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FASTTRACK CLINICAL RESEARCH

Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial

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Aims Mineralocorticoid receptor antagonists (MRAs) improve outcomes in patients with heart failure and reduced left ventricular ejection fraction (HFrEF), but their use is limited by hyperkalaemia and/or worsening renal function (WRF). BAY 94-8862 is a highly selective and strongly potent non-steroidal MRA. We investigated its safety and tolerability in patients with HFrEF associated with mild or moderate chronic kidney disease (CKD).

Methods and results This randomized, controlled, phase II trial consisted of two parts. In part A, the safety and tolerability of oral BAY 94-8862 [2.5, 5, or 10 mg once daily (q.d.)] was assessed in 65 patients with HFrEF and mild CKD. In part B, BAY 94-8862 (2.5, 5, or 10 mg q.d., or 5 mg twice daily) was compared with placebo and open-label spironolactone (25 or 50 mg/day) in 392 patients with HFrEF and moderate CKD. BAY 94-8862 was associated with significantly smaller mean increases in serum potassium concentration than spironolactone (0.04–0.30 and 0.45 mmol/L, respectively, $P < 0.0001$–0.0107) and lower incidences of hyperkalaemia (5.3 and 12.7%, respectively, $P = 0.048$) and WRF. BAY 94-8862 decreased the levels of B-type natriuretic peptide (BNP), amino-terminal proBNP, and albuminuria at least as much as spironolactone. Adverse events related to BAY 94-8862 were infrequent and mostly mild.

Conclusion In patients with HFrEF and moderate CKD, BAY 94-8862 5–10 mg/day was at least as effective as spironolactone 25 or 50 mg/day in decreasing biomarkers of haemodynamic stress, but it was associated with lower incidences of hyperkalaemia and WRF.

Keywords Aldosterone • Antagonist • Chronic kidney disease • Heart failure • Mineralocorticoid receptor

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Introduction

The mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone have been shown to be effective in reducing cardiovascular mortality and hospitalizations for heart failure (HF), as well as total mortality, in patients with chronic HF and a reduced left ventricular ejection fraction (HFrEF).[1,2] However, despite their proven benefits in large-scale, prospective, double-blind, randomized trials and recommendations for their use included in international guidelines,[3,4] they remain under-utilized, in large part owing to the risk of hyperkalaemia and renal dysfunction.

BAY 94-8662 is a next-generation non-steroidal MRA that has shown improved selectivity for the mineralocorticoid receptor (MR) over other steroid hormone receptors compared with spironolactone and improved affinity for the MR compared with eplerenone in pre-clinical studies.[5] In comparative studies using pre-clinical models of hypertension-driven HF and renal dysfunction, BAY 94-8662 has been found to confer more pronounced cardiorenal end-organ protection than the steroidal MRAs.[6,7] The minerAlocorticoid Receptor Antagonist Tolerability Study (ARTS) was designed to assess the safety and tolerability of BAY 94-8662 in patients with HFrEF and mild or moderate chronic kidney disease (CKD), and to select doses for further study in phase III clinical trials.

Methods

Study design

ARTS was a multicentre, randomized, parallel-group, phase II study, with double-blind placebo and open-label spironolactone comparator arms, conducted in patients with HFrEF (left ventricular ejection fraction, $\leq$40%) and mild or moderate CKD [estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) formula, 60 to $<$90 mL/min/1.73 m^2 and 30 to 60 mL/min/1.73 m^2, respectively] at 55 centres in 10 countries worldwide. The design of the trial has been published in detail elsewhere.[8] The investigation conforms to the Declaration of Helsinki and was conducted in keeping with applicable local laws and regulations. Documented approval was obtained from appropriate independent ethics committees or institutional review boards for all participating centres before the start of the study. All patients gave written informed consent to participate in the study.

In part A of the study, the safety, tolerability, and renal effects of oral BAY 94-8862 [2.5, 5, or 10 mg once daily (q.d.)] compared with placebo were investigated in patients with HFrEF and mild CKD. The effects on serum potassium concentration, eGFR, and albuminuria were assessed. An independent data monitoring committee (DMC) reviewed data from part A to confirm the safety and tolerability of BAY 94-8862 in patients with HFrEF and mild CKD before the initiation of part B.

In part B, the primary endpoint was the change in serum potassium concentration after treatment with oral BAY 94-8862 or placebo in patients with HFrEF and moderate CKD, measured at visits 6 and 7 [i.e. the mean of the changes from baseline to visits 6 (day 22 $\pm$ 2) and 7 (day 29 $\pm$ 2)] to reduce the variability associated with isolated measurements. The timing of the primary endpoint assessment was based on observations from the PEARL-HF trial, in which serum potassium concentrations increased in the first 7 days after treatment initialization or up-titration of spironolactone and remained nearly stable thereafter.[9] The effect of oral BAY 94-8862 on serum potassium concentration was also compared with that of oral open-label spironolactone at a dose of 25 mg q.d. up-titrated to 50 mg q.d. as a secondary objective. Other secondary objectives were the safety and tolerability of BAY 94-8862 and its effects on systolic blood pressure (SBP) and levels of serum aldosterone, B-type natriuretic peptide (BNP) and amino-terminal proBNP (NT-proBNP), eGFR, and albuminuria measured at visit 4 (day 15 $\pm$ 1, i.e. before dose up-titration in the spironolactone group) and visit 7 (day 29 $\pm$ 2). Because all secondary endpoints were only exploratory, results at the end of the treatment period were assessed (i.e. visit 7 only rather than visits 6 and 7 combined).

Patients

Inclusion and exclusion criteria for the study are provided in detail elsewhere.[8] Briefly, adult males and females without childbearing potential were eligible for inclusion if they had a clinical diagnosis of HFrEF [New York Heart Association (NYHA) class II–III and left ventricular ejection fraction $\leq$40%] and were treated with evidence-based therapy for HFrEF; if their serum potassium concentration was $\leq$4.8 mmol/L at the screening visit; and if their eGFR was 60 to $<$90 mL/min/1.73 m^2 (part A) or 30 to 60 mL/min/1.73 m^2 (part B) according to the MDRD formula.

Study medication

In both parts of the study, patients received study drug for 4 weeks, starting within 14 days of the initial screening visit. The randomization list was generated using a validated automated system that assigned treatment groups to randomization numbers. In part A, patients were randomized 1:1:1:1 to receive oral BAY 94-8862 at doses of 2.5, 5, or 10 mg q.d., or placebo. In part B, patients were randomized 1:1:1:1:1:1 to receive oral BAY 94-8862 at doses of 2.5, 5, or 10 mg q.d., or 5 mg twice daily (b.i.d.), placebo, or open-label oral spironolactone, which was given at an initial dose of 25 mg q.d. and up-titrated to 50 mg q.d. on day 15 $\pm$ 1 if serum potassium concentration remained below or equal to 4.8 mmol/L.

Investigations

Patients were assessed at the screening visit, at baseline/day 1, day 4 $\pm$ 1 and day 8 $\pm$ 1, and then weekly until the end of the study and at a follow-up visit 14 days after the last intake of study drug. Patients who terminated the study early were assessed as soon as possible after discontinuation of study drug. For patients who received spironolactone at a dose of 50 mg q.d., an additional assessment visit was made at day 18 $\pm$ 1. Details of assessments have been published elsewhere.[8] Briefly, adverse events, vital signs, blood and urinary biomarkers, standard haematology, clinical chemistry, and urinalysis were assessed at each visit.

Statistical considerations

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA). Analyses are presented for two sets: the safety set (all patients who had received at least one dose of study drug) and the full analysis set (all patients from the safety set of part B with baseline and one or more post-baseline serum potassium measurements). Unless otherwise specified in the text, missing values were not imputed.

For part A, all variables were analysed descriptively in the safety set. For part B, the full analysis set was used for the primary analysis. Five different dose–response models were fitted to the serum potassium data from the placebo and BAY 94-8862 groups,[8] but none was considered to provide a better model than analysis of covariance (adjusted for centre and baseline serum potassium concentration). Analysis of covariance was therefore used for the primary analysis, as well as for assessing changes in secondary measurements in the full analysis set. Other safety variables were analysed in the safety set.

In part A, no formal sample size calculation was performed; 15 patients per dose group were considered sufficient to assess the safety and

tolerability of BAY 94-8862 in patients with HFrEF and mild CKD, before investigating its effects in a higher risk population, i.e. patients with HFrEF and moderate CKD, in part B. In part B, based on a planned sample size of 60 patients per group and the assumption that the common standard deviation for the change in serum potassium concentration would be 0.50 mmol/L, each comparison between the BAY 94-8862 groups and the spironolactone or placebo group had 80% power to detect a difference in serum potassium concentration of at least 0.26 mmol/L, using two-sided tests at alpha = 0.05.[8]

Significance levels for secondary variables were not pre-specified, and no adjustment was made for multiple comparisons; the *P*-values for secondary variables should therefore be considered descriptive rather than confirmatory.

Results

Demographics

In total, 782 patients were enrolled and 458 randomized [65 (80% male) in part A; 393 (79% male) in part B] (*Figure 1*). One randomized patient in part B did not receive any study drug and was therefore excluded from the safety analysis set. In the safety sets of parts A and B, the mean ages were 66.3 ± 8.9 and 72.1 ± 7.8 years, respectively. At enrolment, the majority of patients (95.4% in part A and 81.6% in part B) were in NYHA functional class II and the remaining patients were in functional class III (*Table 1*). All randomized patients in part A were naïve to MRA therapy; 56 patients in part B had received MRA therapy previously (stopped 30 days prior to randomization). Further details of study population characteristics are available as Supplementary material online.

Part A

The safety and tolerability of different doses of BAY 94-8862 in patients with HFrEF and mild CKD were confirmed after analysis of data from part A of the study (*Table 2*) by the independent DMC. As a result of this positive outcome, part B was initiated to assess safety and efficacy of BAY 94-8862 in patients with HFrEF and moderate CKD in September 2011.

Part B

The full analysis set comprised 389 patients. Of the 63 patients assigned to receive spironolactone, the dose was up-titrated from 25 to 50 mg q.d. on visit 4 (day 15 ± 1) for 30 (47.6%) patients, resulting in a mean dose of 37 mg/day for this group at visit 7 (day 29 ± 2).

Serum potassium concentrations

Of the 389 patients in the full analysis set, 356, 342, and 336 had serum potassium data at visits 4, 6, and 7, respectively. Patients receiving BAY 94-8862 at doses of 10 mg q.d. and 5 mg b.i.d. showed significantly greater mean increases in serum potassium concentration from baseline at the study endpoint [i.e. the mean of changes at visits 6 (day 22 ± 2) and 7 (day 29 ± 2)] than the placebo group ($P = 0.0243$ and $P = 0.0003$, respectively). However, in the 5 and 2.5 mg q.d. groups, the mean increases in serum potassium concentration were not significantly different from those in the placebo group at visit 4 (day 15 ± 1) or at the study endpoint ($P = 0.1623$ and $P = 0.5745$, respectively) (*Figure 2*). The mean increases in serum potassium concentration were significantly smaller in all four BAY 94-8862 dose groups than in the spironolactone group ($P < 0.0001$ for 2.5, 5, and 10 mg q.d. and $P = 0.0107$ for 5 m.g. b.i.d.) (*Figure 2*). Missing data were few (~12%), and a secondary analysis using the 'last observation carried forward' approach to impute missing data did not alter the conclusions of the original analysis. In a descriptive sub-analysis of patients aged >75 years ($n = 123$), the mean increases in serum potassium concentration from baseline to visit 6/7 remained highest in the spironolactone group. A descriptive sub-analysis comparing patients in NYHA class II and III found no difference in serum potassium results between the two groups. Serum potassium results also showed no marked difference between MRA-naïve and MRA-non-naïve patients.

Estimated glomerular filtration rate

Figure 3 shows the mean change in eGFR from baseline to visits 4 and 7 in part B of ARTS. There was a decrease in eGFR in all BAY 94-8862 groups and the spironolactone group, compared with a small increase in the placebo group. However, the decrease in the spironolactone group was significantly greater than in all BAY 94-8862 groups ($P = 0.0002–0.0133$ at visit 7). A similar trend was observed in the subset of patients aged >75 years. In all treatment groups except the group receiving BAY 94-8862 2.5 mg q.d., patients in NHYA class III showed a greater decrease in eGFR than those in NYHA class II; however, the greatest decrease was still observed in the spironolactone arm.

Systolic blood pressure

In part B of the study, high variability was observed in SBP (determined by cuff measurement) in all groups. However, spironolactone significantly decreased SBP between baseline and visit 7 compared with either placebo ($P = 0.0104$) or all doses of BAY 94-8862 ($P = 0.0023–0.0255$) (*Figure 4*). Changes in SBP in the BAY 94-8862 groups were comparable with those seen in patients receiving placebo.

Serum B-type natriuretic peptide, amino-terminal-pro-B-type natriuretic peptide, and urinary albumin:creatinine ratio

Data from part B of the study showed no significant overall treatment effect on BNP, NT-proBNP, or urinary albumin:creatinine ratio (UACR) ($P > 0.05$), so *P*-values for individual treatment group comparisons were not calculated, and the treatment groups were analysed only descriptively. At visit 4, median concentrations of BNP and NT-proBNP decreased from baseline in all BAY 94-8862 dose groups (*Figure 5A* and *B*). At visit 7, median BNP decreased from baseline in patients receiving BAY 94-8862 10 mg q.d. and 5 mg b.i.d. and showed a small increase from baseline in those receiving BAY 94-8862 2.5 and 5 mg q.d.; median NT-proBNP decreased from baseline in patients receiving BAY 94-8862 ≥5 mg q.d. and increased from baseline in those receiving BAY 94-8862 2.5 mg q.d. In patients receiving spironolactone, median BNP and NT-proBNP decreased from baseline at visits 4 and 7. Median BNP and NT-proBNP concentrations showed a small increase from baseline in the placebo group. The decreases in patients receiving BAY 94-8862 were at least comparable with those recorded in the spironolactone group, with a trend towards greater decreases in the BAY 94-8862 5 mg q.d., 10 mg q.d., and 5 mg b.i.d. dose groups compared with patients receiving spironolactone 25 mg q.d. at visit 4, and in the BAY 94-8862 10 mg q.d. dose group compared with

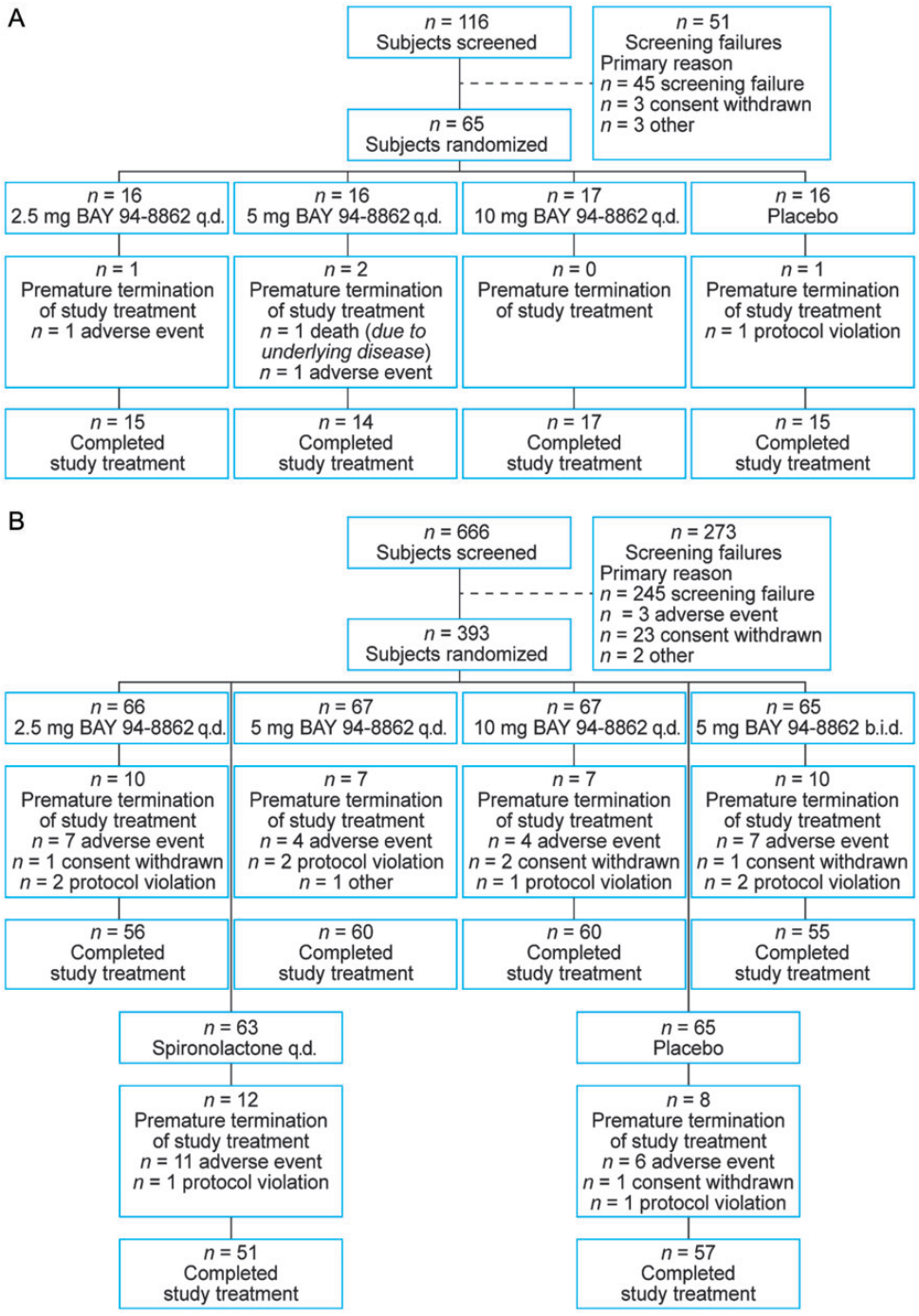


Figure 1 Disposition of patients in part A (*A*) and part B (*B*) of ARTS. b.i.d., twice daily; q.d., once daily.

patients receiving spironolactone 25 or 50 mg q.d. (mean 37 mg) at visit 7. Mean UACRs decreased in all BAY 94-8862 q.d. dose groups and in the spironolactone group, compared with a small increase in the placebo group (*Figure 5C*).

Serum aldosterone concentrations

Figure 6 shows the change in serum aldosterone levels from baseline to visits 4 and 7 in part B. The change from baseline was higher in the BAY 94-8862 groups than in the placebo group. The largest increase from baseline was seen in the patients receiving spironolactone ($P < 0.0001$ compared with placebo and each BAY 94-8862 dose group at visit 7).

Adverse events

In part A of the study, treatment-emergent adverse events (TEAEs) were mostly mild and considered unrelated to study drug (*Table 2*). The number of serious TEAEs was low (occurring in 2 of 65 patients; 3.1%). There was one case of investigator-reported hyperkalaemia in

Table 1 Demographics and baseline characteristics of patients enrolled in ARTS

	Part A ($n = 65$)	Part B ($n = 392$)
Males, *n* (%)	52 (80.0)	312 (79.6)
Mean age (range), years	66.3 (42–85)	72.1 (40–89)
Mean BMI (range), kg/m^2	28.6 (21.5–41.4)	28.8 (18.1–46.9)
Mean systolic blood pressure (range), mmHg	133.8 (83–169)	127.3 (81–180)
NYHA functional class, *n* (%)		
II	62 (95.4)	320 (81.6)
III	3 (4.6)	72 (18.4)
Medical history, *n* (%)		
Ischaemic heart disease	24 (36.9)	251 (64.0)
Atrial fibrillation	24 (36.9)	177 (45.2)
Congestive cardiomyopathy	8 (12.3)	36 (9.2)
Arterial hypertension	28 (43.1)	261 (66.6)
Diabetes mellitus	9 (13.8)	134 (34.2)
Treated with metformin	5 (7.7)	51 (13.0)
Concomitant medication, *n* (%)		
Agents acting on renin–angiotensin system	64 (98.5)	372 (94.9)
Beta-blockers	63 (96.9)	366 (93.4)
Diuretics	46 (70.8)	349 (89.0)
Baseline laboratory values		
Mean serum potassium ± SD, mmol/L	4.23 ± 0.33	4.29 ± 0.42
Median serum creatinine (range), mg/dL	1.000 (0.70–1.30)	1.400 (0.80–3.10)
Mean eGFR (MDRD) ± SD, mL/min/1.73 m^2	69.1 ± 8.43	47.0 ± 10.0
Geometric mean UACR (geometric SD), mg/g	13.67 (3.20)	21.33 (4.87)
Median BNP (range), pg/mL	–	270.0 (10–6382)
Median NT-proBNP (range), pg/mL	–	1381.45 (22.7–32 349.1)
Median serum aldosterone (range), pmol/L	–	279.100 (<LLOQ–2557.70)

The dash indicates data not recorded; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LLOQ, lower limit of quantification (for serum aldosterone, LLOQ = 7.35 pmol/L); MDRD, modification of diet in renal disease; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; UACR, urinary albumin:creatinine ratio.

the BAY 94-8862 10 mg q.d. group at visit 5 (day 22 ± 2) (serum potassium concentration of 5.8 mmol/L as measured by the central laboratory, and 5.2 mmol/L as measured by the local laboratory). Study drug was not withdrawn and no action was taken in this case. Serum potassium concentration stayed within the normal range in this patient throughout the rest of the study.

In part B, TEAEs were mostly mild (*Table 2*). The number of serious TEAEs was also low (occurring in 23 of 392 patients; 5.9%). The highest proportion of serious TEAEs considered to be drug-related was in the spironolactone group (occurring in 5 of 63 patients; 7.9%). The highest proportion of TEAEs leading to discontinuation of study drug was also in the spironolactone group (occurring in 11 of 65 patients; 17.5%). Considering only TEAEs that occurred before visit 4, i.e. before the spironolactone dose was up-titrated, the spironolactone group had the highest proportion of TEAEs (57.1% compared with 29.7–40.3% in the BAY 94-8862 groups) and TEAEs leading to discontinuation of study drug (9.5% compared with 1.5–6.3% in the BAY 94-8862 groups).

In a *post hoc* analysis, data from part B were pooled. Compared with the placebo group, the pooled BAY 94-8862 groups had higher incidences of investigator-reported hyperkalaemia/increased blood potassium levels (5.3 vs. 1.5%, $P = 0.3195$) and renal failure (1.5 vs. 0%, $P = 1.0000$) and a lower incidence of renal impairment (3.8 vs. 9.2%, $P = 0.0996$). The incidence of each of these adverse events was significantly lower in the BAY 94-8862 groups than in the spironolactone group (hyperkalaemia/increased blood potassium levels: 5.3 vs. 12.7%, $P = 0.048$; renal failure: 1.5 vs. 7.9%, $P = 0.0153$; renal impairment: 3.8 vs. 28.6%, $P < 0.0001$). When pooling data from the BAY 94-8862 5 and 10 mg q.d. groups only, the incidence of hyperkalaemia/increased blood potassium levels, renal failure, and renal impairment remained significantly lower in the BAY 94-8862 groups than in the spironolactone group (3.7 vs. 12.7%, $P = 0.0284$; 1.5 vs. 7.9%, $P = 0.0352$; and 6.0 vs. 28.6%, $P < 0.0001$, respectively).

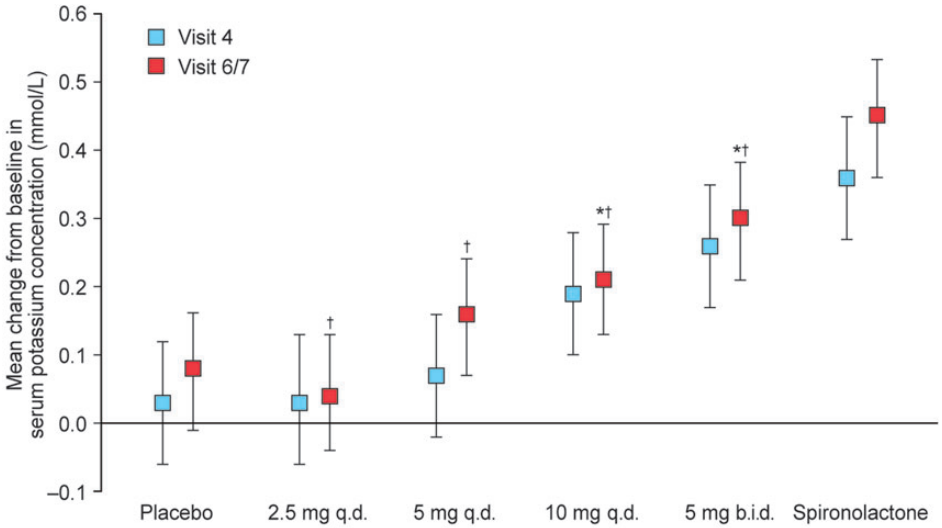
Discussion

ARTS is the first randomized clinical trial of BAY 94-8862, with double-blind placebo and open-label spironolactone comparator arms, to be conducted in patients with HFrEF and mild or moderate CKD. BAY 94-8862 at doses of 5 and 10 mg q.d. decreased the levels of BNP, NT-proBNP, and albuminuria to at least the same, if not a greater degree than spironolactone 25 or 50 mg q.d. Of particular interest is the finding that although these doses of BAY 94-8862 raised serum potassium concentrations as expected, this increase

Table 2 Treatment-emergent adverse events, including serious adverse events, in parts A and B of ARTS

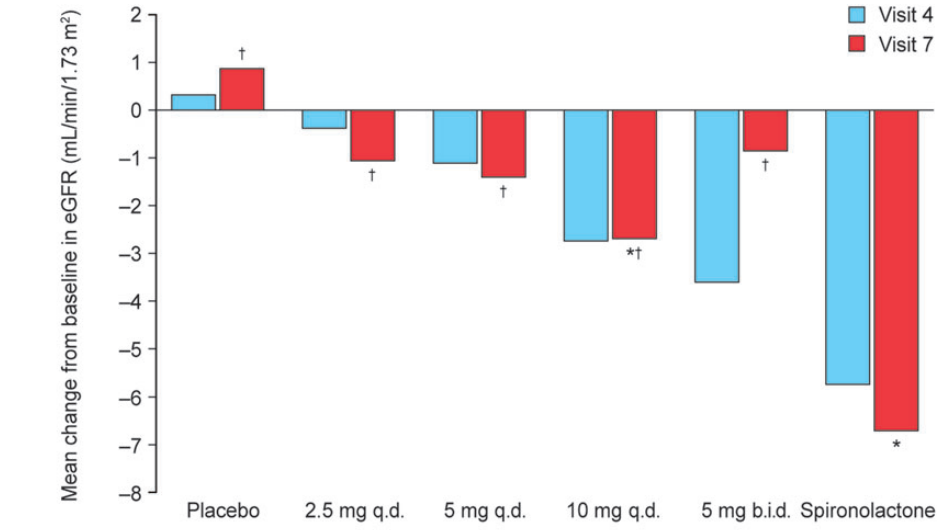
	BAY 94-8862 (2.5 mg q.d.)	BAY 94-8862 (5 mg q.d.)	BAY 94-8862 (10 mg q.d.)	BAY 94-8862 (5 mg b.i.d.) (part B only)	Spironolactone (25 or 50 mg q.d.) (part B only)	Placebo
Part A						
Total patients, *N*	16	16	17	–	–	16
Patients with at least one TEAE, *n* (%)	10 (62.5)	6 (37.5)	5 (29.4)	–	–	6 (37.5)
Cardiac disorders, *n* (%)	1 (6.3)	1 (6.3)	0	–	–	0
Angina pectoris	0	1 (6.3)[a]	0			0
Sinus tachycardia	1 (6.3)	0	0			0
Gastrointestinal disorders, *n* (%)	0	1 (6.3)	2 (11.8)	–	–	0
Constipation	0	1 (6.3)	0			0
Flatulence	0	0	1 (5.9)			0
Nausea	0	0	1 (5.9)			0
Investigations needed, *n* (%)	1 (6.3)	0	0	–	–	2 (12.5)
Blood CPK level increased[b]	1[c] (6.3)	0	0			1 (6.3)
Blood glucose level increased[b]	0	0	0			1[d] (6.3)
Metabolism and nutrition disorders, *n* (%)	1 (6.3)	0	1 (5.9)	–	–	0
Diabetes mellitus	1 (6.3)	0	0			0
Hyperkalaemia[b]	0	0	1 (5.9)			0
Nervous system disorders, *n* (%)	1 (6.3)	0	0	–	–	2 (12.5)
Dizziness	0	0	0			1 (6.3)
Headache	1 (6.3)	0	0			1 (6.3)
Renal disorders, *n* (%)	1 (6.3)	0	0	–	–	0
Pollakiuria	1 (6.3)	0	0			0
Vascular disorders, *n* (%)	0	0	1 (5.9)	–	–	0
Hypotension	0	0	1 (5.9)			0
Part B						
Total patients, *N*	66	67	67	64	63	65
Patients with at least one TEAE, *n* (%)	31 (47.0)	36 (53.7)	34 (50.7)	34 (53.1)	50 (79.4)	33 (50.8)
Withdrawal	7 (10.6)	3 (4.5)	4 (6.0)	6 (9.4)	11 (17.5)	6 (9.2)
Cardiac failure[e], *n* (%)	0	2 (3.0)	3 (4.5)	1 (1.6)	2 (3.2)	3 (4.6)
Withdrawal	0	1 (1.5)	1 (1.5)	0	0	1 (1.5)
Hyperkalaemia/blood K^+ level increased[f], *n* (%)	3 (4.5)	1 (1.5)	3 (4.5)	5 (7.8)	7 (11.1)	1 (1.5)
Withdrawal	2 (3.0)	0	0	2 (3.1)	2 (3.2)	0
Worsening of renal function[g], *n* (%)	1 (1.5)	3 (4.5)	7 (10.4)	4 (6.3)	24 (38.1)	6 (9.2)
Withdrawal	0	0	1 (1.5)	1 (1.6)	5 (7.9)	1 (1.5)
Hypotension, *n* (%)	0	2 (3.0)	1 (1.5)	7 (10.4)	4 (6.3)	0
Withdrawal	0	0	0	1 (1.5)	1 (1.6)	0

b.i.d., twice daily; CPK, creatine phosphokinase; K, potassium; q.d., once daily; TEAE, treatment-emergent adverse event.
[a]This was a serious adverse event that led to discontinuation of study drug.
[b]Investigator-reported events.
[c]Patient with blood CPK concentration of 606 U/L at visit 4 (day 15 ± 1), moderate adverse event, study drug discontinued.
[d]Patient with blood glucose concentration of 128 mg/dL at visit 4, mild adverse event, study drug continued.
[e]Includes cardiac failure, cardiac failure chronic, and cardiac failure congestive.
[f]Any event reported as 'hyperkalaemia' or 'blood potassium increased'.
[g]Any increase in serum creatinine by ≥0.3 mg/dL from baseline and/or decrease in estimated glomerular filtration rate by ≥25% from baseline; includes renal failure chronic, renal injury, and renal impairment.



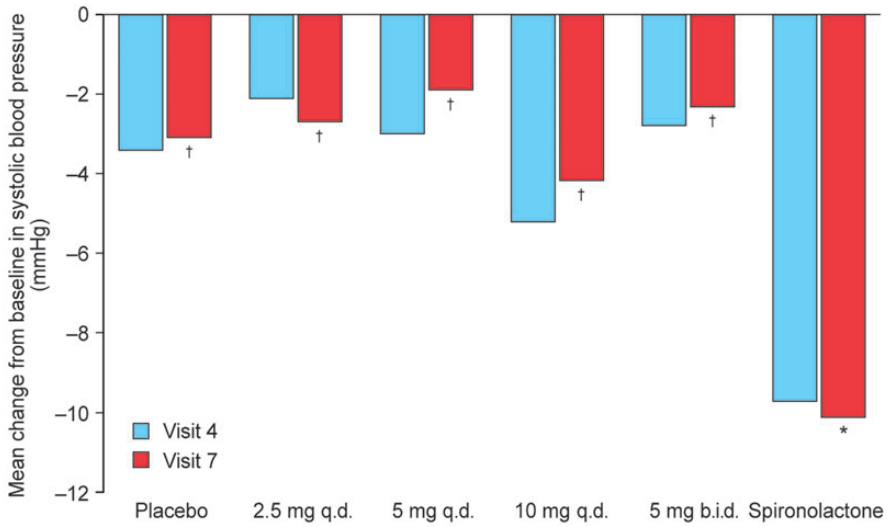
Visit 4, *n*	61	58	61	62	57	57
Visit 6, *n*	55	58	60	61	55	53
Visit 7, *n*	57	56	60	59	53	51

Figure 2 Mean change from baseline to visit 4 (day 15 ± 1) and the mean of visit 6 (day 22) and visit 7 (day 29 ± 2) in serum potassium concentration in patients receiving BAY 94-8862, placebo, or spironolactone in the full analysis set of part B of ARTS. *$P < 0.05$ between the BAY 94-8862 dose group and the placebo group at visit 6/7; †$P < 0.05$ between the BAY 94-8862 dose group and the spironolactone group at visit 6/7. Significance of visit 4 data was not analysed. b.i.d., twice daily; q.d., once daily.



Visit 4, *n*	61	58	61	53	57	59
Mean	0.32	–0.38	–1.11	–2.74	–3.60	–5.73
SD	12.49	7.12	5.45	6.56	11.39	7.49
Visit 7, *n*	57	56	60	59	54	51
Mean	0.87	–1.06	–1.40	–2.69	–0.85	–6.70
SD	10.01	6.90	6.56	6.21	9.09	8.67

Figure 3 Mean change from baseline to visit 4 (day 15 ± 1) and visit 7 (day 29 ± 2) in the estimated glomerular filtration rate (eGFR), as calculated using the modification of diet in renal disease formula, in patients receiving BAY 94-8862, placebo, or spironolactone in the safety analysis set of part B of ARTS. *$P < 0.05$ compared with the placebo group at visit 6/7; †$P < 0.05$ compared with the spironolactone group at visit 6/7. Significance of visit 4 data was not analysed. b.i.d., twice daily; q.d., once daily; SD, standard deviation.



	Placebo	BAY 94-8862 2.5 mg q.d.	BAY 94-8862 5 mg q.d.	BAY 94-8862 10 mg q.d.	BAY 94-8862 5 mg b.i.d.	Spironolactone
Visit 4, *n*	61	59	61	63	58	59
Mean	−3.4	−2.1	−3.0	−5.2	−2.8	−9.7
SD	14.8	15.3	12.5	14.7	12.4	12.0
Visit 7, *n*	57	57	60	60	55	51
Mean	−3.1	−2.7	−1.9	−4.2	−2.3	−10.1
SD	14.7	15.4	14.7	15.5	14.6	15.0

Figure 4 Mean change from baseline to visits 4 (day 15 ± 1) and 7 (day 29 ± 2) in systolic blood pressure in the safety analysis set of part B of ARTS. *$P < 0.05$ compared with the placebo group at visit 6/7; †$P < 0.05$ compared with the spironolactone group at visit 6/7. Significance of visit 4 data was not analysed. b.i.d., twice daily; q.d., once daily; SD, standard deviation.

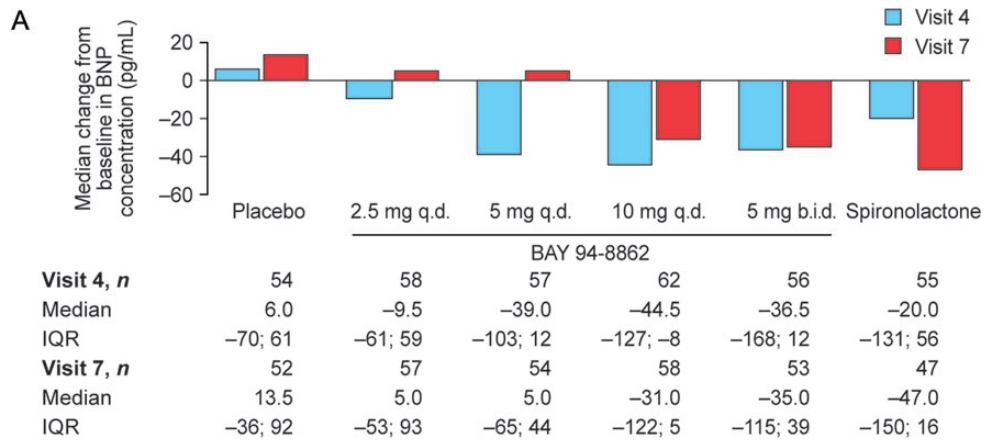
and the incidence of hyperkalaemia associated with these doses were significantly smaller than those recorded for the spironolactone 25 or 50 mg q.d. group. Furthermore, decreases in eGFR were smaller and the incidence of worsening of renal function was lower in all groups of patients receiving BAY 94-8862 than in those receiving spironolactone.

Interestingly, the reduction in SBP and the rise in serum aldosterone levels in patients receiving BAY 94-8862 5 and 10 mg q.d. were smaller than observed in patients receiving spironolactone, which could be an additional benefit for patients with HFrEF whose blood pressure is already well controlled by baseline medications (e.g. angiotensin-converting enzyme inhibitors, beta-blockers, diuretics)[10,11] or whose blood pressure is low due to worsening HF.[4] In other populations, such as those with resistant hypertension, the greater blood pressure-lowering effect of spironolactone would be an advantage.[12] The SBP, BNP, and NT-proBNP findings of the present study are consistent with the findings of a head-to-head comparison of BAY 94-8862 and eplerenone in a pre-clinical model of hypertension-driven HF.[6]

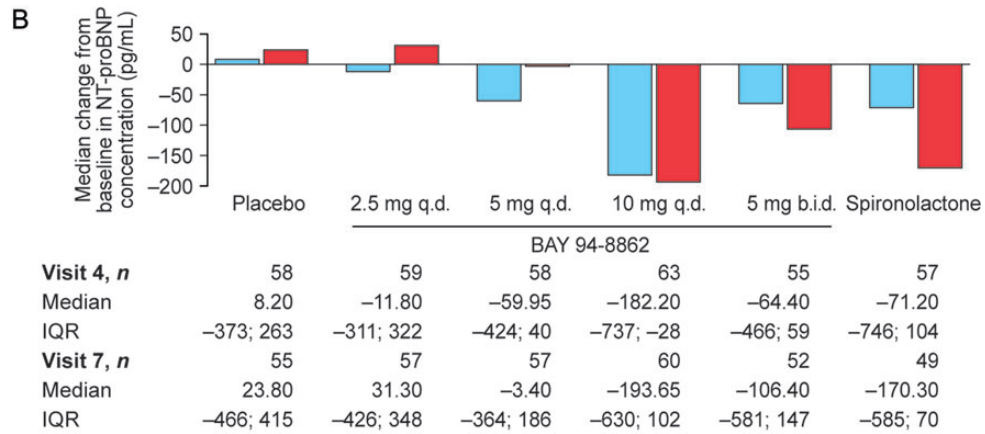
The incidence of adverse events related to study drug was low, with the highest proportion of serious adverse events considered to be drug-related occurring in the spironolactone group. Worsening of renal function was reported as an adverse event in 38% of patients treated with spironolactone, whereas the frequencies in the BAY 94-8862 groups were comparable with the event rate in the placebo group. Analysis of pooled data from part B of the study showed that the incidence of hyperkalaemia was significantly higher in the spironolactone group than in the BAY 94-8862 groups. Of interest, the incidences of adverse and serious adverse events even at the highest doses of BAY 94−8662, 5 and 10 mg q.d., were less than those observed with spironolactone. The effect of eplerenone was not studied in ARTS, and is difficult to predict because of the general lack of direct comparative data for spironolactone and eplerenone in populations with HF. BAY 94-8862 will be compared with eplerenone in a separate clinical trial (ARTS-HF; ClinicalTrials.gov identifier: NCT01807221).

The trend towards a greater reduction in BNP and NT-proBNP levels with BAY 94-8862 5 mg b.i.d. and 10 mg q.d. compared with spironolactone 25 or 50 mg suggests that BAY 94-8862 may exert greater effects on cardiac function and haemodynamic stress at these doses than spironolactone. Studies in rodents have demonstrated that the concentrations of spironolactone and eplerenone in renal tissue are at least six-fold and three-fold higher, respectively, than in the myocardium.[13] In contrast, BAY 94-8862 distributes equally to the kidney and the heart in rats (unpublished data). This suggests that BAY 94-8862 may have cardiac effects even at relatively low dosages and may in part explain the lower incidence of hyperkalaemia with BAY 94-8862 compared with spironolactone. Furthermore, pre-clinical observations have demonstrated that BAY 94-8862 has more pronounced cardiac and renal anti-remodelling effects than the steroidal MRA eplerenone.[6,7,14]

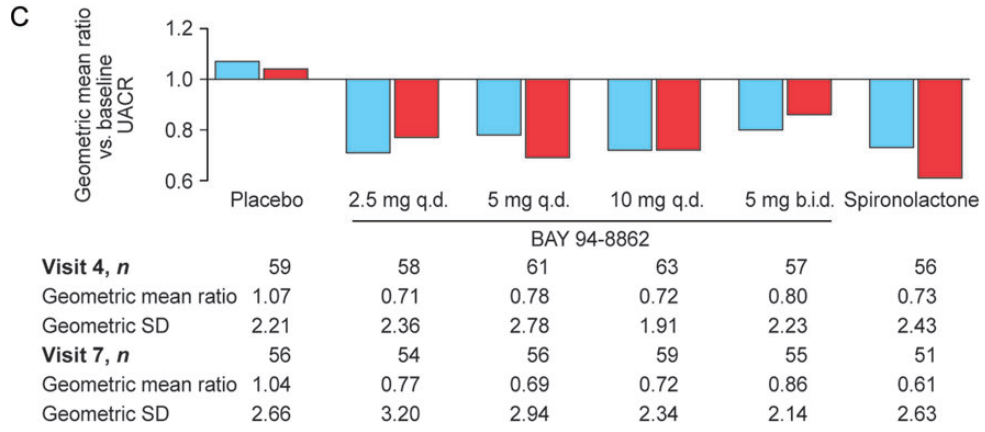
The plasma half-life of BAY 94-8862 is ∼2 h in healthy humans[15] compared with >12 h for spironolactone in healthy volunteers



Visit 4, *n*	54	58	57	62	56	55
Median	6.0	–9.5	–39.0	–44.5	–36.5	–20.0
IQR	–70; 61	–61; 59	–103; 12	–127; –8	–168; 12	–131; 56
Visit 7, *n*	52	57	54	58	53	47
Median	13.5	5.0	5.0	–31.0	–35.0	–47.0
IQR	–36; 92	–53; 93	–65; 44	–122; 5	–115; 39	–150; 16



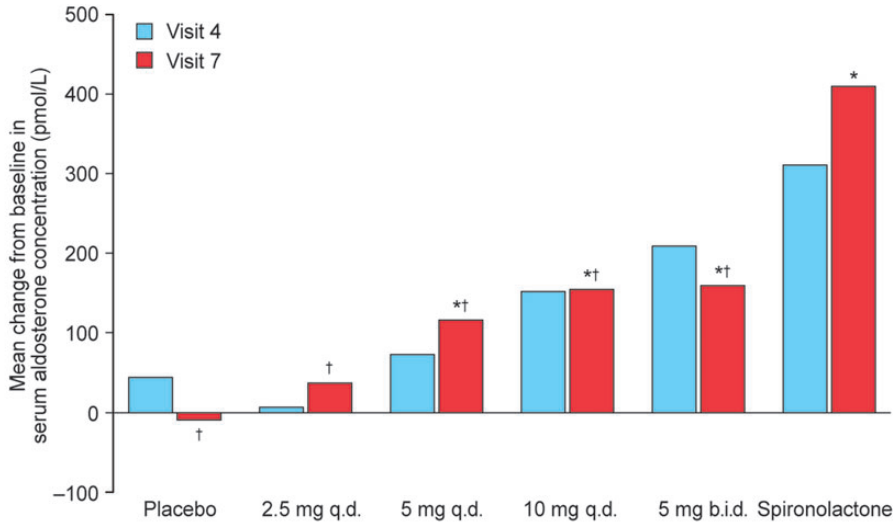
Visit 4, *n*	58	59	58	63	55	57
Median	8.20	–11.80	–59.95	–182.20	–64.40	–71.20
IQR	–373; 263	–311; 322	–424; 40	–737; –28	–466; 59	–746; 104
Visit 7, *n*	55	57	57	60	52	49
Median	23.80	31.30	–3.40	–193.65	–106.40	–170.30
IQR	–466; 415	–426; 348	–364; 186	–630; 102	–581; 147	–585; 70



Visit 4, *n*	59	58	61	63	57	56
Geometric mean ratio	1.07	0.71	0.78	0.72	0.80	0.73
Geometric SD	2.21	2.36	2.78	1.91	2.23	2.43
Visit 7, *n*	56	54	56	59	55	51
Geometric mean ratio	1.04	0.77	0.69	0.72	0.86	0.61
Geometric SD	2.66	3.20	2.94	2.34	2.14	2.63

Figure 5 Change from baseline to visits 4 (day 15 ± 1) and 7 (day 29 ± 2) in serum BNP (*A*: median change), NT-proBNP (*B*: median change), and UACR (*C*: geometric mean change) in the safety analysis set of part B of ARTS. b.i.d., twice daily; BNP, B-type natriuretic peptide; IQR, inter-quartile range; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; q.d., once daily; SD, standard deviation; UACR, urinary albumin:creatinine ratio.

(>24 h in patients with HF) owing to the generation of active metabolites.[13] Although the half-life of BAY 94-8862 is relatively short, there does not seem to be any advantage in twice-daily administration in the present study. The relatively long duration of action of BAY 94-8862 despite its relatively short plasma half-life is similar to that of eplerenone, which has a plasma half-life of 4–6 h in patients with HF[13] but is effective in reducing cardiovascular mortality and hospitalizations for HF at doses of 25 or 50 mg q.d.[16,17] The duration of the effect of an MRA may depend on the biological half-life of the MR in producing its downstream effects in different tissues, such as sodium retention in the kidney or stimulation of pro-inflammatory gene expression, rather than the plasma elimination half-life of the MRA itself.[13] Moreover, the effects of an MRA on pharmacological downstream targets in the kidney, such as the epithelial sodium



	Placebo	2.5 mg q.d.	5 mg q.d.	10 mg q.d.	5 mg b.i.d.	Spironolactone
Visit 4, *n*	59	59	61	62	56	57
Mean	43.5	7.6	72.6	151.8	209.1	311.5
SD	287.1	188.1	166.5	233.7	398.6	318.6
Visit 7, *n*	57	57	58	58	54	51
Mean	−8.3	36.9	116.0	154.6	159.9	410.5
SD	197.1	22.0	232.1	245.0	334.0	464.0

Figure 6 Mean change from baseline to visit 4 (day 15 ± 1) and visit 7 (day 29 ± 2) in serum aldosterone levels in the safety analysis set of part B of ARTS. *$P < 0.05$ compared with the placebo group at visit 6/7; †$P < 0.05$ compared with the spironolactone group at visit 6/7. Significance of visit 4 data was not analysed. b.i.d., twice daily; q.d., once daily; SD, standard deviation.

channel (for sodium excretion) and the renal outer medullary potassium channel (for potassium retention), may take place over longer time frames.

As a consequence of receptor blockade by an antagonist, the serum concentrations of the receptor ligand are expected to rise. The magnitude of this rise is usually associated with the degree of receptor blockade. In ARTS, serum concentrations of the MR ligand aldosterone increased as expected in all BAY 94-8862 groups, and to a greater extent in the spironolactone group. Levels of BNP, NT-proBNP, and albuminuria were reduced by BAY 94-8862 5 and 10 mg q.d. to at least the same degree as spironolactone 25 or 50 mg q.d., despite the lower compensatory rises in aldosterone induced by BAY 94-8862. The finding that spironolactone 25 or 50 mg q.d. resulted in a greater increase in serum aldosterone levels than any dose of BAY 94-8862 may have several reasons (all of which will require further investigation), including: differences in plasma half-life; the effect of the differences in serum potassium concentration on the release of aldosterone from the adrenal gland; and differences in the tissue distribution of the non-steroidal MRA BAY 94-8862 and the steroidal MRA spironolactone.

BAY 94-8862 is highly selective and has a high affinity for the MR, whereas spironolactone also has a high affinity for the MR but is less selective. This accounts for the well-known anti-androgenic and progestonal side effects of spironolactone, which limit patient adherence to therapy. However, the number of patients in this study and the duration of their exposure to BAY 94-8862 are inadequate to provide any definitive information on the relative incidence of these side effects in patients receiving BAY 94-8862.

Further pre-clinical and clinical studies will be required to gain greater insight into the reasons for the apparent differences in cardiac and renal efficacy of BAY 94-8862 5 and 10 mg q.d. compared with spironolactone 25 or 50 mg q.d. However, the results of the present study suggest that, in comparison with the steroidal MRA spironolactone 25 or 50 mg q.d., the non-steroidal MRA BAY 94-8862 5 and 10 mg q.d. may be at least as effective in reducing ventricular remodelling (reflected by a decrease in BNP and NT-proBNP levels), despite exerting less effect on SBP, serum potassium levels, and eGFR, as well as being associated with lower incidences of hyperkalaemia and renal adverse events in patients with HFrEF and moderate CKD. The results of the present study provide a strong impetus for further clinical evaluation of BAY 94-8862 in patients with HFrEF and concomitant CKD.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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