**Clinical Study Synopsis**

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| **Date of study report:** | 26 MAR 2013 |
| **Study title:** | A randomized, double-blind, multi-center study to assess safety and tolerability of different oral doses of BAY 94-8862 in subjects with stable chronic heart failure with left ventricular systolic dysfunction and mild (Part A) or moderate (Part B) chronic kidney disease versus placebo (Part A) or versus placebo and spironolactone (Part B) |
| **Sponsor's study number:** | 14563 |
| **NCT number:** | NCT01345656 |
| **EudraCT number:** | 2011-000301-45 |
| **Sponsor:** | Bayer HealthCare |
| **Clinical phase:** | Phase IIa |
| **Study objectives:** | Part A<br><br>To investigate the safety and tolerability of three oral doses of BAY 94-8862 given once daily (od) over 4 weeks in a randomized, placebo-controlled, double-blind study design in subjects with chronic heart failure (CHF) with left ventricular systolic dysfunction (LVSD) and mild chronic kidney disease (CKD; 60 mL/min/1.73 $m^2$ ≥ estimated glomerular filtration rate [eGFR] < 90 mL/min/1.73 $m^2$). Besides the effects on serum potassium, the effects of these doses on the change in biomarkers of renal function, eGFR using the Modification of Diet in Renal Disease Study Group (MDRD) formula, albuminuria, and pharmacokinetics (PK) of BAY 94-8862 and its metabolites in plasma after multiple oral doses were assessed.<br><br>Part B<br><br>Primary objective: To investigate the change of serum potassium after treatment with four oral dosages of BAY 94-8862 given once or twice daily (bid) over 4 weeks in a randomized, placebo-controlled, double-blind study design versus placebo in subjects with CHF with LVSD and moderate CKD (30 mL/min/1.73 $m^2$ ≤ eGFR ≤ 60 mL/min/1.73 $m^2$).<br><br>Secondary objectives:<br><br>• To investigate the change of serum potassium after treatment with four oral dosages of BAY 94-8862 given once or bid over 4 weeks versus the active comparator spironolactone in subjects with CHF with LVSD and moderate CKD (30 mL/min/1.73 $m^2$ ≤ eGFR ≤60 mL/min/1.73 $m^2$).<br><br>• To assess safety and tolerability of these doses, the effect on cardiac function by changes in concentrations of various biomarkers, and the change in biomarkers of renal function (cystatin C, kidney injury molecule-1 [KIM-1], and neutrophil gelatinase-associated lipocalin [NGAL]), eGFR (MDRD), and albuminuria. In addition, PK of |

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| | BAY 94-8862 and its metabolites in plasma after multiple oral doses were assessed. |
| **Test drug:** | Finerenone (BAY 94-8862) |
| **Name of active ingredient(s):** | Finerenone |
| **Dose:** | Part A: 2.5 mg (2 × 1.25 mg tablet), 5 mg (4 × 1.25 mg tablet), and 10 mg (1 × 10 mg tablet) od<br>Part B: 2.5 mg (2 × 1.25 mg tablet), 5 mg (4 × 1.25 mg tablet), 10 mg (1 × 10 mg tablet) od, and 5 mg (4 × 1.25 mg tablet) twice daily (bid) |
| **Route of administration:** | Oral |
| **Duration of treatment:** | 4 weeks |
| **Reference drug:** | Placebo<br>Active comparator (for part B only): Spironolactone (Aldactone 25 mg) |
| **Dose** | Placebo:<br>Part A: Matching placebo, od; Part B: Matching placebo, bid<br>Active comparator (Part B only): Starting dose of 25 mg (1 × 25 mg tablet) od, up-titration to 50 mg (2 × 25 mg tablet) od after 2 weeks of treatment if serum potassium ≤4.8 mmol/L |
| **Route of administration** | Oral |
| **Duration of treatment** | 4 weeks |
| **Indication:** | CHF with LVSD |
| **Diagnosis and main criteria for inclusion:** | Adult male and female subjects without childbearing potential with clinical diagnosis of CHF (New York Heart Association [NYHA]) class II-III, treated with evidenced-based therapy for CHF [e.g., treatment with beta-blockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as well as diuretics, unless contraindicated or not tolerated]<br>Left ventricular ejection fraction (LVEF) ≤40% measured by any modality in the subject's medical history without intervening revascularization, cardiac surgery, or implantation of biventricular pacemaker in the meantime; for those subjects with cardiac intervention, LVEF was re-assessed and an LVEF ≤40% re-confirmed once after the intervention<br>Part A: 60 mL/min/1.73 $m^2$ ≤ eGFR <90 mL/min/1.73 $m^2$ (MDRD) at screening<br>Part B: 30 mL/min/1.73 $m^2$ ≤ eGFR ≤ 60 mL/min/1.73 $m^2$ (MDRD) at screening<br>Serum potassium ≤4.8 mmol/L at screening |

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| | Systolic blood pressure (BP) ≥90 mmHg without signs or symptoms of hypotension |
| **Study design:** | The study was conducted in:<br><br>Part A: Multi-center, randomized (to one of the 3 BAY 94-8862 dose groups or placebo), double-blind, placebo-controlled, parallel-group design<br><br>Part B: Multi-center, randomized (to one of the 4 BAY 94-8862 dose groups, placebo, or spironolactone), double-blind, placebo-controlled parallel-group design with additional open-label active comparator control group |
| **Methodology:** | Blood samples for clinical chemistry (including serum potassium) were drawn at every visit, ie, at screening, on Days 1, 4, 8, 15, 18, 22, 29, and follow-up in both parts (Day 18 in Part B only).<br><br>Blood and urine samples for biomarkers were collected on Days 1, 15, 29, and at follow-up in both parts.<br><br>Safety including heart rate (HR) and BP and tolerability of study drugs were monitored throughout the study.<br><br>Blood samples for the determination of BAY 94-8862 and its metabolites were drawn before administration of the study drug and approximately 30-90 min and 180-240 min after study drug administration on Days 1, 8, and 15 in each study part. Single post-dose samples were taken on Days 4, 22, and 29. |
| **Study center(s):** | The study was conducted at 51 investigational sites that recruited subjects in 10 countries: 3 centers in Austria, 3 centers in Belgium, 4 centers in the Czech Republic, 11 centers in Denmark, 3 centers in Finland, 8 centers in Germany, 7 centers in Israel, 2 centers in Norway, 5 centers in Poland, and 5 centers in Sweden. |
| **Publication(s) based on the study (references):** | Pitt B, Filippatos G, Gheorghiade M, Kober L, Krum H, Ponikowski P, et al. Rationale and design of ARTS: a randomized, double-blind study of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease. Eur J Heart Fail. 2012 Jun; 14(6): 668-75.<br><br>Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, et al. 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. Eur Heart J. 2013 Aug; 34(31): 2453-63. |
| **Study period:** | **Study Start Date:** 09 MAY 2011<br><br>**Study Completion Date:** 16 JUL 2012 |
| **Early termination:** | Not applicable |

**Number of subjects:**

**Planned:** 60 subjects (15 per treatment group) in Part A; 360 subjects (60 per treatment group) in Part B

**Analyzed:** 65 subjects (safety analysis set [SAF]) in Part A and 392 subjects (SAF) in Part B

**Criteria for evaluation**

***Efficacy:*** Not applicable

***Safety:*** Primary variable

For Part A: Safety and tolerability of BAY 94-8862 (adverse events [AEs], serious AEs [SAEs], electrocardiogram [ECG], safety laboratory parameters)

For Part B: Change in the average of serum potassium values at Visit 6 and Visit 7 from baseline

Secondary variables

For both Part A and Part B:

- Biomarkers of renal function, eGFR (MDRD), and albuminuria
- Change in serum magnesium from baseline
- Number of subjects with serum potassium >5.5 mmol/L
- Incidence of serious hyperkalemia (serum potassium ≥6.0 mmol/L)
- Change in BP and HR

Only for Part A:

- Change in serum potassium from baseline (y)

Only for Part B:

- Safety and tolerability (adverse events [AEs], serious AEs [SAEs], electrocardiogram [ECG], safety laboratory parameters)
- Biomarkers of cardiac function
- Change in serum potassium from baseline to each time point

***Clinical pharmacology:*** Pharmacokinetics (secondary variable): Plasma concentrations of BAY 94-8862 and its metabolites in both Parts A and B of the study

**Statistical methods:** Part A: All variables were summarized by descriptive statistics only. For the change from baseline to the mean of Visit 6 (Day 29 ± 2) in serum potassium, 95% confidence intervals (CIs) were provided for the difference between the BAY 94-8862 dose groups versus placebo. The analyses were performed in the SAF.

Part B: The analysis for the primary variable, the mean change in the average of serum potassium values at Visit 6 (Day 22 ± 2) and Visit 7 (Day 29 ± 2) from baseline, was performed in the full analysis set (FAS) and

per-protocol set (PPS). The primary analysis was based on the FAS and PPS analysis was supportive.

Five different dose-response models were fitted for the serum potassium data from the placebo and BAY 94-8862 groups. The 5 dose-response models were:

Linear: $y_i = \alpha_0 + \alpha_1 Dose$

Quadratic: $y_i = \alpha_0 + \alpha_1 Dose + \alpha_2 Dose^2$

$E_{max}$: $y_i = E_0 + (E_{max} \times DoseB / ED_{50} + DoseB)$

Exponential: $y_i = \alpha_0 \exp(\alpha_1 Dose)$

Logistic: $y_i = 1 / [1 + \exp(-(\alpha_0 + \alpha_1 Dose))]$

where

$y_i$: Individual average change in serum potassium from baseline at Visit 6 and Visit 7

$E_0$: Placebo response

$E_{max}$: Maximum effect achievable above the placebo response

$ED_{50}$: Dose to achieve 50% of $E_{max}$

B: Slope factor

For comparisons between each BAY 94-8862 dose group and spironolactone, 95% CIs for the difference between each dose group and spironolactone were generated from a linear model, which included terms for treatment, pooled centers as the main effects, and baseline value as the covariate. Using the same model, a comparison of placebo and spironolactone was also performed.

All other safety analyses were performed in the SAF.

**Substantial protocol changes:** Protocol Version 2/Amendment 1 from date 25 Nov 2011 introduced the following changes:

- In Part B, the number of subjects per treatment group was increased from 40 to 60 subjects to allow a further formal comparison of BAY 94-8862 dose groups with spironolactone.
- Both Parts A and B were updated to confirm that for both withdrawn and completed subjects, the follow-up visit was to be performed 14 days after the last dose of study drug.
- Exploratory statistical comparisons between the BAY 94-8862 dose groups and the spironolactone and placebo groups were added.
- The placebo, 5 mg BAY 94-8862 bid, and spironolactone groups were not included in the dose-response model.

### Subject disposition and baseline

In Part A of the study, 116 subjects were screened. Sixty-five subjects (mean age 66.3 years, range 42-85 years, mean BMI 28.6 kg/m$^2$, range 21.5-41.4 kg/m$^2$) with CHF and LVSD and mild CKD [52 (80.0% males) and 13 (20.0%) females] were randomized to 2.5 mg BAY 94-8862 od (n = 16), 5 mg od (n = 16), 10 mg od (n = 17), or placebo (n = 16). Fifteen, 14, 17, and 15 subjects of these treatment groups completed the study according to protocol. All subjects randomized in Part A were valid for safety and PK.

In Part B of the study, 666 subjects were screened. Three hundred and ninety-three subjects with CHF and LVSD and moderate CKD were randomized to 2.5 mg BAY 94-8862 od (n = 66), 5 mg od (n = 67), 10 mg od (n = 67), 5 mg bid (n = 65), spironolactone (n = 63), or placebo (n = 65). Fifty-six, 60, 60, 55, 51, and 57 subjects of these treatment groups, respectively, completed the study according to protocol. Of the 393 randomized subjects, 1 subject of the 5 mg BAY 94-8862 bid group did not take any study drug and, therefore, was excluded from the SAF. Therefore, 392 subjects (mean age 72.1 years, range 40-89 years, mean BMI 28.8 kg/m$^2$, range 18.1-46.9 kg/m$^2$), 312 (79.6%) males and 80 (20.4%) females, were valid for safety. This subject and other three subjects were excluded from the FAS. A total of 82 subjects (20.9%) were excluded from the PPS for a variety of reasons, “serum potassium value missing for Visit 6 and Visit 7” (n = 43, 10.9%), “study drug intake not according to protocol” (n = 24, 6.1%), and “noncompliance (<80%)” [n = 10 (2.5%)] were the three most frequent reasons. All subjects of the SAF treated with BAY 94-8862 or placebo were valid for PK. As planned in the protocol, 63 subjects of the spironolactone group were not evaluated for PK.

### Efficacy evaluation

Not applicable

### Safety evaluation

Part A:

In Part A, a 79 year-old white man died (sudden cardiac death) 4 days after the start of study drug (5 mg BAY 94-8862 od). The investigator assessed the event as not related to study drug. The suggested alternative explanation was the coexisting disease, that is, chronic left heart failure with LVSD. Another two subjects experienced SAEs, which recovered. None of the SAEs was assessed as related to study drug.

Twenty seven of 65 subjects (41.5%) experienced at least one treatment-emergent AE (TEAE). In 22 of those 27 subjects, the TEAEs had recovered by the end of the study. The incidence of subjects with any TEAE was similar in the placebo (n=6), 5 mg BAY 94-8862 od (n=6), and 10 mg BAY 94-8862 od (n=5) groups, whereas in the 2.5 mg BAY 94-8862 od, 10 subjects (62.5%) experienced any TEAE, that is, there was no increase in the frequency of TEAEs with increasing BAY 94-8862 dose.

Seven of 65 subjects (10.8%) experienced at least one drug-related TEAE. All drug-related TEAEs were of mild or moderate intensity. There was no increase in the frequency of drug-related TEAEs with increasing BAY 94-8862 dose. Two subjects discontinued study drug due to TEAEs: Non-serious

moderate “blood creatine phosphokinase increased” (2.5 mg BAY 94-8862 od) and serious and severe “angina pectoris” (5 mg BAY 94-8862 od). Both TEAEs recovered.

Only one subject had a single serum potassium value >5.5 mmol/L, that is, 5.8 mmol/L at Visit 5 (Day 22 ± 2).

No signals for study drug-induced clinically relevant laboratory abnormalities, untoward effects on vital signs (including BP and HR) or ECG were detected.

In conclusion, all doses investigated in Part A of the study were safe and well tolerated. Thus, Part B was initiated.

Part B:

The analysis of the primary variable, the mean change in the average of serum potassium values at Visit 6 (Day 22±2) and Visit 7 (Day 29±2) from baseline, was performed to find the dosages of BAY 94-8862 that showed greater increase in serum potassium than the placebo group and smaller increase than the spironolactone group.

In the FAS, the adjusted mean changes from baseline for serum potassium demonstrated an increase in serum potassium change with increasing dose, adjusted mean changes of 0.04 mmol/L, 0.16 mmol/L, and 0.21 mmol/L for the 2.5 mg, 5 mg, and 10 mg BAY 94-8862 od groups, respectively. The adjusted mean change for the 5 mg BAY 94-8862 bid group was 0.30 mmol/L. The placebo group had an adjusted mean change of 0.08 mmol/L, and the spironolactone group had the largest change of any group, 0.45 mmol/L (see Table 1).

**Table 1: Mean change in serum potassium [mmol/L] from baseline to the average of Visit 6 (Day 22 ± 2) and Visit 7 (Day 29 ± 2) in Part B (ANCOVA model, no imputation performed; full analysis set)**

| Treatment group | Adjusted mean | Standard error | 95% confidence interval | |
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| | | | Lower limit | Upper limit |
| 2.5 mg BAY 94-8862 OD | 0.04 | 0.04 | -0.04 | 0.13 |
| 5 mg BAY 94-8862 OD | 0.16 | 0.04 | 0.07 | 0.24 |
| 10 mg BAY 94-8862 OD | 0.21 | 0.04 | 0.13 | 0.29 |
| 5 mg BAY 94-8862 BID | 0.30 | 0.04 | 0.21 | 0.38 |
| Spironolactone | 0.45 | 0.05 | 0.36 | 0.54 |
| Placebo | 0.08 | 0.04 | -0.01 | 0.16 |

In the FAS, the 95% CIs for the differences between the BAY 94-8862 groups and placebo excluded 0 for the 10 mg BAY 94-8862 od group and the 5 mg BAY 94-8862 bid group, demonstrating some evidence of differences between these groups and placebo.

The 95% CIs for the differences between the BAY 94-8862 groups and the spironolactone group excluded 0 for all dose groups, providing further evidence that the potassium increase was larger for the spironolactone group than the BAY 94-8862 groups.

Considering all visits, four subjects in the 5 mg BAY 94-8862 bid group and spironolactone group had serum potassium values >5.5 mmol/L at any visit; there were three such subjects in the 2.5 mg BAY 94-8862 od group and one such subject in the 5 mg BAY 94-8862 od group. Only two subjects

had serum potassium values >6.0 mmol/L at any visit, both in the 2.5 mg BAY 94-8862 od group, that is, at baseline and Visit 2 (Day 4 ± 1). At the subsequent visits, no subject had serum potassium values >6.0 mmol/L.

At the primary endpoint [mean of values at Visit 6 (Day 22 ± 2) and Visit 7 (Day 29 ± 2)], two subjects had serum potassium values >5.5 mmol/L, both in the 5 mg BAY 94-8862 bid group. No subject had serum potassium values >6.0 mmol/L at that time point.

No subject died in Part B. Twenty-three of 392 subjects (5.9%) experienced any SAE. In 21 of those 23 subjects, the SAE had recovered by study end. There was no increase in the frequency of SAEs with increasing BAY 94-8862 dose. The highest incidence of subjects with SAEs was in the spironolactone group [n = 8 (12.7%)]. Eight of 392 subjects (2.0%) experienced drug-related SAEs, five of them in the spironolactone group. Twelve of 392 subjects (3.1%) discontinued study drug due to SAEs, 4 of them in the spironolactone group, 2 in the placebo group, and the remaining 6 subjects in the 4 BAY 94-8862 groups.

Two hundred and eighteen of the 392 subjects (55.6%) experienced at least one TEAE. In 135 of those 218 subjects, the TEAEs had recovered by end of study; in 64 subjects (16.3%), the TEAEs did not recover by the end of the study. The incidence of subjects with any TEAE was similar in the placebo (n = 33, 50.8%) and the 4 BAY 94-8862 groups (2.5 mg od: n = 31, 47.0%; 5 mg od: n = 36, 53.7%; 10 mg od: n = 34, 50.7%; 5 mg bid: n = 34, 53.1%), whereas in the spironolactone group, 50 of the 63 subjects (79.4%) experienced TEAEs.

Eighty-three of 392 subjects (21.2%) experienced at least one drug-related TEAE. Four of the 392 subjects (1.0%) experienced severe drug-related TEAEs. All other drug-related TEAEs were of mild or moderate intensity. Seven of 65 subjects (10.8%) in the placebo group experienced drug-related TEAEs. Ten (15.2%), 13 (19.4%), 13 (19.4%), and 14 subjects (21.9%) experienced drug-related TEAEs in the 2.5 mg od, 5 mg od, 10 mg od, and 5 mg bid BAY 94-8862 groups, respectively. In contrast, 26 of 63 subjects (41.3%) in the spironolactone group experienced drug-related TEAEs.

Thirty-seven of 392 subjects (9.4%) discontinued study drug due to AEs, 12 of those 37 subjects due to SAEs. Discontinuations due to AEs or SAEs were more frequent in the spironolactone group than in any of the four BAY 94-8862 groups, which showed frequencies similar to those in the placebo group.

No signals for study drug-induced clinically relevant laboratory abnormalities, in particular no clinically relevant changes in serum sodium and serum magnesium were detected in the BAY 94-8862 groups.

No signals for study drug-induced untoward effects on vital signs (HR and BP) or ECG were detected. In particular, there was no indication for an untoward prolongation of QT interval corrected for HR (QTc) induced by BAY 94-8862.

At the 5 mg bid and 10 B-tymg od dosage, BAY 94-8862 demonstrated mean decreases in plasma B-type natriuretic peptide (BNP) and plasma N-terminal prohormone BNP (NT-proBNP).

Based on available data, no conclusion can be drawn regarding the effect of study treatment on renal biomarkers.

BAY 94-8862 at doses of 5 and 10 mg od decreased albuminuria to at least the same, if not a greater degree than spironolactone 25 or 50 mg od.

Decreases in eGFR were smaller and the incidence of worsening of renal function was lower in all groups of subjects receiving BAY 94-8862 than in those receiving spironolactone.

### Clinical pharmacology evaluation

Pharmacokinetic evaluation:

Exposure to all four analytes (BAY 94-8862 and its three metabolites) did not raise any concern to continue using this dose range in subjects with CHF and LVSD and mild or moderate CKD or similar study populations.

In both the parts of the study, overall, within a treatment group, plasma concentrations of metabolites increased from Visit 1 (Day 1) after the first dose to Visit 3 (Day 8±1) and Visit 4 (Day 15±1), that is, after multiple dosing.

### Overall conclusions

- Based on the primary analysis of the primary variable in Part B, 10 mg BAY 94-8862 od as well as 5 mg BAY 94-8862 bid demonstrated a significantly higher increase in serum potassium than the placebo group. 2.5 mg, 5 mg, and 10 mg BAY 94-8862 od as well as 5 mg BAY 94-8862 bid demonstrated a significantly smaller increase in serum potassium than the spironolactone group.

- All investigated doses of BAY 94-8862 did show efficacy signals by reducing albuminuria as well as B-type natriuretic peptide (BNP) and N-terminal prohormone BNP (NT-proBNP) levels (with the exception of 2.5 mg BAY 94-8862 od). The effects on natriuretic peptides were at least comparable to those of 25 mg or 50 mg spironolactone in the study population of Part B with stable CHF and LVSD and moderate CKD.

- Treatment with 2.5 mg, 5 mg, or 10 mg BAY 94-8862 od or 5 mg BAY 94-8862 bid over 4 weeks was well tolerated and safe, and did not differ to a relevant degree from placebo with regard to incidence of subjects with TEAEs and pattern of TEAEs, the only exception being a higher number of subjects with “hyperkalemia” in comparison to placebo. In contrast, the incidence of subjects with TEAEs was highest in the spironolactone group, in particular “renal and urinary disorders” and “hyperkalemia.” Virtually, the same applied to the incidence of subjects with drug-related TEAEs.