Efficacy, Safety, and Tolerability of Aliskiren Monotherapy Administered With a Light Meal in Elderly Hypertensive Patients: A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Evaluation Study

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This randomized, double-blind, placebo-controlled study assessed the efficacy, safety, and tolerability of aliskiren 75, 150, and 300 mg to clarify the dose-response relationship and characterize the optimum aliskiren dose when given with a light meal to elderly hypertensive patients. After washout, 754 patients aged ≥65 years with hypertension (mean sitting systolic blood pressure [msSBP] ≥150 and <180 mm Hg; mean sitting diastolic blood pressure [msDBP] <110 mm Hg) were randomized to aliskiren 75, 150, or 300 mg or placebo for 8 weeks; medication was taken each morning with a light meal. The primary efficacy variable was change in msSBP from baseline to week 8 end point. Change from baseline in msDBP and dose-response curves for aliskiren 75, 150, and 300 mg were also assessed. At week 8 end point, all 3 aliskiren doses provided significantly greater least squares mean reductions in msSBP/msDBP (75 mg, 13/5 mm Hg; 150 mg, 15/6 mm Hg; 300 mg, 14/7 mm Hg) compared with placebo (8/4 mm Hg; P < .05). Aliskiren was generally well tolerated at all doses. There was a significant dose-response relationship for aliskiren, with an estimated minimum effective dose of 81.9 mg. In conclusion, aliskiren 150 and 300 mg provided effective blood pressure control in elderly patients when given with a light meal.

Keywords: *aliskiren; hypertension; renin-angiotensin-aldosterone system; elderly; food*

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The prevalence of hypertension increases with age; in developed countries, an estimated 60% to 70% of elderly individuals have hypertension.[1,2] Hypertension is associated with an increased risk of cardiovascular and renal disease, and the absolute risk of cardiovascular events associated with high blood pressure (BP) is greater in elderly patients than in younger individuals.[3] Hypertension thus represents a major and growing health concern in developed countries, as the proportion of elderly individuals continues to rise. However, treatment is often suboptimal for elderly individuals, and fewer than 50% of treated patients achieve BP control.[1,2,4]

Chronic activation of the renin-angiotensin-aldosterone system (RAAS) is implicated in the development of hypertension and cardiovascular and renal disease and is an important target for antihypertensive therapy.[5,6] The direct renin inhibitor aliskiren acts at the rate-limiting step of the RAAS, reducing plasma renin activity (PRA) and so inhibiting the production of angiotensin I and II and aldosterone.[7] Aliskiren differs from angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which also target the RAAS, in that these agents increase PRA.[7] Aliskiren may thus provide greater

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suppression of the RAAS than ACE inhibitors and ARBs.

Aliskiren is approved for the treatment of hypertension at once-daily doses of 150 mg and 300 mg. In the European Union (EU), the current prescribing information states that aliskiren should be taken once a day with a light meal.[8] Aliskiren has relatively low bioavailability, and administration 30 minutes after a high-fat meal has been shown to reduce aliskiren exposure and peak plasma concentration in healthy volunteers.[9] However, a separate study showed that the pharmacodynamic effects of aliskiren were not affected by food, with similar reductions in PRA observed regardless of whether aliskiren was administered in the fed or fasted states.[9] Furthermore, clinical trials, in which aliskiren was administered without regard to meals, have demonstrated the consistent efficacy and safety of aliskiren across patient populations.[10,11] This study was designed to provide further information on the effects of aliskiren when administered with a "typical" European light meal to elderly patients (age ≥65 years) with hypertension and was performed as part of an EU postmarketing commitment mandated by the European Medicines Agency. Our study assessed the efficacy, safety, and tolerability of once-daily aliskiren 75 mg, 150 mg, and 300 mg compared with placebo over 8 weeks of treatment to clarify the dose-response curves and characterize the optimum dose of aliskiren when administered with a light meal.

METHODS

Patients

Men and women aged ≥65 years with essential hypertension (defined as mean sitting systolic BP [msSBP] ≥150 mm Hg and <180 mm Hg and mean sitting diastolic BP [msDBP] <110 mm Hg) were eligible for inclusion in this study. In addition, patients' msSBP had to differ by ≤15 mm Hg between the last two visits of the placebo run-in period for inclusion. The main exclusion criteria were current diagnosis of severe hypertension (msSBP ≥180 mm Hg or msDBP ≥110 mm Hg), heart failure (New York Heart Association class II-IV), symptomatic arrhythmia, or clinically significant valvular heart disease; history or evidence of secondary hypertension or cerebrovascular or cardiovascular disease; known Keith-Wagener grade III or IV hypertensive retinopathy; type 1 diabetes mellitus or type 2 diabetes mellitus with HbA_{1c} >8% at screening; history or evidence of malignancy in the past 5 years; serum potassium >5.5 mEq/L; or estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease formula[12]) at screening.

The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki and was approved by the institutional review board or independent ethics committee at each study center (see appendix for details). Written informed consent was provided by each patient before participation in any study procedures. The trial is registered with ClinicalTrials.gov (identifier: NCT00706134). Patient recruitment and follow-up were between May 26, 2008, and April 15, 2009.

Study Design

This randomized, double-blind, placebo-controlled study was performed at 95 centers in 8 countries (Argentina [n = 179], Czech Republic [n = 29], Germany [n = 262], Iceland [n = 6], Italy [n = 35], the Netherlands [n = 55], Poland [n = 51], and Slovakia [n = 139]).

After screening, eligible patients entered a 1-week washout period, during which antihypertensive medication was withdrawn according to the investigators' instructions and manufacturers' label. The washout period permitted a complete washout of the antihypertensive effect of any prior medication(s) and allowed the assessment of the patient's hypertension profile for study eligibility, the establishment of reliable baseline values, and the evaluation of patient compliance. Prior antihypertensives required at least 1 week discontinuation before entering the next study period, whereas the newly diagnosed patients, who were not under treatment in the week prior to visit 1, could have enrolled directly into the next study period. Following a 1-week washout period, patients entered a 2- or 3-week single-blind, placebo run-in period to establish baseline BP and eligibility for randomization; newly diagnosed patients not receiving antihypertensive treatment in the week before screening entered the run-in period directly after screening. Patients not meeting the BP criteria for randomization after 2 weeks continued the placebo run-in for a further week, after which patients who still did not meet the criteria were excluded from the study. At the end of the placebo run-in period, eligible patients were randomized equally to aliskiren 75 mg, 150 mg, or 300 mg or placebo once daily for 8 weeks. Randomization was stratified by region and age group (≥65 to <75 years

and ≥75 years). To ensure that at least 35% of randomized patients in the study were age ≥75 years (to have ≥30% of patients per group completing the study), enrollment into the ≥65 to <75 years age group was stopped once the target number of patients in this group was reached. Patients were instructed to take their medication in the morning with a light meal, except on the day of a study visit, when the medication was administered by study center staff. To allow for regional variations in a "typical" European light breakfast, the composition of the meal was not prespecified in the study protocol; instead, a region-specific meal was developed by each country based on the cultural and dietary norms of that country. The light meal consisted of a small to medium portion of 1 or 2 of the following: fruit, yogurt, cereal, toast, croissant, bread, cold meat, cheese, or salad, with coffee, tea, juice, or milk.

No dose adjustment of study medication was permitted during the study, but the temporary interruption of study medication was allowed for documented reasons, such as adverse events (AEs). Patients were discontinued from the study for use of cyclosporine or, for safety reasons, if msDBP was ≥110 mm Hg or msSBP was ≥180 mm Hg at any time during the study as no rescue medications were allowed. Patients with msDBP <60 mm Hg or msSBP <100 mm Hg and/or signs or symptoms of clinically significant hypotension were evaluated by the investigator and withdrawn if clinically justified.

An Interactive Voice Response System (IVRS) was used to randomly assign patients to study medication. The IVRS automated the random assignment of patient numbers to randomization numbers, which are linked to the different treatment arms. The medication randomization list was produced by Novartis Drug Supply Management. Placebo tablets were matched to the active study drug, and a double-dummy design was used to ensure study blinding.

Study Assessments

The primary objective of the study was to compare the BP-lowering efficacy of aliskiren 75 mg, 150 mg, and 300 mg with placebo, as assessed by change in msSBP from baseline to week 8 end point. Secondary efficacy assessments included change in msDBP from baseline to week 8 end point and the proportion of patients achieving BP control (msSBP/DBP <140/90 mm Hg) at the week 8 end point. Change in 24-hour ambulatory systolic BP and diastolic BP from baseline at week 8 was assessed in a subset of patients. In addition, the study examined the dose-response effect of aliskiren treatment on msSBP.

Office BP was measured at trough (24 ± 3 hours postdose), at screening, the start of the placebo run-in period, randomization (baseline), and at weeks 2, 4, 6, and 8 during the double-blind treatment period. At each visit, sitting BP was measured at trough using a standard mercury sphygmomanometer (or validated alternative) with the appropriate cuff size. Blood pressure was measured in the arm with the highest sitting DBP reading at screening. Sitting BP was the mean of 3 readings, taken at 1- to 2-minute intervals after the patient had been sitting for 5 minutes. In addition, 24-hour ambulatory BP monitoring (ABPM) was performed in a subset of patients at randomization. Following office BP measurement, the ABPM device (Spacelabs 90207; Medifacts International, Rockville, Maryland) was attached to the nondominant arm of the patient and correlated with the office BP reading. At the end of the 24-hour recording period, the ABPM data were assessed, and if they did not meet the quality criteria, the procedure was repeated within 24 to 72 hours of the start of the first test. Randomization to the first dose of study medication occurred at the end of the 24-hour ABPM period. Patients with successful ABPM readings were assessed again at week 8, and the data were analyzed for this patient subset.

The recording of AEs and serious AEs occurred throughout the study, and all events were assessed by the investigator for severity and for their likely relationship to study treatment. Other safety assessments, including physical examination, regular measurement of vital signs, and regular monitoring of hematology and blood chemistry, were performed throughout the study.

Statistical Analyses

Efficacy analyses were performed on the full analysis set (FAS; all randomized patients, excluding patients who were randomized in error but did not receive study medication); a last-observation-carried-forward approach was used for the week 8 end point analyses. All randomized patients who received at least 1 dose of study medication were included in the safety set. The ABPM analyses were performed on the subset of patients in the FAS with ABPM data available at both baseline and week 8 (ABPM set).

The change in msSBP from baseline at week 8 end point (primary efficacy measure) was assessed by a 2-way analysis of covariance (ANCOVA) model with

treatment, age group (≥65 to <75 years; ≥75 years), and region as factors and baseline msSBP as a covariate. To maintain an overall 2-sided significance level at 5%, Dunnett's procedure was used to adjust for multiple comparisons of the aliskiren doses versus placebo.[13] Changes in msDBP from baseline at week 8 end point were assessed using the same 2-way ANCOVA model, with baseline msDBP as a covariate. The proportion of patients achieving BP control was analyzed using a logistic regression model with treatment, age group, and region as factors and baseline msSBP as a covariate.

An ANCOVA model for repeated measures was used to assess the effects of the study treatments on the changes from baseline in hourly mean ambulatory SBP (MASBP). A 2-way repeated-measures ANCOVA model was fitted with treatment, age group, region, and postdosing hour as factors and baseline 24-hour MASBP as a covariate; the treatment-by-postdosing-hour interaction was also included in the model. The 24-hour mean change from baseline in MASBP between treatment groups was presented with a 95% confidence interval (CI). Mean ambulatory DBP (MADBP) was analyzed as above but with mean 24-hour MADBP as a covariate.

Modeling analysis using multiple comparison procedures[14] was used to assess the overall dose-response with aliskiren for mean change in msSBP from baseline to week 8 end point and to estimate the minimum aliskiren dose required to produce a clinically relevant BP reduction. The best-fit model was selected from a set of 5 candidate dose-response models chosen to cover the possible shapes anticipated for the dose-response relationship: Emax1 (90% of effect at 150 mg), Emax2 (60% of effect at 150 mg), quadratic (maximum effect at 200 mg), logistic (ED_{50}: 60% of effect at 150 mg; 95% of effect at 200 mg), and linear. For each model, the null hypothesis of a constant dose-response curve was tested at a 1-sided α level of 2.5% against the alternative hypothesis of a non-constant dose-response curve. A *t* statistic based on linear combinations using optimal contrast coefficients was derived for each model to test the individual null hypothesis. If the null hypothesis of the maximum *t* statistic was rejected, the overall null hypothesis of a constant dose-response curve was rejected,[14] and a significant dose-response relationship could therefore be established. The most appropriate best-fit model was selected with significant contrast test statistics based on the smallest Akaike information criterion (AIC). This model was then used for dose-response relationship modeling and to estimate the minimum effective dose (MED) of aliskiren. The MED was defined as the smallest dose that showed a clinically relevant and a statistically significant effect.[15] Graphs representing the predicted dose-response curve, its corresponding 95% CI, and the estimated MED were produced for each age group (≥65 to <75 years; ≥75 years) using the selected dose-response model.

A sample size of 668 patients completing the study (167 patients per treatment group) was targeted to provide at least 97% power to detect a treatment difference of 5 mm Hg in msSBP between at least 1 aliskiren dose and placebo, assuming a standard deviation of 14 mm Hg. The study therefore aimed to randomize a total of 744 patients (186 per treatment group).

All statistical analyses were performed using SAS software version 8.2 or higher (SAS Institute, Inc, Cary, North Carolina). The dose-response relationship was analyzed using SAS version 8.2 or higher and S-plus version 6.2 or higher (Statistical Sciences, Inc, Seattle, Washington); sample size calculations were performed using nQuery version 5.0 (Statistical Solutions, Saugus, Massachusetts).

RESULTS

Patient Disposition and Baseline Characteristics

In total, 836 patients were enrolled in the study, of whom 754 completed the placebo run-in period and were randomized to study treatment (Figure 1). A further 2 patients who did not meet the eligibility criteria were randomized to placebo in error but did not receive study medication and so were not included in the efficacy or safety analyses. Overall, 700 patients completed double-blind treatment, with higher completion rates in the aliskiren 150- and 300-mg groups than in the aliskiren 75-mg or placebo groups (Figure 1). The most common reasons for discontinuation were AEs and unsatisfactory therapeutic effect (both 2.6% overall). Discontinuations due to AEs were more frequent with placebo and aliskiren 75 mg than with aliskiren 150 or 300 mg, whereas discontinuations due to unsatisfactory therapeutic effect were higher with placebo than with active treatment (Figure 1).

The treatment groups were generally well matched for baseline and demographic characteristics (Table I). There were more women than men in the study (55.2% vs 44.8%), and almost all patients were white (99.3%). Overall, the mean age was approximately 72 years, and more than 30% of patients in each group were aged ≥75 years, as per the protocol. About one-third of patients were obese, and almost 20% had type

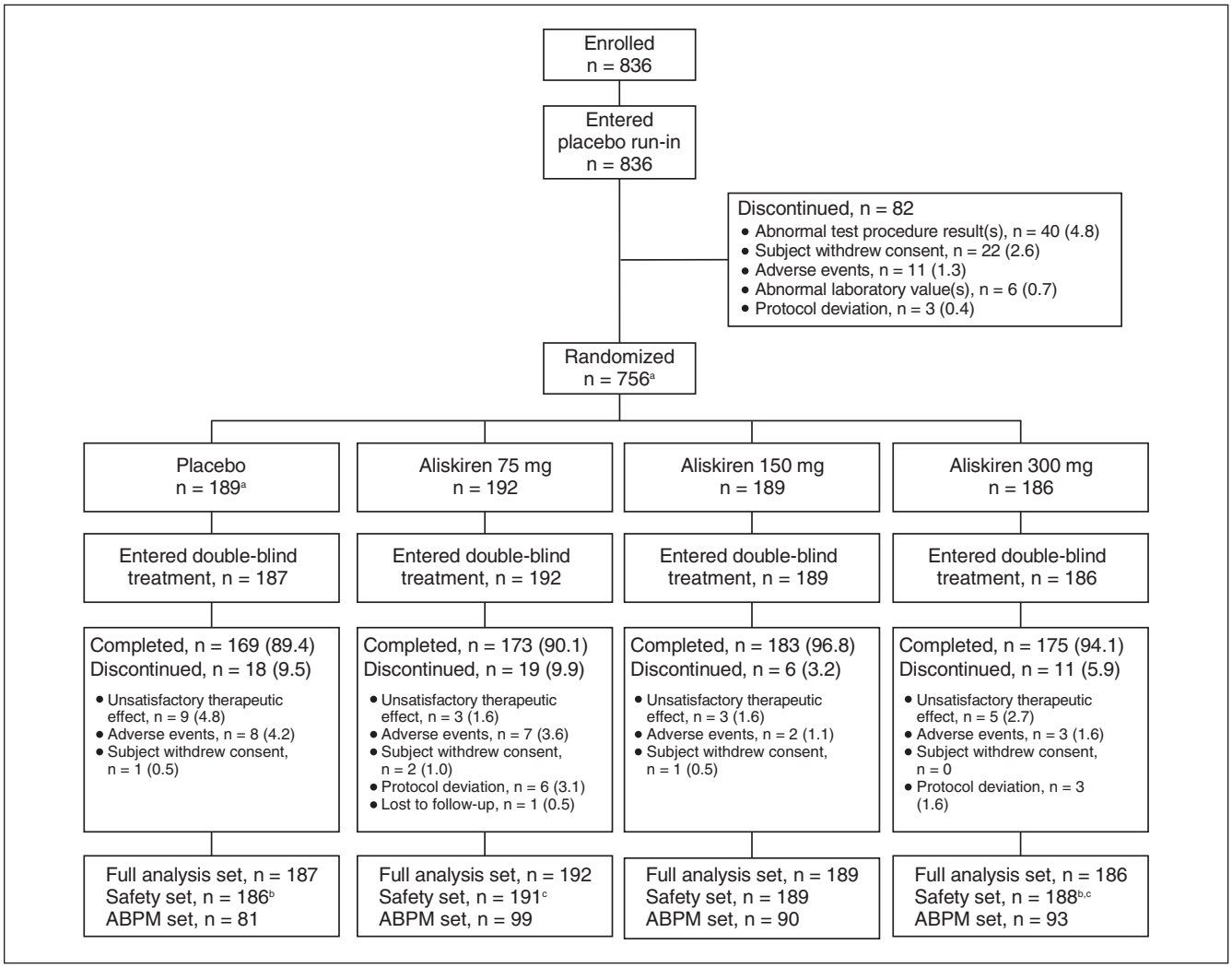

Figure 1. Patient flow diagram. Data are shown as number (%) of patients. Full analysis set is the primary efficacy population. ABPN, ambulatory blood pressure monitoring.

a. Two patients were randomized in error but did not receive study medication.

b. One patient received aliskiren 300 mg in error (day 43 to end of study) and so was included in the aliskiren 300-mg group for safety analyses.

c. One patient received aliskiren 300 mg in error (day 14 to randomization) and so was included in the aliskiren 300-mg group for safety analyses.

2 diabetes mellitus. Obesity was less common in the aliskiren 75-mg arm than in the other treatment groups (Table I), and the incidence of diabetes was lower in both the placebo group and the aliskiren 75-mg group. Approximately 15% of patients had renal impairment (eGFR <60 mL/min/1.73 m^2). Baseline msSBP and msDBP were similar across treatment groups (159-160 mm Hg and 90 mm Hg, respectively).

BP-Lowering Efficacy

All 3 doses of aliskiren provided significantly greater least squares mean reductions in msSBP from baseline at week 8 end point compared with placebo (Figure 2a). Aliskiren 75, 150, and 300 mg showed additional msSBP reductions of 5, 7, and 6 mm Hg, respectively, over placebo (all $P < .01$). Reductions in msDBP with aliskiren at week 8 end point were also significantly greater than those with placebo (Figure 2b), with additional reductions of 2, 3, and 3 mm Hg with the 75-, 150-, and 300-mg doses, respectively (all $P < .05$). Greater reductions in msSBP and msDBP with aliskiren 75, 150, and 300 mg compared with placebo were apparent after 2 weeks of treatment (Figure 3a,b). The larger reductions in BP with active treatment over placebo were maintained throughout the 8-week

Table I Patient Demographics and Baseline Characteristics (Randomized Set)

	Placebo (n = 189)	Aliskiren 75 mg (n = 192)	Aliskiren 150 mg (n = 189)	Aliskiren 300 mg (n = 186)
Age, y	72 ± 5	72 ± 6	72 ± 5	72 ± 6
≥75 years, No. (%)	61 (32.3)	61 (31.8)	60 (31.7)	57 (30.6)
Sex, No. (%)				
Male	89 (47.1)	83 (43.2)	83 (43.9)	84 (45.2)
Female	100 (52.9)	109 (56.8)	106 (56.1)	102 (54.8)
Race, No. (%)				
White	186 (98.4)	192 (100.0)	186 (98.4)	185 (99.5)
Black	0	0	2 (1.1)	0
Other	3 (1.6)	0	1 (0.5)	1 (0.5)
Body mass index,[a] kg/m^2	29 ± 5	28 ± 4	29 ± 4	28 ± 4
Obese,[b] No. (%)	66 (34.9)	53 (27.6)	66 (34.9)	58 (31.2)
Diabetes, No. (%)	30 (15.9)	33 (17.2)	40 (21.2)	37 (19.9)
Duration of hypertension, y	10 ± 7	10 ± 8	10 ± 8	11 ± 8
Treatment-naive patients,[c] No. (%)	3 (1.6)	3 (1.6)	3 (1.6)	3 (1.6)
eGFR, mL/min/1.73 m^2	73 ± 15	73 ± 14	76 ± 16	75 ± 15
eGFR, No. (%)				
<60 mL/min/1.73 m^2	31 (16.4)	33 (17.2)	24 (12.7)	28 (15.1)
Blood pressure, mm Hg				
msSBP	160 ± 8	159 ± 7	160 ± 8	160 ± 8
msDBP	90 ± 9	90 ± 8	90 ± 8	90 ± 8

Data are shown as mean ± SD, unless otherwise indicated. eGFR, estimated glomerular filtration rate; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.
a. Data not available for 1 patient in the placebo group.
b. Defined as body mass index ≥30 kg/m^2.
c. Patients diagnosed with hypertension within 7 days prior to visit 1 or patients not previously treated for essential hypertension or not receiving at least 1 dose of antihypertensive medication within 60 days prior to visit 1.

treatment period.

More patients achieved BP control (<140/90 mm Hg) with aliskiren treatment than with placebo at the week 8 end point. Blood pressure control rates with aliskiren 150 and 300 mg were 37.2% and 38.2%, respectively, significantly higher than with placebo (23.9%; both $P < .01$). Blood pressure control rates with aliskiren 75 mg (32.8%) were also greater than with placebo, although this difference was not statistically significant.

All 3 doses of aliskiren provided greater reductions in mean 24-hour ambulatory BP at the week 8 end point compared with placebo. Aliskiren 75, 150, and 300 mg provided least squares mean reductions from baseline in MASBP/MADBP of 4/3, 5/3, and 5/2 mm Hg, respectively, whereas the reductions in the placebo group were 1/0 mm Hg. Aliskiren treatment thus provided significant additional least squares mean reductions in MASBP over placebo of 4, 5, and 5 mm Hg at the 75-, 150-, and 300-mg doses, respectively ($P < .05$ for 75 mg; $P < .001$ for both 150 and 300 mg). The additional least squares mean reduction in MADBP was 2 mm Hg with both aliskiren 75 and 150 mg. This was statistically significant compared with placebo (both $P < .05$), although the additional reduction of 2 mm Hg with aliskiren 300 mg did not reach significance.

Dose-Response Modeling

Modeling analysis showed a statistically significant ($P < .0001$) dose-response relationship for aliskiren treatment for all 5 of the models tested. The quadratic model showed the best fit based on the lowest AIC score, although the two Emax models also showed a similar fit to the quadratic model. Based on the quadratic model, the quadratic dose parameter was significantly different from zero ($P < .001$), confirming the presence of a dose response. The minimum effective once-daily dose for aliskiren estimated using this model was 81.9 mg. The predicted mean dose-response profile based on the quadratic model showed that the maximum effect of aliskiren on msSBP was reached at approximately 200 mg for both age groups (≥65 to

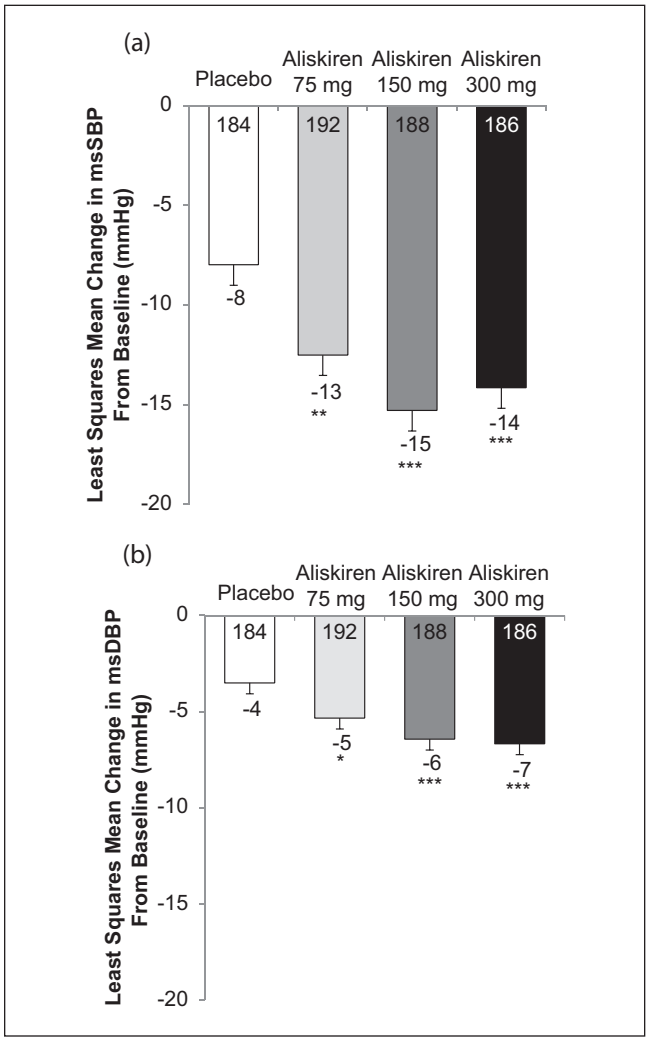

*Figure 2. Change in mean sitting (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP) from baseline at week 8 end point (full analysis set). Data are shown as least squares mean ± standard error of the mean. *P < .05, **P < .01, ***P < .001 vs placebo.*

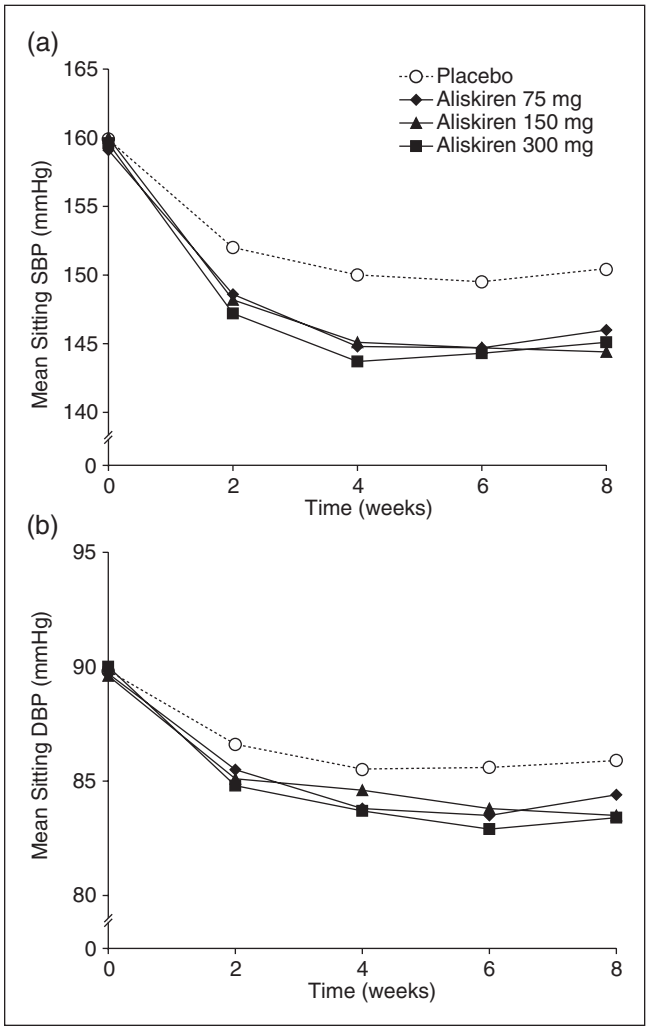

Figure 3. Mean sitting (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP) throughout the double-blind treatment period (full analysis set). Data are shown as means for patients with measurements at baseline and the postbaseline time point indicated.

<75 years; ≥75 years; Figure 4). However, the confidence intervals were too large to draw any meaningful conclusions about the relative effects of aliskiren doses between 200 and 300 mg on msSBP reductions.

Safety and Tolerability

Aliskiren treatment was generally well tolerated. The incidence of AEs reported in each of the 3 aliskiren groups was similar to that observed with placebo (Table II), and most events were transient and mild or moderate in severity. Overall, the most common AEs during treatment were headache and hypertension (both 1.6%). The incidence of headache was low and similar across the treatment groups, whereas hypertension was more common in the placebo and aliskiren 300-mg groups than in the aliskiren 75- or 150-mg groups (Table II). Few patients experienced diarrhea (aliskiren 75 mg, n = 1; placebo, n = 1), hypotension (aliskiren 150 mg, n = 1), or hyperkalemia (aliskiren 150 mg, n = 1); and there were no reports of syncope or hypokalemia. No clinically meaningful differences were observed when AEs were evaluated by age group (≥65 to <75 years; ≥75 years).

Discontinuations due to AEs were more frequent in the placebo and aliskiren 75-mg group than in the aliskiren 150- or 300-mg groups (Table II). Worsening

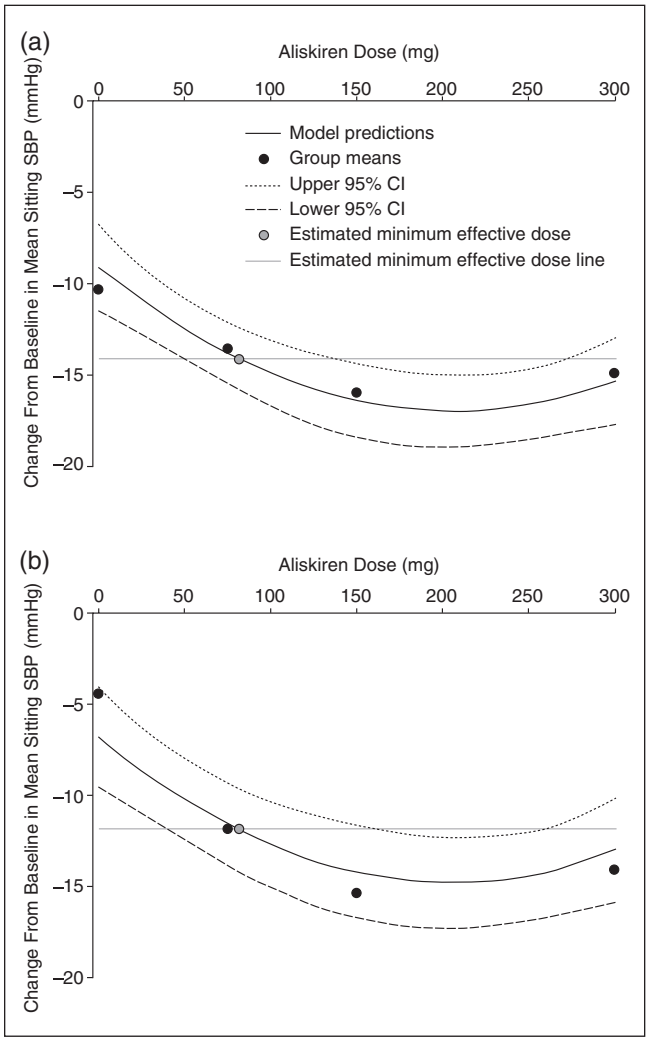

Figure 4. Predicted mean dose-response profile for mean SBP for (a) patients aged ≥65 to <75 years and (b) patients aged ≥75 years (full analysis set). Graphs show predicted mean dose-response profile and point-wise 2-sided 95% confidence intervals for the selected quadratic model. CI, confidence interval; SBP, systolic blood pressure.

hypertension was the most common reason for discontinuation and affected more patients in the placebo group (n = 5) than in the aliskiren groups (75 mg, n = 1; 150 mg, n = 1; 300 mg, n = 2). Serious AEs were uncommon during the study (Table II). One patient died from pneumonia leading to respiratory failure during the follow-up period, approximately 1 month after completing the study; this was not considered to be related to the study medication. There were few clinically meaningful laboratory abnormalities during the study (Table II), with no reports of elevated serum creatinine (>176.8 µmol/L).

DISCUSSION

This study showed that aliskiren 150 and 300 mg provided effective BP lowering and was well tolerated when administered with a light meal to elderly patients with hypertension. The reductions in msSBP/DBP with the aliskiren 150-mg (15/6 mm Hg) and 300-mg (14/7 mm Hg) doses were significantly greater than those with placebo (8/4 mm Hg) after 8 weeks of treatment, with an additional decrease of 7/3 and 6/3 mm Hg, respectively. Aliskiren 150 and 300 mg also enabled almost 40% of patients to achieve their BP goal at the study end point, significantly more than with placebo (24%). The reductions in 24-hour MASBP were consistent with those in msSBP, with both of the approved doses of aliskiren (150 and 300 mg) providing significant additional reductions over placebo.

The current study suggests that administration of aliskiren with a "typical" European light breakfast has no clinically relevant effect on its antihypertensive efficacy, with similar BP reductions to those observed for elderly patients in previous studies where aliskiren was administered without regard to meals. Aliskiren 150 and 300 mg provided msSBP/DBP reductions of approximately 14/6 mm Hg after 8 weeks of treatment in a study of 355 elderly patients (≥65 years) with hypertension (msSBP ≥145 to <180 mm Hg and MASBP ≥135 mm Hg).[16] In the Aliskiren for Geriatric Lowering of Systolic Hypertension (AGELESS) trial, 901 patients aged ≥65 years with hypertension (msSBP ≥140 to <180 mm Hg and msDBP <110 mm Hg) were randomized to aliskiren- or ramipril-based treatment for 36 weeks.[17] At the week 12 end point, aliskiren monotherapy (150 mg, with optional titration to 300 mg for SBP control) provided msSBP/DBP reductions of 14/5 mm Hg, significantly greater than with ramipril (5 mg, with optional titration to 10 mg) alone (12/4 mm Hg, $P < .05$). Similar findings are also apparent from a post hoc subgroup analysis of elderly patients from a randomized, double-blind aliskiren clinical trial in 1797 patients with mild to moderate hypertension. Aliskiren 300 mg showed BP reductions of 15/9 mm Hg from baseline after 8 weeks in patients aged ≥65 years.[18]

Previous studies in healthy volunteers have shown that administration of aliskiren following a high-fat meal significantly reduced aliskiren exposure but that PRA reductions were similar in the fed and fasted states.[9] A more recent study in patients with hypertension compared the pharmacokinetic effects and changes in PRA and BP of 4 weeks' treatment with aliskiren 300 mg administered in the fasted state with

Table II Safety and Tolerability of the Study Treatments (Safety Set)

	Placebo (n = 186[a])	Aliskiren 75 mg (n = 191[a])	Aliskiren 150 mg (n = 189)	Aliskiren 300 mg (n = 188[a])
Any AE	39 (21.0)	36 (18.8)	41 (21.7)	36 (19.1)
Any SAE	1 (0.5)	2 (1.0)	3 (1.6)	0
Discontinuations due to AEs	7 (3.8)	7 (3.7)	1 (0.5)	3 (1.6)
Common AEs (≥2% in any treatment group)				
Hypertension	6 (3.2)	1 (0.5)	1 (0.5)	4 (2.1)
Headache	4 (2.1)	4 (2.1)	2 (1.1)	2 (1.1)
Influenza	1 (0.5)	1 (0.5)	4 (2.1)	2 (1.1)
Laboratory abnormalities	n = 182	n = 191	n = 188	n = 187
Serum potassium				
<3.5 mmol/L	3 (1.6)	2 (1.0)	1 (0.5)	0
>5.5 mmol/L	0	4 (2.1)	4 (2.1)	4 (2.1)
≥6.0 mmol/L	0	2 (1.0)	2 (1.0)	0
Blood urea nitrogen >14.28 mmol/L	1 (0.5)	0	0	1 (0.5)

Data are shown as number (%) of patients. AE, adverse event; SAE, serious adverse event.
a.Two patients, one each in the placebo and aliskiren 75-mg groups, received aliskiren 300 mg in error during the study and so were included in the aliskiren 300-mg group for the safety analyses.

aliskiren 300 mg administered 30 minutes after a light breakfast (Novartis, data on file). Administration following the light meal was associated with marked reductions in aliskiren exposure (67%) and peak plasma concentration (76%) compared with fasted conditions. However, aliskiren provided similar PRA reductions (>60%), regardless of whether it was administered with or without a meal. Importantly, BP reductions were similar in fed (11/10 mm Hg) and fasted (12/11 mm Hg) conditions (Novartis, data on file) and consistent with previous short-term studies of aliskiren 300 mg administered without regard to meals in patients with mild to moderate hypertension.[19,20] Thus, taken together, these findings suggest that aliskiren provides similar antihypertensive efficacy regardless of whether it is taken with a light meal.

Recently, there has been interest in fruit juices that may cause food-drug interactions. Two randomized crossover studies have shown that orange or apple juice[21] and grapefruit juice[22] reduce the plasma concentrations and renin-inhibiting effect of aliskiren after a single dose of aliskiren 150 mg. The extent of this interaction is essentially the same as that with food, and it is not known whether these two effects are additive or whether the juice effect is the same as the food effect.

This newly identified interaction is the principal limitation of this study, as this interaction was not specifically studied. The significance of the fruit juice interaction with repeated dosing is unknown. However, aliskiren has been demonstrated to be generally effective in the clinical trial database submitted for market authorization in the United States when administered without regard to meals. In addition, in this study, even at half the minimum approved treatment dose (75 mg), the BP-lowering effect of aliskiren was clearly demonstrated with statistically significant reductions in both msSBP and msDBP.

Modeling analysis showed a significant dose-response relationship for aliskiren with all 5 models tested in both elderly (aged ≥65 to <75 years) and very elderly patients (≥75 years of age) patients. The quadratic model, with a maximum treatment effect at approximately 200 mg, showed the best fit to the data. This is consistent with the shallow dose response for BP lowering observed with aliskiren in previous clinical studies. Aliskiren monotherapy has demonstrated dose-dependent BP reductions in clinical trials in patients with mild to moderate hypertension.[10,11] In 5 placebo-controlled studies, the aliskiren 150- and 300-mg doses were the most effective, whereas the 75-mg dose showed less consistent BP lowering across the studies.[11] The lower BP reductions and control rates observed with the 75-mg dose in the current study and the calculated minimum effective dose for aliskiren of 81.9 mg are consistent these findings. Moreover, although aliskiren 150 and 300 mg showed similar BP reductions in the present study (as also reflected in the predicted dose-response profiles for msSBP), aliskiren 300 mg has consistently provided greater BP reductions than the 150-mg dose in previous placebo-controlled studies.[10,11]

Aliskiren was well tolerated during the study. The overall incidence of AEs in each of the treatment groups was similar to that with placebo, and there was no evidence of any dose-related AEs with aliskiren. Most events were mild or moderate in severity, and there were few serious AEs or discontinuations due to AEs. Headache and hypertension were the most common AEs reported in the study, although their overall incidence was low (both 1.6%). These findings are consistent with other studies that show that aliskiren is well tolerated in elderly patients with hypertension.[16-18]

This dose-response evaluation study investigated aliskiren at all 3 doses when given with a light meal to elderly hypertensive patients, and the findings suggest that the effects of aliskiren in the elderly are generally similar when administered with a light meal to those when administered "without regard to food," as in the studies provided in the EU submission for aliskiren monotherapy. In conclusion, aliskiren 150 and 300 mg provided effective BP reductions in elderly patients with hypertension when administered with a light meal. Blood pressure reductions were similar to those observed in studies in which aliskiren was administered without regard to the timing of meals, showing that aliskiren provides similar BP-lowering efficacy regardless of whether it is taken with a meal. Aliskiren treatment was well tolerated, with no evidence of any dose-related AEs, and so offers a useful treatment option for elderly patients with hypertension.

APPENDIX

Institutional Review Boards

This study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki and was approved by the following institutional review boards (IRBs) or independent ethics committees:

Thomayer Hospital Ethics committee (Thomayer Hospital, Prague, Czech Republic); Bratislava Ethics Committee (Bratislava, Slovakia); Children's Hospital Ethics Committee (University of Düsseldorf Medical Faculty, Düsseldorf, Germany); Central Ethics Committee of the IRCCS (Salvatore Maugeri Foundation, Pavia, Italy); Prinsengracht IRB (Amsterdam, Netherlands); National Bioethics Committee (Reykjavik, Iceland); Bioethics Committee at the Regional Medical Chamber (Gdansk, Poland); Independent Ethics Committee for Clinical Pharmacology Trials (Pharmacological Studies Foundation and Medicines "Prof. Luis M. Ziehe", Buenos Aires, Argentina).

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