported in patients receiving placebo and were not deemed related to the study drug; one patient suffered cerebral infarction, a second was diagnosed with pancreatic cancer/hepatic metastases of pancreatic cancer and a third presented with infective enteritis. One serious AE was judged to be possibly related to the study drug; this was a case of acute myocardial infarction in a patient receiving aliskiren 75 mg. The one death (in the aliskiren 150 mg group) was not considered related to the study drug. It occurred in a patient receiving concomitant psychiatric treatment for manic depression who was suspected to have overdosed on one of these medications. The extent of the psychiatric illness was not known to the investigator until after the event.

Discussion

This study, which is the first to assess the antihypertensive efficacy and safety of aliskiren in Japanese patients with hypertension, demonstrates that the once-daily oral renin inhibitor aliskiren provides significant, dose-dependent reductions in BP with placebo-like tolerability.

The antihypertensive effects of aliskiren demonstrated in Japanese patients in the present study are consistent with those observed in previous studies on aliskiren conducted in ethnically diverse but predominantly Western populations (*31, 32*). In the present study, the reductions in BP from baseline after 8 weeks treatment with aliskiren 150 mg and 300 mg (8.7/7.8 mmHg and 14.7/10.7 mmHg, respectively) are similar to the reductions recorded in a study of predominantly Western populations (11.4/9.3 mmHg and 15.8/11.8 mmHg for aliskiren 150 mg and 300 mg, respectively) (*32*). In addi-

tion, the dose-dependence of the response in Japanese patients was similar to that seen in Western patients (*32*). In both study populations, while the 150 mg/day dose of aliskiren was an effective BP lowering dose, titration to the 300 mg/day dose could be useful for patients failing to achieve target. Also consistent with the previous clinical trial of aliskiren, the dose-dependent antihypertensive effect of aliskiren was evident within 2 weeks of the first dose (*32*). In general, there do not appear to be significant racial differences in response to aliskiren between Japanese and Western patients with hypertension.

As expected due to the long plasma half-life of aliskiren, this study showed that once-daily dosing with aliskiren provided effective BP control when measured at trough. The convenience of such once-daily dosing is an important factor for improving patient compliance with antihypertensive therapies, and in this clinical trial setting, compliance was excellent. In addition, evidence suggests that sustained 24-h BP control, as observed with aliskiren (*33*), is essential to achieve optimal BP control and to protect against end-organ damage (*35*).

Patient compliance with aliskiren is also aided by its placebo-like safety profile (*32*, *33*, *36*). In this study aliskiren was well-tolerated in all treatment groups, consistent with previous findings that aliskiren has a safety profile equivalent to the ARBs losartan and irbesartan, and placebo (*32*, *33*). Clinically significant elevations in potassium levels were reported in two patients receiving aliskiren 75 mg, but there was no evidence of a dose-related change. Hyperkalemia has been reported with other inhibitors of the RAAS (ARBs and ACE inhibitors) and for these drug classes it is reported as a side effect to be monitored.

This study adds to the growing evidence that the renin inhibitor aliskiren is effective in the short-term for hypertension, but longer-term and larger-scale studies will be needed to confirm its promise in end-organ protection. However, given the effectiveness of RAAS inhibition in hypertension and a wide range of other disease states, it seems likely that aliskiren will become an important addition in the fight against hypertension.

In conclusion, once-daily treatment with aliskiren 75 mg, 150 mg or 300 mg significantly lowered BP in Japanese patients with essential hypertension. This reduction was evident after only 2 weeks of treatment and was long lasting and dose-dependent. In addition, aliskiren demonstrated a safety profile similar to that of placebo, an important consideration in the largely asymptomatic condition of hypertension.

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Appendix

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References

1. Integrated Management of Cardiovascular Risk, Report of a WHO Meeting. Geneva, 9–12 July 2002. Geneva, WHO, 2002.
2. The World Health Report 2002—Reducing Risks, Promoting Healthy Life. Geneva, WHO, 2002.
3. Chobanian AV, Bakris GL, Black HR, *et al*: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**: 1206–1252.
4. Hozawa A, Ohkubo T, Kikuya M, *et al*: Blood pressure control assessed by home, ambulatory and conventional blood pressure measurements in the Japanese general population: the Ohasama study. *Hypertens Res* 2002; **25**: 57–63.
5. Morgan T: Renin angiotensin, sodium and organ damage. *Hypertens Res* 2003; **26**: 349–354.
6. Mori H, Ukai H, Yamamoto H, *et al*: Current status of antihypertensive prescription and associated blood pressure control in Japan. *Hypertens Res* 2006; **29**: 143–151.
7. Dzau VJ: Theodore Cooper Lecture: tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. *Hypertension* 2001; **37**: 1047–1052.
8. Weir MR, Dzau VJ: The renin-angiotensin-aldosterone system: a specific target for hypertension management. *Am J Hypertens* 1999; **12**: 205S–213S.
9. Dahlof B, Devereux RB, Kjeldsen SE, *et al*: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995–1003.
10. Dahlof B, Sever PS, Poulter NR, *et al*: Prevention of cardio-

vascular events with an antihypertensive regimen of amlodipine adding perindopril as required *versus* atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**: 895–906.
11. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, The Heart Outcomes Prevention Evaluation Study Investigators: Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342**: 145–153.
12. Tomiyama H, Kushiro T, Abeta H, *et al*: Kinins contribute to the improvement of insulin sensitivity during treatment with angiotensin converting enzyme inhibitor. *Hypertension* 1994; **23**: 450–455.
13. Israili ZH, Hall WD: Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. *Ann Intern Med* 1992; **117**: 234–242.
14. Hollenberg NK, Fisher ND, Price DA: Pathways for angiotensin II generation in intact human tissue: evidence from comparative pharmacological interruption of the renin system. *Hypertension* 1998; **32**: 387–392.
15. Wolny A, Clozel JP, Rein J, *et al*: Functional and biochemical analysis of angiotensin II–forming pathways in the human heart. *Circ Res* 1997; **80**: 219–227.
16. Okazaki H, Minamino T, Tsukamoto O, *et al*: Angiotensin II type 1 receptor blocker prevents atrial structural remodeling in rats with hypertension induced by chronic nitric oxide inhibition. *Hypertens Res* 2006; **29**: 277–284.
17. Williams B: Angiotensin II and the pathophysiology of cardiovascular remodeling. *Am J Cardiol* 2001; **87**: 10C–17C.
18. Senbonmatsu T, Ichihara S, Price E Jr, Gaffney FA, Inagami T: Evidence for angiotensin II type 2 receptor–mediated cardiac myocyte enlargement during *in vivo* pressure overload. *J Clin Invest* 2000; **106**: R25–R29.
19. Azizi M, Menard J, Bissery A, *et al*: Pharmacologic demonstration of the synergistic effects of a combination of the renin inhibitor aliskiren and the AT1 receptor antagonist valsartan on the angiotensin II-renin feedback interruption. *J Am Soc Nephrol* 2004; **15**: 3126–3133.
20. Nussberger J, Wuerzner G, Jensen C, Brunner HR: Angiotensin II suppression in humans by the orally active renin inhibitor Aliskiren (SPP100): comparison with enalapril. *Hypertension* 2002; **39**: E1–E8.
21. Skeggs LT Jr, Kahn JR, Lentz K, Shumway NP: The preparation, purification, and amino acid sequence of a polypeptide renin substrate. *J Exp Med* 1957; **106**: 439–453.
22. Fisher ND, Hollenberg NK: Renin inhibition: what are the therapeutic opportunities? *J Am Soc Nephrol* 2005; **16**: 592–599.
23. Kokubu T, Hiwada K, Murakami E, Muneta S, Kitami Y, Salmon PF: ES-8891, an orally active inhibitor of human renin. *Hypertension* 1990; **15**: 909–913.
24. Weber MA, Neutel JM, Essinger I, Glassman HN, Boger RS, Luther R: Assessment of renin dependency of hypertension with a dipeptide renin inhibitor. *Circulation* 1990; **81**: 1768–1774.
25. Neutel JM, Luther RR, Boger RS, Weber MA: Immediate blood pressure effects of the renin inhibitor enalkiren and the angiotensin-converting enzyme inhibitor enalaprilat. *Am Heart J* 1991; **122**: 1094–1100.
26. van den Meiracker AH, Admiraal PJ, Derkx FH, *et al*: Comparison of blood pressure and angiotensin responses to the renin inhibitor Ro 42-5892 and the angiotensin converting enzyme inhibitor enalapril in essential hypertension. *J Hypertens* 1993; **11**: 831–838.
27. Kobrin I, Viskoper RJ, Laszt A, Bock J, Weber C, Charlon V: Effects of an orally active renin inhibitor, Ro 42-5892, in patients with essential hypertension. *Am J Hypertens* 1993; **6**: 349–356.
28. Fisher ND, Hollenberg NK: Is there a future for renin inhibitors? *Expert Opin Investig Drugs* 2001; **10**: 417–426.
29. Wood JM, Maibaum J, Rahuel J: Structure-based design of aliskiren, a novel orally effective renin inhibitor. *Biochem Biophys Res Commun* 2003; **308**: 698–705.
30. Rahuel J, Rasetti V, Maibaum J, *et al*: Structure-based drug design: the discovery of novel nonpeptide orally active inhibitors of human renin. *Chem Biol* 2000; **7**: 493–504.
31. Vaidyanathan S, Limoges D, Yeh C-M, Dieterich H-A: Aliskiren, an orally effective renin inhibitor, shows dose linear pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 2006; **79**: P64.
32. Gradman AH, Schmieder RE, Lins RL, *et al*: Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation* 2005; **111**: 1012–1018.
33. Stanton A, Jensen C, Nussberger J, O'Brien E: Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. *Hypertension* 2003; **42**: 1137–1143.
34. Williams B, Poulter NR, Brown MJ, *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.
35. Frattola A, Parati G, Cuspidi C, Albini F, Mancia G: Prognostic value of 24-hour blood pressure variability. *J Hypertens* 1993; **11**: 1133–1137.
36. Neutel JM, Smith DH, Weber MA: Low-dose combination therapy: an important first-line treatment in the management of hypertension. *Am J Hypertens* 2001; **14**: 286–292.