This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes
Title page

A randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy

Short title: Safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy (ARTS-DN)

Test drug: BAY 94-8862

Study purpose: Safety and efficacy

Clinical study phase: IIb Date: 04 Mar 2013

EudraCT no.: 2012-004179-38 Version no.: 1.0

Study no.: BAY 94-8862 / 16243

Sponsor: Bayer HealthCare AG, D-51368 Leverkusen, Germany

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

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Signature of the sponsor’s medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: Christina Nowack, M.D.  Role: Global Clinical Leader

Date: 04/03/2013  Signature: [Signature]
Signature of the investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Date: ___________________________  Signature: ___________________________
## Synopsis

<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>A randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short title</strong></td>
<td>Safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy (ARTS-DN)</td>
</tr>
<tr>
<td><strong>Clinical study phase</strong></td>
<td>IIb</td>
</tr>
</tbody>
</table>
| **Study objectives** | Primary objective of the study is

- To investigate the change of urinary albumin-to-creatinine ratio (UACR) after treatment with different oral doses of BAY 94-8862 given once daily over 90 days in a randomized, placebo-controlled, double-blind study design versus placebo in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy (DN)

Exploratory objectives of the study are

- To assess safety and tolerability of these doses by assessing the effects on serum potassium and renal function
- To assess change in health-related quality of life (HRQoL) from baseline to 90 days of treatment assessed by the Kidney Disease Quality of Life (KDQOL-36) and EuroQol Group 5-dimension, 3-level (EQ-5D-3L) questionnaires |
| **Test drug** | **Name of active ingredient** BAY 94-8862 |
| **Doses** | 1.25 milligram (mg) BAY 94-8862 tablet once daily in the morning or
2.5 mg BAY 94-8862 tablet once daily in the morning or
5 mg BAY 94-8862 tablet once daily in the morning or
7.5 mg BAY 94-8862 tablet once daily in the morning or
10 mg BAY 94-8862 tablet once daily in the morning or
15 mg BAY 94-8862 tablet once daily in the morning or
20 mg BAY 94-8862 tablet once daily in the morning |
| **Route of administration** | Oral |
| **Duration of treatment** | 90 days |
| **Reference drug** | **Name of active ingredient** Placebo |
| **Dose** | Placebo tablet once daily in the morning |
| **Route of administration** | Oral |
| **Duration of treatment** | 90 days |
| **Indication** | Type 2 diabetes mellitus with clinical diagnosis of DN |
Diagnosis and main criteria for inclusion

Adult male subjects and female subjects without childbearing potential with type 2 diabetes mellitus and a clinical diagnosis of DN treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), but not both, for at least 3 months.

The clinical diagnosis of DN must be based on at least 1 of the following criteria:

- Persistent very high albuminuria defined as UACR of ≥300 mg/g (≥34 mg/mmol) in 2 out of 3 first morning void samples and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m² (Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI) (mL = milliliter; min = minute; m² = square meter; g = gram; mmol = millimole) or

- Persistent high albuminuria defined as UACR of ≥30 mg/g but <300 mg/g (≥3.4 mg/mmol but <34 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥30 mL/min/1.73 m² (CKD-EPI)

Subjects with an eGFR of 30 - 45 mL/min/1.73 m² (CKD-EPI) must also be treated with a non-potassium sparing diuretic at randomization.

Serum potassium ≤4.8 mmol/L at screening (L = liter)

Mean sitting systolic blood pressure (SBP) <180 mmHg and mean sitting diastolic blood pressure (DBP) <110 mmHg at the run-in visit and mean sitting SBP <160 mmHg or mean sitting DBP <100 mmHg at the screening visit (mmHg = millimeters of mercury)

Study design

Multi-center, randomized, adaptive, double-blind, placebo-controlled parallel-group design

Methodology

1.25 mg, 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg BAY 94-8862 once daily will be compared to placebo for safety, tolerability, effects on UACR and on cardiac and renal function by changes in concentrations of various biomarkers; pharmacokinetics of BAY 94-8862 and HRQoL will be assessed.

Type of controls

Placebo

Number of subjects

Assuming a screening failure rate of approximately 50%, 1200 (1340 in case that 15 mg and 20 mg BAY 94-8862 will be investigated) subjects will have to be screened to randomize 600 (670) subjects. Assuming a dropout rate of 10% and approximately 90 (75) subjects valid for the full analysis set (FAS) needed per treatment group, in total approximately 540 (600) subjects valid for FAS are expected.

Primary efficacy variable

Ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline

Further exploratory efficacy variables

Please refer to Section 8.3.2.

Safety variables

Please refer to Section 8.3.3.

Plan for statistical analysis

Safety analysis set (SAF): All randomized subjects who have taken at least 1 dose of study drug.

FAS: All subjects of the SAF who have baseline and at least 1 post-baseline UACR value.

Per-protocol analysis set (PPS): All subjects of the FAS who have valid UACR value at Visit 5 (Day 90±2) and have no major protocol deviations.
| Plan for statistical analysis (continued) | An analysis of covariance (ANCOVA) model will be fitted to the logarithmized ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline including a factor for treatment group, factors to adjust for the stratification factors (type of albuminuria and region) and the logarithmized baseline UACR as covariate. |
# Table of contents

Title page............................................... 1
Signature of the sponsor’s medically responsible person........................................... 2
Signature of the investigator......................................................... 3
Synopsis......................................................................................... 4
Table of contents ........................................................................... 7
Table of text tables ........................................................................ 10
Table of text figures ........................................................................ 10
List of abbreviations........................................................................... 11
1. Introduction ................................................................................. 15
   1.1 Background.............................................................................. 15
   1.2 Previous experience in humans ................................................... 16
      1.2.1 Safety............................................................................... 17
      1.2.2 Efficacy ........................................................................... 17
      1.2.3 Pharmacokinetics ................................................................. 18
   1.3 Rationale for the study................................................................. 19
   1.4 Benefit-risk assessment ............................................................... 21
2. Study objectives ......................................................................... 23
3. Investigators and other study personnel ............................................ 23
4. Study design ................................................................................. 24
5. Study population ......................................................................... 30
   5.1 Eligibility ................................................................................. 30
      5.1.1 Inclusion criteria ................................................................. 30
      5.1.2 Exclusion criteria ................................................................. 31
      5.1.3 Justification of selection criteria ........................................... 33
   5.2 Withdrawal of subjects from study .............................................. 33
      5.2.1 Withdrawal ........................................................................ 33
      5.2.2 Replacement ...................................................................... 35
   5.3 Subject identification ................................................................. 35
6. Treatments .................................................................................... 36
   6.1 Treatments to be administered ..................................................... 36
   6.2 Identity of study drug ................................................................ 37
   6.3 Treatment assignment ................................................................. 38
   6.4 Dosage and administration ......................................................... 38
   6.5 Blinding ...................................................................................... 38
      6.5.1 Blinding measures ................................................................. 38
      6.5.2 Unblinding .......................................................................... 38
      6.5.3 Emergency unblinding by the investigator ......................... 39
   6.6 Drug logistics and accountability ................................................. 39
   6.7 Treatment compliance ................................................................. 39
   6.8 Post-study therapy ................................................................. 40
   6.9 Prior and concomitant therapy ................................................. 40
7. Procedures and variables ............................................................... 41
   7.1 Schedule of procedures .............................................................. 41
7.6.5 Iohexol plasma clearance .................................................................................. 66
7.7 Appropriateness of procedures / measurements ....................................................... 66
8. Statistical methods and determination of sample size ...................................................... 67
8.1 General considerations .............................................................................................. 67
8.2 Analysis sets ............................................................................................................. 67
8.3 Variables ................................................................................................................... 68
8.3.1 Primary efficacy variable .................................................................................. 68
8.3.2 Further exploratory efficacy variables ............................................................... 68
8.3.3 Safety and tolerability variables ........................................................................ 68
8.4 Statistical and analytical plans .................................................................................. 68
8.4.1 Analysis of subject characteristics .................................................................... 68
8.4.2 Analysis of primary efficacy variable ............................................................... 68
8.4.3 Analysis of further exploratory efficacy variables ............................................ 70
8.4.3.1 Ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline................................................... 70
8.4.3.2 Decreases in eGFR .................................................................................... 70
8.4.3.3 Changes in albuminuria ............................................................................. 71
8.4.3.4 Efficacy biomarkers ................................................................................... 71
8.4.3.5 Health-related quality of life ........................................................................ 71
8.4.4 Pharmacokinetics .............................................................................................. 72
8.4.5 Safety and tolerability variables ........................................................................ 72
8.4.5.1 Adverse events ........................................................................................... 72
8.4.5.2 Laboratory data .......................................................................................... 73
8.4.5.3 Safety biomarkers ...................................................................................... 73
8.4.5.4 Vital signs, ECG, and ABPM .................................................................... 74
8.4.6 Subgroup analyses ............................................................................................. 74
8.5 Planned interim analyses .......................................................................................... 75
8.6 Determination of sample size ................................................................................... 75
9. Data handling and quality assurance ........................................................................ 77
9.1 Data recording .......................................................................................................... 77
9.2 Monitoring ................................................................................................................ 78
9.3 Data processing ......................................................................................................... 78
9.4 Audit and inspection ................................................................................................. 78
9.5 Archiving .................................................................................................................. 79
10. Premature termination of the study .......................................................................... 79
11. Ethical and legal aspects ......................................................................................... 80
11.1 Ethical and legal conduct of the study .................................................................. 80
11.2 Subject information and consent ......................................................................... 81
11.3 Publication policy .................................................................................................. 82
11.4 Compensation for health damage of subjects / insurance .................................. 82
11.5 Confidentiality ...................................................................................................... 82
12. Reference list .......................................................................................................... 83
13. Protocol amendments ............................................................................................... 87
14. Appendices ............................................................................................................ 87
Table of text tables

Table 1-1: *Post hoc* analyses of randomized clinical studies testing early, treatment-induced changes in albuminuria or proteinuria on long-term renal and cardiovascular outcomes................................................................. 20

Table 4-1: Minimal recommended dose of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (adapted from Kidney Disease Outcomes Quality Initiative clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease; Table 127) .................. 26

Table 4-2: Monitoring of serum potassium during the treatment period .................. 28

Table 6-1: Identity of test drug / BAY 94-8862 and matching placebo .................... 37

Table 7-1: Schedule of procedures ............................................................................. 42

Table 8-1: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862 ................................................................. 76

Table 8-2: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg BAY 94-8862 ................................................................. 77

Table of text figures

Figure 4-1: Study design ............................................................................................... 25
List of abbreviations

τ  dosing interval
%CV  percent coefficient of variation
AASK  African-American Study of Kidney disease and hypertension
ABPM  ambulatory blood pressure monitoring
ACE  angiotensin-converting enzyme
ACEI  angiotensin-converting enzyme inhibitor
AE  adverse event
ALT  alanine aminotransferase
ANCOVA  analysis of covariance
ANOVA  analysis of variance
AP  alkaline phosphatase
ARB  angiotensin receptor blocker
ARTS  MinerAlocorticoid Receptor Antagonist Tolerability Study
AST  aspartate aminotransferase
AUC  area under the plasma concentration vs. time curve of total (bound and unbound) drug from zero to infinity after single (first) dose
AUC_{τ, Day 10}  AUC during the dosing interval τ on Day 10 of dosing
BMI  body mass index
BNP  B-type natriuretic peptide
BP  blood pressure
C\textsubscript{max}  maximum total (bound and unbound) drug concentration in plasma after single dose administration
CK  creatine kinase
CKD  chronic kidney disease
CKD-EPI  Chronic Kidney Disease Epidemiology Collaboration
CRO  contract research organization
CV  cardiovascular
CVD  cardiovascular disease
CYP  cytochrome P450
CYP2C8  cytochrome P450 isoenzyme 2C8
CYP3A4  cytochrome P450 isoenzyme 3A4
DBP  diastolic blood pressure
DCCT  Diabetes Control and Complications Trial
DMC  Data Monitoring Committee
DN  diabetic nephropathy
ECG  electrocardiogram
eCRF  electronic case report form
e.g.  exempli gratia, for example
eGFR  estimated glomerular filtration rate
EQ-5D-3L  EuroQol Group 5-dimension, 3-level questionnaire
ESRD  end-stage renal disease
etc.  et cetera, and so on
EU  European Union
FAS  full analysis set
FU follow-up
g gram
GCP Good Clinical Practice
GFR glomerular filtration rate
GGT gamma glutamyl transpeptidase
GLM generalized linear model
GMP Good Manufacturing Practice
HbA1c glycated hemoglobin
HDL high density lipoprotein
HFrEF heart failure with reduced ejection fraction
HR heart rate
HRQoL health-related quality of life
hs-CRP high-sensitivity C-reactive protein
IB Investigator’s Brochure
ICH International Conference on Harmonization
IDNT Irbesartan Diabetic NephropathyTrial
i.e. id est, that is
IEC Independent Ethics Committee
IR immediate release
IRB Institutional Review Board
IRMA-2 (study) Irbesartan in MicroAlbuminuria, type 2 diabetic nephropathy (study)
IXRS Interactive Voice / Web Response System
KDQOL Kidney Disease Quality of Life
L liter
LDH lactate dehydrogenase
LDL low density lipoprotein
LLOQ lower limit of quantification
ln natural logarithm, i.e. logarithm to the base e, a constant approximately equal to 2.718
log logarithm
LOCF last observation carried forward
LOS listing only set
LVSD left ventricular systolic dysfunction
m² square meter
MCH mean corpuscular hemoglobin
MCHC mean corpuscular hemoglobin concentration
MCV mean corpuscular volume
M.D. doctor of medicine
mg milligram
min minute
mL milliliter
μm micrometer
mmHg millimeters of mercury
mmol millimole
MR mineralocorticoid receptor
MRA mineralocorticoid receptor antagonist
NGSP National Glycohemoglobin Standardization Program
NONMEM non-linear mixed effect modeling
NT-proBNP N-terminal prohormone B-type natriuretic peptide
NYHA New York Heart Association
ONTARGET ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
PD premature discontinuation
PEG polyethylene glycol
PK pharmacokinetic(s)
PKS pharmacokinetic analysis set
PP polypropylene
PPS per-protocol analysis set
PR PR interval in ECG
QA quality assurance
QRS QRS interval in ECG
QRSD QRS duration
QT QT interval in ECG
QTc QT interval corrected for heart rate
RAS renin-angiotensin system
RAVE electronic data capturing system
RBC red blood cells
REGWQ Ryan-Einot-Gabriel-Welsch Q
REIN (study) Ramipril Efficacy In Nephropathy (study)
RENAAL (study) Reduction in Endpoints in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (study)
ROAD (study) Renoprotection of Optimal Antiproteinuric Doses (study)
SAE serious adverse event
SAF safety analysis set
SAS Statistical Analysis System
SBP systolic blood pressure
SD standard deviation
SID subject identification
SOC standard of care
SUSAR suspected, unexpected serious adverse reaction
t_{\text{max}} time to reach C_{\text{max}} in plasma after single (first) dose
TEAE treatment-emergent adverse event
TOSCA Tools for Syntactic Corpus Analysis (database)
TRANSCEEND Telmisartan Randomized Assessment Study in ACE iNtolerant subjects with cardiovascular Disease
UACR urinary albumin-to-creatinine ratio
US United States (of America)
VAS visual analogue scale
vs. versus, as opposed to
WBC white blood cells
WHO  
World Health Organization
1. Introduction

1.1 Background

According to the World Health Organization (WHO), diabetes mellitus currently affects more than 240 million people worldwide, and the number is predicted to rise to more than 360 million by 2030.\(^{(1)}\) Diabetic nephropathy (DN) represents the most common cause of end-stage renal failure in the United States (US) and accounts for approximately 40% of all new patients entering end-stage renal disease (ESRD) programs and approximately 45% of patients receiving renal replacement therapy.\(^{(2,3)}\)

Overall approximately 20 to 30% of patients with type 1 or type 2 diabetes mellitus develop evidence of nephropathy although there is considerable variability by type in terms of disease progression.

- Approximately 25 to 45% of type 1 diabetes mellitus patients will develop DN and signs of high albuminuria. Within those, 80 to 90% will progress to overt DN within 5 to 10 years.\(^{(4)}\)

- About 50% of type 2 diabetes mellitus patients will have high albuminuria at the time of presentation, typically secondary to hypertension.\(^{(5)}\) Only 10 to 20% will progress to overt DN within 5 to 10 years.

Until recently, DN was very much a disease of Western countries, but in the future, Asian countries are likely to represent the bulk of the DN population, due to their size but also to the predilection of Asian diabetic patients to develop renal complications.\(^{(6)}\) In cross-sectional surveys, up to 60% of Asian diabetic patients have high or very high albuminuria compared to 30 to 40% reported in Western diabetic populations.\(^{(7)}\)

Hyperglycemia is a primary initiator of DN – in the absence of elevated glycemia, nephropathy is much less likely to develop.\(^{(8)}\) As a result, long-standing uncontrolled or poorly controlled diabetes is the single most important risk factor for the development of DN. Other risk factors include hypertension and hyperlipidemia.

In patients with DN, albuminuria at baseline is a much more important factor to predict ESRD than is hypertension at baseline. In addition to lowering albuminuria, it is now clearly demonstrated that interruption of the renin-angiotensin system (RAS) reduces the risk of progression to ESRD. However, an impact on overall survival has not yet been demonstrated.\(^{(9)}\)

Despite significant progress over the last decade, the ultimate goal of preventing the development of ESRD in DN is still far from being reached. Without therapy, the average time from diagnosed chronic kidney disease (CKD) to ESRD is about 4 to 5 years. On therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor
blockers (ARBs), this time is extended by 1 to 2 years only.\(^{(9,10)}\) DN remains the primary diagnosis leading to ESRD in the US and 1 of the top 2 or 3 in most other countries.\(^{(11)}\)

Current therapies for DN rely on the control of albuminuria through inhibition of the RAS with ACEIs or ARBs. Despite initial down-regulation of the release of aldosterone by the adrenal glands, up to 50% of the patients treated with a RAS blocker develop an increase in plasma aldosterone within 6 to 12 months after the initiation of treatment.\(^{(12)}\) Several studies have shown a direct relationship between increases in plasma aldosterone after ACEI treatment and increases in albuminuria and decreases in kidney function. Explorative clinical studies in adults have shown a potential role for mineralocorticoid receptor antagonists (MRAs), when added to RAS blockers, to delay the development of ESRD further.\(^{(13-16)}\)

BAY 94-8862 is a novel non-steroidal MRA. In vitro investigations have demonstrated superior selectivity vs. spironolactone and improved potency vs. eplerenone.\(^{(17)}\) These properties have also been demonstrated in a number of nonclinical in vivo investigations, which showed BAY 94-8862 to be effective in reducing mortality in models of heart failure and stroke; and in reducing cardiac remodeling and end-organ lesions.

In Study 14563 (Mineralocorticoid Receptor Antagonist Tolerability Study, ARTS), a multicenter, randomized, double-blind, placebo-controlled study, BAY 94-8862 was investigated in subjects with heart failure with reduced ejection fraction (HFrEF) and mild to moderate CKD.\(^{(18)}\) ARTS demonstrated the improved safety of all once-daily investigated doses of BAY 94-8862 (2.5 - 10 mg) in comparison to spironolactone (25 / 50 mg once daily), in particular with regards to increase of serum potassium and change in renal function. During the observation period of 28 days, a reduction of B-type natriuretic peptide (BNP) and N-terminal-prohormone B-type natriuretic peptide (NT-proBNP) similar to spironolactone (25 / 50 mg once daily) was demonstrated for doses higher than 5 mg BAY 94-8862 once daily in that high-risk population for hyperkalemia. Albuminuria was also reduced by all doses of BAY 94-8862, in particular in subjects with high and very high albuminuria at baseline.

Based on the aforementioned properties, BAY 94-8862 is expected to have the potential to address the unmet medical needs in patients with type 2 diabetes mellitus and the clinical diagnosis of DN. When added to standard therapy with RAS blocker treatment with 1.25 to 20 mg BAY 94-8862 given once daily might lead to a reduction in albuminuria compared with placebo on top of standard of care (SOC). In Study 16243, safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN will be investigated over 90 days of treatment.

### 1.2 Previous experience in humans

A detailed description of the properties of BAY 94-8862 and the results of the nonclinical and clinical pharmacology studies as well as the first clinical study (Study 14563, ARTS) conducted so far are given in the Investigator’s Brochure (IB). A brief overview of the results is provided in the following sections.
1.2.1 Safety

The dose range investigated so far in healthy subjects was safe and well tolerated and covered single oral doses of 1 to 40 mg BAY 94-8862 polyethylene glycol solution (Studies 13782, 13784, and 13786) and 1.25 to 80 mg BAY 94-8862 administered as immediate-release (IR) tablets (Studies 13784, 13786, 14504, 14506, 14508, 14509, 15526, 15528, and 15481) as well as multiple oral doses of 10 and 20 mg twice daily and 40 mg once daily for 10 days administered as 10 mg IR tablets (Studies 13785 and 15171). There were no drug-related serious adverse events (SAEs). All observed treatment-emergent adverse events (TEAEs) were of mild or moderate intensity.

In MinerAlocorticoid Receptor Antagonist Tolerability Study (ARTS, Study 14563), BAY 94-8862 was investigated in subjects with stable chronic heart failure and mild (Part A) or moderate (Part B) CKD. In total, 65 subjects were enrolled in Part A and 393 in Part B which was the main part of the study. Safety and tolerability as well as the effects on different biomarkers of cardiac and renal function were compared to placebo as well as to 25 / 50 mg spironolactone once daily after 28 days of study drug treatment. Primary variable in Part B was the change in serum potassium from baseline to Visit 6 (Day 22±2) and Visit 7 (Day 29±2). All doses of BAY 94-8862 tested in Study 14563 (2.5 mg, 5 mg, and 10 mg once daily as well as 5 mg twice daily) were safe and well tolerated. Although only approximately 50% of all subjects in the spironolactone treatment group could be up-titrated from 25 mg to 50 mg after 14 days of treatment, all doses of BAY 94-8862 showed less potassium increase than spironolactone.

In the tested dose range, BAY 94-8862 was well tolerated and safe and did not differ to a relevant degree from placebo with regard to overall number of adverse events (AEs) and types of AEs, the only exception being a higher number of subjects with hyperkalemia in comparison to placebo. In contrast, the number of subjects with AEs was highest in the spironolactone treatment group; in particular, “renal and urinary disorders” and “hyperkalemia” occurred more frequently in the spironolactone treatment group than in the other treatment groups.

1.2.2 Efficacy

ARTS (Study 14563) was not designed to detect any statistically significant differences in the efficacy of BAY 94-8862 in comparison to spironolactone. In addition, the treatment period of 28 days was too short to fully exploit the beneficial anti-fibrotic effects of MR antagonism on heart and kidney. Nevertheless, the short-term effects of BAY 94-8862 on albuminuria (measured as urinary albumin-to creatinine ratio, UACR) were measured in both parts of the study as well as the effects on biomarkers of cardiac function such as BNP and NT-proBNP in Part B of the study only. Serum aldosterone which can be used as biomarker for activity of the MRA at the MR was also assessed in Part B. Since MR antagonism is associated with a feedback increase in plasma renin activity, increasing angiotensin II and aldosterone levels can be observed under treatment with an MRA.
In ARTS (Study 14563), a dose-dependent increase in serum aldosterone was demonstrated at all investigated doses of BAY 94-8862 as well as spironolactone.

Since baseline values of UACR were rather low in Part A of the study, only small decreases in UACR were observed at all doses of BAY 94-8862. In Part B, all doses of BAY 94-8862 decreased UACR to a similar extent as 25 mg spironolactone once daily after 2 weeks of treatment but less than 25 / 50 mg spironolactone once daily at the end of the observation period. Since the mean baseline values in the 5 mg BAY 94-8862 twice-daily treatment group were low in comparison to the other groups, no remarkable effects on reduction in albuminuria were seen in this group.

Starting at a dose of 5 mg BAY 94-8862 once daily, a decrease in BNP and NT-proBNP was observed during the course of the study. For the 10 mg BAY 94-8862 once-daily and 5 mg BAY 94-8862 twice-daily treatment groups, the mean changes from baseline were more pronounced than in the spironolactone treatment group. However, as already known for BNP and NT-proBNP, high inter-subject variability was observed for these parameters.

In summary, all investigated doses of BAY 94-8862 showed efficacy signals by reducing albuminuria as well as BNP and NT-proBNP levels (with the exception of 2.5 mg once daily). The effects on natriuretic peptides were at least comparable to those following 25 / 50 mg spironolactone once daily in the investigated subject population with stable HFrEF and moderate CKD (Part B).

1.2.3 Pharmacokinetics

Based on the available clinical-pharmacological studies in healthy volunteers the pharmacokinetics (PK) of BAY 94-8862 can be summarized as follows: BAY 94-8862 was rapidly absorbed with a median time to maximum concentration (t\text{max}) between 0.5 and 1.5 hours [fasted administration of immediate-release (IR) tablet] and rapidly eliminated from plasma with a terminal half-life (t\text{1/2}) of 2 - 3 hours. After administration of 1.25 to 10 mg IR tablets, the area under the plasma concentration vs. time curve (AUC) increased in proportion to the dose. A high-fat, high-calorie meal had little effect on the AUC of 10 mg BAY 94-8862 IR tablet (10% increase) and resulted in a reduced absorption rate [32% decrease in maximum total drug concentration in plasma (C\text{max}) and 1.75 h increase in the time to reach C\text{max} in plasma (t\text{max})]. Following administration of IR tablets for 10 days [10 mg or 20 mg (two 10 mg tablets) twice daily, 40 mg (four 10 mg tablets) once daily], a 10 - 32% increase in AUC during the dosing interval τ on Day 10 of dosing (AUC\text{τ,Day 10}) over AUC on Day 1 was observed, while there was no consistent effect on maximum plasma concentrations. BAY 94-8862 starting from 20 mg twice daily onwards was a weak inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4) as multiple doses increased the AUC of the prototypical CYP3A4 substrate midazolam by 21%.

Renal elimination of unchanged BAY 94-8862 by glomerular filtration was a minor route of elimination and accounted for 0.57 - 1.4% of the dose. Mild renal impairment had no effect on BAY 94-8862 exposure. Moderate or severe renal impairment resulted in an increase in
BAY 94-8862 AUC (+47% to 57% for unbound AUC) and had no effect on C_{\text{max}} in comparison to healthy controls. Age-related increases in BAY 94-8862 AUC (+34%) and C_{\text{max}} (+51%) were observed when comparing subjects aged \geq 65 years with subjects aged \leq 45 years while gender had no effect on the drug’s pharmacokinetics. Omeprazole or Maalox had no effect on the AUC of BAY 94-8862 (10 mg IR tablet) and no relevant effect on its C_{\text{max}}.

Based on available data, 4 days pre-treatment with and concomitant administration of the moderate CYP3A4 inhibitor erythromycin (500 mg 3 times daily) results in an increase in AUC (+250%) and C_{\text{max}} (+90%) of BAY 94-8862 (1.25 mg IR tablet) compared to BAY 94-8862 administered alone.

1.3 Rationale for the study

Treatment with MRAs has become a 1A recommendation in international guidelines for patients with HFrEF, New York Heart Association (NYHA) class II - IV who remain symptomatic despite treatment with both ACEIs and beta-blockers.\(^{(20, 21)}\) Although these agents are still underused or used at a low dose in clinical practice partly due to concerns raised about their safety,\(^{(22, 23)}\) there is consensus that in all symptomatic patients with HFrEF, an MRA is an appropriate addition to ACEIs and beta-blockers, proven to provide additional reductions in morbidity and mortality.\(^{(21, 24)}\)

There is also evidence that treatment with ACEIs and ARBs slows progression of kidney disease; however, used alone or in combination, these classes of drugs have not been proven to reduce cardiovascular (CV) morbidity and mortality.\(^{(25, 26)}\) There is an urgent need to evaluate novel therapies to improve CV and renal outcomes in patients with DN.\(^{(27)}\) No treatment regimens have been shown to stop progression of kidney disease or prevent CV events in patients with diabetes mellitus, including anemia treatment.\(^{(28)}\)

Although the precedent of MRAs in DN is limited to explorative studies with MRAs given on top of optimized SOC, the results suggest that administration of therapeutic agents that block the MR may improve outcomes in patients with CKD. In these studies, the MRAs spironolactone and eplerenone showed to reduce albuminuria.\(^{(13-16)}\) However, the ultimate goal of slowing progression of kidney disease and improving CV morbidity / mortality has not yet been demonstrated in long-term outcome studies.
Table 1-1: *Post hoc* analyses of randomized clinical studies testing early, treatment-induced changes in albuminuria or proteinuria on long-term renal and cardiovascular outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Renal outcomes</th>
<th>Cardiovascular outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmieder et al. (29)</td>
<td>23,480 subjects with vascular disease or high-risk diabetes included in the ONTARGET and TRANSCEND</td>
<td>Each halving of albuminuria level during the first 2 years was associated with a decrease in the combined renal outcome by 27% during the 1.7 years of follow-up</td>
<td>Each halving of albuminuria level during the first 2 years was associated with a decrease in the combined CV outcome by 15% after 1.7 years of follow-up</td>
</tr>
<tr>
<td>Xie et al. (30)</td>
<td>339 Chinese nondiabetic CKD subjects with overt proteinuria included in the ROAD study</td>
<td>Every 0.5 g reduction in residual proteinuria was associated with a risk reduction by 50% for the combined end point during 3.7 years of follow-up</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Lea et al. (31)</td>
<td>1,094 African Americans with hypertensive renal disease included in the AASK</td>
<td>Each doubling of proteinuria level in the first 6 months was associated with a relative risk for ESRD of 2.11 (95% confidence interval: 1.89 - 2.36) over a median follow-up of 3.8 years</td>
<td>Not assessed</td>
</tr>
<tr>
<td>de Zeeuw et al. (32, 33)</td>
<td>1,513 subjects with overt diabetic nephropathy included in the RENAAL study</td>
<td>Each halving of albuminuria level during the first 6 months was associated with a reduction in the risk for the combined renal end point by 45% during 3.4 years of follow-up</td>
<td>Each halving of albuminuria level during the first 6 months was associated with a reduction in CV risk by 18% after 3.4 years of follow-up</td>
</tr>
<tr>
<td>Hunsicker et al. (34)</td>
<td>1,715 subjects with type 2 diabetes mellitus included in the IDNT</td>
<td>Each halving of proteinuria level during the first 12 months was associated with a risk reduction in ESRD by 56% during 2.9 years of follow-up</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Ruggenenti et al. (35)</td>
<td>273 nondiabetic subjects with chronic proteinuric nephropathies included in the REIN study</td>
<td>Short-term changes in proteinuria independently predicted GFR decline over a median follow-up of 2.6 years</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Hellemons et al. (36)</td>
<td>531 diabetic subjects with microalbuminuria included in the IRMA-2 study</td>
<td>Each halving of proteinuria level was associated with a risk reduction for development of overt nephropathy by 44% over 2 years of follow-up</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Holtkamp et al. (37)</td>
<td>2,900 subjects with diabetic nephropathy included in the RENAAAL study and the IDNT</td>
<td>Not assessed</td>
<td>Each log unit decrease in albuminuria level was associated with a 13% risk reduction for CV events</td>
</tr>
</tbody>
</table>

AASK, African-American Study of Kidney disease and hypertension; CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease; GFR, glomerular filtration rate; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA-2, IRbesartan in MicroAlbuminuria, type 2 diabetic nephropathy; ONTARGET, ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; REIN, Ramipril Efficacy In Nephropathy; RENAAL, Reduction in Endpoints in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan; ROAD, Renoprotection of Optimal Antiproteinuric Doses; TRANSCEND, Telmisartan Randomized AssessmeNT Study in ACE iNtolerant subjects with cardiovascular Disease
Albuminuria is a surrogate marker of kidney damage (reflecting underlying glomerular disease or renal tubular dysfunction) and has been proposed to be a marker of CKD progression. Patients with higher baseline albuminuria experience a relatively faster rate of glomerular filtration rate (GFR) decline.\(^{(38)}\) Urinary protein reduction is associated with a decline in the rate of kidney disease progression, which leads to disease stabilization and, in some cases, even to recovery of renal function.\(^{(39)}\) Post hoc analyses of randomized clinical studies that have aimed to evaluate the relationships between changes in albuminuria and disease outcome have consistently found that a short-term reduction in albuminuria is invariably associated with reduction in CV mortality and morbidity as well as slower GFR decline and progression to ESRD in the long term (see Table 1-1).

In Study 14563 (ARTS), albuminuria was reduced by all investigated doses of BAY 94-8862. In particular in subjects with high and very high albuminuria, UACR was decreased by up to 52% and 74% from baseline, respectively. The observed effects were comparable to the effects following the administration of 25 / 50 mg spironolactone in subjects with HFrEF and moderate CKD. All doses of BAY 94-8862, i.e. 2.5 to 10 mg given once daily as well as 5 mg given twice daily, were safe and well tolerated and showed less potassium increase than the comparator spironolactone.

This study (Study 16243) will investigate short-term efficacy and safety of different oral doses of BAY 94-8862 given once daily over 90 days in comparison to placebo in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN.

Based on its specific profile with its favorable balanced activity on heart and kidney, BAY 94-8862 might have the potential to address the unmet medical needs in patients with type 2 diabetes mellitus and the clinical diagnosis of DN and to demonstrate a delay in the progression to ESRD and a reduction of CV mortality and morbidity, on top of ACEIs or ARBs, in this high-risk patient population.

1.4 Benefit-risk assessment

In recent years, large-scale clinical studies\(^{(9, 10, 40)}\) have shown that the interruption of the RAS with either ACEIs or ARBs has renoprotective effects in patients with DN. Both, ACEIs and ARBs, significantly reduce proteinuria and the risk of ESRD by about 20% to 30%.\(^{(41)}\) Therefore, guidelines recommend these treatments in hypertensive and normotensive patients with DN.\(^{(42)}\)

However, it has also been demonstrated that despite initial down-regulation of the release of aldosterone by the adrenal glands in patients treated with ACEIs or ARBs, up to 50% of the patients develop an increase in plasma aldosterone within 6 - 12 months.\(^{(12)}\) Several studies have shown a direct relationship between increases in plasma aldosterone after ACEI treatment and increases in proteinuria and decreases in kidney function.\(^{(13, 43-45)}\) Aldosterone breakthrough during blockade of the RAS in DN is associated with enhanced decline in GFR due to the unsuppressed actions of aldosterone leading to fibrotic and pro-inflammatory effects at a number of target organs, including the kidneys.\(^{(13, 43-45)}\) Increased aldosterone
levels are associated with enhanced albuminuria and a faster rate of decline in renal function.\(^{(13, 43)}\)

In this study (Study 16243), subjects with type 2 diabetes mellitus and the clinical diagnosis of DN will be treated with different oral doses of BAY 94-8862 or placebo given once daily for 90 days. At least minimal recommended doses of either an ACEI or ARB, but not both, will continue concomitantly. Given the aforementioned aldosterone breakthrough under treatment with ACEIs and ARBs as well as the observed benefits of MRAs in ameliorating albuminuria and glomerular podocyte damage,\(^{(46, 47)}\) subjects participating in this study may already benefit from short-term treatment with different oral doses of BAY 94-8862. In Study 14563 (ARTS), all doses planned to be initially evaluated in this study were proven to be safe and well tolerated and demonstrated after 28 days of treatment beneficial effects on NT-proBNP, BNP, and albuminuria in subjects with HFrEF and moderate CKD.

The 1.25 mg BAY 94-8862 dose was not investigated in Study 14563 (ARTS). However, based on the effects on UACR seen with the lowest dose investigated in Study 14563 (ARTS), i.e. 2.5 mg (15% or 68.8% reduction in UACR from baseline to Visit 7 in subjects with high or very high albuminuria at baseline, respectively), the 1.25 mg dose was chosen as additional dose for this Phase IIb study in order to find out if this dose is effective. Once the safety and tolerability of doses up to 10 mg BAY 94-8862 once daily have been confirmed by an independent data monitoring committee (DMC), higher doses will also be tested. Higher doses will provide a higher level of MR blockade and therefore, subjects might also benefit from this treatment.

Because of its potential favorable balance of cardiac anti-remodeling effects vs. renal (electrolyte) effects, it is anticipated that BAY 94-8862 may provide a high level of MR antagonism accompanied by an acceptable safety profile at all investigated doses. Considering the detrimental effects of albuminuria on renal function as well as the increased CV risk in patients with type 2 diabetes mellitus, subjects participating in this study should allow full breadth of beneficial effects of MR antagonism with BAY 94-8862 to be investigated.

Given the increased risk of CV events in patients with type 2 diabetes mellitus and the clinical diagnosis of DN with the substantial risk of progression to ESRD, a next-generation MRA with an improved efficacy and safety profile could help to prevent progression of kidney disease, CV mortality and non-fatal CV events as well as save healthcare resources utilized in this population.

The main risks identified from previous studies with MRAs are the development of hyperkalemia and worsening of renal function.\(^{(48)}\) In this study, serum potassium levels and renal function will be closely monitored, in particular after changes in the subject’s clinical status that influences serum electrolyte levels or fluid balance. Precise and well-defined stopping rules for permanent discontinuation of study drug have been included into this protocol. In addition, before higher doses of BAY 94-8862 will be introduced into the study, safety and tolerability of lower doses have been reviewed and confirmed by an independent DMC.
All procedures in the study [e.g. recording of electrocardiogram (ECG), measurement of blood pressure (BP), drawing of blood and urine samples] are established and routine procedures in the management of patients with DN. As no specific invasive procedures are included in the study protocol, no specific risk linked to the study has been identified.

Considering this clinical setting, the risk-benefit assessment is in favor of the participation of subjects in this study.

2. **Study objectives**

Primary objective of the study is

- To investigate the change of UACR after treatment with different oral doses of BAY 94-8862 given once daily from baseline to Visit 5 (Day 90±2)

Further exploratory objectives of the study are

- To assess safety and tolerability of these doses by assessing the effects on serum potassium and renal function

- To assess change in health-related quality of life (HRQoL) from baseline to 90 days of treatment assessed by the Kidney Disease Quality of Life (KDQOL-36) and EuroQol Group 5-dimension, 3-level (EQ-5D-3L) questionnaires

3. **Investigators and other study personnel**

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center’s investigator site file.

The principal investigator of each center must sign the protocol signature sheet before subject recruitment may start at the respective center. Likewise, all protocol amendments / integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor study file.

The global sponsor of this study is identified on the title page of this protocol.

If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.
The coordinating investigator for this study is:

Prof. Luis Miguel Ruilope
Complutense University
12 de Octubre Hospital, 28041 Madrid, Spain

4. Study design

Design overview

This study will be conducted in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN using a multi-center, randomized, adaptive, double-blind, placebo-controlled, parallel-group design.

Planned number of subjects valid for the full analysis set: approximately 90 subjects in each treatment group. Approximately 75 subjects in each of the BAY 94-8862 treatment groups and the placebo group if at least 1 of the additional treatment groups will be added and not closed due to safety reasons during the further course of the study.

Following an open-label run-in and screening period of up to 12 weeks in total, eligible subjects will be randomized to 1 of up to 7 doses of BAY 94-8862 or placebo on top of SOC to receive a 90-day study drug treatment. Initially, the following 5 doses of BAY 94-8862 will be compared to placebo in a double-blind manner: 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg once daily. After safety and tolerability of these doses have been assessed by an independent DMC, none or up to 2 further doses of BAY 94-8862 may be introduced: 15 mg and 20 mg once daily.
Open-label run-in period (up to 12 weeks)

Following a run-in visit, subjects meeting all of the inclusion and none of the exclusion criteria will be enrolled in the open-label run-in period. During this period, subjects’ eligibility for randomization into this study will be evaluated. At the end of this run-in period, each subject should receive at least the minimal recommended dose of conventional therapy according to local guidelines which consists either of an ACEI or ARB, but not both.

Table 4-1 shows the minimal recommended dose of the ACEIs and ARBs that were used in the major controlled studies. Variation of minimal recommended doses may exist in local clinical guidelines.
Table 4-1: Minimal recommended dose of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (adapted from Kidney Disease Outcomes Quality Initiative clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease; Table 127)

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Minimal recommended dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td></td>
</tr>
<tr>
<td>Benazepril</td>
<td>20</td>
</tr>
<tr>
<td>Captopril</td>
<td>25</td>
</tr>
<tr>
<td>Enalapril</td>
<td>10</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>20</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>20</td>
</tr>
<tr>
<td>Moexipril</td>
<td>5</td>
</tr>
<tr>
<td>Perindopril</td>
<td>4</td>
</tr>
<tr>
<td>Quinapril</td>
<td>20</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>2</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>16</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>400</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>150</td>
</tr>
<tr>
<td>Losartan</td>
<td>50</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>20</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>40</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80</td>
</tr>
</tbody>
</table>

Subjects with an estimated glomerular filtration rate (eGFR) (CKD-EPI)\(^{50}\) of 30 - 45 mL/min/1.73 m\(^2\) at the run-in visit must also be treated with a non-potassium-sparing diuretic at randomization. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. At the screening visit, subject’s treatment should be stable and without any adjustments for at least 4 weeks as documented in the subject’s medical records.

As part of the 12-week run-in period, a screening visit to confirm the subject’s eligibility will take place within ≤14 days prior to the planned randomization. At this visit, it will be assessed whether the subject still meets all the inclusion and none of the exclusion criteria while on at least the minimal recommended dose of an ACEI or ARB according to the local guidelines.

If the subject already receives an ACEI or ARB for at least 3 months and is on the minimal recommended dose of the ACEI or ARB at the run-in visit and this dose has not been adjusted for at least 4 weeks, the run-in visit will be considered as the screening visit and the subject can be randomized within the next 14 days. Before randomization, investigators should check if the subject is still eligible for the study.
Double-blind study period (90 days)

Subjects who meet all the inclusion and none of the exclusion criteria will be randomized to receive 1 of 5 fixed oral doses of BAY 94-8862 or placebo on top of their conventional treatment for 90 days. After safety and tolerability of these doses have been assessed by an independent DMC, none or up to 2 fixed oral doses of BAY 94-8862 may introduced into the study.

The goal of this study is to assess the relative effects of BAY 94-8862 on UACR as well as safety and tolerability in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN.

Blood pressure control

According to international guidelines, target blood pressure for subjects with type 2 DN is <140/80 mmHg.\(^{(51, 52)}\) However, the individual target blood pressure for each subject may vary dependent on concomitant diseases and individual well-being. If blood pressure is considered uncontrolled by the investigator during the double-blind study period, non-potassium-sparing diuretics should be added as first choice to the treatment regimen if not already included. Thereafter, antihypertensive medications can be added according to local guideline recommendations. If the blood pressure is still not considered sufficient by the investigator although these medications were added, the subject has to be withdrawn from the study.

Monitoring of serum potassium during the treatment period

Subjects will maintain their normal diet throughout the study and will not be given any specific advice on dietary sodium or potassium restrictions. If there is a change in the subject’s clinical status of which the investigator is aware of that influences serum electrolyte levels or fluid balance (e.g. vomiting or / and diarrhea >1 day), it is recommended to reassess serum potassium levels as soon as possible after the acute event.

If any re-assessment of serum potassium is required, always locally and centrally analyzed blood samples must be taken.

If serum potassium is ≥5.6 and ≤6.0 mmol/L measured in the central or local laboratory, a second blood sample has to be taken as soon as possible but at the latest within 48 hours. If serum potassium is again ≥5.6 mmol/L in the locally or centrally analyzed blood sample, study drug has to be discontinued permanently.

If serum potassium is >6.0 mmol/L in the centrally analyzed blood sample but <5.6 mmol/L in the locally analyzed sample, treatment with study drug can be continued. If serum potassium is >6.0 mmol/L in the centrally analyzed blood sample and ≥5.6 mmol/L in the locally analyzed sample, study drug has to be discontinued permanently.
Inappropriate transport conditions or lengthy transport time to the central laboratory may result in falsely elevated serum potassium values in the centrally analyzed blood sample. Therefore, the results of the locally analyzed blood sample will also be taken into account. If the locally analyzed blood sample is missing or the result is inconclusive and the central laboratory result is not available, another blood sample must be taken as soon as possible but at the latest within 48 hours.

If serum potassium is >6.0 mmol/L in the locally analyzed blood sample, study drug has to be discontinued permanently.

Hemolytic blood samples or serum potassium values >6.0 mmol/L in the centrally analyzed blood sample which cannot be confirmed by the locally analyzed sample (serum potassium locally <5.6 mmol/L) will not be considered for analysis.

<table>
<thead>
<tr>
<th>Result of first serum potassium measurement</th>
<th>&lt;5.6 mmol/L</th>
<th>5.6 - 6.0 mmol/L</th>
<th>&gt;6.0 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central lab</td>
<td>Continue study drug</td>
<td>Repeat serum potassium measurement within 48 hoursa</td>
<td>Check serum potassium in locally analyzed sampleb</td>
</tr>
<tr>
<td>Local lab</td>
<td>Continue study drug</td>
<td>Repeat serum potassium measurement within 48 hoursa</td>
<td>Discontinue study drug permanently</td>
</tr>
</tbody>
</table>

a If serum potassium is again ≥5.6 mmol/L in the repeat blood sample, discontinue study drug permanently.
If serum potassium is <5.6 mmol/L in the repeat blood sample, continue study drug.

b If serum potassium is ≥5.6 mmol/L in the (first) locally analyzed blood sample, discontinue study drug permanently.
If serum potassium is <5.6 mmol/L in the (first) locally analyzed blood sample, continue study drug.

**Potassium supplementation**

Any potassium supplementation should be stopped prior to randomization if serum potassium levels are within the normal range. If serum potassium levels are low at randomization or at any of the following visits, potassium supplementation can be continued or re-started until serum potassium values are within the normal range again. In general, investigators should monitor serum potassium carefully at each visit and if potassium supplementation is prescribed, they should adapt the dose of potassium supplementation in accordance with the serum potassium value measured at each visit or discontinue potassium supplementation once the serum potassium is within the normal range.

**Medical management**

It is recommended that all subjects receive at least the minimal recommended dose of an ACEI or ARB and optimal antihypertensive therapy for renal and cardiovascular disease (CVD) protection, according to local guidelines. Statins, anti-platelets, and beta-blockers are
also recommended according to the local guidelines. It is advised that other guideline recommendations for management of CVD and CKD are also followed. Glycemic control should be performed according to local guidelines.

**Note:** It is preferable that any medical therapy (e.g. antidiabetic, antihypertensive therapy as well as therapy with statins) will not be changed during study drug treatment, i.e. between the screening visit and the last dose of study drug. However, if this is necessary, the subject does not need to be withdrawn from study drug.

### Data Monitoring Committee

Data will be reviewed for safety and tolerability by an independent DMC. One DMC has been established for the BAY 94-8862 Phase IIb studies, incorporating this study and Study 14564. The first DMC meeting will take place when a combined total number of 30 subjects has been randomized in both BAY 94-8862 Phase IIb studies. Thereafter, DMC meetings will take place approximately every other month. In addition, an overview regarding SAEs reported in the 2 studies will be sent to the DMC chair on a weekly basis. When a minimum of 150 subjects have been randomized in this study, a dose decision meeting will take place. During this meeting, the 5 initial treatment groups of BAY 94-8862 will be assessed for safety and tolerability (in particular changes in serum potassium, e.g. number of subjects with hyperkalemia, and changes in eGFR, e.g. number of subjects with an eGFR decrease ≥30%) by the DMC. Based on this assessment, none or up to 2 of the additional treatment groups will be introduced into the study. The detailed plan for these assessments will be covered in the DMC charter.

### Primary efficacy variable

The primary variable will be the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline.

### Justification of the design

For study objectives, please see Section 2.

A multi-center, randomized, adaptive, double-blind, placebo-controlled, parallel-group design is considered adequate to evaluate the safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and a clinical diagnosis of DN. As only doses up to 10 mg BAY 94-8862 once daily were tested in Study 14563 (ARTS), higher doses of up to 20 mg BAY 94-8862 once daily will only be introduced after an independent DMC has assessed the ongoing data from the study for safety and tolerability.

The 1.25 mg BAY 94-8862 dose was not investigated in Study 14563 (ARTS). However, based on the effects on UACR seen with the lowest dose investigated in Study 14563 (ARTS), i.e. 2.5 mg, the 1.25 mg dose was chosen as additional dose for this study in order to find out if the 1.25 mg dose is effective.
End of study

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject for the main study has occurred for all study sites in the respective country.

The end of the study as a whole will be reached as soon as the end of the study according to the above definition has been reached in all participating countries (EU and non-EU).

The primary completion date for this study according to the Food and Drug Administration (FDA) Amendment Act is specified in a separate document (not part of this clinical study protocol).

5. Study population

5.1 Eligibility

Subjects with type 2 diabetes mellitus and a clinical diagnosis of DN treated with at least the minimal recommended dose of an ACEI or ARB, but not both, who meet all the inclusion criteria and none of the exclusion criteria will be eligible for enrollment in this study.

5.1.1 Inclusion criteria

- Written informed consent signed before any study-specific procedure

- Men aged 18 years and older, confirmed postmenopausal women or women aged 18 years and older without childbearing potential based on surgical treatment such as bilateral tubal ligation, bilateral ovariectomy, or hysterectomy. Men enrolled in this study must agree to use adequate barrier birth control measures during the treatment period of the study. The lower age limit may be higher if legally required in the participating country

- Subjects with type 2 diabetes mellitus fulfilling at least 1 of the following criteria
  a) are on oral antidiabetics and / or insulin,
  b) have a documented fasting glucose ≥7.0 mmol/L in the medical history,
  c) have a 2-hour plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test in the medical history, or
  d) have a glycated hemoglobin (HbA1c) ≥6.5% [National Glycohemoglobin Standardization Program (NGSP) / Diabetes Control and Complications Trial (DCCT)] in the medical history or at the run-in visit

- Subjects with a clinical diagnosis of DN based on at least 1 of the following criteria at the run-in and the screening visit:
Persistent very high albuminuria defined as UACR of $\geq 300$ mg/g ($\geq 34$ mg/mmol) in 2 out of 3 first morning void samples and estimated glomerular filtration rate (eGFR) $\geq 30$ mL/min/1.73 m$^2$ (CKD-EPI)$^{(50)}$

or

Persistent high albuminuria defined as UACR of $\geq 30$ mg/g but $< 300$ mg/g ($\geq 3.4$ mg/mmol but $< 34$ mg/mmol) in 2 out of 3 first morning void samples and eGFR $\geq 30$ mL/min/1.73 m$^2$ (CKD-EPI)$^{(50)}$

Note: 1 re-assessment of eGFR is allowed at the run-in visit and the screening visit. If 1 of the 3 UACR measurements is missing, but the other 2 are consistent, these values can be used to assess subject’s eligibility for this study.

- Subjects treated with at least the minimal recommended dose of an ACEI or ARB, but not both, for at least 3 months without any adjustments to this therapy for at least 4 weeks prior to the screening visit; subjects with an eGFR of 30 - 45 mL/min/1.73 m$^2$ (CKD-EPI)$^{(50)}$ must also be treated with a non-potassium sparing diuretic at the screening visit and without any adjustments to this therapy for at least 4 weeks prior to the screening visit

- Serum potassium $\leq 4.8$ mmol/L at both the run-in visit and the screening visit

Note: 1 re-assessment of serum potassium is allowed at the run-in visit and the screening visit.

- Ability to understand and follow study-related instructions

5.1.2 Exclusion criteria

Medical and surgical history

- Non-diabetic renal disease (confirmed by biopsy)

- Known bilateral clinically relevant renal artery stenosis (>75%)

- HbA$_{1c}$ $> 12\%$ at the run-in visit or the screening visit

- UACR $> 3000$ mg/g (339 mg/mmol) in any of the urinary first morning void samples at the run-in visit or screening visit

- Hypertension with mean sitting systolic blood pressure (SBP) $\geq 180$ mmHg or mean sitting diastolic blood pressure (DBP) $\geq 110$ mmHg at the run-in visit or mean sitting SBP $\geq 160$ mmHg or mean sitting DBP $\geq 100$ mmHg at the screening visit
Subjects with a clinical diagnosis of heart failure with reduced ejection fraction (HFrEF) and persistent symptoms (New York Heart Association class II - IV) at the run-in visit

Stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening heart failure, in the last 30 days prior to the run-in visit

Known hypersensitivity to the study drug (active substance or excipients)

Addison’s disease

Dialysis for acute renal failure within the previous 6 months prior to the run-in visit

Renal allograft in place or a scheduled kidney transplant within the next 18 weeks (being on a waiting list does not exclude the subject)

Congenital or acquired solitary kidney

Hepatic insufficiency classified as Child-Pugh B or C

**Medication, drug use, and special behavioral patterns**

Concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued for the run-in and the treatment period

Concomitant therapy with high-dose acetylsalicylic acid (≥500 mg/day) or continuous treatment with other non-steroidal anti-inflammatory agents

Concomitant therapy with potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors or inducers (to be stopped at least 7 days before randomization) or strong CYP2C8 inhibitors (to be stopped at least 7 days before randomization) such as gemfibrozil

**Note:** The investigators will be provided with a list of the most common concomitant medications considered as potent CYP3A4 inhibitors or inducers or strong CYP2C8 inhibitors

**Other**

Participation in another clinical study or treatment with another investigational product 30 days prior to randomization (i.e. Phase I - III clinical studies)

Any other condition or therapy, which would make the subject unsuitable for this study and will not allow participation for the full planned study period

Previous enrolment in this study
5.1.3 Justification of selection criteria

The selection criteria were chosen to exclude subjects from the study who may potentially be exposed to specific risks after administering the study drug as well as subjects with conditions that may have an impact on the aims of the study.

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

Subjects must be withdrawn from the study drug for the following reasons:

- At their own request or at the request of their legally acceptable representative at any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

- If, in the investigator’s opinion, continuation of the study would be harmful to the subject’s well-being, for example, uncontrolled blood pressure (see Section 4).

- If any AE occurred which is not acceptable in the opinion of the investigator and/or participating subject.

- If any investigational drug other than the study drug is used.

- If serum potassium is $\geq 5.6$ and $\leq 6.0$ mmol/L measured in the central or local laboratory, a second blood sample has to be taken as soon as possible but at the latest within 48 hours. If serum potassium is again $\geq 5.6$ mmol/L in the locally or centrally analyzed blood sample, study drug has to be discontinued permanently (see Table 4-2).

- If serum potassium is $> 6.0$ mmol/L in the centrally analyzed blood sample but $< 5.6$ mmol/L in the locally analyzed sample, treatment with study drug can be continued. If serum potassium is $> 6.0$ mmol/L in the centrally analyzed blood sample and $\geq 5.6$ mmol/L in the locally analyzed sample, study drug has to be discontinued permanently (see Table 4-2).

- If serum potassium is $> 6.0$ mmol/L in the locally analyzed blood sample, study drug has to be discontinued permanently (see Table 4-2).

Discontinuation of study drug due to an increase in serum potassium is considered an adverse event of special interest (see Section 7.5.1.6) and has to be reported to the sponsor along the timelines set for SAEs, i.e. within 24 hours of the investigator’s awareness as described in Section 7.5.1.4. In any case, adverse events of special interest fulfilling any seriousness criterion, should be reported as SAE (see also Section 7.5.1.1).
Subjects may be withdrawn from the study drug for the following reasons:

- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns)

- If any exclusion criterion applies during treatment

- If a significant violation of the protocol occurs, as defined by the sponsor and the coordinating investigator

- Temporary withdrawal of study drug for at least 5 consecutive days of the treatment period or, starting from Visit 4 (Day 60±2) onwards, a total number of temporary withdrawal days ≥10% of the total duration of the treatment period completed at that time

- If the randomization code is broken via Interactive Voice / Web Response System (IXRS)

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of “dropout” (see below) is regarded a “screening failure”.

A subject who discontinues study participation prematurely for any reason is defined as a “dropout” if the subject has been randomized (even if no study drug has been taken).

Any subject removed from the study will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be recorded in the electronic case report form (eCRF) and in the subject’s medical records.

If a subject prematurely withdraws from the study and if any study drug has been taken, the subject must be advised to return to the study center for the premature discontinuation visit as soon as possible and to the follow-up visit 30±5 days after the last intake of study drug.

A subject may withdraw from further participation in the study and still allow further release of information. In this situation, the subject’s consent to the collection of further data should be documented in the site’s source document.

Information regarding adverse events, or at a minimum information regarding potential adverse drug reaction, should be obtained and documented in the eCRF for subjects who withdraw consent to participate further in the study. The information should be collected in the eCRF until the follow-up visit 30±5 days after the last intake of study drug. Adverse events which occur within 30±5 days after the last dose of study drug will be followed up until resolution if possible.
At a minimum, the following information should be obtained and documented in the eCRF for subjects who still allow further release of information but withdraw consent to participate further in the study:

- Vital status and any hospitalization
- Adverse events

For subjects who withdraw consent for release of information, vital status only should be obtained. The measures taken for follow-up must be documented in the source data. Vital status should be obtained at the end of the follow-up period (i.e. 30±5 days after last intake of study drug).

Details for the premature termination of the study as a whole [or components thereof (e.g. centers, treatment groups, dose steps)] are provided in Section 10.

5.2.2 Replacement

Randomized subjects who withdraw prematurely will not be replaced.

5.3 Subject identification

Upon signing the informed consent form and registering the subject in IXRS, each subject will be assigned an unique 9-digit subject identification (SID) number for unambiguous identification throughout the study; it is constructed as follows:

- Digits 1 - 2: Unique country number
- Digits 3 - 5: Study center number, unique within any country
- Digits 6 - 9: Subject number, unique within any study center of a given country. Sequential number reflecting the order in which the subjects signed the informed consent form at the center

SID numbers must be used in sequence and no number should be skipped, substituted, or reused.
6. Treatments

6.1 Treatments to be administered

BAY 94-8862 IR tablets are light orange film-coated tablets, oval (modified oblong), containing 1.25 mg, 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg BAY 94-8862 (Table 6-1). Placebo tablets (matching BAY 94-8862 tablets) will be supplied in this double-blind, placebo-controlled clinical study.

Following a screening visit, eligible subjects will be randomized 1:1:1:1:1:1 within ≤14 days after the screening to 1 of the following 6 treatment groups and will receive study drug dispensed per visit schedule (see Section 7.1) for a total of 90 days treatment with either

- 1.25 mg BAY 94-8862 tablet once daily in the morning or
- 2.5 mg BAY 94-8862 tablet once daily in the morning or
- 5 mg BAY 94-8862 tablet once daily in the morning or
- 7.5 mg BAY 94-8862 tablet once daily in the morning or
- 10 mg BAY 94-8862 tablet once daily in the morning or
- Placebo tablet once daily in the morning

After safety and tolerability of these doses have been assessed by an independent DMC, none or up to 2 fixed oral doses of BAY 94-8862 may be introduced into the study:

- 15 mg BAY 94-8862 tablet once daily in the morning or
- 20 mg BAY 94-8862 tablet once daily in the morning

If treatment groups will be added, the randomization will be adapted in order to obtain equally balanced sample sizes across all treatment groups at the end of the study.

Following screening and randomization of the subject, the IXRS will determine the bottle number for the study site investigator or designee to select for the subject. Subjects are to take 1 tablet once daily in the morning as directed by the study site investigator. The first dose of study drug must be taken on the same day as Visit 1 (Day 1) which must be in the morning.

At Visit 5 (Day 90±2), study drug will be administered at the study center by study personnel in the morning. On all other days during the 90-day study drug treatment, study drug will be taken in the morning by the subjects on an ambulatory basis.
### 6.2 Identity of study drug

#### Table 6-1: Identity of test drug / BAY 94-8862 and matching placebo

<table>
<thead>
<tr>
<th>Sponsor's substance code</th>
<th>BAY 94-8862</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name / brand name</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Sponsor's material name and number</td>
<td></td>
</tr>
<tr>
<td>BAY 94-8862 TABL 1.25 MG 150 COAT</td>
<td>Material no: 81128758</td>
</tr>
<tr>
<td>BAY 94-8862 TABL 2.5 MG 250 COAT</td>
<td>Material no: 81128766</td>
</tr>
<tr>
<td>BAY 94-8862 TABL 5 MG 350 COAT</td>
<td>Material no: 81128774</td>
</tr>
<tr>
<td>BAY 94-8862 TABL 7.5 MG 750 COAT</td>
<td>Material no: 81128782</td>
</tr>
<tr>
<td>BAY 94-8862 TABL 10 MG 450 COAT</td>
<td>Material no: 81128790</td>
</tr>
<tr>
<td>BAY 94-8862 TABL 15 MG 860 COAT</td>
<td>Material no: 81559635</td>
</tr>
<tr>
<td>BAY 94-8862 TABL 20 MG 850 COAT</td>
<td>Material no: 81559643</td>
</tr>
<tr>
<td>BAY 94-8862 PLAC TABL 002 COAT</td>
<td>Material no: 81128804</td>
</tr>
</tbody>
</table>

**Formulation**
- Film-coated tablet

**Tablet strength**
- 1.25 mg, 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg or placebo

**Composition**

*Active ingredient:*
- BAY 94-8862 micronized

*Other ingredients:*
- Cellulose microcrystalline, croscarmellose sodium, hypromellose 5 cP, lactose monohydrate, magnesium stearate, sodium laurilsulfate, talc, titanium dioxide, ferric oxide

*Placebo:*
- Cellulose microcrystalline, hypromellose 5 cP, lactose monohydrate, magnesium stearate, talc, titanium dioxide, ferric oxide

**Type of primary packaging**
- Plastic bottle high-density polyethylene white opaque closed with screw cap polypropylene (PP) / PP white with sealing insert

**Marketing Authorization Holder if applicable**
- Not applicable

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance (QA) group.
A complete record of batch numbers and expiry dates of all study drug as well as the labels will be maintained in the sponsor study file.

Study drugs need to be stored according to the label text.

### 6.3 Treatment assignment

Following a screening visit, eligible subjects will be randomized within \( \leq 14 \) days after the screening visit and receive a 90-day study drug treatment.

The randomization will be stratified by region (Europe, North America, Asia, others), and type of albuminuria (very high albuminuria or high albuminuria at baseline). No formal caps will be applied within the stratification levels. However, a ratio of approximately 50:50 for high and very high albuminuria is planned to be reached. An initial randomization list including the initial treatment groups will be generated before study start. Additional possible randomization lists will be generated before the DMC decision. The computer-generated randomization lists will be provided to the IXRS supplier by Bayer Global Biostatistics. The name and address for the IXRS service provider can be found in the documentation supplied by the vendor.

For further details, please refer to Section 6.1.

### 6.4 Dosage and administration

Please refer to Section 6.1.

### 6.5 Blinding

#### 6.5.1 Blinding measures

BAY 94-8862 IR tablets containing 1.25 mg, 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg BAY 94-8862 and placebo tablets will be identical in appearance (size, shape, color). The packaging and labeling will be designed to maintain the blinding of the investigator’s team and to the subjects. The study data will remain blinded for each treatment group, until database lock and authorization of data release according to standard operating procedures.

Appropriate measures will be taken to maintain blinding while bioanalysis is ongoing.

#### 6.5.2 Unblinding

In compliance with applicable regulations, in the event of a suspected, unexpected serious adverse reaction (SUSAR, see Section 7.5.1.5), the subject’s treatment code will usually be unblinded before reporting to the health authorities, Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), and investigators (see Section 7.5.1.4).
6.5.3 Emergency unblinding by the investigator

In case of emergency or any finding that requires unblinding, the investigator will be able to break the blind for an individual subject via IXRS according to the unblinding procedure outlined in the manual. This will allow breaking the blind for an individual subject without impairing the study as a whole unless safety findings required unblinding.

This system allows the investigator, or other responsible person, to identify the study drug in case of an emergency, without jeopardizing the double-blind integrity of the remainder of the study.

The code can be broken by the investigator, or other responsible person, when knowledge of the subject's treatment is required for the clinical management of the subject. Whenever possible, the sponsor is to be contacted to discuss the case before the code is broken. If it becomes necessary to know the individual treatment during the study and thus to break the code for that subject, the date, and reason are to be recorded in the relevant eCRF page. The investigator is required to promptly document and explain to the sponsor any premature unblinding (e.g. unblinding due to a serious adverse event) of the study drug.

6.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate / contract research organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor’s study file. The site-specific elements of this information will be available in the investigator's site file. The responsible site personnel will confirm receipt of the study drug via IXRS and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of the study drug must be properly documented according to the sponsor’s agreed and specified procedures.

Written instructions on study drug destruction will be made available to affected parties as applicable.

6.7 Treatment compliance

To monitor compliance, the investigator will be required to complete a drug dispensing log for each subject. Overall compliance with study drug intake should be between 80% and 120% of the scheduled dose at the end of study drug treatment. The date of dispensing the study drug to the subject will be documented.

Study drug will be dispensed at Visit 1 (Day 1), Visit 3 (Day 30±2), and Visit 4 (Day 60±2).Subjects will return at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) or at the premature discontinuation visit, if applicable, with all remaining unused study drug.
Accountability has to be determined for all tablets of study drug at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) or at the premature discontinuation visit, if applicable. To facilitate this, subjects must be instructed to return all of the study drug packaging including unused study drug and empty packaging.

6.8 Post-study therapy

Subjects completing the 90-day treatment period will not be given further free access to study drug. The investigator will decide in consultation with the individual subject if additional treatment is required and choose from existing treatment options.

The investigator must provide follow-up medical care for all subjects who complete the study or who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care as required.

6.9 Prior and concomitant therapy

Subjects must be on an ACEI or ARB for at least 3 months and treated with at least the minimal recommended dose of that ACEI or ARB, but not both, for at least 4 weeks prior to the screening visit. Subjects with an eGFR of 30 - 45 mL/min/1.73 m² (CKD-EPI) must also be treated with a non-potassium sparing diuretic at randomization. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. At the screening visit, subject’s treatment should be stable and without any adjustments for at least 4 weeks as documented in the subject’s medical records.

All concomitant medications including therapy for type 2 diabetes mellitus and DN administered after signing of informed consent until the follow-up visit will be recorded in the eCRF.

It is preferable that any medical therapy (e.g. antidiabetic, antihypertensive therapy as well as therapy with statins) will not be changed during study drug treatment, i.e. between the screening visit and the last dose of study drug. However, if this is necessary, the subject does not need to be withdrawn from study drug.

Prior and concomitant medications not allowed during the study include:

- Concomitant treatment with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued for the run-in and the treatment periods

Note: Any potassium supplementation should be stopped at randomization if serum potassium levels are within the normal range. If serum potassium levels are low at randomization or at any of the following visits, potassium supplementation can be continued or re-started until serum potassium values are within the normal range again.
- Combined use of an ACEI and an ARB

- Concomitant therapy with high-dose acetylsalicylic acid (>500 mg/d) or daily treatment with other non-steroidal anti-inflammatory agents for more than 5 consecutive days

- Potent CYP3A4 inhibitors or inducers (to be stopped at least 7 days prior to randomization)

- Strong CYP2C8 inhibitors such as gemfibrozil (to be stopped at least 7 days prior to randomization)

The investigators will be provided with a list of the most common concomitant medications considered as potent CYP3A4 inhibitors or inducers or strong CYP2C8 inhibitors.

**Caution:** Increases in BAY 94-8862 exposure in combination with the following moderate CYP3A4 inhibitors cannot be excluded: amiodarone, aprepitant, bicalutamide, chloramphenicol, imatinib, mifepristone, norfloxacin, tacrolimus, verapamil, lapatinib, dasatinib, and nilotinib.

It cannot be ruled out that higher plasma concentrations of BAY 94-8862 are associated with an increase in frequency or severity of AEs.

See also Section 5.1.2.

7. **Procedures and variables**

7.1 **Schedule of procedures**

Time deviations from the given visit schedule will be documented as protocol deviations, if applicable. Respective time windows are specified in the sections below.

7.1.1 **Tabulated overview**

Table 7-1 summarizes the schedule of procedures.
**Table 7-1: Schedule of procedures**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Run-in visit ≤ -12 weeks</th>
<th>Screening visit ≤ -14 days</th>
<th>Visit 1* (Baseline) (Day 1)</th>
<th>Visit 2 (Day 7±2)</th>
<th>Visit 3 (Day 30±2)</th>
<th>Visit 4 (Day 60±2)</th>
<th>Visit 5 (Day 90±2)</th>
<th>PD visit</th>
<th>FU visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signed written informed consent available a</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Check of in- and exclusion criteria</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Demographic data</td>
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<tr>
<td>Randomization (IXRS)</td>
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<tr>
<td>Dispense study drug</td>
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<td>X</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug accountability, collect unused study drug</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>Smoking status, a and alcohol consumption</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Previous medications</td>
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<td>X</td>
<td></td>
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<tr>
<td>Physical examination, including height, waist &amp; hip circumference measures, and weight f</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Vital signs (blood pressure and heart rate) g</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>12-lead ECG h</td>
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<td>X</td>
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</tr>
<tr>
<td>Blood sample (full central lab)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Blood sample (clinical chemistry, central lab)</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Blood sample (local lab)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Blood sample (HbA1c, central lab)</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sample (biomarkers, central lab)</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>PK blood sample (single) a</td>
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<tr>
<td>PK blood sample (study drug intake at home)</td>
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<tr>
<td>PK blood sample (study drug intake at study center)</td>
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<tr>
<td>Urine sample (central lab)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis (local lab)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>KDQOL-36 and EQ-5D-3L (HRQoL)</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recording of AEs and concomitant medications</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory blood pressure monitoring a</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood samples for iohexol plasma clearance a</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table continued
Table 7-1: Schedule of procedures (continued)

<table>
<thead>
<tr>
<th>FU = follow-up; PD = premature discontinuation; PK = pharmacokinetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Randomization has to occur within ≤14 days after the screening visit.</td>
</tr>
<tr>
<td>b Only for subjects who have discontinued the study prematurely: to be performed as soon as possible after withdrawal of study drug.</td>
</tr>
<tr>
<td>c For all subjects who have taken any study drug: to be performed 30±5 days after last intake of study drug.</td>
</tr>
<tr>
<td>d The signed written informed consent must be available before any study procedures are conducted.</td>
</tr>
<tr>
<td>e Smoking status and alcohol consumption to be recorded at run in visit. Smoking status to be checked at all visits.</td>
</tr>
<tr>
<td>f Height as well as waist and hip circumference will only be measured once at the run-in visit.</td>
</tr>
<tr>
<td>g Resting for at least 10 min, 3 measurements at 2-min intervals in sitting position. At Visit 5 (Day 90±2), blood pressure must be measured before study drug intake.</td>
</tr>
<tr>
<td>h Resting for at least 10 min; ECG to be recorded in supine position.</td>
</tr>
<tr>
<td>i Single post-dose (towards the end of the visit) blood sample.</td>
</tr>
<tr>
<td>j Study drug intake at home followed by 2 samples collected in the interval approximately 60 to 120 min and 240 to 300 min post administration, respectively.</td>
</tr>
<tr>
<td>k Pre-dose PK sample before study drug administration at study center followed by 2 samples collected in the interval approximately 30 to 90 min and 180 to 240 min post administration, respectively.</td>
</tr>
<tr>
<td>l On 3 consecutive days, first morning void urine samples will be collected at the subject’s home.</td>
</tr>
<tr>
<td>m Local dipstick test of central lab samples to confirm sample validity for analysis.</td>
</tr>
<tr>
<td>n At selected sites only (see Section 7.6.5).</td>
</tr>
<tr>
<td>o In all <strong>Italian</strong> centers, subjects who are not sensitive to iodine or other iodinated contrast agents can be included in this sub-study, if they consent.</td>
</tr>
</tbody>
</table>
7.1.2 Timing of assessments

All visit from Visit 1 (Day 1, Baseline) to the last visit under treatment, i.e. Visit 5 (Day 90±2) for subjects who will complete the study, must be performed in the morning.

If not stated otherwise, the measures listed in the following sections will be performed by or under the supervision of a study site investigator.

7.1.3 Informed consent

Before any study-specific examination takes place, potentially eligible subjects will be given a full explanation as to what the study would involve. This will be done both verbally and in writing in the form of a written subject information leaflet. Subjects will be given sufficient time to consider their participation in the study and to ask any questions concerning the study. Subjects who are willing to take part in the study will then be asked to sign an informed consent form prior to the run-in visit. The signed informed consent form must be available before any study-specific procedure will be performed at the run-in visit.

Run-in examinations will only be performed after having received the subject’s written informed consent.

Due to the fact that not all subjects may fulfill the inclusion criteria and not meet any of the exclusion criteria, a higher number of subjects than needed for the evaluation of the study will be asked to participate in the run-in examination.

7.1.4 Run-in visit

The following procedures and assessments will be performed at this visit:

- Confirm signed informed consent is available
- Allocation of a unique SID number (see Section 5.3)
- Demographic data and other population characteristics including sex, race, ethnic group, year of birth, age, smoking history, and alcohol consumption at the run-in visit (see Section 7.2.1)
- Medical history (see Section 7.2.2)
- Prior and concomitant medications (see Section 6.9)
- Physical examination including height, waist and hip circumference measurements, and weight [Note: body mass index (BMI) will be calculated automatically in the eCRF]
• 12-lead ECG in supine position after resting for at least 10 min

• Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart

• Continuous assessment of AEs will start immediately after signing the informed consent until the follow-up visit (if applicable) (see Section 7.5)

• Laboratory examinations in blood including hematology, clinical chemistry (full central lab), and HbA1c (to be analyzed at central laboratory, see Section 7.6.1)

• Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)

• Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

• Assess inclusion and exclusion criteria (see Section 5.1)

• In all subjects, 1 re-assessment of eGFR and serum potassium is allowed at the run-in visit. If 1 of the 3 UACR measurements is missing, but the other 2 are consistent, these values can be used to assess subject’s eligibility for this study.

• Schedule the screening visit for ≤12 weeks after the run-in visit

  **Note:** At the end of this run-in period, each subject should receive at least the minimal recommended dose of conventional therapy according to local guidelines which consists either of an ACEI or ARB, but not both. Subjects with an eGFR of 30 - 45 mL/min/1.73 m² (CKD-EPI) must also be treated with a non-potassium-sparing diuretic at randomization. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. The treatment should be stable and without any adjustments for at least 4 weeks before the screening visit.

### 7.1.5 Screening visit

The following procedures and assessments will be performed within ≤14 days prior to randomization but after the run-in visit (for a subject who is already treated with an ACEI or ARB for at least 3 months and on at least the minimal recommended dose of that ACEI or ARB and without any adjustments for at least 4 weeks, the run-in visit will be considered as screening visit and the subject can be randomized within the next 14 days if she / he meets all the inclusion and none of the exclusion criteria):

• Assess inclusion and exclusion criteria (see Section 5.1)

• Smoking status
• Concomitant medications planned to be continued during the study and previous medications that were stopped in order to comply with the inclusion and exclusion criteria, if applicable (see Section 6.9)

• Physical examination including weight (Note: BMI will be calculated automatically in the eCRF)

• 12-lead ECG in supine position after resting for at least 10 min

• Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart

• Laboratory examinations in blood including hematology, clinical chemistry (full central lab), and HbA1c (to be analyzed at central laboratory, see Section 7.6.1)

• Iohexol plasma clearance (at selected sites only, see Section 7.6.5) [If the run-in visit is considered as screening visit, iohexol plasma clearance can be performed at any time before Visit 1 (Day 1).]

• Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)

• Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

• Adverse events (see Section 7.5)

• In all subjects, 1 re-assessment of eGFR and serum potassium is allowed at the screening visit. If 1 of the 3 UACR measurements is missing, but the other 2 are consistent, these values can be used to assess subject’s eligibility for this study.

• At selected sites only: ambulatory blood pressure monitoring (ABPM) (see Section 7.6.4) Note: The ABPM does not necessarily need to be started at the screening visit if this is not convenient. However, the screening ABPM must be completed prior to randomization at Visit 1 (Day 1)

• Schedule Visit 1 (Baseline) for ≤14 days after the screening visit

7.1.6 Visit 1 (Baseline and randomization) - Day 1

The following procedures and assessments will be performed during this visit:

• KDQOL-36 and EQ-5D-3L (see Section 7.3.3)

• Assess inclusion and exclusion criteria (see Section 5.1)
• Concomitant medications (see Section 6.9)

• Smoking status

• Adverse events (see Section 7.5)

• Physical examination including weight (Note: BMI will be calculated automatically in the eCRF)

• 12-lead ECG in supine position after resting for at least 10 min

• Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart

• Laboratory examinations in blood including hematology and clinical chemistry (full central lab) (to be analyzed at central laboratory, see Section 7.6.1)

• Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)

• Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

• Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at local laboratory, see Section 7.6.1)

• Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)

• Randomization to BAY 94-8862 or placebo once daily (see Section 6.1)

• Dispense study drug for 36 days and instruct the subject on how to take the study drug

• Subject to take first dose of study drug

• Schedule Visit 2 for Day 7±2

7.1.7 Visit 2 - Day 7±2

The following procedures and assessments will be performed during this visit:

• Concomitant medications (see Section 6.9)

• Adverse events (see Section 7.5)

• Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at central laboratory, see Section 7.6.1)

Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at local laboratory, see Section 7.6.1)

Single post-dose (towards the end of the visit) blood sample for BAY 94-8862 pharmacokinetics (see Section 7.4)

Schedule Visit 3 for Day 30±2

### 7.1.8 Visit 3 - Day 30±2

The following procedures and assessments will be performed during this visit:

- KDQOL-36 and EQ-5D-3L (see Section 7.3.3)
- Concomitant medications (see Section 6.9)
- Smoking status
- Adverse events (see Section 7.5)
- 12-lead ECG in supine position after resting for at least 10 min
- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Laboratory examinations in blood including hematology and clinical chemistry (full central lab) (to be analyzed at central laboratory, see Section 7.6.1)
- Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)
- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)
- Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at local laboratory, see Section 7.6.1)
- Post-dose blood samples (approximately 60 to 120 minutes and 240 to 300 min after study drug intake at home) for BAY 94-8862 pharmacokinetics (see Section 7.4)
- Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)
- Collect unused study drug and perform accountability to assess compliance
Dispense study drug for 36 days and instruct the subject on how to take the study drug

Schedule Visit 4 for Day 60±2

7.1.9 Visit 4 - Day 60±2

The following procedures and assessments will be performed during this visit:

- Concomitant medications (see Section 6.9)
- Smoking status
- Adverse events (see Section 7.5)
- 12-lead ECG in supine position after resting for at least 10 min
- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Laboratory examinations in blood including hematology and clinical chemistry (full central lab) (to be analyzed at central laboratory, see Section 7.6.1)
- Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)
- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)
- Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at local laboratory, see Section 7.6.1)
- Single post-dose (towards the end of the visit) blood sample for BAY 94-8862 pharmacokinetics (see Section 7.4)
- Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)
- Collect unused study drug and perform accountability to assess compliance
- Dispense study drug for 36 days and instruct the subject on how to take the study drug
- At selected sites only: start ABPM (see Section 7.6.4)
- Schedule Visit 5 for Day 90±2
7.1.10 Visit 5 - Day 90±2

The following procedures and assessments will be performed during this visit:

- KDQOL-36 and EQ-5D-3L (see Section 7.3.3)
- Concomitant medications (see Section 6.9)
- Smoking status
- Adverse events (see Section 7.5)
- Physical examination including weight (Note: BMI will be calculated automatically in the eCRF)
- 12-lead ECG in supine position after resting for at least 10 min
- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart; these must be performed before study drug intake
- Pre-dose blood sample for BAY 94-8862 pharmacokinetics (see Section 7.4)
- Laboratory examinations in blood including hematology, clinical chemistry (full central lab), and HbA1c (to be analyzed at central laboratory, see Section 7.6.1)
- Iohexol plasma clearance (at selected sites only, see Section 7.6.5)
- Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)
- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)
- Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at local laboratory, see Section 7.6.1)
- Intake of study drug
- Post-dose blood samples (approximately 30 to 90 minutes and 180 to 240 min after study drug administration at the study center) for BAY 94-8862 pharmacokinetics (see Section 7.4)
- Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)
- Collect unused study drug and perform accountability to assess compliance
• At selected sites only: start ABPM (see Section 7.6.4)
• Schedule follow-up visit for 30±5 days after last intake of study drug

7.1.11 Premature discontinuation visit

This visit will take place as soon as possible after premature discontinuation of study drug due to any reason except death or lost to follow-up. The investigator should make every possible effort to ensure that the visit takes place and the following procedures and assessments are performed during this visit:

• KDQOL-36 and EQ-5D-3L (see Section 7.3.3)
• Concomitant medications (see Section 6.9)
• Smoking status
• Adverse events (see Section 7.5) [In case a (serious) adverse event has occurred, the event must be adequately followed-up. If an SAE has occurred, this should be followed up until the subject’s condition has resolved or stabilized. Additional local legal requirements for follow-up procedures of AEs and SAEs have to be fulfilled if applicable.]
• Physical examination including weight (Note: BMI will be calculated automatically in the eCRF)
• 12-lead ECG in supine position after resting for at least 10 min
• Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
• Laboratory examinations in blood including hematology, clinical chemistry (full central lab), and HbA1c (to be analyzed at central laboratory, see Section 7.6.1)
• Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)
• Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)
• Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)
• Collect unused study drug and perform accountability to assess compliance
• Schedule follow-up visit 30±5 days after last intake of study drug
7.1.12 Follow-up visit (30±5 days after last intake of study drug)

The following procedures and assessments will be performed during this visit:

- KDQOL-36 and EQ-5D-3L (see Section 7.3.3)
- Concomitant medications (see Section 6.9)
- Adverse events (see Section 7.5) [In case a (serious) adverse event has occurred, the event must be adequately followed-up. If an SAE has occurred, this should be followed up until the subject’s condition has resolved or stabilized. Additional local legal requirements for follow-up procedures of AEs and SAEs have to be fulfilled if applicable.]
- Physical examination including weight (Note: BMI will be calculated automatically in the eCRF)
- 12-lead ECG in supine position after resting for at least 10 min
- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Laboratory examinations in blood including hematology and clinical chemistry (full central lab) (to be analyzed at central laboratory, see Section 7.6.1)
- Iohexol plasma clearance [at selected sites only, if Visit 5 (Day 90±2) was performed; see Section 7.6.5]
- Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)
- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)
- Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)

7.2 Population characteristics

7.2.1 Demographic

The following demographic data will be collected in the eCRF:

- Year of birth and age at the run-in visit
- Ethnic group
- Race
• Sex

• Smoking habits and alcohol consumption

### 7.2.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases, or surgeries) meeting all criteria listed below will be collected:

• Started prior to signing the informed consent

• Pertaining to the study indication (e.g. teething problems or orthopedic surgery which are not related to the development of diabetic nephropathy do not need to be entered)

• Considered relevant to the study (e.g. cardiovascular and metabolic diseases)

• Medical history related to concomitant medication

Detailed instructions on the differentiation between medical history and AEs can be found in Section 7.5.1.1.

### 7.2.3 Physical examination

All diagnoses, symptoms, signs, or findings during physical examination at the run-in visit that have a start date before signing the informed consent will be recorded in the medical history, all others (with a start date after signing informed consent) will be recorded as AEs (see Section 7.5.1.1).

### 7.3 Efficacy

The following parameters will be used to assess the efficacy of the study drug treatments.

#### 7.3.1 Primary efficacy variable

The primary efficacy variable will be the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline.

#### 7.3.2 Further exploratory efficacy variables

In addition, the following parameters will be used to assess the efficacy of the study drug treatments:

• Ratio of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline
• Decrease in eGFR (CKD-EPI)\(^{50}\) of ≥30%, ≥40%, and ≥57%

• Regression of albuminuria, defined as change of very high albuminuria to high albuminuria or albuminuria [UACR ≤30 mg/g (3.4 mg/mmol)] or high albuminuria to albuminuria, in all cases accompanied by a change of more than 30% from baseline to Visit 5 (Day 90±2)

• Efficacy biomarkers (NT-proBNP, BNP, aldosterone, and galectin-3)

• HRQoL: KDQOL-36 and EQ-5D-3L

### 7.3.3 Health-related quality of life

The following HRQoL questionnaires will be used: Kidney Disease Quality of Life (KDQOL-36) and the EuroQol Group 5-dimension, 3-level questionnaire (EQ-5D-3L). The subject will be instructed to fill in the questionnaires himself / herself before any other procedure of each visit. Subsequently, a member of the site investigator’s team will enter the responses into the eCRF.

**KDQOL-36** is a specific measure of health-related quality of life for CKD that includes effects and burden of kidney disease as well as physical and mental health scores. 2 forms of the KDQOL exist, the KDQOL-SF and the KDQOL-36. Both were developed in 1994 and later by the Kidney Disease Quality of Life Working Group at RAND Corporation.

The KDQOL-SF is based on the SF-36 with additional questions specific to kidney disease concerning symptoms and problems, effects of kidney disease on daily life, burden of kidney disease, cognitive function, work status, sexual function, quality of social interaction, and sleep.\(^{54}\) It was developed for use with a dialysis patient population but it has also been found to be valid and reliable in a kidney transplant patient population.\(^{55}\) Studies using the KDQOL revealed that psychological factors, including depression, were a much stronger determinant of quality of life than biological measures like dialysis adequacy.\(^{56}\)

While the KDQOL-SF has 134 questions the shorter form KDQOL-36 consists of 36 questions and contains the SF-12. The items of the KDQOL-36 are grouped as follows:

• Items 1-12: SF-12; Physical Component Summary (PCS) on physical functioning, role-physical, bodily pain, general health; Mental Component Summary (MCS) on vitality, social functioning, role-emotional, mental health

• Items 13-16: Burden of Kidney Disease (4); interference with daily life, time to deal with kidney disease, frustration, feeling like a burden

• Items 17-28: Symptoms / Problems (12); general health, activity limits, ability to accomplish desired tasks, depression/anxiety, energy level, social activities
● Items 29-36: Effects of Kidney Disease (8); impact of fluid & diet limits, ability to work around the house and to travel, feeling depending on medical team, stress or worries, sex life, personal appearance

The EQ-5D-3L was introduced in 1990. The EQ-5D-3L essentially consists of 2 pages - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The respondent is asked to indicate his / her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent’s self-rated health on a vertical, visual analogue scale where the endpoints are labeled ‘best imaginable health state’ and ‘worst imaginable health state’. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. It should be noted that the numerals 1 - 3 have no arithmetic properties and should not be used as a cardinal score.

7.3.4 Efficacy biomarkers

The following efficacy biomarkers will be measured: NT-proBNP, BNP, aldosterone, and galectin-3.

7.4 Pharmacokinetics

For the investigation of systemic exposure to BAY 94-8862 and its relationship with treatment effects, the plasma concentrations of BAY 94-8862 will be determined at different time points using a sparse sampling approach in all participating subjects (see Table 7-1). The plasma concentration vs. time data of Visit 3 (Day 30±2) and Visit 5 (Day 90±2) will be evaluated descriptively separated by dose and visit. Plots will be prepared pooling all individual plasma concentrations (naive pooling) vs. actual relative study times (time of sample collection after time of study drug administration). The plasma concentration vs. time data of Visit 3 (Day 30±2) and Visit 5 (Day 90±2) will also be sorted in categories and descriptive statistics [geometric mean and percent coefficient of variation (%CV), arithmetic mean and %CV, median and range] will be presented by category in tabular form.

Furthermore, the pharmacokinetic data and the relationship of markers of BAY 94-8862 exposure (e.g. C\text{max}, AUC) with treatment effects will be evaluated using non-linear mixed effect modeling (NONMEM). The latter evaluation will be described in a separate analysis plan and will be reported under separate cover.

At Visit 3 (Day 30±2), blood samples for the determination of BAY 94-8862 plasma concentrations will be drawn approximately 60 to 120 minutes and 240 to 300 minutes after study drug administration. Study drug will be taken at home. At this visit, the exact time of study drug intake, the exact sampling times, and the start time of breakfast will be recorded in the eCRF. At Visit 5 (Day 90±2), blood samples for the determination of BAY 94-8862 plasma concentrations will be drawn pre-dose, approximately 30 to 90 minutes and 180 to 240
minutes after study drug administration. At this visit, study drug will be administered at the study center by study personnel and the exact time of study drug intake, the exact sampling times, the start time of breakfast, and the time of study drug intake on the day before the visit will be recorded in the eCRF.

At Visit 2 (Day 7±2) and Visit 4 (Day 60±2), single post-dose blood samples for the determination of BAY 94-8862 plasma concentrations will be drawn towards the end of the visit. At these 2 visits, the time of study drug intake and the exact sampling time will be recorded in the eCRF.

The PK bioanalysis will be performed at the Bayer HealthCare Bioanalytics Laboratory, Bayer Pharma AG, GDD-GED-DMPK Bioanalytics, 42096 Wuppertal, Germany.

7.5 Safety

7.5.1 Adverse events

7.5.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term “condition” may include abnormal physical examination findings, symptoms, diseases, laboratory, or ECG findings.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).

- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis).

- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.
Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

The term “life-threatening” in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 24 hours
- The admission is pre-planned (i.e. elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of "medically important" and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

e. Is a congenital anomaly / birth defect

f. Is another medically important serious event as judged by the investigator

7.5.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.
7.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.5.1.1.

7.5.1.2.2 Intensity

The intensity of an AE is classified according to the following categories, taking into account the possible range of the intensity of the event:

- Mild - usually transient in nature and generally not interfering with normal activities
- Moderate - sufficiently discomforting to interfere with normal activities
- Severe - prevents normal activities

7.5.1.2.3 Causal relationship

Causal relationship to study drug

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF.

The causality assessment should be done as detailed in the eCRF.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question. Possible answers are “yes” or “no”.

An assessment of “no” would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site

or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
• Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):

• Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.

• Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

• Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

• The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject’s pharmacodynamics should be considered.

### Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a “reasonable causal relationship” to protocol-required procedure(s). Possible answers are “yes” or “no”.

#### 7.5.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment as detailed in the eCRF.

• Drug withdrawn

• Drug interrupted

• Dose not changed

• Not applicable

• Unknown
7.5.1.2.5 Other specific treatments of adverse events

- None
- Remedial drug therapy
- Other

7.5.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

7.5.1.3 Assessments and documentation of adverse events

Attention is to be paid to the occurrence of AEs at all stages of the examination. Thus, the subject should be closely observed by the investigator.

Adverse events (AEs) observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the patient will be documented. The observation period for AEs will start with signing the informed consent, and will end with the last visit of follow-up. In case of ongoing study-related adverse events and medically relevant adverse events at the end of the study, the investigator is urged to monitor the subject and document the outcome on the subject's source document.

The investigator is responsible for the grading of each category mentioned. An assessment of the seriousness of the event will be made by the investigator, who is to complete a special form provided by the sponsor in the case of a SAE. However, SAEs will also be recorded on the AE page of the eCRF.

The sponsor has to carry out a separate assessment for expectedness, seriousness, and causal relationship to study drug.
Emerging AEs will be allocated to the period in which they have started, e.g. a symptom starting in the treatment period and continuing in the follow-up period without deterioration will only be documented in the treatment period.

When assigning the cause of death, “death” should not be recorded as an AE on the AE page. Instead, “death” is the outcome of underlying AE(s).

7.5.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 7.5.1.1.

Investigator’s notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

All SAEs occurring during the observation period defined in Section 7.5.1.3 must immediately (within 24 hours of the investigator’s awareness) be reported to the recipient detailed in the instructions for SAE reporting included in the investigator site file. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g. suspected, unexpected, serious adverse reactions (SUSARs)) will be performed by the sponsor and / or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor’s notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.
7.5.1.5 Expected adverse events

For this study, the applicable reference document is the most recent version of the IB for BAY 94-8862.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

7.5.1.6 Adverse events of special safety interest

A confirmed increase in serum potassium ≥5.6 mmol/L and subsequent discontinuation of study treatment is considered an adverse event of special interest and has to be reported to the sponsor according to the timelines set for SAEs, i.e. within 24 hours of the investigator’s awareness as described in Section 7.5.1.4. In any case, adverse events of special interest fulfilling the seriousness criteria, should be reported as SAE (see also Section 7.5.1.1).

7.5.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a study subject, or in his partner, during the subject’s participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any outcome (normal as well as abnormal) of the mother or the child should be reported.

For the pregnancy of a study subject’s partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner’s consent.

For all reports, the forms provided are to be used.

7.5.3 Safety biomarkers

The following safety biomarkers will be measured: troponin T and cystatin C.

7.6 Other procedures and variables

The following safety procedures and variables will be assessed during the study (see Table 7-1 and Section 7.1 for frequency of assessments):

- Blood sample for laboratory parameter measurements (see Section 7.6.1)
- Physical examination
- 12-lead ECG
• Vital signs

• 24-hour ABPM (at selected sites only)

• Data regarding AEs will be collected at all visits after signing of the informed consent (see Section 7.5.1.1)

7.6.1 Laboratory parameter measurement

7.6.1.1 Central laboratory

The name and the address for the central lab service provider can be found in the documentation supplied by the vendor. Only centrally analyzed blood samples will be considered for analysis and the following laboratory tests will be performed centrally:

**Hematology:** white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelets will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit.

**Clinical chemistry:** aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), cholesterol [high density lipoprotein (HDL), low density lipoprotein (LDL), total], triglycerides, creatinine, eGFR (CKD-EPI\(^{[50]}\)), blood urea nitrogen, uric acid, bilirubin, sodium, potassium, magnesium, total protein, albumin, and high-sensitivity C-reactive protein (hs-CRP) will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit.

At Visit 2 (Day 7±2), a limited range of clinical chemistry parameters will be analyzed: creatinine, eGFR (CKD-EPI\(^{[50]}\)), LDH, CK, sodium, and potassium.

**HbA1c:** Measurement of HbA1c will be performed at the run-in visit, screening visit, and Visit 5 (Day 90±2) or the premature discontinuation visit, if applicable.

**Blood sample for biomarkers:** NT-proBNP, BNP, troponin T, aldosterone, cystatin C, and galectin-3 will be performed at Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or the premature discontinuation visit as well as at the follow-up visit.

If the blood sample for the central laboratory taken at any visit is hemolytic or not evaluable, the measurements have to be repeated as soon as possible.

**Urinalysis:** urine albumin-to-creatinine ratio (measured in first morning void urine samples collected at the subject’s home on 3 consecutive days) and urinary sodium-potassium ratio
will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit.

**Albuminuria**

The determination of albuminuria will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit.

For the determination of albuminuria, first morning void urine collections will be used which can be collected at the subject’s home on 3 consecutive days. Subjects must use the first morning urine after getting up for these first morning void urine samples.

If one of the following cases is reported, the subject will be asked to repeat urine sampling as soon as practical and come again to the study center: febrile illness, flu, urinary tract infection, menstruation, or unusual physical exercises.

7.6.1.2 **Local laboratory**

Beside the samples analyzed at the central laboratory, an additional blood safety sample will be taken which will be analyzed at the local laboratory.

It is expected that the local lab results will be available earlier than the central lab results allowing the investigator to take any required action as soon as possible. Regarding withdrawal of subjects because of increase in serum potassium, Table 4-2 outlines how to manage differences in results between the central and local labs. Local urinalysis using a dipstick will also be conducted.

**Clinical chemistry [from Visit 1 (Day 1) to Visit 5 (Day 90±2)]**

- Potassium
- Creatinine

**Urinalysis [at the run-in visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), Visit 5 (Day 90±2) or the premature discontinuation visit, and the follow-up visit]**

- Dipstick (to confirm sample validity for analysis)

7.6.2 **Electrocardiogram**

Standard electrocardiograms (12-lead ECG) according to Goldberger / Einthoven and Wilson will be recorded in supine position after resting for at least 10 min in a supine position at the run-in visit, screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and
Visit 5 (Day 90±2) or at the premature discontinuation visit as well as at the follow-up visit. All ECG print-outs will be identified with the SID as well as date and time of recording and will be attached to the subject’s file.

ECG printouts will be examined locally by the investigator on the day of recording for safety and quality. Any clinically relevant abnormality will be documented as an AE.

In addition, the medical reading and interpretation of ECGs will be performed centrally by an expert in cardiology who will provide expert assessment and interpretation of all ECGs performed. If applicable, the following parameters will be assessed: heart rate (HR), PR interval (PR), QRS duration (QRSD), QT interval (QT), and QT interval corrected for HR (QTc). If the ECG is considered valid for QT analysis, QTc will be calculated according to the formulas of Bazett and Fridericia.

The name and address for the ECG service provider can be found in the documentation supplied by the vendor.

### 7.6.3 Vital signs

After the subject has rested for at least 10 min, 3 measurements of vital signs, i.e. BP and HR, will be performed in sitting position at 2-min intervals at the run-in visit, screening visit, Visit 1 (Day 1), Visit 2 (Day 7±2), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) or at the premature discontinuation visit as well at the follow-up visit. At Visit 5 (Day 90±2), vital signs must be measured before study drug intake.

### 7.6.4 Ambulatory blood pressure monitoring

At selected sites, 24-hour ABPM will be performed at the screening visit, Visit 4 (Day 60±2), and Visit 5 (Day 90±2). The name and address for the ABPM service provider can be found in the documentation supplied by the vendor.

The screening ABPM must be completed prior to randomization at Visit 1 (Day 1) but does not have to be started during the screening visit if this is not convenient. For Visit 4 (Day 60±2) and Visit 5 (Day 90±2), the ABPM will start during the visit and will finish 24 hours later on the following day when the subject will need to return to the study center to return the device.

The 24-hour profiles will be recorded with standard ABPM devices at the following intervals:

- At 15-min intervals from 06:00 to <22:00 (daytime)
- At 30-min intervals from 22:00 to <06:00 (night-time)

During the recording of 24-hour ABPM, subjects will be obliged to refrain from physical exertion. The printouts will be attached to the subject’s file.
7.6.5 Iohexol plasma clearance

In a subgroup of the study population, iohexol plasma clearance will be assessed at the screening visit, Visit 5 (Day 90±2), and the follow-up visit if Visit 5 (Day 90±2) was performed. In all Italian centers, subjects who consent to participate in this sub-study and who are not sensitive to iodine or other iodinated contrast agents can be included in this sub-study. Iohexol is a non-ionic iodinated contrast agent.

Iohexol plasma clearance will be measured as follows:

On the morning of the respective visit, a Teflon cannula will be inserted in an antecubital vein for the injection of the marker substance, and another in the contralateral arm for subsequent blood sampling. A pre-iohexol blood sample (blank sample, 3 mL) will be collected. This sample will be used to find out whether any of the subject’s concomitant medications interferes with the iohexol chromatography. The Teflon cannula will be kept open with saline solution (0.9%).

Subjects will receive a slow intravenous injection (2 min) of 5 mL Omnipaque 300 containing 3.235 g iohexol into the injection cannula.

Note the exact time of injection (time 0) and use the same clock for timing throughout the procedure.

For iohexol determination, blood samples (3 mL) will be collected at different times according to the eGFR (CKD-EPI)(50) at the run-in visit:

- For eGFR (CKD-EPI)(50) >40 mL/min sampling at pre-iohexol as well as 120, 150, 180, 210, 240 min post-dose
- For eGFR (CKD-EPI)(50) ≤40 mL/min sampling at pre-iohexol as well as 120, 180, 240, 300, 360, 420, and 480 min post-dose
- If the run-in visit is considered as the screening visit, the iohexol plasma clearance can be performed at any time before Visit 1 (Day 1). The name and address for the iohexol plasma clearance service provider can be found in the documentation supplied by the central lab vendor.

7.7 Appropriateness of procedures / measurements

All parameters, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate, and relevant.
8. **Statistical methods and determination of sample size**

8.1 **General considerations**

Statistical analyses will be performed using the Statistical Analysis System (SAS) software package; the version used will be specified in the statistical analysis plan (SAP).

All subjects will be analyzed according to the actual treatment. Data from subjects who prematurely terminated the study will be used to the maximum extent possible.

Doses which will be closed prematurely due to safety concerns will not be included in the primary analysis and in the ANCOVA models.

In case of any unexpected finding, further exploratory analyses might be performed.

8.2 **Analysis sets**

Safety analysis set (SAF): All randomized subjects who have taken at least 1 dose of study drug.

Full analysis set (FAS): All subjects of the SAF who have baseline and at least 1 post-baseline UACR value.

Per-protocol analysis set (PPS): All subjects of the FAS who have valid UACR data at Visit 5 (Day 90±2) and have no major protocol deviations. Major protocol deviations are for example:

- Intake of any prohibited concomitant medication
- Overall compliance with study drug intake of <80% or >120%

Listing only set (LOS): All other subjects screened who did not receive any dose of study drug or for whom no data after beginning of treatment are available will be classified as LOS. Their data will be presented in the individual subject data listings but will not be included in any statistical analysis.

Pharmacokinetic analysis set (PKS): All BAY 94-8862-treated subjects with at least 1 valid BAY 94-8862 plasma concentration and without protocol deviation, which would interfere with the evaluation of the PK data.

The allocation of each subject to analysis sets will be documented before the database lock. Final decisions regarding validity of subjects to analysis sets assignment will be made during the Validity Review Meetings and documented in the Validity Review Reports.
8.3 Variables

8.3.1 Primary efficacy variable

- Ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline

8.3.2 Further exploratory efficacy variables

- HRQoL: KDQOL-36 and EQ-5D-3L

Further exploratory efficacy variables are described in Section 7.3.

8.3.3 Safety and tolerability variables

- Serum potassium
- eGFR (CKD-EPI)\(^{(50)}\)

Safety and tolerability variables are described in Section 7.5.

8.4 Statistical and analytical plans

8.4.1 Analysis of subject characteristics

All demographic data and baseline characteristics will be tabulated by treatment group and overall. The demographic tables will also be presented by the stratification factor (type of albuminuria and region). The analyses will be performed in the SAF and the description of all main baseline characteristics, which will be specified in the SAP, will be repeated for all other analysis sets if they differ from the SAF.

8.4.2 Analysis of primary efficacy variable

The analysis of the primary efficacy variable, the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline, will be performed in the FAS (primary analysis) and PPS (supportive analysis). The primary analysis will focus on the on-treatment data.

The UACR will be determined 3 times at each visit from first morning void urine samples collected on 3 consecutive days. For all analyses of UACR, the 3 measurements at 1 visit will be combined as follows: First, the coefficient of variation will be calculated for the 3 values. If the coefficient of variation exceeds 25%, the median from the measurements will be used for the analyses. The median in case of an even number of values will be defined as the geometric mean from the 2 middle values. If the coefficient of variation is 25% at the most, the geometric mean will be used.
In order to describe the course of UACR and the ratio of UACR to baseline for all visits, descriptive statistics will be provided including the geometric means, geometric standard deviations (SDs), and geometric coefficients of variation by treatment group and time point. This will be done overall and separately for all subgroups defined in Section 8.4.6. Graphs displaying the geometric group means and SDs of the ratios vs. time will be generated.

Primarily, the aim is to demonstrate a dose-dependent effect of BAY 94-8862 with respect to the primary variable. For this purpose, an ANCOVA model will be fitted to the logarithmized ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline including a factor for treatment group, factors to adjust for the stratification factors (type of albuminuria and region) and the logarithmized baseline UACR as covariate. The UACR values and ratios will be transformed since the primary variable is considered to be approximately log-normally distributed, i.e. the log-values are considered to be normally distributed. In the event of a region with a relatively small number of subjects, this region might be pooled with another region for this analysis. The decision will be made during the blind data review meeting and documented in the Validity Report.

The primary hypothesis $H_0$: $L' \mu = 0$ will be tested by means of the F-test with a 1-sided significance level of 5%, where $\mu = (\mu_1, \ldots, \mu_k)'$ with $\mu_i =$ expected value for $\ln$(UACR at Visit 5 (Day 90±2)) – $\ln$(UACR at baseline) adjusted for baseline log-UACR and the stratification factors (type of albuminuria and region), where $i = 1,\ldots,k$ means the different $k$ dose groups. The alternative hypothesis $H_1$: $L' \mu > 0$ which shall demonstrate a linear trend in the group means will be tested by applying the linear contrast $L_k'$ which reflects the intervals between the dose groups. In case, the dose groups will be placebo (= 0 mg), 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862, the linear contrast will be $L_6' = (3.5, 2.5, 1.5, -0.5, -2.5, -4.5)$. If 15 mg BAY 94-8862 will be added, the linear contrast will be $L_7' = (4.714, 3.714, 2.714, 0.716, -1.286, -3.286, -7.286)$. If 15 mg and 20 mg BAY 94-8862 will be added the linear contrast will be $L_8' = (6.125, 5.125, 4.125, 2.125, 0.125, -1.875, -5.875, -9.875)$.

The distributional model assumptions will be checked by inspection of residual plots of studentized residuals vs. normal order scores to check normality, and studentized residuals vs. predicted values to check homogeneity of variance.

In the 90-day treatment period of this study, a dropout rate of approximately 30% is expected, i.e. there will be a high number of missing UACR values at Visit 5 (Day 90±2). 10% of the subjects are expected to drop out during the first month and another 20% during the following 2 months. Dropouts after the first month are expected to be due to worsening renal function or uncontrolled hypertension. The remaining dropouts are expected to be due to clinical outcomes or hyperkalemia. While albuminuria might not be influenced in subjects with clinical outcomes or hyperkalemia, a worsening albuminuria is expected in cases of worsening renal function or uncontrolled hypertension.

In the primary analysis for imputation of missing UACR values at Visit 5 (Day 90±2), the last observation carried forward (LOCF) method will be applied. Thereby, the higher UACR
value from the premature discontinuation measurement (to be collected as soon as possible after premature discontinuation) and follow-up measurement (30±5 days after premature discontinuation) will be used to carry forward for subjects, who prematurely terminated the study drug.

Extensive sensitivity analyses for the imputation method will be conducted with the intention to learn more about the missing data process in this special population.

If the primary hypothesis could be rejected, the single dose groups will be compared to placebo by a hierarchical procedure starting with the highest dose of BAY 94-8862 vs. placebo within the same ANCOVA model in order to investigate the dose-response relationship further. The 1-sided significance level of 10% will be kept for each pairwise comparison and the procedure will stop when the first hypothesis could not be rejected.

Furthermore, it will be aimed to detect which group means of the logarithmized ratios are different from each other as an exploratory analysis. Therefore, the REGWQ (Ryan-Einot-Gabriel-Welsch Q) option of the SAS GLM (generalized linear model) procedure will be applied with a 2-sided significance level of 10%. The option performs a Ryan-Einot-Gabriel-Welsch multiple range test, which tests subsets of the group means for equality. This option is available only for unadjusted means.

8.4.3 Analysis of further exploratory efficacy variables

All exploratory efficacy variables will be analyzed in FAS and PPS.

8.4.3.1 Ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline

The logarithmized ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline will be analyzed by a mixed-effects repeated measures model with treatment group as the main effect, factors for the stratification levels (type of albuminuria and region), a factor for time, the interaction factor between treatment and time and the logarithmized baseline value as covariate.

The overall treatment effect, as well as treatment effects at each time point will be estimated.

Details for the analysis, e.g. the specification of the covariance structure, will be outlined in the statistical analysis plan.

8.4.3.2 Decreases in eGFR

Frequency tables will be generated for the number and incidence of subjects with a decrease in eGFR of ≥30% from baseline eGFR, of ≥40% from baseline eGFR, and of ≥57% from baseline eGFR. The analysis will be performed for each time point and overall (subjects with at least 1 event in the respective category after start of study drug administration).
8.4.3.3 Changes in albuminuria

A shift table will be provided displaying the number and incidence of subjects who changed from baseline to Visit 5 (Day 90±2) from very high albuminuria to high albuminuria, from very high albuminuria to albuminuria, from high albuminuria to albuminuria, from high albuminuria to very high albuminuria, and albuminuria to high albuminuria by treatment group and overall. The albuminuria category changes will only be considered as shifts, if they are accompanied by a UACR change of more than 30% from baseline to Visit 5 (Day 90±2).

8.4.3.4 Efficacy biomarkers

The analyses of efficacy biomarkers will be performed in FAS and PPS.

Efficacy biomarkers will be summarized descriptively by treatment group and visit including absolute changes to baseline. These analyses will be performed overall and separated by the stratification factor (type of albuminuria and region). Group means and standard deviations of absolute values and changes to baseline (non-stratified) will be plotted versus time including medical threshold levels, if applicable.

The change in biomarkers from baseline to Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (type of albuminuria and region) and baseline value as covariate. In case of signs for not approximately normal data, nonparametric methods or transformation of the data will be considered.

8.4.3.5 Health-related quality of life

The health-related quality of life questionnaires will be analyzed in FAS and PPS. For a detailed description of the questionnaires, please refer to Section 7.3.3.

The KDQOL-36 results will be described by visit and treatment group by presenting the summary scores (PCS, MCS, Burden of Kidney Disease, Symptoms / Problems, and Effects of Kidney Disease) by means of number of observations, minimum, first quartile, median, third quartile, and maximum, including the changes from baseline. It is not sensible to calculate an overall summary score. In addition, the frequencies of answers to individual questions will be displayed by treatment group and overall by visit. The frequencies of changes from baseline at Visit 3 (Day 30±2), Visit 5 (Day 90±2), and the follow-up visit will be presented regarding the categories improvement / no change / worsening for the summary scores and single items. Incidences of improvement and improvement / no change will be compared between the BAY 94-8862 treatment groups and the placebo treatment group by means of the \( \chi^2 \) test.

With regard to the EQ-5D-3L, the summary score and the scores for each dimension including changes from baseline will be described by treatment group and overall by visit using number of observations, minimum, first quartile, median, third quartile, and maximum, including the
changes from baseline. The above specified statistics plus the arithmetic mean and standard deviations will be provided for the EQ VAS and its changes to baseline. Furthermore, the frequencies of answers to all individual questions will be provided by treatment group and overall by visit. The frequencies of changes from baseline at Visit 3 (Day 30±2), Visit 5 (Day 90±2), and the follow-up visit will be presented regarding the categories improvement / no change / worsening for the summary score, each dimension and the EQ VAS. Incidences of improvement and of improvement/no change in the summary scores and the EQ VAS will be compared between the BAY 94-8862 treatment groups and the placebo treatment group by means of the χ² test.

8.4.4 Pharmacokinetics

For all planned pharmacokinetic analyses, please refer to Section 7.4.

Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value, a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked. Measurements that were not taken within the pre-defined time windows for Visit 3 (Day 30±2) and Visit 5 (Day 90±2) [60 to 120 minutes and 240 to 300 minutes after study drug administration for Visit 3 (Day 30±2); pre-administration, 30 to 90 minutes and 180 to 240 minutes after drug administration for Visit 5 (Day 90±2)] will be excluded from the descriptive statistics.

8.4.5 Safety and tolerability variables

All analyses on safety and tolerability data will be performed in the SAF.

8.4.5.1 Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, latest version available prior to data base freeze). A listing will be provided linking the original investigator terms and the coded terms.

AEs that occurred or worsened on or after the date of the first dose of study drug up to 3 days after the date of the last dose of study drug will be considered as TEAEs.

An overall summary of all TEAEs will be generated.

The number and incidence of non-treatment-emergent (pre-treatment) AEs, TEAEs, treatment-emergent SAEs, treatment-emergent study drug-related AEs, treatment-emergent study drug-related SAEs, treatment-emergent AEs causing discontinuation of study drug and treatment-emergent non-serious AEs will be summarized by treatment group and overall in total and using MedDRA terms grouped by system organ class and preferred terms.
In case of events with different intensity within a subject, the maximum reported intensity will be used. If intensity is missing, the event will be considered as severe. Similarly, if the same event is reported as both unrelated and related to the study drug within a subject, the event will be reported as related to study drug. If the drug relationship is missing, the event will be considered as being related to the study drug.

Deaths, SAEs, and AEs leading to study discontinuation will be listed separately (if applicable).

Separate tables summarizing TEAEs, treatment-emergent study drug-related AEs, and SAEs that occurred in more than 5% of the subjects will be provided.

8.4.5.2 Laboratory data

Only the data provided by the central laboratory will be used for analysis, values from local laboratories will not be used.

For potassium values only, in the cases in which tests are repeated, the following approach will be used. If the new (retest) potassium value is ≥5.6 mmol/L, the higher of the 2 values (original value and retest value) will be used. If the new (retest) value is <5.6 mmol/L, the new value will be used for analysis. However, all potassium values will be listed.

Summary statistics including changes to baseline will be calculated by treatment group and visit for all quantitative laboratory parameters. For log10(10×urinary sodium / potassium ratio), a normal distribution can be assumed. Therefore, geometric statistics and ratios to baseline will be presented for this parameter.

The number of subjects with transitions from baseline with respect to reference ranges categories (low, normal, high) will be provided by visit and treatment group.

In addition, for the special safety parameter serum potassium, the means and standard deviations of absolute values and changes to baseline by treatment group will be plotted versus time.

Serum potassium will be further assessed by displaying the number and incidence of serum potassium values ≥5.6 mmol/L and >6 mmol/L by treatment, visit, and overall. This will also be done stratified by the subgroups, specified in Section 8.4.6.

Summary statistics including changes to baseline will be calculated by treatment group and visit for iohexol plasma clearance.

8.4.5.3 Safety biomarkers

Safety biomarkers (troponin T and cystatin C) will be summarized descriptively by treatment group and visit including absolute changes to baseline. These analyses will be performed overall and separated by the stratification factor (type of albuminuria). Group means and
standard deviations of absolute values and changes to baseline (non-stratified) will be plotted versus time including medical threshold levels, if applicable.

The change in biomarkers from baseline to Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) will be analyzed by separate analysis of a covariance (ANCOVA) models with treatment group as the main effect, factors for the stratification levels (type of albuminuria and region), and baseline value as covariate. In case of signs for not approximately normal data, nonparametric methods or transformations of the data will be considered.

8.4.5.4 Vital signs, ECG, and ABPM

Vital sign values, ECG parameters, and measurements from the ABPM will be summarized by treatment group and visit using descriptive statistics including absolute changes from baseline.

3 measurements of vital signs parameters will be taken at time intervals of about 2 minutes. Averages of these 3 measurements will be calculated and used for the statistical analysis.

Subjects with abnormal overall ECG evaluation will be listed.

8.4.6 Subgroup analyses

The following subgroups will be considered for the descriptive and exploratory analysis of the primary variable:

- Age (18 to ≤45 years, >45 to ≤65 years, >65 to ≤75 years, and >75 years)
- Age (≤ median and > median)
- Region (Europe, North America, Asia, others)
- Gender (male, female)
- Race (white, black, Asian, other)
- Baseline BMI (≤30, >30)
- Baseline serum potassium value (≤ median and > median)
- eGFR values (CKD-EPI(50)) (≤ median and > median)
- Concomitant medication (ACEI or ARB)
- Very high albuminuria (UACR ≥300 mg/g) vs. high albuminuria (UACR ≥30 mg/g but <300 mg/g) at baseline

- Systolic blood pressure at baseline (>90 to <140 mmHg, ≥140 to <180 mmHg, and ≥180 mmHg; ≤ median and > median)

- Concomitant medication (beta-blocker vs. no beta-blocker at baseline, diuretic vs. no diuretic at baseline)

- Potassium supplementation vs. no potassium supplementation at any time during the study

However, if the total number of subjects in a subgroup category is <15, the analysis for that level of the subgroup will not be performed.

### 8.5 Planned interim analyses

No interim analysis is planned. However, data will be reviewed for safety and tolerability by an independent DMC.

### 8.6 Determination of sample size

With the primary analysis, dose-dependent effects on the primary variable, the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline, shall be demonstrated. Considering the method to detect an overall effect described in Section 8.4.2 (without covariate and adjustment for stratification factors), we estimated the power in 4 different scenarios for 6 treatment groups, as well as for 7 treatment groups (for the case of the addition of the 15 mg BAY 94-8862 once daily treatment group) with several sample sizes of subjects valid for FAS per treatment group. We simplified the planned ANCOVA to an analysis of variance (ANOVA) for the determination of sample size. We consider this approach as valid because the inclusion of the baseline log-UACR as a covariate will rather increase the power to detect a dose-dependent effect. For sample size calculations, the software nQuery Advisor® 7.0 was used.

The 4 scenarios used for the power calculations were designed based on the geometric means and geometric standard deviations of the UACR ratios from Study 14563 (ARTS) in subjects with high or very high albuminuria at baseline.

The results of the power estimations for 6 treatment groups (5 BAY 94-8862 groups and 1 placebo group) for sample sizes between 70 and 120 subjects per treatment group are summarized in Table 8-1.
Table 8-1: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862

<table>
<thead>
<tr>
<th>Sample size per treatment group</th>
<th>Total sample size</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
<th>SD of difference on log scale</th>
</tr>
</thead>
<tbody>
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<td>70</td>
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<td>80</td>
<td>92</td>
<td>91</td>
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<td>100</td>
<td>600</td>
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<td>120</td>
<td>720</td>
<td>95</td>
<td>99</td>
<td>98</td>
<td>94</td>
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</tr>
</tbody>
</table>

a Standard deviation of ln (UACR at Visit 5 (Day 90±2)) - ln (UACR at baseline)

The different assumed scenarios are (expected values of the logarithmized UACR ratios for the different treatments placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862):
- Scenario 1: ln(0.91), ln(0.87), ln(0.82), ln(0.74), ln(0.66), ln(0.59)
- Scenario 2: ln(0.91), ln(0.87), ln(0.82), ln(0.69), ln(0.60), ln(0.55)
- Scenario 3: ln(0.91), ln(0.82), ln(0.73), ln(0.58), ln(0.56), ln(0.55)
- Scenario 4: ln(0.91), ln(0.73), ln(0.64), ln(0.60), ln(0.57), ln(0.55)

A sample size of 90 subjects valid for FAS per treatment group would lead to 88% power in the worst case scenario. For the best case assumed, the primary analysis would demonstrate a power of 96%.

With 90 evaluable subjects per treatment group, a total of 540 evaluable subjects are needed. Considering an assumed screening failure rate of up to 50% and an assumed dropout rate of 10%, 100 subjects per treatment group should be randomized and approximately 1200 subjects need to be enrolled.

The results of the power estimations in the case that 1 treatment group with 15 mg BAY 94-8862 will be added after the DMC decision, i.e. for 6 BAY 94-8862 treatment groups and 1 placebo group, are summarized in Table 8-2 for sample sizes between 70 and 80 subjects per treatment group (fewer subjects than in Table 8-1 are considered here since the additional dose leads to an increase in power).
Table 8-2: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg BAY 94-8862

<table>
<thead>
<tr>
<th>Sample size per treatment group</th>
<th>Total sample size</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
<th>SD of difference on log scale a</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>490</td>
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<td>99</td>
<td>99</td>
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<td>89</td>
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</tr>
</tbody>
</table>

a Standard deviation of ln (UACR at Visit 5 (Day 90±2)) - ln (UACR at baseline)

The different assumed scenarios are (expected values of the logarithmized UACR ratios for the different treatments placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, and 15 mg BAY 94-8862):
- Scenario 1: ln(0.91), ln(0.87), ln(0.82), ln(0.74), ln(0.59), ln(0.46)
- Scenario 2: ln(0.91), ln(0.87), ln(0.82), ln(0.69), ln(0.60), ln(0.55), ln(0.48)
- Scenario 3: ln(0.91), ln(0.82), ln(0.73), ln(0.58), ln(0.56), ln(0.55), ln(0.54)
- Scenario 4: ln(0.91), ln(0.73), ln(0.64), ln(0.60), ln(0.57), ln(0.55), ln(0.52)

A sample size of 75 subjects valid for FAS per treatment group would lead to a power between 87% (worst case scenario) and 99% (best case scenario).

With the same assumptions on screening failure and dropout rate, a total of 83 subjects per treatment group should be randomized. The approximate number of enrolled subjects would not exceed 1200 subjects, as calculated for 6 treatment groups.

Sample size considerations for adding the 20 mg BAY 94-8862 treatment group as well are not considered here since reliable assumptions can hardly be made and it is expected that the power will even increase with 75 additional subjects valid for FAS for 20 mg BAY 94-8862.

Sample size considerations for adding the 20 mg BAY 94-8862 treatment group are not considered here. It is expected that the power will increase even in case a plateau will be reached with 75 additional subjects valid for FAS for 20 mg BAY 94-8862.

9. Data handling and quality assurance

9.1 Data recording

Specific data (race and ethnic group) may be entered directly into the eCRF, for all other data, source documentation must be available at the site. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.
9.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor’s / CRO’s procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor / designee will monitor the site activity to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study drug being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.3 Data processing

The data collection tool for this study will be a validated electronic system called RAVE. Subject data necessary for analysis and reporting will be entered / transmitted into a validated database or data system (e.g. Tools for Syntactic Corpus Analysis [TOSCA], SAS). Clinical data management will be performed in accordance with applicable sponsor’s standards and data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (e.g. laboratory).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

9.4 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor’s (or a designated CRO’s) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator / institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s) / IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator / institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his / her time and the time of his / her staff to the auditor /
inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

9.5 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator / institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor’s approval.

The investigator’s contract will contain all regulations relevant for the study center.

10. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment groups, dose steps, centers]) at any time, which may be due but not limited to the following reasons:

- If the risk-benefit ratio becomes unacceptable owing to, for example:
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity)
  - If the study conduct (e.g. recruitment rate, dropout rate, data quality, protocol compliance) does not suggest a proper completion of the study within a reasonable time frame

The investigator has the right to close his / her center at any time.
For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties
- All affected institutions (e.g. IEC(s) / IRB(s), competent authority(ies), study center, head of study center) must be informed as applicable according to local law
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner

Details for individual subject's withdrawal can be found in Section 5.2.1.

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s) / IRB(s) will be obtained for all participating centers / countries before start of the study, according to GCP, local laws, regulations, and organizations. When necessary, an extension, amendment or renewal of the IEC / IRB approval must be obtained and also forwarded to the Sponsor. The responsible unit (e.g. IEC / IRB, head of the study center / medical institution) must supply to the sponsor, upon request, a list of the IEC / IRB members involved in the vote and a statement to confirm that the IEC / IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change in the protocol to eliminate an immediate hazard(s) to the study subjects without prior IEC / IRB / sponsor approval / favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC / IRB / head of medical
institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 10.

11.2 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject / legal representative or proxy consenter (if the subject is under legal protection), prior to his / her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IEC / IRB has been obtained.

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the subject’s note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject’s clinical record must clearly show that informed consent was obtained prior to these procedures.

If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

For subjects under legal protection, consent shall be given by the legal guardian(s). The consent of a subject under legal protection shall also be requested where such a person is able to express his own will. His refusal or the withdrawal of his consent may not be disregarded.
The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject’s consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC’s / IRB’s approval / favorable opinion in advance of use.

11.3 Publication policy

The sponsor is interested in the publication of the results of every study it performs.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator / institution.

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

11.4 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

11.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC / IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject’s identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.
12. Reference list


21. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-847.


13. Protocol amendments

Not applicable.

14. Appendices

Not applicable.
Cover page of the integrated protocol

A randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy

This protocol version is an integration of the following documents / sections:

- Original protocol, Version 1.0, dated 04 MAR 2013
- Amendment 1 (described in Section 13.1) forming integrated protocol Version 2.0, dated 04 DEC 2013

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol.
Title page

A randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy

Short title: Safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy (ARTS-DN)

Test drug: BAY 94-8862

Study purpose: Safety and efficacy

Clinical study phase: IIb

Date: 04 DEC 2013

EudraCT no.: 2012-004179-38

Version no.: 2.0

Study no.: BAY 94-8862 / 16243

Sponsor: Bayer HealthCare AG, D-51368 Leverkusen, Germany

Sponsor’s medical expert: Anna Carolina Ferreira, M.D.
Study Medical Expert
Bayer S.A.
Bayer HealthCare
04779-900 São Paulo, Brasil
Phone no.: +55 11 5694 7132

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Confidential

The information provided in this document is strictly confidential and is intended solely for the guidance of the clinical investigation. Reproduction or disclosure of this document - whether in part or in full - to parties not associated with the clinical investigation, or its use for any other purpose, without the prior written consent of the sponsor is not permitted.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.
Signature of the sponsor’s medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: Christina Nowack, M.D.          Role: Global Clinical Leader

Date: 04. December 2013          Signature: [Signature]
Signature of the investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Date: ___________________________  Signature: __________________________________
### Synopsis

*This section was modified in AMD 1, see Section 13.1.2.1*

<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>A randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short title</strong></td>
<td>Safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy (ARTS-DN)</td>
</tr>
<tr>
<td><strong>Clinical study phase</strong></td>
<td>IIb</td>
</tr>
</tbody>
</table>
| **Study objectives** | **Primary objective of the study is**
- To investigate the change of urinary albumin-to-creatinine ratio (UACR) after treatment with different oral doses of BAY 94-8862 given once daily over 90 days in a randomized, placebo-controlled, double-blind study design versus placebo in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy (DN)

**Exploratory objectives of the study are**
- To assess safety and tolerability of these doses by assessing the effects on serum potassium and renal function
- To assess change in health-related quality of life (HRQoL) from baseline to 90 days of treatment assessed by the Kidney Disease Quality of Life (KDQOL-36) and EuroQol Group 5-dimension, 3-level (EQ-5D-3L) questionnaires. |
| **Test drug** | **Name of active ingredient** BAY 94-8862

- 1.25 milligram (mg) BAY 94-8862 tablet once daily in the morning
- 2.5 mg BAY 94-8862 tablet once daily in the morning
- 5 mg BAY 94-8862 tablet once daily in the morning
- 7.5 mg BAY 94-8862 tablet once daily in the morning
- 10 mg BAY 94-8862 tablet once daily in the morning
- 15 mg BAY 94-8862 tablet once daily in the morning
- 20 mg BAY 94-8862 tablet once daily in the morning |
| **Route of administration** | Oral |
| **Duration of treatment** | 90 days |
| **Reference drug** | **Name of active ingredient** Placebo

- Placebo tablet once daily in the morning |
| **Route of administration** | Oral |
| **Duration of treatment** | 90 days |
| **Indication** | Type 2 diabetes mellitus with clinical diagnosis of DN |
### Diagnosis and main criteria for inclusion

Adult male and female subjects with type 2 diabetes mellitus and a clinical diagnosis of DN treated with an angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB), for at least 3 months. The clinical diagnosis of DN must be based on at least 1 of the following criteria:

- Very high albuminuria defined as UACR of \( \geq 300 \text{ mg/g} \) \((\geq 34 \text{ mg/mmol})\) in 2 out of 3 first morning void samples and estimated glomerular filtration rate (eGFR) \( \geq 30 \text{ mL/min/1.73 m}^2 \) but < 90 \( \text{ mL/min/1.73 m}^2 \) (Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI) (mL = milliliter; min = minute; m² = square meter; g = gram; mmol = millimole)

- Persistent high albuminuria defined as UACR of \( \geq 30 \text{ mg/g} \) but < 300 mg/g (\( \geq 3.4 \text{ mg/mmol} \) but < 34 mg/mmol) in 2 out of 3 first morning void samples and eGFR \( \geq 30 \text{ mL/min/1.73 m}^2 \) but < 90 \( \text{ mL/min/1.73 m}^2 \) (CKD-EPI)

Subjects with an eGFR of 30 - 45 \( \text{ mL/min/1.73 m}^2 \) (CKD-EPI) must also be treated with a non-potassium sparing diuretic at randomization

- Serum potassium \( \leq 4.8 \text{ mmol/L} \) at screening (L = liter)

- Mean sitting systolic blood pressure (SBP) < 180 mmHg and mean sitting diastolic blood pressure (DBP) < 110 mmHg at the run-in visit and mean sitting SBP < 160 mmHg or mean sitting DBP < 100 mmHg at the screening visit (mmHg = millimeters of mercury)

### Study design

Multi-center, randomized, adaptive, double-blind, placebo-controlled parallel-group design

### Methodology

1.25 mg, 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg BAY 94-8862 once daily will be compared to placebo for safety, tolerability, effects on UACR and on cardiac and renal function by changes in concentrations of various biomarkers; pharmacokinetics of BAY 94-8862 and HRQoL will be assessed

### Type of controls

Placebo

### Number of subjects

Assuming a screening failure rate of approximately 50%, 1200 (1340 in case that 15 mg and 20 mg BAY 94-8862 will be investigated) subjects will have to be screened to randomize 600 (670) subjects. Assuming a dropout rate of 10% and approximately 90 (75) subjects valid for the full analysis set (FAS) needed per treatment group, in total approximately 540 (600) subjects valid for FAS are expected.

### Primary efficacy variable

Ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline

### Further exploratory efficacy variables

Please refer to Section 8.3.2.

### Safety variables

Please refer to Section 8.3.3.
### Plan for statistical analysis

<table>
<thead>
<tr>
<th><strong>Safety analysis set (SAF)</strong></th>
<th>All randomized subjects who have taken at least 1 dose of study drug and with data after beginning of treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAS</strong></td>
<td>All subjects of the SAF who have baseline and at least 1 post-baseline UACR value.</td>
</tr>
<tr>
<td><strong>Per-protocol analysis set (PPS)</strong></td>
<td>All subjects of the FAS who have valid UACR value at Visit 5 (Day 90±2) and have no major protocol deviations.</td>
</tr>
</tbody>
</table>

### Plan for statistical analysis (continued)

| An analysis of covariance (ANCOVA) model will be fitted to the logarithmized ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline including a factor for treatment group, factors to adjust for the stratification factors (type of albuminuria and region) and the logarithmized baseline UACR as covariate. |
Table of contents

Cover page of the integrated protocol ................................................................. 1
Title page .............................................................................................................. 2
Signature of the sponsor’s medically responsible person .................................... 3
Signature of the investigator .................................................................................. 4
Synopsis .................................................................................................................. 5
Table of contents .................................................................................................. 8
Table of text tables ............................................................................................... 12
Table of text figures ............................................................................................. 12
List of abbreviations ............................................................................................ 13

1. Introduction ...................................................................................................... 17
   1.1 Background .................................................................................................... 17
   1.2 Previous experience in humans ................................................................. 18
      1.2.1 Safety ..................................................................................................... 19
      1.2.2 Efficacy ................................................................................................. 19
      1.2.3 Pharmacokinetics .................................................................................. 20
   1.3 Rationale for the study ................................................................................ 21
   1.4 Benefit-risk assessment ............................................................................. 23

2. Study objectives ............................................................................................... 25

3. Investigators and other study personnel ......................................................... 25

4. Study design .................................................................................................... 26

5. Study population ............................................................................................ 32
   5.1 Eligibility ...................................................................................................... 32
      5.1.1 Inclusion criteria .................................................................................... 32
      5.1.2 Exclusion criteria .................................................................................. 34
      5.1.3 Justification of selection criteria ............................................................ 35
   5.2 Withdrawal of subjects from study ............................................................ 36
      5.2.1 Withdrawal ........................................................................................... 36
      5.2.2 Replacement ......................................................................................... 38
   5.3 Subject identification .................................................................................. 38

6. Treatments ....................................................................................................... 38
   6.1 Treatments to be administered ................................................................. 38
   6.2 Identity of study drug ................................................................................... 40
   6.3 Treatment assignment ............................................................................... 41
   6.4 Dosage and administration ....................................................................... 41
   6.5 Blinding ....................................................................................................... 41
      6.5.1 Blinding measures ............................................................................... 41
      6.5.2 Unblinding ......................................................................................... 42
      6.5.3 Emergency unblinding by the investigator ............................................ 42
   6.6 Drug logistics and accountability ................................................................. 42
   6.7 Treatment compliance ............................................................................... 43
   6.8 Post-study therapy .................................................................................... 43
   6.9 Prior and concomitant therapy ................................................................ 43
7. Procedures and variables

7.1 Schedule of procedures

7.1.1 Tabulated overview

7.1.2 Timing of assessments

7.1.3 Informed consent

7.1.4 Run-in visit

7.1.5 Screening visit

7.1.6 Visit 1 (Baseline and randomization) - Day 1

7.1.7 Visit 2 - Day 7

7.1.8 Visit 3 - Day 30

7.1.9 Visit 4 - Day 60

7.1.10 Visit 5 - Day 90

7.1.11 Premature discontinuation visit

7.1.12 Follow-up visit (30±5 days after last intake of study drug)

7.2 Population characteristics

7.2.1 Demographic

7.2.2 Medical history

7.2.3 Physical examination

7.3 Efficacy

7.3.1 Primary efficacy variable

7.3.2 Further exploratory efficacy variables

7.3.3 Health-related quality of life

7.3.4 Efficacy biomarkers

7.4 Pharmacokinetics

7.5 Safety

7.5.1 Adverse events

7.5.1.1 Definitions

7.5.1.2 Classifications for adverse event assessment

7.5.1.2.1 Seriousness

7.5.1.2.2 Intensity

7.5.1.2.3 Causal relationship

7.5.1.2.4 Action taken with study treatment

7.5.1.2.5 Other specific treatments of adverse events

7.5.1.2.6 Outcome

7.5.1.3 Assessments and documentation of adverse events

7.5.1.4 Reporting of serious adverse events

7.5.1.5 Expected adverse events

7.5.1.6 Adverse events of special safety interest

7.5.2 Pregnancies

7.5.3 Safety biomarkers

7.6 Other procedures and variables

7.6.1 Laboratory parameter measurement

7.6.1.1 Central laboratory

7.6.1.2 Local laboratory
7.6.2 Electrocardiogram ....................................................... 70
7.6.3 Vital signs ................................................................. 70
7.6.4 Ambulatory blood pressure monitoring ......................... 70
7.6.5 Iohexol plasma clearance ........................................... 71
7.7 Appropriateness of procedures / measurements .................. 72
8. Statistical methods and determination of sample size ............... 72
  8.1 General considerations .................................................. 72
  8.2 Analysis sets ................................................................. 72
  8.3 Variables ....................................................................... 73
    8.3.1 Primary efficacy variable .......................................... 73
    8.3.2 Further exploratory efficacy variables ......................... 73
    8.3.3 Safety and tolerability variables .................................. 73
  8.4 Statistical and analytical plans .......................................... 73
    8.4.1 Analysis of subject characteristics ............................... 73
    8.4.2 Analysis of primary efficacy variable ............................ 73
    8.4.3 Analysis of further exploratory efficacy variables .......... 75
      8.4.3.1 Ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline ......................... 76
      8.4.3.2 Decreases in eGFR ............................................. 76
      8.4.3.3 Changes in albuminuria ........................................ 76
      8.4.3.4 Efficacy biomarkers ............................................ 76
      8.4.3.5 Health-related quality of life .................................. 77
    8.4.4 Pharmacokinetics ..................................................... 77
    8.4.5 Safety and tolerability variables .................................. 77
      8.4.5.1 Adverse events .................................................. 78
      8.4.5.2 Laboratory data ................................................ 78
      8.4.5.3 Safety biomarkers .............................................. 79
      8.4.5.4 Vital signs, ECG, and ABPM ................................. 79
    8.4.6 Subgroup analyses .................................................. 79
  8.5 Planned interim analyses ................................................ 80
  8.6 Determination of sample size ........................................... 80
9. Data handling and quality assurance ...................................... 83
  9.1 Data recording ............................................................. 83
  9.2 Monitoring ................................................................. 83
  9.3 Data processing .......................................................... 83
  9.4 Audit and inspection ...................................................... 84
  9.5 Archiving ....................................................................... 84
10. Premature termination of the study ....................................... 84
11. Ethical and legal aspects .................................................... 85
    11.1 Ethical and legal conduct of the study ............................. 85
    11.2 Subject information and consent ................................. 86
    11.3 Publication policy ...................................................... 87
    11.4 Compensation for health damage of subjects / insurance .... 87
    11.5 Confidentiality .......................................................... 87
12. Reference list.................................................................................................................................................. 88
13. Protocol amendments ..................................................................................................................................... 93
  13.1 Amendment 1 ................................................................................................................................................. 93
         13.1.1 Overview of changes .............................................................................................................................. 93
         13.1.2 Changes to the protocol text .................................................................................................................. 94
                    13.1.2.1 Synopsis section .............................................................................................................................. 95
                    13.1.2.2 Section 4 Study design .................................................................................................................. 96
                    13.1.2.3 Section 5.1.1 Inclusion criteria ....................................................................................................... 100
                    13.1.2.4 Section 5.2.1 Withdrawal .............................................................................................................. 102
                    13.1.2.5 Section 6.3 Treatment assignment ................................................................................................ 104
                    13.1.2.6 Section 6.9 Prior concomitant therapy .............................................................................................. 105
                    13.1.2.7 Section 7.1.1 Tabulated overview ................................................................................................... 107
                    13.1.2.8 Section 7.1.4 Run-in visit ................................................................................................................ 109
                    13.1.2.9 Section 7.1.5 Screening visit ........................................................................................................... 110
                    13.1.2.10 Section 7.1.6 Visit 1 (Baseline and randomization) - Day 1 ...................................................... 111
                    13.1.2.11 Section 7.1.7 Visit 2 – Day 7±2 ....................................................................................................... 111
                    13.1.2.12 Section 7.1.10 Visit 5 – Day 90±2 ................................................................................................ 112
                    13.1.2.13 Section 7.3.3 Health-related quality of life .................................................................................... 112
                    13.1.2.14 Section 7.5.1.6 Adverse events of special safety interest ................................................................. 113
                    13.1.2.15 Section 7.6.1.1 Central laboratory .................................................................................................. 113
                    13.1.2.16 Section 7.6.1.2 Local laboratory .................................................................................................... 115
                    13.1.2.17 Section 8.1 General considerations .................................................................................................. 116
                    13.1.2.18 Section 8.2 Analysis sets ................................................................................................................ 117
                    13.1.2.19 Section 8.4.2 Analysis of primary efficacy variable ......................................................................... 117
                    13.1.2.20 Section 8.4.3.1 Ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline ........................................................................................................... 120
                    13.1.2.21 Section 8.4.3.5 Health-related quality of life .................................................................................... 120
                    13.1.2.22 Section 8.4.5.1 Adverse events ........................................................................................................ 121
                    13.1.2.23 Section 8.4.5.2 Laboratory data ...................................................................................................... 122
                    13.1.2.24 Section 8.5 Planned interim analyses ............................................................................................... 122
                    13.1.2.25 Section 8.6 Determination of sample size ...................................................................................... 123
14. Appendices ....................................................................................................................................................... 126
Table of text tables

Table 1-1: *Post hoc* analyses of randomized clinical studies testing early, treatment-induced changes in albuminuria or proteinuria on long-term renal and cardiovascular outcomes ............................................................................................................ 22

Table 4-1: Minimal recommended dose of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (adapted from Kidney Disease Outcomes Quality Initiative clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease; Table 127).......................................................... 28

Table 4-2: Monitoring of potassium during the treatment period .................................. 30

Table 6-1: Identity of test drug / BAY 94-8862 and matching placebo ............................ 40

Table 7-1: Schedule of procedures ...................................................................................... 46

Table 8-1: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862.............................. 81

Table 8-2: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg BAY 94-8862 .......................... 82

Table 8-1: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862.............................. 123

Table 8-2: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg BAY 94-8862 ........................ 124

Table 8-1: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862.............................. 125

Table 8-2: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg BAY 94-8862 ........................ 126

Table of text figures

Figure 4-1: Study design............................................................................................................. 27
List of abbreviations

\(\tau\)  
\(\%CV\)  
AASK  
ABPM  
ACE  
ACEI  
AE  
ALT  
ANCOVA  
ANOVA  
AP  
ARB  
ARTS  
AST  
AUC  
AUC\(_{\tau,\text{Day 10}}\)  
BMI  
BNP  
BP  
\(C_{max}\)  
CK  
CKD  
CKD-EPI  
CRO  
CV  
CVD  
CYP  
CYP2C8  
CYP3A4  
DBP  
DCCT  
DMC  
DN  
ECG  
eCRF  
e.g.  
eGFR  
EQ-5D-3L  
ESRD  
etc.
EU  European Union
FAS  full analysis set
FU  follow-up
g  gram
GCP  Good Clinical Practice
GFR  glomerular filtration rate
GGT  gamma glutamyl transpeptidase
GLM  generalized linear model
GMP  Good Manufacturing Practice
HbA1c  glycated hemoglobin
HDL  high density lipoprotein
HFrEF  heart failure with reduced ejection fraction
HR  heart rate
HRQoL  health-related quality of life
hs-CRP  high-sensitivity C-reactive protein
IB  Investigator’s Brochure
ICH  International Conference on Harmonization
IDNT  Irbesartan Diabetic Nephropathy Trial
i.e.  id est, that is
IEC  Independent Ethics Committee
IR  immediate release
IRB  Institutional Review Board
IRMA-2 (study)  Irbesartan in MicroAlbuminuria, type 2 diabetic nephropathy (study)
IXRS  Interactive Voice / Web Response System
KDQOL  Kidney Disease Quality of Life
L  liter
LDH  lactate dehydrogenase
LDL  low density lipoprotein
LLOQ  lower limit of quantification
ln  natural logarithm, i.e. logarithm to the base e, a constant approximately equal to 2.718
log  logarithm
LOCF  last observation carried forward
LOS  listing only set
LVSD  left ventricular systolic dysfunction
m²  square meter
MCH  mean corpuscular hemoglobin
MCHC  mean corpuscular hemoglobin concentration
MCV  mean corpuscular volume
M.D.  doctor of medicine
mg  milligram
min  minute
mL  milliliter
μm  micrometer
mmHg millimeters of mercury
mmol millimole
MR mineralocorticoid receptor
MRA mineralocorticoid receptor antagonist
NGSP National Glycohemoglobin Standardization Program
NONMEM non-linear mixed effect modeling
NT-proBNP N-terminal prohormone B-type natriuretic peptide
NYHA New York Heart Association
ONTARGET ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
PD premature discontinuation
PEG polyethylene glycol
PK pharmacokinetic(s)
PKS pharmacokinetic analysis set
PP polypropylene
PPS per-protocol analysis set
PR PR interval in ECG
QA quality assurance
QRS QRS interval in ECG
QRSD QRS duration
QT QT interval in ECG
QTc QT interval corrected for heart rate
RAS renin-angiotensin system
RAVE electronic data capturing system
RBC red blood cells
REGWQ Ryan-Einot-Gabriel-Welsch Q
REIN (study) Ramipril Efficacy In Nephropathy (study)
RENAAL (study) Reduction in Endpoints in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (study)
ROAD (study) Renoprotection of Optimal Antiproteinuric Doses (study)
SAE serious adverse event
SAF safety analysis set
SAS Statistical Analysis System
SBP systolic blood pressure
SD standard deviation
SID subject identification
SOC standard of care
SUSAR suspected, unexpected serious adverse reaction
t_{max} time to reach C_{max} in plasma after single (first) dose
TEAE treatment-emergent adverse event
TOSCA Tools for Syntactic Corpus Analysis (database)
TRANSCEND Telmisartan Randomized Assessment Study in ACE iNtolerant subjects with cardiovascular Disease
UACR urinary albumin-to-creatinine ratio
US  United States (of America)
VAS  visual analogue scale
vs.  versus, as opposed to
WBC  white blood cells
WHO  World Health Organization
1. Introduction

1.1 Background

According to the World Health Organization (WHO), diabetes mellitus currently affects more than 240 million people worldwide, and the number is predicted to rise to more than 360 million by 2030. Diabetic nephropathy (DN) represents the most common cause of end-stage renal failure in the United States (US) and accounts for approximately 40% of all new patients entering end-stage renal disease (ESRD) programs and approximately 45% of patients receiving renal replacement therapy.

Overall approximately 20 to 30% of patients with type 1 or type 2 diabetes mellitus develop evidence of nephropathy although there is considerable variability by type in terms of disease progression.

- Approximately 25 to 45% of type 1 diabetes mellitus patients will develop DN and signs of high albuminuria. Within those, 80 to 90% will progress to overt DN within 5 to 10 years.

- About 50% of type 2 diabetes mellitus patients will have high albuminuria at the time of presentation, typically secondary to hypertension. Only 10 to 20% will progress to overt DN within 5 to 10 years.

Until recently, DN was very much a disease of Western countries, but in the future, Asian countries are likely to represent the bulk of the DN population, due to their size but also to the predilection of Asian diabetic patients to develop renal complications. In cross-sectional surveys, up to 60% of Asian diabetic patients have high or very high albuminuria compared to 30 to 40% reported in Western diabetic populations.

Hyperglycemia is a primary initiator of DN – in the absence of elevated glycemia, nephropathy is much less likely to develop. As a result, long-standing uncontrolled or poorly controlled diabetes is the single most important risk factor for the development of DN. Other risk factors include hypertension and hyperlipidemia.

In patients with DN, albuminuria at baseline is a much more important factor to predict ESRD than is hypertension at baseline. In addition to lowering albuminuria, it is now clearly demonstrated that interruption of the renin-angiotensin system (RAS) reduces the risk of progression to ESRD. However, an impact on overall survival has not yet been demonstrated.

Despite significant progress over the last decade, the ultimate goal of preventing the development of ESRD in DN is still far from being reached. Without therapy, the average time from diagnosed chronic kidney disease (CKD) to ESRD is about 4 to 5 years. On therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor
blockers (ARBs), this time is extended by 1 to 2 years only.\(^{(9,10)}\) DN remains the primary diagnosis leading to ESRD in the US and 1 of the top 2 or 3 in most other countries.\(^{(11)}\)

Current therapies for DN rely on the control of albuminuria through inhibition of the RAS with ACEIs or ARBs. Despite initial down-regulation of the release of aldosterone by the adrenal glands, up to 50% of the patients treated with a RAS blocker develop an increase in plasma aldosterone within 6 to 12 months after the initiation of treatment.\(^{(12)}\) Several studies have shown a direct relationship between increases in plasma aldosterone after ACEI treatment and increases in albuminuria and decreases in kidney function. Explorative clinical studies in adults have shown a potential role for mineralocorticoid receptor antagonists (MRAs), when added to RAS blockers, to delay the development of ESRD further.\(^{(13-16)}\)

BAY 94-8862 is a novel non-steroidal MRA. In vitro investigations have demonstrated superior selectivity vs. spironolactone and improved potency vs. eplerenone.\(^{(17)}\) These properties have also been demonstrated in a number of nonclinical in vivo investigations, which showed BAY 94-8862 to be effective in reducing mortality in models of heart failure and stroke; and in reducing cardiac remodeling and end-organ lesions.

In Study 14563 (Mineralocorticoid Receptor Antagonist Tolerability Study, ARTS), a multicenter, randomized, double-blind, placebo-controlled study, BAY 94-8862 was investigated in subjects with heart failure with reduced ejection fraction (HFrEF) and mild to moderate CKD.\(^{(18)}\) ARTS demonstrated the improved safety of all once-daily investigated doses of BAY 94-8862 (2.5 - 10 mg) in comparison to spironolactone (25 / 50 mg once daily), in particular with regards to increase of serum potassium and change in renal function. During the observation period of 28 days, a reduction of B-type natriuretic peptide (BNP) and N-terminal-prohormone B-type natriuretic peptide (NT-proBNP) similar to spironolactone (25 / 50 mg once daily) was demonstrated for doses higher than 5 mg BAY 94-8862 once daily in that high-risk population for hyperkalemia. Albuminuria was also reduced by all doses of BAY 94-8862, in particular in subjects with high and very high albuminuria at baseline.

Based on the aforementioned properties, BAY 94-8862 is expected to have the potential to address the unmet medical needs in patients with type 2 diabetes mellitus and the clinical diagnosis of DN. When added to standard therapy with RAS blocker treatment with 1.25 to 20 mg BAY 94-8862 given once daily might lead to a reduction in albuminuria compared with placebo on top of standard of care (SOC). In Study 16243, safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN will be investigated over 90 days of treatment.

### 1.2 Previous experience in humans

A detailed description of the properties of BAY 94-8862 and the results of the nonclinical and clinical pharmacology studies as well as the first clinical study (Study 14563, ARTS)
conducted so far are given in the Investigator’s Brochure (IB). A brief overview of the results is provided in the following sections.

1.2.1 Safety

The dose range investigated so far in healthy subjects was safe and well tolerated and covered single oral doses of 1 to 40 mg BAY 94-8862 polyethylene glycol solution (Studies 13782, 13784, and 13786) and 1.25 to 80 mg BAY 94-8862 administered as immediate-release (IR) tablets (Studies 13784, 13786, 14504, 14506, 14508, 14509, 15526, 15528, and 15481) as well as multiple oral doses of 10 and 20 mg twice daily and 40 mg once daily for 10 days administered as 10 mg IR tablets (Studies 13785 and 15171). There were no drug-related serious adverse events (SAEs). All observed treatment-emergent adverse events (TEAEs) were of mild or moderate intensity.

In MinerAlocorticoid Receptor Antagonist Tolerability Study (ARTS, Study 14563), BAY 94-8862 was investigated in subjects with stable chronic heart failure and mild (Part A) or moderate (Part B) CKD. In total, 65 subjects were enrolled in Part A and 393 in Part B which was the main part of the study. Safety and tolerability as well as the effects on different biomarkers of cardiac and renal function were compared to placebo as well as to 25 / 50 mg spironolactone once daily after 28 days of study drug treatment. Primary variable in Part B was the change in serum potassium from baseline to Visit 6 (Day 22±2) and Visit 7 (Day 29±2). All doses of BAY 94-8862 tested in Study 14563 (2.5 mg, 5 mg, and 10 mg once daily as well as 5 mg twice daily) were safe and well tolerated. Although only approximately 50% of all subjects in the spironolactone treatment group could be up-titrated from 25 mg to 50 mg after 14 days of treatment, all doses of BAY 94-8862 showed less potassium increase than spironolactone.

In the tested dose range, BAY 94-8862 was well tolerated and safe and did not differ to a relevant degree from placebo with regard to overall number of adverse events (AEs) and types of AEs, the only exception being a higher number of subjects with hyperkalemia in comparison to placebo. In contrast, the number of subjects with AEs was highest in the spironolactone treatment group; in particular, “renal and urinary disorders” and “hyperkalemia” occurred more frequently in the spironolactone treatment group than in the other treatment groups.

1.2.2 Efficacy

ARTS (Study 14563) was not designed to detect any statistically significant differences in the efficacy of BAY 94-8862 in comparison to spironolactone. In addition, the treatment period of 28 days was too short to fully exploit the beneficial anti-fibrotic effects of MR antagonism on heart and kidney. Nevertheless, the short-term effects of BAY 94-8862 on albuminuria (measured as urinary albumin-to creatinine ratio, UACR) were measured in both parts of the study as well as the effects on biomarkers of cardiac function such as BNP and NT-proBNP in Part B of the study only. Serum aldosterone which can be used as biomarker for activity of the MRA at the MR(19) was also assessed in Part B. Since MR antagonism is associated with
a feedback increase in plasma renin activity, increasing angiotensin II and aldosterone levels can be observed under treatment with an MRA.

In ARTS (Study 14563), a dose-dependent increase in serum aldosterone was demonstrated at all investigated doses of BAY 94-8862 as well as spironolactone.

Since baseline values of UACR were rather low in Part A of the study, only small decreases in UACR were observed at all doses of BAY 94-8862. In Part B, all doses of BAY 94-8862 decreased UACR to a similar extent as 25 mg spironolactone once daily after 2 weeks of treatment but less than 25 / 50 mg spironolactone once daily at the end of the observation period. Since the mean baseline values in the 5 mg BAY 94-8862 twice-daily treatment group were low in comparison to the other groups, no remarkable effects on reduction in albuminuria were seen in this group.

Starting at a dose of 5 mg BAY 94-8862 once daily, a decrease in BNP and NT-proBNP was observed during the course of the study. For the 10 mg BAY 94-8862 once-daily and 5 mg BAY 94-8862 twice-daily treatment groups, the mean changes from baseline were more pronounced than in the spironolactone treatment group. However, as already known for BNP and NT-proBNP, high inter-subject variability was observed for these parameters.

In summary, all investigated doses of BAY 94-8862 showed efficacy signals by reducing albuminuria as well as BNP and NT-proBNP levels (with the exception of 2.5 mg once daily). The effects on natriuretic peptides were at least comparable to those following 25 / 50 mg spironolactone once daily in the investigated subject population with stable HFrEF and moderate CKD (Part B).

### 1.2.3 Pharmacokinetics

Based on the available clinical-pharmacological studies in healthy volunteers the pharmacokinetics (PK) of BAY 94-8862 can be summarized as follows: BAY 94-8862 was rapidly absorbed with a median time to maximum concentration ($t_{\text{max}}$) between 0.5 and 1.5 hours [fasted administration of immediate-release (IR) tablet] and rapidly eliminated from plasma with a terminal half-life ($t_{1/2}$) of 2 - 3 hours. After administration of 1.25 to 10 mg IR tablets, the area under the plasma concentration vs. time curve (AUC) increased in proportion to the dose. A high-fat, high-calorie meal had little effect on the AUC of 10 mg BAY 94-8862 IR tablet (10% increase) and resulted in a reduced absorption rate [32% decrease in maximum total drug concentration in plasma ($C_{\text{max}}$) and 1.75 h increase in the time to reach $C_{\text{max}}$ in plasma ($t_{\text{max}}$)]. Following administration of IR tablets for 10 days [10 mg or 20 mg (two 10 mg tablets) twice daily, 40 mg (four 10 mg tablets) once daily], a 10 - 32% increase in AUC during the dosing interval $\tau$ on Day 10 of dosing (AUC$_{\tau,\text{Day 10}}$) over AUC on Day 1 was observed, while there was no consistent effect on maximum plasma concentrations. BAY 94-8862 starting from 20 mg twice daily onwards was a weak inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4) as multiple doses increased the AUC of the prototypical CYP3A4 substrate midazolam by 21%.
Renal elimination of unchanged BAY 94-8862 by glomerular filtration was a minor route of elimination and accounted for 0.57 - 1.4% of the dose. Mild renal impairment had no effect on BAY 94-8862 exposure. Moderate or severe renal impairment resulted in an increase in BAY 94-8862 AUC (+47% to 57% for unbound AUC) and had no effect on Cmax in comparison to healthy controls. Age-related increases in BAY 94-8862 AUC (+34%) and Cmax (+51%) were observed when comparing subjects aged ≥65 years with subjects aged ≤45 years while gender had no effect on the drug’s pharmacokinetics. Omeprazole or Maalox® had no effect on the AUC of BAY 94-8862 (10 mg IR tablet) and no relevant effect on its Cmax.

Based on available data, 4 days pre-treatment with and concomitant administration of the moderate CYP3A4 inhibitor erythromycin (500 mg 3 times daily) results in an increase in AUC (+250%) and Cmax (+90%) of BAY 94-8862 (1.25 mg IR tablet) compared to BAY 94-8862 administered alone.

1.3 Rationale for the study

Treatment with MRAs has become a 1A recommendation in international guidelines for patients with HFrEF, New York Heart Association (NYHA) class II - IV who remain symptomatic despite treatment with both ACEIs and beta-blockers. Although these agents are still underused or used at a low dose in clinical practice partly due to concerns raised about their safety, there is consensus that in all symptomatic patients with HFrEF, an MRA is an appropriate addition to ACEIs and beta-blockers, proven to provide additional reductions in morbidity and mortality.

There is also evidence that treatment with ACEIs and ARBs slows progression of kidney disease; however, used alone or in combination, these classes of drugs have not been proven to reduce cardiovascular (CV) morbidity and mortality. There is an urgent need to evaluate novel therapies to improve CV and renal outcomes in patients with DN. No treatment regimens have been shown to stop progression of kidney disease or prevent CV events in patients with diabetes mellitus, including anemia treatment.

Although the precedent of MRAs in DN is limited to explorative studies with MRAs given on top of optimized SOC, the results suggest that administration of therapeutic agents that block the MR may improve outcomes in patients with CKD. In these studies, the MRAs spironolactone and eplerenone showed to reduce albuminuria. However, the ultimate goal of slowing progression of kidney disease and improving CV morbidity / mortality has not yet been demonstrated in long-term outcome studies.
Table 1-1: *Post hoc* analyses of randomized clinical studies testing early, treatment-induced changes in albuminuria or proteinuria on long-term renal and cardiovascular outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Renal outcomes</th>
<th>Cardiovascular outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmieder et al. (29)</td>
<td>23,480 subjects with vascular disease or high-risk diabetes included in the ONTARGET and TRANSCEND</td>
<td>Each halving of albuminuria level during the first 2 years was associated with a decrease in the combined renal outcome by 27% during the 1.7 years of follow-up</td>
<td>Each halving of albuminuria level during the first 2 years was associated with a decrease in the combined CV outcome by 15% after 1.7 years of follow-up</td>
</tr>
<tr>
<td>Xie et al. (30)</td>
<td>339 Chinese nondiabetic CKD subjects with overt proteinuria included in the ROAD study</td>
<td>Every 0.5 g reduction in residual proteinuria was associated with a risk reduction by 50% for the combined end point during 3.7 years of follow-up</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Lea et al. (31)</td>
<td>1,094 African Americans with hypertensive renal disease included in the AASK</td>
<td>Each doubling of proteinuria level in the first 6 months was associated with a relative risk for ESRD of 2.11 (95% confidence interval: 1.89 - 2.36) over a median follow-up of 3.8 years</td>
<td>Not assessed</td>
</tr>
<tr>
<td>de Zeeuw et al. (32, 33)</td>
<td>1,513 subjects with overt diabetic nephropathy included in the RENAAL study</td>
<td>Each halving of albuminuria level during the first 6 months was associated with a reduction in the risk for the combined renal end point by 45% during 3.4 years of follow-up</td>
<td>Each halving of albuminuria level during the first 6 months was associated with a reduction in CV risk by 18% after 3.4 years of follow-up</td>
</tr>
<tr>
<td>Hunsicker et al. (34)</td>
<td>1,715 subjects with type 2 diabetes mellitus included in the IDNT</td>
<td>Each halving of proteinuria level during the first 12 months was associated with a risk reduction in ESRD by 56% during 2.9 years of follow-up</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Ruggenenti et al. (35)</td>
<td>273 nondiabetic subjects with chronic proteinuric nephropathies included in the REIN study</td>
<td>Short-term changes in proteinuria independently predicted GFR decline over a median follow-up of 2.6 years</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Hellemons et al. (36)</td>
<td>531 diabetic subjects with microalbuminuria included in the IRMA-2 study</td>
<td>Each halving of proteinuria level was associated with a risk reduction for development of overt nephropathy by 44% over 2 years of follow-up</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Holtkamp et al. (37)</td>
<td>2,900 subjects with diabetic nephropathy included in the RENAAL study and the IDNT</td>
<td>Not assessed</td>
<td>Each log unit decrease in albuminuria level was associated with a 13% risk reduction for CV events</td>
</tr>
</tbody>
</table>

AASK, African-American Study of Kidney disease and hypertension; CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease; GFR, glomerular filtration rate; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA-2, Irbesartan in Microalbuminuria, type 2 diabetic nephropathy; ONTARGET, Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; REIN, Ramipril Efficacy In Nephropathy; RENAAL, Reduction in Endpoints in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan; ROAD, Renoprotection of Optimal Antiproteinuric Doses; TRANSCEND, Telmisartan Randomized AssessmeNT Study in ACE iNTolerant subjects with cardiovascular Disease
Albuminuria is a surrogate marker of kidney damage (reflecting underlying glomerular disease or renal tubular dysfunction) and has been proposed to be a marker of CKD progression. Patients with higher baseline albuminuria experience a relatively faster rate of glomerular filtration rate (GFR) decline.\(^{(38)}\) Urinary protein reduction is associated with a decline in the rate of kidney disease progression, which leads to disease stabilization and, in some cases, even to recovery of renal function.\(^{(39)}\) Post hoc analyses of randomized clinical studies that have aimed to evaluate the relationships between changes in albuminuria and disease outcome have consistently found that a short-term reduction in albuminuria is invariably associated with reduction in CV mortality and morbidity as well as slower GFR decline and progression to ESRD in the long term (see Table 1-1).

In Study 14563 (ARTS), albuminuria was reduced by all investigated doses of BAY 94-8862. In particular in subjects with high and very high albuminuria, UACR was decreased by up to 52% and 74% from baseline, respectively. The observed effects were comparable to the effects following the administration of 25 / 50 mg spironolactone in subjects with HFrEF and moderate CKD. All doses of BAY 94-8862, i.e. 2.5 to 10 mg given once daily as well as 5 mg given twice daily, were safe and well tolerated and showed less potassium increase than the comparator spironolactone.

This study (Study 16243) will investigate short-term efficacy and safety of different oral doses of BAY 94-8862 given once daily over 90 days in comparison to placebo in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN.

Based on its specific profile with its favorable balanced activity on heart and kidney, BAY 94-8862 might have the potential to address the unmet medical needs in patients with type 2 diabetes mellitus and the clinical diagnosis of DN and to demonstrate a delay in the progression to ESRD and a reduction of CV mortality and morbidity, on top of ACEIs or ARBs, in this high-risk patient population.

### 1.4 Benefit-risk assessment

In recent years, large-scale clinical studies\(^{(9, 10, 40)}\) have shown that the interruption of the RAS with either ACEIs or ARBs has renoprotective effects in patients with DN. Both, ACEIs and ARBs, significantly reduce proteinuria and the risk of ESRD by about 20% to 30%\(^{(41)}\). Therefore, guidelines recommend these treatments in hypertensive and normotensive patients with DN.\(^{(42)}\)

However, it has also been demonstrated that despite initial down-regulation of the release of aldosterone by the adrenal glands in patients treated with ACEIs or ARBs, up to 50% of the patients develop an increase in plasma aldosterone within 6 - 12 months\(^{(12)}\). Several studies have shown a direct relationship between increases in plasma aldosterone after ACEI treatment and increases in proteinuria and decreases in kidney function.\(^{(13, 43-45)}\) Aldosterone breakthrough during blockade of the RAS in DN is associated with enhanced decline in GFR
due to the unsuppressed actions of aldosterone leading to fibrotic and pro-inflammatory effects at a number of target organs, including the kidneys. Increased aldosterone levels are associated with enhanced albuminuria and a faster rate of decline in renal function.

In this study (Study 16243), subjects with type 2 diabetes mellitus and the clinical diagnosis of DN will be treated with different oral doses of BAY 94-8862 or placebo given once daily for 90 days. At least minimal recommended doses of either an ACEI or ARB, but not both, will continue concomitantly. Given the aforementioned aldosterone breakthrough under treatment with ACEIs and ARBs as well as the observed benefits of MRAs in ameliorating albuminuria and glomerular podocyte damage, subjects participating in this study may already benefit from short-term treatment with different oral doses of BAY 94-8862. In Study 14563 (ARTS), all doses planned to be initially evaluated in this study were proven to be safe and well tolerated and demonstrated after 28 days of treatment beneficial effects on NT-proBNP, BNP, and albuminuria in subjects with HFrEF and moderate CKD.

The 1.25 mg BAY 94-8862 dose was not investigated in Study 14563 (ARTS). However, based on the effects on UACR seen with the lowest dose investigated in Study 14563 (ARTS), i.e. 2.5 mg (15% or 68.8% reduction in UACR from baseline to Visit 7 in subjects with high or very high albuminuria at baseline, respectively), the 1.25 mg dose was chosen as additional dose for this Phase IIb study in order to find out if this dose is effective. Once the safety and tolerability of doses up to 10 mg BAY 94-8862 once daily have been confirmed by an independent data monitoring committee (DMC), higher doses will also be tested. Higher doses will provide a higher level of MR blockade and therefore, subjects might also benefit from this treatment.

Because of its potential favorable balance of cardiac anti-remodeling effects vs. renal (electrolyte) effects, it is anticipated that BAY 94-8862 may provide a high level of MR antagonism accompanied by an acceptable safety profile at all investigated doses. Considering the detrimental effects of albuminuria on renal function as well as the increased CV risk in patients with type 2 diabetes mellitus, subjects participating in this study should allow full breadth of beneficial effects of MR antagonism with BAY 94-8862 to be investigated.

Given the increased risk of CV events in patients with type 2 diabetes mellitus and the clinical diagnosis of DN with the substantial risk of progression to ESRD, a next-generation MRA with an improved efficacy and safety profile could help to prevent progression of kidney disease, CV mortality and non-fatal CV events as well as save healthcare resources utilized in this population.

The main risks identified from previous studies with MRAs are the development of hyperkalemia and worsening of renal function. In this study, serum potassium levels and renal function will be closely monitored, in particular after changes in the subject’s clinical status that influences serum electrolyte levels or fluid balance. Precise and well-defined stopping rules for permanent discontinuation of study drug have been included into this
protocol. In addition, before higher doses of BAY 94-8862 will be introduced into the study, safety and tolerability of lower doses have been reviewed and confirmed by an independent DMC.

All procedures in the study [e.g. recording of electrocardiogram (ECG), measurement of blood pressure (BP), drawing of blood and urine samples] are established and routine procedures in the management of patients with DN. As no specific invasive procedures are included in the study protocol, no specific risk linked to the study has been identified.

Considering this clinical setting, the risk-benefit assessment is in favor of the participation of subjects in this study.

2. **Study objectives**

Primary objective of the study is

- To investigate the change of UACR after treatment with different oral doses of BAY 94-8862 given once daily from baseline to Visit 5 (Day 90±2)

Further exploratory objectives of the study are

- To assess safety and tolerability of these doses by assessing the effects on serum potassium and renal function

- To assess change in health-related quality of life (HRQoL) from baseline to 90 days of treatment assessed by the Kidney Disease Quality of Life (KDQOL-36) and EuroQol Group 5-dimension, 3-level (EQ-5D-3L) questionnaires

3. **Investigators and other study personnel**

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center’s investigator site file.

The principal investigator of each center must sign the protocol signature sheet before subject recruitment may start at the respective center. Likewise, all protocol amendments / integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor study file.

The global sponsor of this study is identified on the title page of this protocol.
If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

The coordinating investigator for this study is:

Prof. Luis Miguel Ruilope
Complutense University
12 de Octubre Hospital, 28041 Madrid, Spain

4. Study design

Design overview

This study will be conducted in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN using a multi-center, randomized, adaptive, double-blind, placebo-controlled, parallel-group design.

Planned number of subjects valid for the full analysis set: approximately 90 subjects in each treatment group. Approximately 75 subjects in each of the BAY 94-8862 treatment groups and the placebo group if at least 1 of the additional treatment groups will be added and not closed due to safety reasons during the further course of the study.

Following an open-label run-in and screening period of up to 12 weeks in total, eligible subjects will be randomized to 1 of up to 7 doses of BAY 94-8862 or placebo on top of SOC to receive a 90-day study drug treatment. Initially, the following 5 doses of BAY 94-8862 will be compared to placebo in a double-blind manner: 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg once daily. After safety and tolerability of these doses have been assessed by an independent DMC, none or up to 2 further doses of BAY 94-8862 may be introduced: 15 mg and 20 mg once daily.
Open-label run-in period (up to 12 weeks)

*The whole paragraph was modified in AMD 1, see Section 13.1.2.2.*

Following a run-in visit, subjects meeting all of the inclusion and none of the exclusion criteria will be enrolled in the open-label run-in period. Only subjects already treated with an ACEI and/or ARB for at least two weeks before enrolment can be considered for the study. During this period, subjects’ eligibility for randomization into this study will be evaluated. At the end of this run-in period, each subject should receive at least the minimal recommended dose of conventional therapy according to local guidelines which consists either of an ACEI or ARB, but not both.

Table 4-1 shows the minimal recommended dose of the ACEIs and ARBs that were used in the major controlled studies. Variation of minimal recommended doses may exist in local clinical guidelines.
Table 4-1: Minimal recommended dose of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (adapted from Kidney Disease Outcomes Quality Initiative clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease; Table 127)

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Minimal recommended dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td></td>
</tr>
<tr>
<td>Benazepril</td>
<td>20</td>
</tr>
<tr>
<td>Captopril</td>
<td>25</td>
</tr>
<tr>
<td>Enalapril</td>
<td>10</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>20</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>20</td>
</tr>
<tr>
<td>Moexipril</td>
<td>5</td>
</tr>
<tr>
<td>Perindopril</td>
<td>4</td>
</tr>
<tr>
<td>Quinapril</td>
<td>20</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>2</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>16</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>400</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>150</td>
</tr>
<tr>
<td>Losartan</td>
<td>50</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>20</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>40</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80</td>
</tr>
</tbody>
</table>

Subjects with an estimated glomerular filtration rate (eGFR) (CKD-EPI)\(^{50}\) of 30 - 45 mL/min/1.73 m\(^2\) at the run-in visit must also be treated with a non-potassium-sparing diuretic at screening. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. At the screening visit, subject’s treatment should be stable and without any adjustments for at least 4 weeks as documented in the subject’s medical records.

As part of the 12-week run-in period, a screening visit to confirm the subject’s eligibility will take place within ≤14 days prior to the planned randomization. At this visit, it will be assessed whether the subject still meets all the inclusion and none of the exclusion criteria while on at least the minimal recommended dose of an ACEI or ARB according to the local guidelines.

If the subject already receives an ACEI and/or ARB for at least 3 months and is on the minimal recommended dose of the ACEI or ARB at the run-in visit and this dose has not been adjusted for at least 4 weeks, the run-in visit may be considered as the screening visit and the subject can be randomized within the next 14 days. Before randomization, investigators should check if the subject is still eligible for the study.
Double-blind study period (90 days)

Subjects who meet all the inclusion and none of the exclusion criteria will be randomized to receive 1 of 5 fixed oral doses of BAY 94-8862 or placebo on top of their conventional treatment for 90 days. After safety and tolerability of these doses have been assessed by an independent DMC, none or up to 2 fixed oral doses of BAY 94-8862 may introduced into the study.

The goal of this study is to assess the relative effects of BAY 94-8862 on UACR as well as safety and tolerability in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN.

Blood pressure control

According to international guidelines, target blood pressure for subjects with type 2 DN is <140/80 mmHg.(51, 52) However, the individual target blood pressure for each subject may vary dependent on concomitant diseases and individual well-being. If blood pressure is considered uncontrolled by the investigator during the double-blind study period, non-potassium-sparing diuretics should be added as first choice to the treatment regimen if not already included. Thereafter, antihypertensive medications can be added according to local guideline recommendations. If the blood pressure is still not considered sufficient by the investigator although these medications were added, the subject has to be withdrawn from the study.

Monitoring of blood potassium during the treatment period

Subjects will maintain their normal diet throughout the study and will not be given any specific advice on dietary sodium or potassium restrictions. If there is a change in the subject’s clinical status of which the investigator is aware of that influences serum electrolyte levels or fluid balance (e.g. vomiting or / and diarrhea >1 day), it is recommended to reassess potassium levels as soon as possible after the acute event.

If any re-assessment of potassium is required, always locally and centrally analyzed blood samples must be taken.

Upon receipt of the laboratory results at each of the regular visits under study drug treatment (considered as first potassium measurement), different scenarios are possible:

- If potassium is ≥5.6 and ≤6.0 mmol/L measured in the central or local laboratory, a second blood sample has to be taken as soon as possible but at the latest within 48 hours. If potassium is again ≥5.6 mmol/L in the locally or centrally analyzed blood sample (considered as second potassium measurement), study drug has to be discontinued permanently.
- If potassium is >6.0 mmol/L in the centrally analyzed blood sample but <5.6 mmol/L in the locally analyzed sample, treatment with study drug can be continued. If potassium is >6.0 mmol/L in the centrally analyzed blood sample and ≥5.6 mmol/L in the locally analyzed sample, study drug has to be discontinued permanently.

- If potassium is >6.0 mmol/L in the locally analyzed blood sample, study drug has to be discontinued permanently.

Inappropriate transport conditions or lengthy transport time to the central laboratory may result in falsely elevated serum potassium values in the centrally analyzed blood sample. Therefore, the results of the locally analyzed blood sample will also be taken into account. If the locally analyzed blood sample is missing or the result is inconclusive and the central laboratory result is not available, another blood sample must be taken as soon as possible but at the latest within 48 hours after becoming aware of the results.

### Table 4-2: Monitoring of potassium during the treatment period

<table>
<thead>
<tr>
<th>Result of first potassium measurement</th>
<th>&lt;5.6 mmol/L</th>
<th>5.6 - 6.0 mmol/L</th>
<th>&gt;6.0 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central lab</td>
<td>Continue study drug</td>
<td>Repeat potassium measurement within 48 hours(^a)</td>
<td>Check potassium in locally analyzed sample(^b)</td>
</tr>
<tr>
<td>Local lab</td>
<td>Continue study drug</td>
<td>Repeat potassium measurement within 48 hours(^a)</td>
<td>Discontinue study drug permanently</td>
</tr>
</tbody>
</table>

\(^a\) If potassium is again ≥5.6 mmol/L in the repeat blood sample, discontinue study drug permanently.

\(^b\) If potassium is ≥5.6 mmol/L in the (first) locally analyzed blood sample, discontinue study drug permanently.

If in the re-test potassium is ≥ 5.6 mmol/L in the locally or centrally analyzed blood sample, study drug has to be discontinued permanently.

Potassium values >6.0 mmol/L in the centrally analyzed blood sample which cannot be confirmed by the locally analyzed sample (potassium locally <5.6 mmol/L) will not be considered for analysis.

**Potassium supplementation**

*The whole paragraph including header was modified in AMD 1, see Section 13.1.2.2.*

Any potassium supplementation should be stopped prior to randomization if potassium levels are within the normal range. If potassium levels are low at randomization or at any of the following visits, potassium supplementation can be continued or re-started until potassium values are within the normal range again. In general, investigators should monitor potassium carefully at each visit and if potassium supplementation is prescribed, they should adapt the
dose of potassium supplementation in accordance with the potassium value measured at each visit or discontinue potassium supplementation once the potassium is within the normal range.

**Potassium lowering agents**

*This paragraph was added in AMD 1, see Section 13.1.2.2.*

With the exception of non-potassium sparing diuretics, potassium-lowering agents (e.g. sodium polystyrene sulfonate, calcium polystyrene sulfonate, insulin and glucose infusion) are not allowed to be started during treatment with study drug. In case of hyperkalemia occurring during study treatment, the study treatment should be discontinued prior to starting a potassium lowering agent.

**Medical management**

It is recommended that all subjects receive at least the minimal recommended dose of an ACEI or ARB and optimal antihypertensive therapy for renal and cardiovascular disease (CVD) protection, according to local guidelines. Statins, anti-platelets, and beta-blockers are also recommended according to the local guidelines. It is advised that other guideline recommendations for management of CVD and CKD are also followed. Glycemic control should be performed according to local guidelines.

**Note:** It is preferable that any medical therapy (e.g. antidiabetic, antihypertensive therapy as well as therapy with statins) will not be changed during study drug treatment, i.e. between the screening visit and the last dose of study drug. However, if this is necessary, the subject does not need to be withdrawn from study drug.

**Data Monitoring Committee**

Data will be reviewed for safety and tolerability by an independent DMC. One DMC has been established for the BAY 94-8862 Phase IIb studies, incorporating this study and Study 14564. The first DMC meeting will take place when a combined total number of 30 subjects has been randomized in both BAY 94-8862 Phase IIb studies. Thereafter, DMC meetings will take place approximately every other month. In addition, an overview regarding SAEs reported in the 2 studies will be sent to the DMC chair on a weekly basis. When a minimum of 150 subjects have been randomized in this study, a dose decision meeting will take place. During this meeting, the 5 initial treatment groups of BAY 94-8862 will be assessed for safety and tolerability (in particular changes in serum potassium, e.g. number of subjects with hyperkalemia, and changes in eGFR, e.g. number of subjects with an eGFR decrease ≥30%) by the DMC. Based on this assessment, none or up to 2 of the additional treatment groups will be introduced into the study. The detailed plan for these assessments will be covered in the DMC charter.
Primary efficacy variable

The primary variable will be the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline.

Justification of the design

For study objectives, please see Section 2.

A multi-center, randomized, adaptive, double-blind, placebo-controlled, parallel-group design is considered adequate to evaluate the safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and a clinical diagnosis of DN. As only doses up to 10 mg BAY 94-8862 once daily were tested in Study 14563 (ARTS), higher doses of up to 20 mg BAY 94-8862 once daily will only be introduced after an independent DMC has assessed the ongoing data from the study for safety and tolerability.

The 1.25 mg BAY 94-8862 dose was not investigated in Study 14563 (ARTS). However, based on the effects on UACR seen with the lowest dose investigated in Study 14563 (ARTS), i.e. 2.5 mg, the 1.25 mg dose was chosen as additional dose for this study in order to find out if the 1.25 mg dose is effective.

End of study

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject for the main study has occurred for all study sites in the respective country.

The end of the study as a whole will be reached as soon as the end of the study according to the above definition has been reached in all participating countries (EU and non-EU).

The primary completion date for this study according to the Food and Drug Administration (FDA) Amendment Act is specified in a separate document (not part of this clinical study protocol).

5. Study population

5.1 Eligibility

Subjects with type 2 diabetes mellitus and a clinical diagnosis of DN treated with at least the minimal recommended dose of an ACEI or ARB, but not both, who meet all the inclusion criteria and none of the exclusion criteria will be eligible for enrollment in this study.

5.1.1 Inclusion criteria

This section was modified in AMD 1, see Section 13.1.2.3.
• Written informed consent signed before any study-specific procedure

• Men and women aged 18 years and older. The lower age limit may be higher if legally required in the participating country

• Women of childbearing potential can only be included in the study if a pregnancy test is negative and if they agree to use adequate contraception when sexually active. Adequate contraception is defined as any combination of at least 2 effective methods of birth control, of which at least one is a physical barrier (e.g. condoms with hormonal contraception or implants or combined oral contraceptives, certain intrauterine devices)

• Subjects with **type 2 diabetes mellitus** fulfilling at least 1 of the following criteria
  a) are on oral antidiabetics and/or insulin,
  b) have a documented fasting glucose ≥7.0 mmol/L in the medical history,
  c) have a 2-hour plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test in the medical history, or
  d) have a glycated hemoglobin (HbA1c) ≥6.5% [National Glycohemoglobin Standardization Program (NGSP) / Diabetes Control and Complications Trial (DCCT)] in the medical history or at the run-in visit

• Subjects with a clinical diagnosis of DN based on at least 1 of the following criteria at the run-in and the screening visit:

  Persistent very high albuminuria defined as UACR of ≥300 mg/g (≥34 mg/mmol) in 2 out of 3 first morning void samples and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m² but < 90 mL/min/1.73 m² (CKD-EPI)

  or

  Persistent high albuminuria defined as UACR of ≥30 mg/g but < 300 mg/g (≥3.4 mg/mmol but < 34 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥30 mL/min/1.73 m² but < 90 mL/min/1.73 m² (CKD-EPI)

**Note:** 1 re-assessment of eGFR is allowed at the run-in visit and the screening visit. If 1 of the 3 UACR measurements is missing, but the other 2 are consistent, these values can be used to assess subject’s eligibility for this study.

• Subjects treated with at least the minimal recommended dose of an ACEI and/or ARB for at least 3 months without any adjustments to this therapy for at least 4 weeks prior to the screening visit; subjects with an eGFR of 30 - 45 mL/min/1.73 m² (CKD-EPI) must also be treated with a non-potassium sparing diuretic at the screening visit and without any adjustments to this therapy for at least 4 weeks prior to the screening visit
• Serum potassium ≤4.8 mmol/L at both the run-in visit and the screening visit

**Note:** 1 re-assessment of serum potassium is allowed at the run-in visit and the screening visit.

• Ability to understand and follow study-related instructions

### 5.1.2 Exclusion criteria

**Medical and surgical history**

• Non-diabetic renal disease (confirmed by biopsy)

• Known bilateral clinically relevant renal artery stenosis (>75%)

• HbA₁c >12% at the run-in visit or the screening visit

• UACR >3000 mg/g (339 mg/mmol) in any of the urinary first morning void samples at the run-in visit or screening visit

• Hypertension with mean sitting systolic blood pressure (SBP) ≥180 mmHg or mean sitting diastolic blood pressure (DBP) ≥110 mmHg at the **run-in visit** or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the **screening visit**

• Subjects with a clinical diagnosis of heart failure with reduced ejection fraction (HFrEF) and persistent symptoms (New York Heart Association class II - IV) at the run-in visit

• Stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening heart failure, in the last 30 days prior to the run-in visit

• Known hypersensitivity to the study drug (active substance or excipients)

• Addison’s disease

• Dialysis for acute renal failure within the previous 6 months prior to the run-in visit

• Renal allograft in place or a scheduled kidney transplant within the next 18 weeks (being on a waiting list does not exclude the subject)

• Congenital or acquired solitary kidney

• Hepatic insufficiency classified as Child-Pugh B or C^{[53]}
Medication, drug use, and special behavioral patterns

- Concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued for the run-in and the treatment period

- Concomitant therapy with high-dose acetylsalicylic acid (>500 mg/day) or continuous treatment with other non-steroidal anti-inflammatory agents

- Concomitant therapy with potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors or inducers (to be stopped at least 7 days before randomization) or strong CYP2C8 inhibitors (to be stopped at least 7 days before randomization) such as gemfibrozil
  Note: The investigators will be provided with a list of the most common concomitant medications considered as potent CYP3A4 inhibitors or inducers or strong CYP2C8 inhibitors

Other

- Participation in another clinical study or treatment with another investigational product 30 days prior to randomization (i.e. Phase I - III clinical studies)

- Any other condition or therapy, which would make the subject unsuitable for this study and will not allow participation for the full planned study period

- Previous enrolment in this study

5.1.3 Justification of selection criteria

The selection criteria were chosen to exclude subjects from the study who may potentially be exposed to specific risks after administering the study drug as well as subjects with conditions that may have an impact on the aims of the study.
5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

Subjects must be withdrawn from the study drug for the following reasons:

- At their own request or at the request of their legally acceptable representative at any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

- If, in the investigator’s opinion, continuation of the study would be harmful to the subject’s well-being, for example, uncontrolled blood pressure (see Section 4).

- If any AE occurred which is not acceptable in the opinion of the investigator and / or participating subject.

- If any investigational drug other than the study drug is used.

- Please refer to section 4 (chapter Monitoring of blood potassium) for discontinuation due to hyperkalemia.

- If the randomization code is broken.

Discontinuation of study drug due to an increase in potassium is considered an adverse event of special interest (see Section 7.5.1.6) and has to be reported to the sponsor as SAEs, i.e. within 24 hours of the investigator’s awareness as described in Section 7.5.1.4.

Subjects may be withdrawn from the study drug for the following reasons:

- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).

- If any exclusion criterion applies during treatment.

- If a significant violation of the protocol occurs, as defined by the sponsor and the coordinating investigator.

- Temporary withdrawal of study drug for at least 5 consecutive days of the treatment period or, starting from Visit 4 (Day 60±2) onwards, a total number of temporary withdrawal days ≥10% of the total duration of the treatment period completed at that time.
A subject who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before the time point used for the definition of “dropout” (see below) is regarded a “screening failure”.

A subject who discontinues study participation prematurely for any reason is defined as a “dropout” if the subject has been randomized (even if no study drug has been taken).

Any subject removed from the study will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be recorded in the electronic case report form (eCRF) and in the subject’s medical records.

If a subject prematurely withdraws from the study and if any study drug has been taken, the subject must be advised to return to the study center for the premature discontinuation visit as soon as possible and to the follow-up visit 30±5 days after the last intake of study drug.

A subject may withdraw from further participation in the study and still allow further release of information. In this situation, the subject’s consent to the collection of further data should be documented in the site’s source document.

Information regarding adverse events, or at a minimum information regarding potential adverse drug reaction, should be obtained and documented in the eCRF for subjects who withdraw consent to participate further in the study. The information should be collected in the eCRF until the follow-up visit 30±5 days after the last intake of study drug. Adverse events which occur within 30±5 days after the last dose of study drug will be followed up until resolution if possible.

At a minimum, the following information should be obtained and documented in the eCRF for subjects who still allow further release of information but withdraw consent to participate further in the study:

- Vital status and any hospitalization
- Adverse events

For subjects who withdraw consent for release of information, no follow-up data can be obtained.

The measures taken for follow-up must be documented in the source data. Vital status should be obtained at the end of the follow-up period (i.e., 30±5 days after last intake of study drug).

Details for the premature termination of the study as a whole [or components thereof (e.g., centers, treatment groups, dose steps)] are provided in Section 10.
5.2.2 Replacement

Randomized subjects who withdraw prematurely will not be replaced.

5.3 Subject identification

Upon signing the informed consent form and registering the subject in IXRS, each subject will be assigned an unique 9-digit subject identification (SID) number for unambiguous identification throughout the study; it is constructed as follows:

- Digits 1 - 2: Unique country number
- Digits 3 - 5: Study center number, unique within any country
- Digits 6 - 9: Subject number, unique within any study center of a given country.
  Sequential number reflecting the order in which the subjects signed the informed consent form at the center

SID numbers must be used in sequence and no number should be skipped, substituted, or re-used.

6. Treatments

6.1 Treatments to be administered

BAY 94-8862 IR tablets are light orange film-coated tablets, oval (modified oblong), containing 1.25 mg, 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg BAY 94-8862 (Table 6-1). Placebo tablets (matching BAY 94-8862 tablets) will be supplied in this double-blind, placebo-controlled clinical study.

Following a screening visit, eligible subjects will be randomized 1:1:1:1:1:1 within ≤14 days after the screening to 1 of the following 6 treatment groups and will receive study drug dispensed per visit schedule (see Section 7.1) for a total of 90 days treatment with either

- 1.25 mg BAY 94-8862 tablet once daily in the morning or
- 2.5 mg BAY 94-8862 tablet once daily in the morning or
- 5 mg BAY 94-8862 tablet once daily in the morning or
- 7.5 mg BAY 94-8862 tablet once daily in the morning or
- 10 mg BAY 94-8862 tablet once daily in the morning or
- **Placebo** tablet once daily in the morning

After safety and tolerability of these doses have been assessed by an independent DMC, none or up to 2 fixed oral doses of BAY 94-8862 may be introduced into the study:

- 15 mg **BAY 94-8862** tablet once daily in the morning **or**
- 20 mg **BAY 94-8862** tablet once daily in the morning

If treatment groups will be added, the randomization will be adapted in order to obtain equally balanced sample sizes across all treatment groups at the end of the study.

Following screening and randomization of the subject, the IXRS will determine the bottle number for the study site investigator or designee to select for the subject. Subjects are to take 1 tablet once daily in the morning as directed by the study site investigator. The first dose of study drug must be taken on the same day as Visit 1 (Day 1) which must be in the morning.

At Visit 5 (Day 90±2), study drug will be administered at the study center by study personnel in the morning. On all other days during the 90-day study drug treatment, study drug will be taken in the morning by the subjects on an ambulatory basis.
6.2 Identity of study drug

Table 6-1: Identity of test drug / BAY 94-8862 and matching placebo

<table>
<thead>
<tr>
<th>Sponsor's substance code</th>
<th>BAY 94-8862</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name / brand name</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Sponsor's material name and number</td>
<td>BAY 94-8862 TABL 1.25 MG 150 COAT</td>
</tr>
<tr>
<td></td>
<td>Material no: 81128758</td>
</tr>
<tr>
<td></td>
<td>BAY 94-8862 TABL 2.5 MG 250 COAT</td>
</tr>
<tr>
<td></td>
<td>Material no: 81128766</td>
</tr>
<tr>
<td></td>
<td>BAY 94-8862 TABL 5 MG 350 COAT</td>
</tr>
<tr>
<td></td>
<td>Material no: 81128774</td>
</tr>
<tr>
<td></td>
<td>BAY 94-8862 TABL 7.5 MG 750 COAT</td>
</tr>
<tr>
<td></td>
<td>Material no: 81128782</td>
</tr>
<tr>
<td></td>
<td>BAY 94-8862 TABL 10 MG 450 COAT</td>
</tr>
<tr>
<td></td>
<td>Material no: 81128790</td>
</tr>
<tr>
<td></td>
<td>BAY 94-8862 TABL 15 MG 860 COAT</td>
</tr>
<tr>
<td></td>
<td>Material no: 81559635</td>
</tr>
<tr>
<td></td>
<td>BAY 94-8862 TABL 20 MG 850 COAT</td>
</tr>
<tr>
<td></td>
<td>Material no: 81559643</td>
</tr>
<tr>
<td></td>
<td>BAY 94-8862 PLAC TABL 002 COAT</td>
</tr>
<tr>
<td></td>
<td>Material no: 81128804</td>
</tr>
</tbody>
</table>

Formulation: Film-coated tablet

Tablet strength: 1.25 mg, 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg or placebo

Composition:
- **Active ingredient:** BAY 94-8862 micronized
- **Other ingredients:** Cellulose microcrystalline, croscarmellose sodium, hypromellose 5 cP, lactose monohydrate, magnesium stearate, sodium laurilsulfate, talc, titanium dioxide, ferric oxide
- **Placebo:** Cellulose microcrystalline, hypromellose 5 cP, lactose monohydrate, magnesium stearate, talc, titanium dioxide, ferric oxide

Type of primary packaging: Plastic bottle high-density polyethylene white opaque closed with screw cap polypropylene (PP) / PP white with sealing insert

Marketing Authorization Holder if applicable: Not applicable

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance (QA) group.

A complete record of batch numbers and expiry dates of all study drug as well as the labels will be maintained in the sponsor study file.
Study drugs need to be stored according to the label text.

### 6.3 Treatment assignment

*This section was modified in AMD 1, see Section 13.1.2.5.*

Following a screening visit, eligible subjects will be randomized within ≤14 days after the screening visit and receive a 90-day study drug treatment.

The randomization will be stratified by region (Europe, North America, Asia, others [Australia, Israel and South Africa]), and type of albuminuria (very high albuminuria or high albuminuria at screening). No formal caps will be applied within the stratification levels. However, a ratio of approximately 50:50 for high and very high albuminuria is planned to be reached with an imbalance of up to 65:35 being considered as acceptable. In order to achieve a proportion of at least 35% of subjects with very high albuminuria, single centers or countries predominantly recruiting subjects with high albuminuria may be closed during the course of the study. In case that less than 35% of subjects randomized were diagnosed with very high albuminuria, the sample size may be increased to approximately 90 subjects in each treatment group (in case it can be reduced to 75 subjects per treatment arm after the dose decision meeting) in order to increase the amount of available safety data per treatment arm for the subjects with very high albuminuria. An initial randomization list including the initial treatment groups will be generated before study start. Additional possible randomization lists will be generated before the DMC decision. The computer-generated randomization lists will be provided to the IXRS supplier by Bayer Global Biostatistics. The name and address for the IXRS service provider can be found in the documentation supplied by the vendor.

For further details, please refer to Section 6.1.

### 6.4 Dosage and administration

Please refer to Section 6.1.

### 6.5 Blinding

#### 6.5.1 Blinding measures

BAY 94-8862 IR tablets containing 1.25 mg, 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg BAY 94-8862 and placebo tablets will be identical in appearance (size, shape, color). The packaging and labeling will be designed to maintain the blinding of the investigator’s team and to the subjects. The study data will remain blinded for each treatment group, until database lock and authorization of data release according to standard operating procedures.

Appropriate measures will be taken to maintain blinding while bioanalysis is ongoing.
6.5.2 Unblinding

In compliance with applicable regulations, in the event of a suspected, unexpected serious adverse reaction (SUSAR, see Section 7.5.1.5), the subject’s treatment code will usually be unblinded before reporting to the health authorities, Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), and investigators (see Section 7.5.1.4).

6.5.3 Emergency unblinding by the investigator

In case of emergency or any finding that requires unblinding, the investigator will be able to break the blind for an individual subject via IXRS according to the unblinding procedure outlined in the manual. This will allow breaking the blind for an individual subject without impairing the study as a whole unless safety findings required unblinding.

This system allows the investigator, or other responsible person, to identify the study drug in case of an emergency, without jeopardizing the double-blind integrity of the remainder of the study.

The code can be broken by the investigator, or other responsible person, when knowledge of the subject's treatment is required for the clinical management of the subject. Whenever possible, the sponsor is to be contacted to discuss the case before the code is broken. If it becomes necessary to know the individual treatment during the study and thus to break the code for that subject, the date, and reason are to be recorded in the relevant eCRF page. The investigator is required to promptly document and explain to the sponsor any premature unblinding (e.g. unblinding due to a serious adverse event) of the study drug.

6.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate / contract research organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor’s study file. The site-specific elements of this information will be available in the investigator's site file. The responsible site personnel will confirm receipt of the study drug via IXRS and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of the study drug must be properly documented according to the sponsor’s agreed and specified procedures.

Written instructions on study drug destruction will be made available to affected parties as applicable.
6.7 Treatment compliance

To monitor compliance, the investigator will be required to complete a drug dispensing log for each subject. Overall compliance with study drug intake should be between 80% and 120% of the scheduled dose at the end of study drug treatment. The date of dispensing the study drug to the subject will be documented.

Study drug will be dispensed at Visit 1 (Day 1), Visit 3 (Day 30±2), and Visit 4 (Day 60±2). Subjects will return at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) or at the premature discontinuation visit, if applicable, with all remaining unused study drug.

Accountability has to be determined for all tablets of study drug at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) or at the premature discontinuation visit, if applicable. To facilitate this, subjects must be instructed to return all of the study drug packaging including unused study drug and empty packaging.

6.8 Post-study therapy

Subjects completing the 90-day treatment period will not be given further free access to study drug. The investigator will decide in consultation with the individual subject if additional treatment is required and choose from existing treatment options.

The investigator must provide follow-up medical care for all subjects who complete the study or who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care as required.

6.9 Prior and concomitant therapy

This section was modified in AMD 1, see Section 13.1.2.6.

Subjects must be on an ACEI and/or ARB for at least 3 months and treated with at least the minimal recommended dose of that ACEI or ARB but not both, for at least 4 weeks prior to the screening visit. Subjects with an eGFR of 30 - 45 mL/min/1.73 m² (CKD-EPI)(50) must also be treated with a non-potassium sparing diuretic at screening. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. At the screening visit, subject’s treatment should be stable and without any adjustments for at least 4 weeks as documented in the subject’s medical records.

Prior medication that was discontinued to comply with the eligibility criteria of the study should also be recorded in the eCRF.

All concomitant medications including therapy for type 2 diabetes mellitus and DN administered after signing of informed consent until the follow-up visit will be recorded in the eCRF.
It is preferable that any medical therapy (e.g. antidiabetic, antihypertensive therapy as well as therapy with statins) will not be changed during study drug treatment, i.e. between the screening visit and the last dose of study drug. However, if this is necessary, the subject does not need to be withdrawn from study drug.

Prior and concomitant medications not allowed during the study include:

- Concomitant treatment with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued for the run-in and the treatment periods

**Note:** Any potassium supplementation should be stopped at randomization if potassium levels are within the normal range. If potassium levels are low at randomization or at any of the following visits, potassium supplementation can be continued or re-started until potassium values are within the normal range again.

- Concomitant treatment with an ACEI and an ARB

- Concomitant therapy with high-dose acetylsalicylic acid (>500 mg/d) or daily treatment with other non-steroidal anti-inflammatory agents for more than 5 consecutive days

- Potent CYP3A4 inhibitors or inducers (to be stopped at least 7 days prior to randomization)

- Strong CYP2C8 inhibitors such as gemfibrozil (to be stopped at least 7 days prior to randomization)

The investigators will be provided with a list of the most common concomitant medications considered as potent CYP3A4 inhibitors or inducers or strong CYP2C8 inhibitors.

**Caution:** Increases in BAY 94-8862 exposure in combination with the following moderate CYP3A4 inhibitors cannot be excluded: amiodarone, apreptant, bicalutamide, chloramphenicol, imatinib, mifepristone, norfloxacine, tacrolimus, verapamil, lapatinib, dasatinib, and nilotinib.

It cannot be ruled out that higher plasma concentrations of BAY 94-8862 are associated with an increase in frequency or severity of AEs.

See also Section 5.1.2.
7. Procedures and variables

7.1 Schedule of procedures

Time deviations from the given visit schedule will be documented as protocol deviations, if applicable. Respective time windows are specified in the sections below.

7.1.1 Tabulated overview

The table was modified in AMD 1, see Section 13.1.2.7.

Table 7-1 summarizes the schedule of procedures.


<table>
<thead>
<tr>
<th>Table 7-1: Schedule of procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Run-in visit ≤ -12 weeks</strong></td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Signed written informed consent available</td>
</tr>
<tr>
<td>Check of in- and exclusion criteria</td>
</tr>
<tr>
<td>Demographic data</td>
</tr>
<tr>
<td>Randomization (IXRS)</td>
</tr>
<tr>
<td>Dispense study drug</td>
</tr>
<tr>
<td>Drug accountability, collect unused study drug</td>
</tr>
<tr>
<td>Smoking status, a and alcohol consumption</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Previous medications</td>
</tr>
<tr>
<td>Physical examination, including height, waist &amp; hip circumference measurements, and weight</td>
</tr>
<tr>
<td>Vital signs (blood pressure and heart rate)</td>
</tr>
<tr>
<td>12-lead ECG b</td>
</tr>
<tr>
<td>Blood sample (full central lab)</td>
</tr>
<tr>
<td>Blood sample (clinical chemistry, central lab)</td>
</tr>
<tr>
<td>Blood sample (local lab)</td>
</tr>
<tr>
<td>Blood sample (HbA1c, central lab)</td>
</tr>
<tr>
<td>Blood sample (biomarkers, central lab)</td>
</tr>
<tr>
<td>PK blood sample (single)</td>
</tr>
<tr>
<td>PK blood sample (study drug intake at home)</td>
</tr>
<tr>
<td>PK blood sample (study drug intake at study center)</td>
</tr>
<tr>
<td>Urine sample (central lab)</td>
</tr>
<tr>
<td>Urinalysis (local lab) c</td>
</tr>
<tr>
<td>KDQOL-36 and EQ-5D-3L (HRQoL)</td>
</tr>
<tr>
<td>Recording of AEs and concomitant medications</td>
</tr>
<tr>
<td>Ambulatory blood pressure monitoring</td>
</tr>
<tr>
<td>Blood samples for iohexol plasma clearance</td>
</tr>
<tr>
<td>Pregnancy test</td>
</tr>
</tbody>
</table>

Table continued
Table 7-1: Schedule of procedures (continued)

<table>
<thead>
<tr>
<th>FU = follow-up; PD = premature discontinuation; PK = pharmacokinetic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a Randomization has to occur within ≤14 days after the screening visit.</td>
<td></td>
</tr>
<tr>
<td>b Only for subjects who have discontinued the study prematurely: to be performed as soon as possible after withdrawal of study drug.</td>
<td></td>
</tr>
<tr>
<td>c For all subjects who have taken any study drug: to be performed 30±5 days after last intake of study drug.</td>
<td></td>
</tr>
<tr>
<td>d The signed written informed consent must be available before any study procedures are conducted.</td>
<td></td>
</tr>
<tr>
<td>e Smoking status and alcohol consumption to be recorded at run in visit. Smoking status to be checked at all visits, except at Follow up visit.</td>
<td></td>
</tr>
<tr>
<td>f Height as well as waist and hip circumference will only be measured once at the run-in visit.</td>
<td></td>
</tr>
<tr>
<td>g Resting for at least 10 min, 3 measurements at 2-min intervals in sitting position. At Visit 5 (Day 90±2), blood pressure must be measured before study drug intake.</td>
<td></td>
</tr>
<tr>
<td>h Resting for at least 10 min; ECG to be recorded in supine position.</td>
<td></td>
</tr>
<tr>
<td>i Single post-dose (towards the end of the visit) blood sample.</td>
<td></td>
</tr>
<tr>
<td>j Study drug intake at home followed by 2 samples collected in the interval approximately 60 to 120 min and 240 to 300 min post administration, respectively.</td>
<td></td>
</tr>
<tr>
<td>k Pre-dose PK sample before study drug administration at study center followed by 2 samples collected in the interval approximately 30 to 90 min and 180 to 240 min post administration, respectively.</td>
<td></td>
</tr>
<tr>
<td>l On 3 consecutive days, first morning void urine samples will be collected at the subject’s home.</td>
<td></td>
</tr>
<tr>
<td>m Local dipstick test of central lab samples to confirm sample validity for analysis.</td>
<td></td>
</tr>
<tr>
<td>n At selected sites only (see Section 7.6.5).</td>
<td></td>
</tr>
<tr>
<td>o In all Italian centers, subjects who are not sensitive to iodine or other iodinated contrast agents can be included in this sub-study, if they consent.</td>
<td></td>
</tr>
<tr>
<td>p All 3 urine samples should be taken before first intake of study drug.</td>
<td></td>
</tr>
<tr>
<td>q All 3 urine samples should be taken before last intake of study drug.</td>
<td></td>
</tr>
</tbody>
</table>
7.1.2 Timing of assessments

All visits from Visit 1 (Day 1, Baseline) to the last visit under treatment, i.e., Visit 5 (Day 90±2) for subjects who will complete the study, must be performed in the morning.

If not stated otherwise, the measures listed in the following sections will be performed by or under the supervision of a study site investigator.

7.1.3 Informed consent

Before any study-specific examination takes place, potentially eligible subjects will be given a full explanation as to what the study would involve. This will be done both verbally and in writing in the form of a written subject information leaflet. Subjects will be given sufficient time to consider their participation in the study and to ask any questions concerning the study. Subjects who are willing to take part in the study will then be asked to sign an informed consent form prior to the run-in visit. The signed informed consent form must be available before any study-specific procedure will be performed at the run-in visit.

Run-in examinations will only be performed after having received the subject’s written informed consent.

Due to the fact that not all subjects may fulfill the inclusion criteria and not meet any of the exclusion criteria, a higher number of subjects than needed for the evaluation of the study will be asked to participate in the run-in examination.

7.1.4 Run-in visit

This section was modified in AMD 1, see Section 13.1.2.8.

The following procedures and assessments will be performed at this visit:

- Confirm signed informed consent is available
- Allocation of a unique SID number (see Section 5.3)
- Demographic data and other population characteristics including sex, race, ethnic group, year of birth, age, smoking history, and alcohol consumption at the run-in visit (see Section 7.2.1)
- Medical history (see Section 7.2.2)
- Prior and concomitant medications (see Section 6.9)
- Physical examination including height, waist and hip circumference measurements, and weight [Note: body mass index (BMI) will be calculated automatically in the eCRF]
12-lead ECG in supine position after resting for at least 10 min

Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart

Continuous assessment of AEs will start immediately after signing the informed consent until the follow-up visit (if applicable) (see Section 7.5)

Laboratory examinations in blood including hematology, clinical chemistry (full central lab), and HbA1c (to be analyzed at central laboratory, see Section 7.6.1)

Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)

Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

Pregnancy test (to be performed at local laboratory, see Section 7.6.1.2)

Assess inclusion and exclusion criteria (see Section 5.1)

In all subjects, 1 re-assessment of eGFR and serum potassium is allowed at the run-in visit. If 1 of the 3 UACR measurements is missing, but the other 2 are consistent, these values can be used to assess subject’s eligibility for this study.

Schedule the screening visit if applicable

Note: At the end of this run-in period, each subject should receive at least the minimal recommended dose of conventional therapy according to local guidelines which consists either of an ACEI or ARB, but not both. Subjects with an eGFR of 30 - 45 mL/min/1.73 m² (CKD-EPI)(50) must also be treated with a non-potassium-sparing diuretic at screening. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. The treatment should be stable and without any adjustments for at least 4 weeks before the screening visit.

7.1.5 Screening visit

This section was modified in AMD 1, see Section 13.1.2.9.

The following procedures and assessments will be performed within ≤14 days prior to randomization but after the run-in visit (for a subject who is already treated with an ACEI and/or ARB for at least 3 months and on at least the minimal recommended dose of that ACEI or ARB and without any adjustments for at least 4 weeks, the run-in visit may be considered
as screening visit and the subject can be randomized within the next 14 days if she / he meets all the inclusion and none of the exclusion criteria):

- Assess inclusion and exclusion criteria (see Section 5.1)
- Smoking status
- Concomitant medications planned to be continued during the study and previous medications that were stopped in order to comply with the inclusion and exclusion criteria, if applicable (see Section 6.9)
- Physical examination including weight (Note: BMI will be calculated automatically in the eCRF)
- 12-lead ECG in supine position after resting for at least 10 min
- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Laboratory examinations in blood including hematology, clinical chemistry (full central lab), and HbA1c (to be analyzed at central laboratory, see Section 7.6.1)
- Iohexol plasma clearance (at selected sites only, see Section 7.6.5) [If the run-in visit is considered as screening visit, iohexol plasma clearance can be performed at any time before Visit 1 (Day 1).]
- Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)
- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)
- Pregnancy test (to be analyzed at the local laboratory, see Section 7.6.1.2)
- Adverse events (see Section 7.5)
- In all subjects, 1 re-assessment of eGFR and serum potassium is allowed at the screening visit. If 1 of the 3 UACR measurements is missing, but the other 2 are consistent, these values can be used to assess subject’s eligibility for this study.
- At selected sites only: ambulatory blood pressure monitoring (ABPM) (see Section 7.6.4)
  **Note:** The ABPM does not necessarily need to be started at the screening visit if this is not convenient. However, the screening ABPM must be completed prior to randomization at Visit 1 (Day 1)
Schedule Visit 1 (Baseline) for ≤14 days after the screening visit

7.1.6 Visit 1 (Baseline and randomization) - Day 1

This section was modified in AMD 1, see Section 13.1.2.10.

The following procedures and assessments will be performed during this visit:

- KDQOL-36 and EQ-5D-3L (see Section 7.3.3)
- Assess inclusion and exclusion criteria (see Section 5.1)
- Concomitant medications (see Section 6.9)
- Smoking status
- Adverse events (see Section 7.5)
- Physical examination including weight (Note: BMI will be calculated automatically in the eCRF)
- 12-lead ECG in supine position after resting for at least 10 min
- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Laboratory examinations in blood including hematology and clinical chemistry (full central lab) (to be analyzed at central laboratory, see Section 7.6.1)
- Urinalysis (to be analyzed at central laboratory, see Section 7.6.1). All 3 urine samples for this visit should be collected before first study drug intake.
- Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)
- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)
- Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at local laboratory, see Section 7.6.1)
- Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)
- Randomization to BAY 94-8862 or placebo once daily (see Section 6.1)
- Dispense study drug for 36 days and instruct the subject on how to take the study drug
Subject to take first dose of study drug

Schedule Visit 2 for Day 7±2

7.1.7 Visit 2 - Day 7±2

This section was modified in AMD 1, see Section 13.1.2.11.

The following procedures and assessments will be performed during this visit:

- Smoking status
- Concomitant medications (see Section 6.9)
- Adverse events (see Section 7.5)
- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at central laboratory, see Section 7.6.1)
- Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at local laboratory, see Section 7.6.1)
- Single post-dose (towards the end of the visit) blood sample for BAY 94-8862 pharmacokinetics (see Section 7.4)

Schedule Visit 3 for Day 30±2

7.1.8 Visit 3 - Day 30±2

The following procedures and assessments will be performed during this visit:

- KDQOL-36 and EQ-5D-3L (see Section 7.3.3)
- Concomitant medications (see Section 6.9)
- Smoking status
- Adverse events (see Section 7.5)
- 12-lead ECG in supine position after resting for at least 10 min
• Vital signs in sitting position (BP and HR after resting for at least 10 min),
  3 measurements, 2 min apart

• Laboratory examinations in blood including hematology and clinical chemistry (full
  central lab) (to be analyzed at central laboratory, see Section 7.6.1)

• Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)

• Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

• Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at
  local laboratory, see Section 7.6.1)

• Post-dose blood samples (approximately 60 to 120 minutes and 240 to 300 min after
  study drug intake at home) for BAY 94-8862 pharmacokinetics (see Section 7.4)

• Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)

• Collect unused study drug and perform accountability to assess compliance

• Dispense study drug for 36 days and instruct the subject on how to take the study drug

• Schedule Visit 4 for Day 60±2

7.1.9 Visit 4 - Day 60±2

The following procedures and assessments will be performed during this visit:

• Concomitant medications (see Section 6.9)

• Smoking status

• Adverse events (see Section 7.5)

• 12-lead ECG in supine position after resting for at least 10 min

• Vital signs in sitting position (BP and HR after resting for at least 10 min),
  3 measurements, 2 min apart

• Laboratory examinations in blood including hematology and clinical chemistry (full
  central lab) (to be analyzed at central laboratory, see Section 7.6.1)

• Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)
• Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

• Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at local laboratory, see Section 7.6.1)

• Single post-dose (towards the end of the visit) blood sample for BAY 94-8862 pharmacokinetics (see Section 7.4)

• Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)

• Collect unused study drug and perform accountability to assess compliance

• Dispense study drug for 36 days and instruct the subject on how to take the study drug

• At selected sites only: start ABPM (see Section 7.6.4)

• Schedule Visit 5 for Day 90±2

7.1.10 Visit 5 - Day 90±2

This section was modified in AMD 1, see Section 13.1.2.12.

The following procedures and assessments will be performed during this visit:

• KDQOL-36 and EQ-5D-3L (see Section 7.3.3)

• Concomitant medications (see Section 6.9)

• Smoking status

• Adverse events (see Section 7.5)

• Physical examination including weight (Note: BMI will be calculated automatically in the eCRF)

• 12-lead ECG in supine position after resting for at least 10 min

• Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart; these must be performed before study drug intake

• Pre-dose blood sample for BAY 94-8862 pharmacokinetics (see Section 7.4)

• Laboratory examinations in blood including hematology, clinical chemistry (full central lab), and HbA1c (to be analyzed at central laboratory, see Section 7.6.1)
• Iohexol plasma clearance (at selected sites only, see Section 7.6.5)

• Urinalysis (to be analyzed at central laboratory, see Section 7.6.1). All 3 urine samples for this visit should be collected before last study drug intake.

• Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

• Laboratory examinations in blood (limited range of clinical chemistry to be analyzed at local laboratory, see Section 7.6.1)

• Intake of study drug

• Post-dose blood samples (approximately 30 to 90 minutes and 180 to 240 min after study drug administration at the study center) for BAY 94-8862 pharmacokinetics (see Section 7.4)

• Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)

• Collect unused study drug and perform accountability to assess compliance

• At selected sites only: start ABPM (see Section 7.6.4)

• Schedule follow-up visit for 30±5 days after last intake of study drug

7.1.11 Premature discontinuation visit

This visit will take place as soon as possible after premature discontinuation of study drug due to any reason except death or lost to follow-up. The investigator should make every possible effort to ensure that the visit takes place and the following procedures and assessments are performed during this visit:

• KDQOL-36 and EQ-5D-3L (see Section 7.3.3)

• Concomitant medications (see Section 6.9)

• Smoking status

• Adverse events (see Section 7.5) [In case a (serious) adverse event has occurred, the event must be adequately followed-up. If an SAE has occurred, this should be followed up until the subject’s condition has resolved or stabilized. Additional local legal requirements for follow-up procedures of AEs and SAEs have to be fulfilled if applicable.]
- Physical examination including weight (Note: BMI will be calculated automatically in the eCRF)

- 12-lead ECG in supine position after resting for at least 10 min

- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart

- Laboratory examinations in blood including hematology, clinical chemistry (full central lab), and HbA1c (to be analyzed at central laboratory, see Section 7.6.1)

- Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)

- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

- Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)

- Collect unused study drug and perform accountability to assess compliance

- Schedule follow-up visit 30±5 days after last intake of study drug

### 7.1.12 Follow-up visit (30±5 days after last intake of study drug)

The following procedures and assessments will be performed during this visit:

- KDQOL-36 and EQ-5D-3L (see Section 7.3.3)

- Concomitant medications (see Section 6.9)

- Adverse events (see Section 7.5) [In case a (serious) adverse event has occurred, the event must be adequately followed-up. If an SAE has occurred, this should be followed up until the subject’s condition has resolved or stabilized. Additional local legal requirements for follow-up procedures of AEs and SAEs have to be fulfilled if applicable.]

- Physical examination including weight (Note: BMI will be calculated automatically in the eCRF)

- 12-lead ECG in supine position after resting for at least 10 min

- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
• Laboratory examinations in blood including hematology and clinical chemistry (full central lab) (to be analyzed at central laboratory, see Section 7.6.1)

• Iohexol plasma clearance [at selected sites only, if Visit 5 (Day 90±2) was performed; see Section 7.6.5]

• Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)

• Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

• Blood sample for biomarkers (to be analyzed at central laboratory, see Section 7.6.1)

7.2 Population characteristics

7.2.1 Demographic

The following demographic data will be collected in the eCRF:

• Year of birth and age at the run-in visit

• Ethnic group

• Race

• Sex

• Smoking habits and alcohol consumption

7.2.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases, or surgeries) meeting all criteria listed below will be collected:

• Started prior to signing the informed consent

• Pertaining to the study indication (e.g. teething problems or orthopedic surgery which are not related to the development of diabetic nephropathy do not need to be entered)

• Considered relevant to the study (e.g. cardiovascular and metabolic diseases)

• Medical history related to concomitant medication

Detailed instructions on the differentiation between medical history and AEs can be found in Section 7.5.1.1.
7.2.3 Physical examination

All diagnoses, symptoms, signs, or findings during physical examination at the run-in visit that have a start date before signing the informed consent will be recorded in the medical history, all others (with a start date after signing informed consent) will be recorded as AEs (see Section 7.5.1.1).

7.3 Efficacy

The following parameters will be used to assess the efficacy of the study drug treatments.

7.3.1 Primary efficacy variable

The primary efficacy variable will be the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline.

7.3.2 Further exploratory efficacy variables

In addition, the following parameters will be used to assess the efficacy of the study drug treatments:

- Ratio of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline
- Decrease in eGFR (CKD-EPI)(50) of ≥30%, ≥40%, and ≥57%
- Regression of albuminuria, defined as change of very high albuminuria to high albuminuria or albuminuria [UACR ≤30 mg/g (3.4 mg/mmol)] or high albuminuria to albuminuria, in all cases accompanied by a change of more than 30% from baseline to Visit 5 (Day 90±2)
- Efficacy biomarkers (NT-proBNP, BNP, aldosterone, and galectin-3)
- HRQoL: KDQOL-36 and EQ-5D-3L

7.3.3 Health-related quality of life

This section was modified in AMD 1, see Section 13.1.2.13.

The following HRQoL questionnaires will be used: Kidney Disease Quality of Life (KDQOL-36) and the EuroQol Group 5-dimension, 3-level questionnaire (EQ-5D-3L). The subject will be instructed to fill in the questionnaires himself / herself before any other procedure of each visit. Subsequently, a member of the site investigator’s team will enter the responses into the eCRF.

KDQOL-36 is a specific measure of health-related quality of life for CKD that includes effects and burden of kidney disease as well as physical and mental health scores. 2 forms of
the KDQOL exist, the KDQOL-SF and the KDQOL-36. Both were developed in 1994 and later by the Kidney Disease Quality of Life Working Group at RAND Corporation.

The KDQOL-SF is based on the SF-36 with additional questions specific to kidney disease concerning symptoms and problems, effects of kidney disease on daily life, burden of kidney disease, cognitive function, work status, sexual function, quality of social interaction, and sleep.\(^{(54)}\) It was developed for use with a dialysis patient population but it has also been found to be valid and reliable in a kidney transplant patient population.\(^{(55)}\) Studies using the KDQOL revealed that psychological factors, including depression, were a much stronger determinant of quality of life than biological measures like dialysis adequacy.\(^{(56)}\)

While the KDQOL-SF has 134 questions the shorter form KDQOL-36 consists of 36 questions and contains the SF-12. The items of the KDQOL-36 are grouped as follows:

- Items 1-12: SF-12; Physical Component Summary (PCS) on physical functioning, role-physical, bodily pain, general health; Mental Component Summary (MCS) on vitality, social functioning, role-emotional, mental health
- Items 13-16: Burden of Kidney Disease (4); interference with daily life, time to deal with kidney disease, frustration, feeling like a burden
- Items 17-28: Symptoms / Problems (12); general health, activity limits, ability to accomplish desired tasks, depression/anxiety, energy level, social activities (item 28 not applicable in this study)
- Items 29-36: Effects of Kidney Disease (8); impact of fluid & diet limits, ability to work around the house and to travel, feeling depending on medical team, stress or worries, sex life, personal appearance

The EQ-5D-3L was introduced in 1990. The EQ-5D-3L essentially consists of 2 pages - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The respondent is asked to indicate his / her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent’s self-rated health on a vertical, visual analogue scale where the endpoints are labeled ‘best imaginable health state’ and ‘worst imaginable health state’. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. It should be noted that the numerals 1 - 3 have no arithmetic properties and should not be used as a cardinal score.

### 7.3.4 Efficacy biomarkers

The following efficacy biomarkers will be measured: NT-proBNP, BNP, aldosterone, and galectin-3.
7.4 Pharmacokinetics

For the investigation of systemic exposure to BAY 94-8862 and its relationship with treatment effects, the plasma concentrations of BAY 94-8862 will be determined at different time points using a sparse sampling approach in all participating subjects (see Table 7-1). The plasma concentration vs. time data of Visit 3 (Day 30±2) and Visit 5 (Day 90±2) will be evaluated descriptively separated by dose and visit. Plots will be prepared pooling all individual plasma concentrations (naive pooling) vs. actual relative study times (time of sample collection after time of study drug administration). The plasma concentration vs. time data of Visit 3 (Day 30±2) and Visit 5 (Day 90±2) will also be sorted in categories and descriptive statistics [geometric mean and percent coefficient of variation (%CV), arithmetic mean and %CV, median and range] will be presented by category in tabular form.

Furthermore, the pharmacokinetic data and the relationship of markers of BAY 94-8862 exposure (e.g. C\text{max}, AUC) with treatment effects will be evaluated using non-linear mixed effect modeling (NONMEM). The latter evaluation will be described in a separate analysis plan and will be reported under separate cover.

At Visit 3 (Day 30±2), blood samples for the determination of BAY 94-8862 plasma concentrations will be drawn approximately 60 to 120 minutes and 240 to 300 minutes after study drug administration. Study drug will be taken at home. At this visit, the exact time of study drug intake, the exact sampling times, and the start time of breakfast will be recorded in the eCRF. At Visit 5 (Day 90±2), blood samples for the determination of BAY 94-8862 plasma concentrations will be drawn pre-dose, approximately 30 to 90 minutes and 180 to 240 minutes after study drug administration. At this visit, study drug will be administered at the study center by study personnel and the exact time of study drug intake, the exact sampling times, the start time of breakfast, and the time of study drug intake on the day before the visit will be recorded in the eCRF.

At Visit 2 (Day 7±2) and Visit 4 (Day 60±2), single post-dose blood samples for the determination of BAY 94-8862 plasma concentrations will be drawn towards the end of the visit. At these 2 visits, the time of study drug intake and the exact sampling time will be recorded in the eCRF.

The PK bioanalysis will be performed at the Bayer HealthCare Bioanalytics Laboratory, Bayer Pharma AG, GDD-GED-DMPK Bioanalytics, 42096 Wuppertal, Germany.
7.5 Safety

7.5.1 Adverse events

7.5.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term “condition” may include abnormal physical examination findings, symptoms, diseases, laboratory, or ECG findings.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).

- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis).

- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

The term “life-threatening” in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 24 hours
- The admission is pre-planned (i.e. elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE (e.g. social hospitalization for purposes of respite care).
- However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of "medically important" and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

e. Is a congenital anomaly / birth defect

f. Is another medically important serious event as judged by the investigator

7.5.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

7.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.5.1.1.

7.5.1.2.2 Intensity

The intensity of an AE is classified according to the following categories, taking into account the possible range of the intensity of the event:

- Mild - usually transient in nature and generally not interfering with normal activities
- Moderate - sufficiently discomforting to interfere with normal activities
• Severe - prevents normal activities

7.5.1.2.3 Causal relationship

Causal relationship to study drug

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF.

The causality assessment should be done as detailed in the eCRF.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question. Possible answers are “yes” or “no”.

An assessment of “no” would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site

   or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

• The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.

• Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):

• Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.

• Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

• Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be
examined to determine whether any of them may be suspected to cause the event in question.

- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject’s pharmacodynamics should be considered.

**Causal relationship to protocol-required procedure(s)**

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a “reasonable causal relationship” to protocol-required procedure(s). Possible answers are “yes” or “no”.

**7.5.1.2.4 Action taken with study treatment**

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Dose not changed
- Not applicable
- Unknown

**7.5.1.2.5 Other specific treatments of adverse events**

- None
- Remedial drug therapy
- Other
7.5.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

7.5.1.3 Assessments and documentation of adverse events

Attention is to be paid to the occurrence of AEs at all stages of the examination. Thus, the subject should be closely observed by the investigator.

Adverse events (AEs) observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the patient will be documented. The observation period for AEs will start with signing the informed consent, and will end with the last visit of follow-up. In case of ongoing study-related adverse events and medically relevant adverse events at the end of the study, the investigator is urged to monitor the subject and document the outcome on the subject's source document.

The investigator is responsible for the grading of each category mentioned. An assessment of the seriousness of the event will be made by the investigator, who is to complete a special form provided by the sponsor in the case of a SAE. However, SAEs will also be recorded on the AE page of the eCRF.

The sponsor has to carry out a separate assessment for expectedness, seriousness, and causal relationship to study drug.

Emerging AEs will be allocated to the period in which they have started, e.g. a symptom starting in the treatment period and continuing in the follow-up period without deterioration will only be documented in the treatment period.

When assigning the cause of death, “death” should not be recorded as an AE on the AE page. Instead, “death” is the outcome of underlying AE(s).
7.5.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 7.5.1.1.

Investigator’s notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

All SAEs occurring during the observation period defined in Section 7.5.1.3 must immediately (within 24 hours of the investigator’s awareness) be reported to the recipient detailed in the instructions for SAE reporting included in the investigator site file. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g. suspected, unexpected, serious adverse reactions (SUSARs)) will be performed by the sponsor and / or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor’s notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

7.5.1.5 Expected adverse events

For this study, the applicable reference document is the most recent version of the IB for BAY 94-8862.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.
7.5.1.6 Adverse events of special safety interest

This section was modified in AMD 1, see Section 13.1.2.14.

An increase in potassium ≥5.6 mmol/L and subsequent discontinuation of study treatment is considered an adverse event of special interest and has to be reported to the sponsor as SAE, i.e. within 24 hours of the investigator’s awareness as described in Section 7.5.1.4.

7.5.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a study subject, or in his partner, during the subject’s participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any outcome (normal as well as abnormal) of the mother or the child should be reported.

For the pregnancy of a study subject’s partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner’s consent.

For all reports, the forms provided are to be used.

7.5.3 Safety biomarkers

The following safety biomarkers will be measured: troponin T and cystatin C.

7.6 Other procedures and variables

The following safety procedures and variables will be assessed during the study (see Table 7-1 and Section 7.1 for frequency of assessments):

- Blood sample for laboratory parameter measurements (see Section 7.6.1)
- Physical examination
- 12-lead ECG
- Vital signs
- 24-hour ABPM (at selected sites only)
- Data regarding AEs will be collected at all visits after signing of the informed consent (see Section 7.5.1.1)
7.6.1 Laboratory parameter measurement

7.6.1.1 Central laboratory

This section was modified in AMD 1, see Section 13.1.2.15.

The name and the address for the central lab service provider can be found in the documentation supplied by the vendor. Only centrally analyzed blood samples will be considered for analysis and the following laboratory tests will be performed centrally:

**Hematology:** white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelets will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit.

**Clinical chemistry:** aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), cholesterol [high density lipoprotein (HDL), low density lipoprotein (LDL), total], triglycerides, creatinine, eGFR (CKD-EPI(50)), blood urea nitrogen, uric acid, bilirubin, sodium, serum potassium, magnesium, total protein, albumin, and high-sensitivity C-reactive protein (hs-CRP) will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit.

At Visit 2 (Day 7±2), a limited range of clinical chemistry parameters will be analyzed: creatinine, eGFR (CKD-EPI(50)), LDH, CK, sodium, and potassium.

**HbA1c:** Measurement of HbA1c will be performed at the run-in visit, screening visit, and Visit 5 (Day 90±2) or the premature discontinuation visit, if applicable.

**Blood sample for biomarkers:** NT-proBNP, BNP, troponin T, aldosterone, cystatin C, and galectin-3 will be performed at Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or the premature discontinuation visit as well as at the follow-up visit.

If the blood sample for the central laboratory taken at any visit is missing or not evaluable, the measurements have to be repeated as soon as possible.

**Urinalysis:** urine albumin-to-creatinine ratio and urinary sodium-potassium ratio will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit and will be measured in the first morning void urine samples collected at the subject’s home on 3 consecutive days.
Subjects must use the first morning urine after getting up for these first morning void urine samples.

If one of the following cases is reported, the subject will be asked to repeat urine sampling as soon as practical and come again to the study center: febrile illness, flu, urinary tract infection, menstruation, or unusual physical exercises.

All 3 urine samples on Visit 1 (Day 1) and Visit 5 (Day 90±2) should be collected before the respective study drug intake.

### 7.6.1.2 Local laboratory

*This section was modified in AMD 1, see Section 13.1.2.16.*

Beside the samples analyzed at the central laboratory, an additional blood safety sample will be taken which will be analyzed at the local laboratory.

It is expected that the local lab results will be available earlier than the central lab results allowing the investigator to take any required action as soon as possible. Regarding withdrawal of subjects because of increase in potassium, Table 4-2 outlines how to manage differences in results between the central and local labs. Local urinalysis using a dipstick will also be conducted.

**Clinical chemistry [from Visit 1 (Day 1) to Visit 5 (Day 90±2)]**

- Potassium
- Creatinine

**Urinalysis [at the run-in visit, screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), Visit 5 (Day 90±2) or the premature discontinuation visit, and the follow-up visit]**

- Dipstick (to confirm sample validity for analysis). Results of the dipstick and confirmation about samples validity should be recorded in the source notes only. If more than 1 of the 3 UACR measurements is missing or invalid urine sample collection should be repeated (3 first morning void samples taken on 3 consecutive days).

**Pregnancy test [at the run-in visit and the screening visit]**

- Both serological as well as urine test is acceptable
- In case the run-in visit is regarded as screening visit it is sufficient to perform the pregnancy test at the run-in visit only
7.6.2 Electrocardiogram

Standard electrocardiograms (12-lead ECG) according to Goldberger / Einthoven and Wilson will be recorded in supine position after resting for at least 10 min in a supine position at the run-in visit, screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) or at the premature discontinuation visit as well as at the follow-up visit. All ECG print-outs will be identified with the SID as well as date and time of recording and will be attached to the subject’s file.

ECG printouts will be examined locally by the investigator on the day of recording for safety and quality. Any clinically relevant abnormality will be documented as an AE.

In addition, the medical reading and interpretation of ECGs will be performed centrally by an expert in cardiology who will provide expert assessment and interpretation of all ECGs performed. If applicable, the following parameters will be assessed: heart rate (HR), PR interval (PR), QRS duration (QRSD), QT interval (QT), and QT interval corrected for HR (QTc). If the ECG is considered valid for QT analysis, QTc will be calculated according to the formulas of Bazett and Fridericia.

The name and address for the ECG service provider can be found in the documentation supplied by the vendor.

7.6.3 Vital signs

After the subject has rested for at least 10 min, 3 measurements of vital signs, i.e. BP and HR, will be performed in sitting position at 2-min intervals at the run-in visit, screening visit, Visit 1 (Day 1), Visit 2 (Day 7±2), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) or at the premature discontinuation visit as well as at the follow-up visit. At Visit 5 (Day 90±2), vital signs must be measured before study drug intake.

7.6.4 Ambulatory blood pressure monitoring

At selected sites, 24-hour ABPM will be performed at the screening visit, Visit 4 (Day 60±2), and Visit 5 (Day 90±2). The name and address for the ABPM service provider can be found in the documentation supplied by the vendor.

The screening ABPM must be completed prior to randomization at Visit 1 (Day 1) but does not have to be started during the screening visit if this is not convenient. For Visit 4 (Day 60±2) and Visit 5 (Day 90±2), the ABPM will start during the visit and will finish 24 hours later on the following day when the subject will need to return to the study center to return the device.

The 24-hour profiles will be recorded with standard ABPM devices at the following intervals:
- At 15-min intervals from 06:00 to <22:00 (daytime)
- At 30-min intervals from 22:00 to <06:00 (night-time)

During the recording of 24-hour ABPM, subjects will be obliged to refrain from physical exertion. The printouts will be attached to the subject’s file.

7.6.5 Iohexol plasma clearance

In a subgroup of the study population, iohexol plasma clearance will be assessed at the screening visit, Visit 5 (Day 90±2), and the follow-up visit if Visit 5 (Day 90±2) was performed. In all Italian centers, subjects who consent to participate in this sub-study and who are not sensitive to iodine or other iodinated contrast agents can be included in this sub-study. Iohexol is a non-ionic iodinated contrast agent.

Iohexol plasma clearance will be measured as follows:

On the morning of the respective visit, a Teflon cannula will be inserted in an antecubital vein for the injection of the marker substance, and another in the contralateral arm for subsequent blood sampling. A pre-iohexol blood sample (blank sample, 3 mL) will be collected. This sample will be used to find out whether any of the subject’s concomitant medications interferes with the iohexol chromatography. The Teflon cannula will be kept open with saline solution (0.9%).

Subjects will receive a slow intravenous injection (2 min) of 5 mL Omnipaque 300 containing 3.235 g iohexol into the injection cannula.

Note the exact time of injection (time 0) and use the same clock for timing throughout the procedure.

For iohexol determination, blood samples (3 mL) will be collected at different times according to the eGFR (CKD-EPI)(50) at the run-in visit:

- For eGFR (CKD-EPI)(50) >40 mL/min sampling at pre-iohexol as well as 120, 150, 180, 210, 240 min post-dose
- For eGFR (CKD-EPI)(50) ≤40 mL/min sampling at pre-iohexol as well as 120, 180, 240, 300, 360, 420, and 480 min post-dose
- If the run-in visit is considered as the screening visit, the iohexol plasma clearance can be performed at any time before Visit 1 (Day 1). The name and address for the iohexol plasma clearance service provider can be found in the documentation supplied by the central lab vendor.
7.7  Appropriateness of procedures / measurements

All parameters, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate, and relevant.

8.  Statistical methods and determination of sample size

8.1  General considerations

This section was modified in AMD 1, see Section 13.1.2.17.

Statistical analyses will be performed using the Statistical Analysis System (SAS) software package; the version used will be specified in the statistical analysis plan (SAP).

All subjects will be analyzed according to the actual treatment. Data from subjects who prematurely terminated the study will be used to the maximum extent possible.

Doses which will be closed prematurely due to safety concerns will not be included in the primary analysis and in the ANCOVA models.

Baseline values will be defined as the last non-missing measurement before the first intake of study treatment. In case the last observation available prior to treatment is the measurement from the screening visit, this would be used as the baseline value. If the last observation prior to treatment is the measurement from the run-in visit, this value will only be used in case the run-in visit is the same visit as the screening visit. Otherwise baseline will be missing.

In case of any unexpected finding, further exploratory analyses might be performed.

8.2  Analysis sets

This section was modified in AMD 1, see Section 13.1.2.18;

Safety analysis set (SAF): All randomized subjects who have taken at least 1 dose of study drug and with data after beginning of treatment.

Full analysis set (FAS): All subjects of the SAF who have baseline and at least 1 post-baseline UACR value.

Per-protocol analysis set (PPS): All subjects of the FAS who have valid UACR data at Visit 5 (Day 90±2) and have no major protocol deviations. Major protocol deviations are for example:

- Intake of any prohibited concomitant medication
Overall compliance with study drug intake of <80% or >120%

Listing only set (LOS): All other subjects screened who did not receive any dose of study drug or for whom no data after beginning of treatment are available will be classified as LOS. Their data will be presented in the individual subject data listings but will not be included in any statistical analysis.

Pharmacokinetic analysis set (PKS): All BAY 94-8862-treated subjects with at least 1 valid BAY 94-8862 plasma concentration and without protocol deviation, which would interfere with the evaluation of the PK data.

The allocation of each subject to analysis sets will be documented before the database lock. Final decisions regarding validity of subjects to analysis sets assignment will be made during the Validity Review Meetings and documented in the Validity Review Reports.

8.3 Variables

8.3.1 Primary efficacy variable

- Ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline

8.3.2 Further exploratory efficacy variables

- HRQoL: KDQOL-36 and EQ-5D-3L

Further exploratory efficacy variables are described in Section 7.3.

8.3.3 Safety and tolerability variables

- Serum potassium

- eGFR (CKD-EPI)\(^{50}\)

Safety and tolerability variables are described in Section 7.5.

8.4 Statistical and analytical plans

8.4.1 Analysis of subject characteristics

All demographic data and baseline characteristics will be tabulated by treatment group and overall. The demographic tables will also be presented by the stratification factor (type of albuminuria and region). The analyses will be performed in the SAF and the description of all main baseline characteristics, which will be specified in the SAP, will be repeated for all other analysis sets if they differ from the SAF.

8.4.2 Analysis of primary efficacy variable

*This section was modified in AMD 1, see Section 13.1.2.19.*
The analysis of the primary efficacy variable, the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline, will be performed in the FAS (primary analysis) and PPS (supportive analysis). The primary analysis will focus on the on-treatment data.

The UACR will be determined 3 times at each visit from first morning void urine samples collected on 3 consecutive days. For all analyses of UACR, the 3 measurements at 1 visit will be combined as follows: First, the coefficient of variation will be calculated for the 3 values. If the coefficient of variation exceeds 25%, the median from the measurements will be used for the analyses. The median in case of an even number of values will be defined as the geometric mean from the 2 middle values. If the coefficient of variation is 25% at the most, the geometric mean will be used. If a scheduled measurement is missing or invalid and an additional unscheduled measurement was performed instead, this unscheduled measurement should be used to determine the UACR if the measurement was within two days after the last scheduled measurement. If all three assessments have been repeated, then these will be used for analysis. For Visit 1 (Day 1), only measurements taken prior to the first intake of study drug will be used to determine the respective visit assessment. If only one UACR measurement at a visit is available, then this measurement will not be used for analysis.

In order to describe the course of UACR and the ratio of UACR to baseline for all visits, descriptive statistics will be provided including the geometric means, geometric standard deviations (SDs), and geometric coefficients of variation by treatment group and time point. This will be done overall and separately for all subgroups defined in Section 8.4.6. Graphs displaying the geometric group means and SDs of the ratios vs. time will be generated.

Primarily, the aim is to demonstrate a dose-dependent effect of BAY 94-8862 with respect to the primary variable. For this purpose, an ANCOVA model will be fitted to the logarithmized ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline including a factor for treatment group, factors to adjust for the stratification factors (type of albuminuria and region) and the logarithmized baseline UACR as covariate nested within type of albuminuria. The UACR values and ratios will be transformed since the primary variable is considered to be approximately log-normally distributed, i.e. the log-values are considered to be normally distributed. In the event of a region with a relatively small number of subjects, this region might be pooled with another region for this analysis. The decision will be made during the blind data review meeting and documented in the Validity Report.

The primary hypothesis \( H_0: L_k' \cdot \mu = 0 \) will be tested by means of the F-test with a 1-sided significance level of 5%, where \( \mu = (\mu_1, \ldots, \mu_k)^t \) with \( \mu_i = \text{expected value for ln(UACR at Visit 5 (Day 90±2))} - \ln(\text{UACR at baseline}) \) adjusted for baseline log-UACR and the stratification factors (type of albuminuria and region), where \( i = 1,\ldots,k \) means the different k dose groups. The alternative hypothesis \( H_1: L_k' \cdot \mu > 0 \) which shall demonstrate a linear trend in the group means will be tested by applying the linear contrast \( L_k' \) which reflects the intervals between the dose groups. In case, the dose groups will be placebo (= 0 mg), 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862, the linear contrast will be \( L_6' = (3.5, 2.5, 1.5, -0.5, -2.5, -4.5) \). If 15 mg BAY 94-8862 will be added, the linear contrast will be \( L_7' = (4.714, 3.714, 2.714, 0.716, -1.286, -3.286, -7.286) \). If 15 mg and 20 mg
BAY 94-8862 will be added the linear contrast will be $L_s' = (6.125, 5.125, 4.125, 2.125, 0.125, -1.875, -5.875, -9.875)$.

The distributional model assumptions will be checked by inspection of residual plots of studentized residuals vs. normal order scores to check normality, and studentized residuals vs. predicted values to check homogeneity of variance.

In the 90-day treatment period of this study, a dropout rate of approximately 30% is expected, i.e. there will be a high number of missing UACR values at Visit 5 (Day 90±2). 10% of the subjects are expected to drop out during the first month and another 20% during the following 2 months. Dropouts after the first month are expected to be due to worsening renal function or uncontrolled hypertension. The remaining dropouts are expected to be due to clinical outcomes or hyperkalemia. While albuminuria might not be influenced in subjects with clinical outcomes or hyperkalemia, a worsening albuminuria is expected in cases of worsening renal function or uncontrolled hypertension.

In the primary analysis for imputation of missing UACR values at Visit 5 (Day 90±2), the last observation carried forward (LOCF) method will be applied. Thereby, the higher UACR value from the premature discontinuation measurement (to be collected as soon as possible after premature discontinuation) and follow-up measurement (30±5 days after premature discontinuation) will be used to carry forward for subjects, who prematurely terminated the study drug.

Extensive sensitivity analyses for the imputation method will be conducted with the intention to learn more about the missing data process in this special population.

If the primary hypothesis could be rejected, the single dose groups will be compared to placebo by a hierarchical procedure starting with the highest dose of BAY 94-8862 vs. placebo within the same ANCOVA model in order to investigate the dose-response relationship further. The 1-sided significance level of 5% will be kept for each pairwise comparison and the procedure will stop when the first hypothesis could not be rejected.

Furthermore, it will be aimed to detect which group means of the logarithmized ratios are different from each other as an exploratory analysis. Therefore, the REGWQ (Ryan-Einot-Gabriel-Welsch Q) option of the SAS GLM (generalized linear model) procedure will be applied with a 2-sided significance level of 10%. The option performs a Ryan-Einot-Gabriel-Welsch multiple range test, which tests subsets of the group means for equality. This option is available only for unadjusted means.

8.4.3 Analysis of further exploratory efficacy variables
All exploratory efficacy variables will be analyzed in FAS and PPS.
8.4.3.1 Ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline

This section was modified in AMD 1, see Section 13.1.2.20.
The logarithmized ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline will be analyzed by a mixed-effects repeated measures model with treatment group as the main effect, factors for the stratification levels (type of albuminuria and region), a factor for time, the interaction factor between treatment and time and the logarithmized baseline value as covariate nested within type of albuminuria.
The overall treatment effect, as well as treatment effects at each time point will be estimated.
Details for the analysis, e.g. the specification of the covariance structure, will be outlined in the statistical analysis plan.

8.4.3.2 Decreases in eGFR

Frequency tables will be generated for the number and incidence of subjects with a decrease in eGFR of ≥30% from baseline eGFR, of ≥40% from baseline eGFR, and of ≥57% from baseline eGFR. The analysis will be performed for each time point and overall (subjects with at least 1 event in the respective category after start of study drug administration).

8.4.3.3 Changes in albuminuria

A shift table will be provided displaying the number and incidence of subjects who changed from baseline to Visit 5 (Day 90±2) from very high albuminuria to high albuminuria, from very high albuminuria to albuminuria, from high albuminuria to albuminuria, from high albuminuria to very high albuminuria, and albuminuria to high albuminuria by treatment group and overall. The albuminuria category changes will only be considered as shifts, if they are accompanied by a UACR change of more than 30% from baseline to Visit 5 (Day 90±2).

8.4.3.4 Efficacy biomarkers

The analyses of efficacy biomarkers will be performed in FAS and PPS.

Efficacy biomarkers will be summarized descriptively by treatment group and visit including absolute changes to baseline. These analyses will be performed overall and separated by the stratification factor (type of albuminuria and region). Group means and standard deviations of absolute values and changes to baseline (non-stratified) will be plotted versus time including medical threshold levels, if applicable.

The change in biomarkers from baseline to Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (type of albuminuria and region) and
baseline value as covariate. In case of signs for not approximately normal data, nonparametric methods or transformation of the data will be considered.

8.4.3.5 Health-related quality of life

This section was modified in AMD 1, see Section 13.1.2.21.

The health-related quality of life questionnaires will be analyzed in FAS and PPS. For a detailed description of the questionnaires, please refer to Section 7.3.3.

The KDQOL-36 results will be described by visit and treatment group by presenting the summary scores (PCS, MCS, Burden of Kidney Disease, Symptoms / Problems, and Effects of Kidney Disease) by means of number of observations, minimum, first quartile, median, third quartile, and maximum, including the changes from baseline. It is not sensible to calculate an overall summary score. In addition, the frequencies of answers to individual questions will be displayed by treatment group and overall by visit. The frequencies of changes from baseline at Visit 3 (Day 30±2), Visit 5 (Day 90±2), and the follow-up visit will be presented regarding the categories improvement / no change / worsening for the single items. With regard to the EQ-5D-3L, the summary score including changes from baseline will be described by treatment group and overall by visit using number of observations, minimum, first quartile, median, third quartile, and maximum, including the changes from baseline. The above specified statistics plus the arithmetic mean and standard deviations will be provided for the EQ VAS and its changes to baseline. Furthermore, the frequencies of answers to all individual questions will be provided by treatment group and overall by visit. The frequencies of changes from baseline at Visit 3 (Day 30±2), Visit 5 (Day 90±2), and the follow-up visit will be presented regarding the categories improvement / no change / worsening for each dimension.

8.4.4 Pharmacokinetics

For all planned pharmacokinetic analyses, please refer to Section 7.4.

Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value, a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked. Measurements that were not taken within the pre-defined time windows for Visit 3 (Day 30±2) and Visit 5 (Day 90±2) [60 to 120 minutes and 240 to 300 minutes after study drug administration for Visit 3 (Day 30±2); pre-administration, 30 to 90 minutes and 180 to 240 minutes after drug administration for Visit 5 (Day 90±2)] will be excluded from the descriptive statistics.

8.4.5 Safety and tolerability variables

All analyses on safety and tolerability data will be performed in the SAF.
8.4.5.1 Adverse events

This section was modified in AMD 1, see Section 13.1.2.22.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, latest version available prior to data base freeze). A listing will be provided linking the original investigator terms and the coded terms.

AEs that occurred or worsened on or after the first dose of study drug up to 3 days after the date of the last dose of study drug will be considered as TEAEs.

An overall summary of all TEAEs will be generated.

The number and incidence of subjects with non-treatment-emergent (pre-treatment) AEs, TEAEs, treatment-emergent SAEs, treatment-emergent study drug-related AEs, treatment-emergent study drug-related SAEs, treatment-emergent AEs causing discontinuation of study drug and treatment-emergent non-serious AEs will be summarized by treatment group and overall in total and using MedDRA terms grouped by system organ class and preferred terms.

In case of events with different intensity within a subject, the maximum reported intensity will be used. If intensity is missing, the event will be considered as severe. Similarly, if the same event is reported as both unrelated and related to the study drug within a subject, the event will be reported as related to study drug. If the drug relationship is missing, the event will be considered as being related to the study drug.

Deaths, SAEs, and AEs leading to study discontinuation will be listed separately (if applicable).

Separate tables summarizing TEAEs, treatment-emergent study drug-related AEs, and SAEs that occurred in more than 5% of the subjects will be provided.

8.4.5.2 Laboratory data

This section was modified in AMD 1, see Section 13.1.2.23.

Only the data provided by the central laboratory will be used for analysis, values from local laboratories will not be used.

For potassium values only, in the cases in which tests are repeated, the following approach will be used. If the new (retest) potassium value is ≥5.6 mmol/L, the higher of the 2 values (original value and retest value) will be used. If the new (retest) value is <5.6 mmol/L, the new value will be used for analysis. However, all potassium values will be listed.

Summary statistics including changes to baseline will be calculated by treatment group and visit for all quantitative laboratory parameters. For log10(10*urinary sodium / potassium ratio), a normal distribution can be assumed. Therefore, geometric statistics and ratios to baseline will be presented for this parameter.
The number of subjects with transitions from baseline with respect to reference ranges categories (low, normal, high) will be provided by visit and treatment group.

In addition, for the special safety parameter serum potassium, the means and standard deviations of absolute values and changes to baseline by treatment group will be plotted versus time.

Serum potassium will be further assessed by displaying the number and incidence of subjects with serum potassium values ≥5.6 mmol/L and >6 mmol/L by treatment, visit, and overall. This will also be done stratified by the subgroups, specified in Section 8.4.6.

Summary statistics including changes to baseline will be calculated by treatment group and visit for iohexol plasma clearance.

8.4.5.3 Safety biomarkers

Safety biomarkers (troponin T and cystatin C) will be summarized descriptively by treatment group and visit including absolute changes to baseline. These analyses will be performed overall and separated by the stratification factor (type of albuminuria). Group means and standard deviations of absolute values and changes to baseline (non-stratified) will be plotted versus time including medical threshold levels, if applicable.

The change in biomarkers from baseline to Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) will be analyzed by separate analysis of a covariance (ANCOVA) models with treatment group as the main effect, factors for the stratification levels (type of albuminuria and region), and baseline value as covariate. In case of signs for not approximately normal data, nonparametric methods or transformations of the data will be considered.

8.4.5.4 Vital signs, ECG, and ABPM

Vital sign values, ECG parameters, and measurements from the ABPM will be summarized by treatment group and visit using descriptive statistics including absolute changes from baseline.

3 measurements of vital signs parameters will be taken at time intervals of about 2 minutes. Averages of these 3 measurements will be calculated and used for the statistical analysis.

Subjects with abnormal overall ECG evaluation will be listed.

8.4.6 Subgroup analyses

The following subgroups will be considered for the descriptive and exploratory analysis of the primary variable:

- Age (18 to ≤45 years, >45 to ≤65 years, >65 to ≤75 years, and >75 years)
8.3 Baseline characteristics

- Age (≤ median and > median)
- Region (Europe, North America, Asia, others)
- Gender (male, female)
- Race (white, black, Asian, other)
- Baseline BMI (≤30, >30)
- Baseline serum potassium value (≤ median and > median)
- eGFR values (CKD-EPI(50)) (≤ median and > median)
- Concomitant medication (ACEI or ARB)
- Very high albuminuria (UACR ≥300 mg/g) vs. high albuminuria (UACR ≥30 mg/g but <300 mg/g) at baseline
- Systolic blood pressure at baseline (>90 to <140 mmHg, ≥140 to <180 mmHg, and ≥180 mmHg; ≤ median and > median)
- Concomitant medication (beta-blocker vs. no beta-blocker at baseline, diuretic vs. no diuretic at baseline)
- Potassium supplementation vs. no potassium supplementation at any time during the study

However, if the total number of subjects in a subgroup category is <15, the analysis for that level of the subgroup will not be performed.

8.5 Planned interim analyses

This section was modified in AMD 1, see Section 13.1.2.24.

No formal interim analysis is planned. However, data will be reviewed for safety and tolerability by an independent DMC.

8.6 Determination of sample size

This section was modified in AMD 1, see Section 13.1.2.25.

With the primary analysis, dose-dependent effects on the primary variable, the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline, shall be demonstrated. Considering the method to detect an overall effect described in Section 8.4.2 (without covariate and adjustment for
stratification factors), we estimated the power in 4-5 different scenarios for 6 treatment groups, as well as for 7 treatment groups (for the case of the addition of the 15 mg BAY 94-8862 once daily treatment group) with several sample sizes of subjects valid for FAS per treatment group. We simplified the planned ANCOVA to an analysis of variance (ANOVA) for the determination of sample size. We consider this approach as valid because the inclusion of the baseline log-UACR as a covariate will rather increase the power to detect a dose-dependent effect. For sample size calculations, the software nQuery Advisor® 7.0 was used.

The 5 scenarios used for the power calculations were designed based on the geometric means and geometric standard deviations of the UACR ratios from Study 14563 (ARTS) in subjects with high or very high albuminuria at baseline, where the fifth scenario should reflect a reduced effect in case of a much higher rate of high albuminuria subjects compared to very high albuminuria subjects.

The results of the power estimations for 6 treatment groups (5 BAY 94-8862 groups and 1 placebo group) for sample sizes between 70 and 120 subjects per treatment group are summarized in Table 8-1.

<table>
<thead>
<tr>
<th>Sample size per treatment group</th>
<th>Total sample size</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
<th>Scenario 5</th>
<th>SD of difference on log scale a</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>420</td>
<td>80</td>
<td>92</td>
<td>91</td>
<td>80</td>
<td>71</td>
<td>1.25</td>
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<td></td>
</tr>
<tr>
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<td>600</td>
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<td>90</td>
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<td>95</td>
<td>99</td>
<td>98</td>
<td>94</td>
<td>89</td>
<td></td>
</tr>
</tbody>
</table>

a Standard deviation of ln (UACR at Visit 5 (Day 90±2)) - ln (UACR at baseline)

The different assumed scenarios are (expected values of the logarithmized UACR ratios for the different treatments placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862):

- Scenario 1: ln(0.91), ln(0.87), ln(0.82), ln(0.74), ln(0.66), ln(0.59)
- Scenario 2: ln(0.91), ln(0.87), ln(0.82), ln(0.69), ln(0.60), ln(0.55)
- Scenario 3: ln(0.91), ln(0.82), ln(0.73), ln(0.58), ln(0.56), ln(0.55)
- Scenario 4: ln(0.91), ln(0.73), ln(0.64), ln(0.60), ln(0.57), ln(0.55)
- Scenario 5: ln(0.95), ln(0.91), ln(0.86), ln(0.79), ln(0.71), ln(0.65)

A sample size of 90 subjects valid for FAS per treatment group would lead to 88% power in the worst case among scenarios 1 to 4 and still to a power of 80% for Scenario 5. For the best case assumed, the primary analysis would demonstrate a power of 96%.
With 90 evaluable subjects per treatment group, a total of 540 evaluable subjects are needed. Considering an assumed screening failure rate of up to 50% and an assumed dropout rate of 10%, 100 subjects per treatment group should be randomized and approximately 1200 subjects need to be enrolled.

The results of the power estimations in the case that 1 treatment group with 15 mg BAY 94-8862 will be added after the DMC decision, i.e. for 6 BAY 94-8862 treatment groups and 1 placebo group, are summarized in Table 8-2 for sample sizes between 70 and 90 subjects per treatment group (fewer subjects than in Table 8-1 are considered here since the additional dose leads to an increase in power).

**Table 8-2: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg BAY 94-8862**

<table>
<thead>
<tr>
<th>Sample size per treatment group</th>
<th>Total sample size</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
<th>Scenario 5</th>
<th>SD of difference on log scale *</th>
</tr>
</thead>
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<td>88</td>
<td></td>
</tr>
</tbody>
</table>

* Standard deviation of ln (UACR at Visit 5 (Day 90±2)) - ln (UACR at baseline)

The different assumed scenarios are (expected values of the logarithmized UACR ratios for the different treatments placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, and 15 mg BAY 94-8862):

- **Scenario 1**: ln(0.91), ln(0.87), ln(0.82), ln(0.74), ln(0.66), ln(0.59), ln(0.46)
- **Scenario 2**: ln(0.91), ln(0.87), ln(0.82), ln(0.69), ln(0.60), ln(0.55), ln(0.48)
- **Scenario 3**: ln(0.91), ln(0.82), ln(0.73), ln(0.58), ln(0.56), ln(0.55), ln(0.54)
- **Scenario 4**: ln(0.91), ln(0.73), ln(0.64), ln(0.60), ln(0.57), ln(0.55), ln(0.52)
- **Scenario 5**: ln(0.95), ln(0.91), ln(0.86), ln(0.79), ln(0.71), ln(0.65), ln(0.64)

A sample size of 75 subjects valid for FAS per treatment group would lead to a power among scenarios 1 to 4 between 87% (worst case scenario) and 99% (best case scenario) and for scenario 5 to a power of 83%.

With the same assumptions on screening failure and dropout rate, a total of 83 subjects per treatment group should be randomized. The approximate number of enrolled subjects would not exceed 1200 subjects, as calculated for 6 treatment groups.

Sample size considerations for adding the 20 mg BAY 94-8862 treatment group are not considered here. It is expected that the power will increase even in case a plateau will be reached with 75 additional subjects valid for FAS for 20 mg BAY 94-8862.
9. **Data handling and quality assurance**

9.1 **Data recording**

Specific data (race and ethnic group) may be entered directly into the eCRF, for all other data, source documentation must be available at the site. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

9.2 **Monitoring**

In accordance with applicable regulations, GCP, and sponsor’s / CRO’s procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor / designee will monitor the site activity to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study drug being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.3 **Data processing**

The data collection tool for this study will be a validated electronic system called RAVE. Subject data necessary for analysis and reporting will be entered / transmitted into a validated database or data system (e.g. Tools for Syntactic Corpus Analysis [TOSCA], SAS). Clinical data management will be performed in accordance with applicable sponsor’s standards and data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (e.g. laboratory).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.
9.4 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor’s (or a designated CRO’s) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator / institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s) / IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator / institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his / her time and the time of his / her staff to the auditor / inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

9.5 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator / institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor’s approval.

The investigator’s contract will contain all regulations relevant for the study center.

10. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment groups, dose steps, centers]) at any time, which may be due but not limited to the following reasons:

- If the risk-benefit ratio becomes unacceptable owing to, for example:

- Safety findings from this study (e.g. SAEs)

- Results of any interim analysis
Results of parallel clinical studies

Results of parallel animal studies
(on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity)

If the study conduct (e.g. recruitment rate, dropout rate, data quality, protocol compliance) does not suggest a proper completion of the study within a reasonable time frame

The investigator has the right to close his / her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties

- All affected institutions (e.g. IEC(s) / IRB(s), competent authority(ies), study center, head of study center) must be informed as applicable according to local law

- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction

- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner

Details for individual subject's withdrawal can be found in Section 5.2.1.

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s) / IRB(s) will be obtained for all participating centers / countries before start of the study, according to GCP, local laws, regulations, and organizations. When necessary, an extension, amendment or renewal of the IEC / IRB approval must be obtained and also forwarded to the Sponsor. The responsible unit (e.g. IEC / IRB, head of the study center / medical institution) must supply to the sponsor, upon request, a list of the IEC / IRB members involved in the vote and a statement to confirm that the IEC / IRB is organized and operates according to GCP and applicable laws and regulations.
Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change in the protocol to eliminate an immediate hazard(s) to the study subjects without prior IEC / IRB / sponsor approval / favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC / IRB / head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 10.

11.2 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject / legal representative or proxy consenter (if the subject is under legal protection), prior to his / her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IEC / IRB has been obtained.

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the subject's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject’s clinical record must clearly show that informed consent was obtained prior to these procedures.
If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

For subjects under legal protection, consent shall be given by the legal guardian(s). The consent of a subject under legal protection shall also be requested where such a person is able to express his own will. His refusal or the withdrawal of his consent may not be disregarded.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject’s consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC’s / IRB’s approval / favorable opinion in advance of use.

11.3 Publication policy

The sponsor is interested in the publication of the results of every study it performs.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator / institution.

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

11.4 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

11.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that
representatives of the sponsor, IEC / IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

### 12. Reference list


21. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-847.


13. Protocol amendments

13.1 Amendment 1

In this amendment changes to ensure consistency within the document and the central and local laboratory as well as clarifications of the study procedure have been implemented.

The changes made to the protocol under Amendment 1 are described in section 13.1.2 and are incorporated into this integrated protocol.

13.1.1 Overview of changes

The reasons for this protocol amendment are as follows:

- Minor changes to ensure consistency within the document and the central and local laboratory. Sections: Synopsis
  
  This section was modified in AMD 1, see Section 13.1.2.1

- 4. Study design, 5.1.1 Inclusion criteria, 5.2.1 Withdrawal, 6.3 Treatment assignment, 6.9 Prior and concomitant therapy, 7.1 Schedule of procedures, 7.5.1 Adverse events, 7.6.1 Laboratory parameter measurement, 8.1 General considerations, 8.4 Statistical and analytical plans, 8.5 Planned interim analyses

- Minor clarification of study procedures. Sections: Synopsis
  
  This section was modified in AMD 1, see Section 13.1.2.1

- 4. Study design, 5.2.1 Withdrawal, 6.3 Treatment assignment, 6.9 Prior and concomitant therapy, 7.1 Schedule of procedures, 7.3.3 Health-related quality of life, 7.5.1 Adverse events, 7.6.1 Laboratory parameter measurement, 8.1 General considerations, 8.2 Analysis sets, 8.4 Statistical and analytical plans, 8.6 Determination of sample size
• Inclusion criteria was modified with respect to the inclusion of women with childbearing potential Section 5.1.1.

• Inclusion criteria regarding clinical diagnosis of DN based on albuminuria levels and eGFR was modified Section 5.1.1.

• Minor changes to the schedule of procedures Section 7.1 Schedule of procedures.

13.1.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the “old text” refers to the protocol version preceding this amendment. Deletions are crossed out in the “old text”. Additions are underlined in the “new text”. Corrections of typing errors or omissions are not highlighted in this section.
13.1.2.1 Synopsis section

Old:

[...]

Diagnosis and main criteria for inclusion

Adult male subjects and female subjects without childbearing potential with type 2 diabetes mellitus and a clinical diagnosis of DN treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), but not both, for at least 3 months

- Persistent very high albuminuria defined as UACR of ≥300 mg/g (≥34 mg/mmol) in 2 out of 3 first morning void samples and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m² (Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI) (mL = milliliter; min = minute; m² = square meter; g = gram; mmol = millimole) or

- Persistent high albuminuria defined as UACR of ≥30 mg/g but <300 mg/g (≥3.4 mg/mmol but <34 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥30 mL/min/1.73 m² (CKD-EPI)

[...]

New:

[...]

Diagnosis and main criteria for inclusion

Adult male and female subjects with type 2 diabetes mellitus and a clinical diagnosis of DN treated with an angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB), for at least 3 months.

- Persistent very high albuminuria defined as UACR of ≥300 mg/g (≥34 mg/mmol) in 2 out of 3 first morning void samples and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m² but < 90 mL/min/1.73 m² (Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI) (mL = milliliter; min = minute; m² = square meter; g = gram; mmol = millimole) or

- Persistent high albuminuria defined as UACR of ≥30 mg/g but <300 mg/g (≥3.4 mg/mmol but <34 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥30 mL/min/1.73 m² but < 90 mL/min/1.73 m² (CKD-EPI)

[...]
Plan for statistical analysis
Safety analysis set (SAF): All randomized subjects who have taken at least 1 dose of study drug and with data after beginning of treatment.

13.1.2 Section 4 Study design

*Old:*

**Open-label run-in period (up to 12 weeks)**

Following a run-in visit, subjects meeting all of the inclusion and none of the exclusion criteria will be enrolled in the open-label run-in period. During this period, subjects’ eligibility for randomization into this study will be evaluated. At the end of this run-in period, each subject should receive at least the minimal recommended dose of conventional therapy according to local guidelines which consists either of an ACEI or ARB, but not both.

[...]

Subjects with an estimated glomerular filtration rate (eGFR) (CKD-EPI)\(^{(50)}\) of 30 - 45 mL/min/1.73 m\(^2\) at the run-in visit must also be treated with a non-potassium-sparing diuretic at randomization. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. At the screening visit, subject’s treatment should be stable and without any adjustments for at least 4 weeks as documented in the subject’s medical records.

[...]

If the subject already receives an ACEI or ARB for at least 3 months and is on the minimal recommended dose of the ACEI or ARB at the run-in visit and this dose has not been adjusted for at least 4 weeks, the run-in visit will be considered as the screening visit and the subject can be randomized within the next 14 days. Before randomization, investigators should check if the subject is still eligible for the study.

[...]

**Monitoring of serum potassium during the treatment period**

Subjects will maintain their normal diet throughout the study and will not be given any specific advice on dietary sodium or potassium restrictions. If there is a change in the subject’s clinical status of which the investigator is aware of that influences serum electrolyte levels or fluid balance (e.g. vomiting or / and diarrhea >1 day), it is recommended to reassess serum potassium levels as soon as possible after the acute event.
If any re-assessment of serum potassium is required, always locally and centrally analyzed blood samples must be taken.

If serum potassium is ≥5.6 and ≤6.0 mmol/L measured in the central or local laboratory, a second blood sample has to be taken as soon as possible but at the latest within 48 hours. If serum potassium is again ≥5.6 mmol/L in the locally or centrally analyzed blood sample, study drug has to be discontinued permanently.

If serum potassium is >6.0 mmol/L in the centrally analyzed blood sample but <5.6 mmol/L in the locally analyzed sample, treatment with study drug can be continued. If serum potassium is >6.0 mmol/L in the centrally analyzed blood sample and ≤5.6 mmol/L in the locally analyzed sample, study drug has to be discontinued permanently.

Inappropriate transport conditions or lengthy transport time to the central laboratory may result in falsely elevated serum potassium values in the centrally analyzed blood sample. Therefore, the results of the locally analyzed blood sample will also be taken into account. If the locally analyzed blood sample is missing or the result is inconclusive and the central laboratory result is not available, another blood sample must be taken as soon as possible but at the latest within 48 hours.

If serum potassium is >6.0 mmol/L in the locally analyzed blood sample, study drug has to be discontinued permanently.

Hemolytic blood sample or serum potassium values >6.0 mmol/L in the centrally analyzed blood sample which cannot be confirmed by the locally analyzed sample (serum potassium locally <5.6 mmol/L) will not be considered for analysis.

<table>
<thead>
<tr>
<th>Central lab</th>
<th>Result of first serum potassium measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.6 mmol/L</td>
<td>Continue study drug</td>
</tr>
<tr>
<td>5.6 - 6.0 mmol/L</td>
<td>Repeat serum potassium measurement within 48 hours&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;6.0 mmol/L</td>
<td>Check serum potassium in locally analyzed sample&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Local lab</th>
<th>Result of first serum potassium measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.6 mmol/L</td>
<td>Continue study drug</td>
</tr>
<tr>
<td>5.6 - 6.0 mmol/L</td>
<td>Repeat serum potassium measurement within 48 hours&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;6.0 mmol/L</td>
<td>Discontinue study drug permanently</td>
</tr>
</tbody>
</table>

<sup>a</sup> If serum potassium is again ≥5.6 mmol/L in the repeat blood sample, discontinue study drug permanently.

<sup>b</sup> If serum potassium is <5.6 mmol/L in the (first) locally analyzed blood sample, continue study drug.

Potassium supplementation

Any potassium supplementation should be stopped prior to randomization if serum potassium levels are within the normal range. If serum potassium levels are low at randomization or at
any of the following visits, potassium supplementation can be continued or re-started until serum potassium values are within the normal range again. In general, investigators should monitor serum potassium carefully at each visit and if potassium supplementation is prescribed, they should adapt the dose of potassium supplementation in accordance with the serum-potassium value measured at each visit or discontinue potassium supplementation once the serum potassium is within the normal range.

[...]

New:

**Open-label run-in period (up to 12 weeks)**

Following a run-in visit, subjects meeting all of the inclusion and none of the exclusion criteria will be enrolled in the open-label run-in period. Only subjects already treated with an ACEI and/or ARB for at least two weeks before enrolment can be considered for the study. During this period, subjects’ eligibility for randomization into this study will be evaluated. At the end of this run-in period, each subject should receive at least the minimal recommended dose of conventional therapy according to local guidelines which consists either of an ACEI or ARB, but not both.

[...]

Subjects with an estimated glomerular filtration rate (eGFR) (CKD-EPI) of 30 - 45 mL/min/1.73 m² at the run-in visit must also be treated with a non-potassium-sparing diuretic at screening. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. At the screening visit, subject’s treatment should be stable and without any adjustments for at least 4 weeks as documented in the subject’s medical records.

[...]

If the subject already receives an ACEI and/or ARB for at least 3 months and is on the minimal recommended dose of the ACEI or ARB at the run-in visit and this dose has not been adjusted for at least 4 weeks, the run-in visit may be considered as the screening visit and the subject can be randomized within the next 14 days. Before randomization, investigators should check if the subject is still eligible for the study.

[...]

**Monitoring of blood potassium during the treatment period**

Subjects will maintain their normal diet throughout the study and will not be given any specific advice on dietary sodium or potassium restrictions. If there is a change in the subject’s clinical status of which the investigator is aware of that influences serum electrolyte
levels or fluid balance (e.g. vomiting or / and diarrhea >1 day), it is recommended to reassess potassium levels as soon as possible after the acute event.

If any re-assessment of potassium is required, always locally and centrally analyzed blood samples must be taken.

Upon receipt of the scheduled laboratory results (considered as first potassium measurement), different scenarios are possible:

- If potassium is ≥5.6 and ≤6.0 mmol/L measured in the central or local laboratory, a second blood sample has to be taken as soon as possible but at the latest within 48 hours. If potassium is again ≥5.6 mmol/L in the locally or centrally analyzed blood sample (considered as second potassium measurement), study drug has to be discontinued permanently.

- If potassium is >6.0 mmol/L in the centrally analyzed blood sample but <5.6 mmol/L in the locally analyzed sample, treatment with study drug can be continued. If potassium is >6.0 mmol/L in the centrally analyzed blood sample and ≥5.6 mmol/L in the locally analyzed sample, study drug has to be discontinued permanently.

- If potassium is >6.0 mmol/L in the locally analyzed blood sample, study drug has to be discontinued permanently.

Inappropriate transport conditions or lengthy transport time to the central laboratory may result in falsely elevated potassium values in the centrally analyzed blood sample. Therefore, the results of the locally analyzed blood sample will also be taken into account. If the locally analyzed blood sample is missing or the result is inconclusive and the central laboratory result is not available, another blood sample must be taken as soon as possible but at the latest within 48 hours after becoming aware of the results.

**Table 4-2: Monitoring of potassium during the treatment period**

<table>
<thead>
<tr>
<th>Result of first potassium measurement</th>
<th>&lt;5.6 mmol/L</th>
<th>5.6 - 6.0 mmol/L</th>
<th>&gt;6.0 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central lab</td>
<td>Continue study drug</td>
<td>Repeat potassium measurement within 48 hours</td>
<td>Check potassium in locally analyzed sample</td>
</tr>
<tr>
<td>Local lab</td>
<td>Continue study drug</td>
<td>Repeat potassium measurement within 48 hours</td>
<td>Discontinue study drug permanently</td>
</tr>
</tbody>
</table>

*a If potassium is again ≥5.6 mmol/L in the repeat blood sample, discontinue study drug permanently.

*b If potassium is <5.6 mmol/L in the (first) locally analyzed blood sample, continue study drug permanently.

If in the re-test potassium is ≥5.6 mmol/L in the locally or centrally analyzed blood sample, study drug has to be discontinued permanently.
Potassium values >6.0 mmol/L in the centrally analyzed blood sample which cannot be confirmed by the locally analyzed sample (potassium locally <5.6 mmol/L) will not be considered for analysis.

**Potassium supplementation**

Any potassium supplementation should be stopped prior to randomization if potassium levels are within the normal range. If potassium levels are low at randomization or at any of the following visits, potassium supplementation can be continued or re-started until potassium values are within the normal range again. In general, investigators should monitor potassium carefully at each visit and if potassium supplementation is prescribed, they should adapt the dose of potassium supplementation in accordance with the potassium value measured at each visit or discontinue potassium supplementation once the potassium is within the normal range.

**Potassium lowering agents**

With the exception of non-potassium sparing diuretics, potassium-lowering agents (e.g. sodium polystyrene sulfonate, calcium polystyrene sulfonate, insulin and glucose infusion) are not allowed to be started during treatment with study drug. In case of hyperkalemia occurring during study treatment, the study treatment should be discontinued prior to starting a potassium lowering agent.

[...]

### 13.1.2.3 Section 5.1.1 Inclusion criteria

**Old:**

[...]

- Men aged 18 years and older, confirmed postmenopausal women or women aged 18 years and older without childbearing potential based on surgical treatment such as bilateral tubal ligation, bilateral ovariectomy, or hysterectomy. Men enrolled in this study must agree to use adequate barrier birth control measures during the treatment period of the study. The lower age limit may be higher if legally required in the participating country

[...]

- Subjects with a clinical diagnosis of DN based on at least 1 of the following criteria at the run-in and the screening visit:
Persistent very high albuminuria defined as UACR of ≥300 mg/g (≥34 mg/mmol) in 2 out of 3 first morning void samples and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m² (CKD-EPI)\(^{(50)}\)

or

Persistent high albuminuria defined as UACR of ≥30 mg/g but <300 mg/g (≥3.4 mg/mmol but <34 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥30 mL/min/1.73 m² (CKD-EPI)\(^{(50)}\)

[...]

- Subjects treated with at least the minimal recommended dose of an ACEI or ARB, but not both, for at least 3 months without any adjustments to this therapy for at least 4 weeks prior to the screening visit; subjects with an eGFR of 30 - 45 mL/min/1.73 m² (CKD-EPI)\(^{(50)}\) must also be treated with a non-potassium sparing diuretic at the screening visit and without any adjustments to this therapy for at least 4 weeks prior to the screening visit

[...]

New:

[...]

- Men and women aged 18 years and older. The lower age limit may be higher if legally required in the participating country

- Women of childbearing potential can only be included in the study if a pregnancy test is negative and if they agree to use adequate contraception when sexually active. Adequate contraception is defined as any combination of at least 2 effective methods of birth control, of which at least one is a physical barrier (e.g. condoms with hormonal contraception or implants or combined oral contraceptives, certain intrauterine devices)

[...]

- Subjects with a clinical diagnosis of DN based on at least 1 of the following criteria at the run-in and the screening visit:

  Persistent very high albuminuria defined as UACR of ≥300 mg/g (≥34 mg/mmol) in 2 out of 3 first morning void samples and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m² but < 90 mL/min/1.73 m² (CKD-EPI)\(^{(50)}\)

  or
Persistent high albuminuria defined as UACR of $\geq 30 \text{ mg/g}$ but $< 300 \text{ mg/g}$ ($\geq 3.4 \text{ mg/mmol}$ but $< 34 \text{ mg/mmol}$) in 2 out of 3 first morning void samples and eGFR $\geq 30 \text{ mL/min/1.73 m}^2$ but $< 90 \text{ mL/min/1.73 m}^2$ (CKD-EPI)\(^{(50)}\)

[...]

- Subjects treated with at least the minimal recommended dose of an ACEI and/or ARB for at least 3 months without any adjustments to this therapy for at least 4 weeks prior to the screening visit; subjects with an eGFR of $30 - 45 \text{ mL/min/1.73 m}^2$ (CKD-EPI)\(^{(50)}\) must also be treated with a non-potassium sparing diuretic at the screening visit and without any adjustments to this therapy for at least 4 weeks prior to the screening visit

[...]

13.1.2.4 Section 5.2.1 Withdrawal

Old:

[...]

- If any investigational drug other than the study drug is used

- If serum potassium is $\geq 5.6$ and $\leq 6.0$ mmol/L measured in the central or local laboratory, a second blood sample has to be taken as soon as possible but at the latest within 48 hours. If serum potassium is again $\geq 5.6$ mmol/L in the locally or centrally analyzed blood sample, study drug has to be discontinued permanently (see Table 4-2).

- If serum potassium is $>6.0$ mmol/L in the centrally analyzed blood sample but $\leq 5.6$ mmol/L in the locally analyzed sample, treatment with study drug can be continued. If serum potassium is $>6.0$ mmol/L in the centrally analyzed blood sample and $\geq 5.6$ mmol/L in the locally analyzed sample, study drug has to be discontinued permanently (see Table 4-2).

- If serum potassium is $>6.0$ mmol/L in the locally analyzed blood sample, study drug has to be discontinued permanently (see Table 4-2).

Discontinuation of study drug due to an increase in serum potassium is considered an adverse event of special interest (see Section 7.5.1.6) and has to be reported to the sponsor along the timelines set for SAEs, i.e. within 24 hours of the investigator’s awareness as described in Section 7.5.1.4. In any case, adverse events of special interest fulfilling any seriousness criterion should be reported as SAE (see also Section 7.5.1.1)

[...]
- Temporary withdrawal of study drug for at least 5 consecutive days of the treatment period or, starting from Visit 4 (Day 60±2) onwards, a total number of temporary withdrawal days ≥10% of the total duration of the treatment period completed at that time

- If the randomization code is broken via Interactive Voice / Web Response System (IXRS)

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of “dropout” (see below) is regarded a “screening failure”.

[...]

- Adverse events

For subjects who withdraw consent for release of information, vital status only should be obtained. The measures taken for follow-up must be documented in the source data. Vital status should be obtained at the end of the follow-up period (i.e. 30±5 days after last intake of study drug).

[...]

New:

[...]

- If any investigational drug other than the study drug is used

- Please refer to section 4 (chapter Monitoring of blood potassium) for discontinuation due to hyperkalemia

- If the randomization code is broken

Discontinuation of study drug due to an increase in potassium is considered an adverse event of special interest (see Section 7.5.1.6) and has to be reported to the sponsor along the timelines set for SAEs, i.e. within 24 hours of the investigator’s awareness as described in Section 7.5.1.4.

[...]

- Temporary withdrawal of study drug for at least 5 consecutive days of the treatment period or, starting from Visit 4 (Day 60±2) onwards, a total number of temporary withdrawal days ≥10% of the total duration of the treatment period completed at that time
A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of “dropout” (see below) is regarded a “screening failure”.

 […]

- Adverse events

For subjects who withdraw consent for release of information, no follow-up data can be obtained.

The measures taken for follow-up must be documented in the source data. Vital status should be obtained at the end of the follow-up period (i.e. 30±5 days after last intake of study drug).

 […]

### 13.1.2.5 Section 6.3 Treatment assignment

**Old:**

 […]

The randomization will be stratified by region (Europe, North America, Asia, others), and type of albuminuria (very high albuminuria or high albuminuria at baseline). No formal caps will be applied within the stratification levels. However, a ratio of approximately 50:50 for high and very high albuminuria is planned to be reached.

 […]

**New:**

 […]

The randomization will be stratified by region (Europe, North America, Asia, others [Australia, Israel and South Africa]), and type of albuminuria (very high albuminuria or high albuminuria at screening). No formal caps will be applied within the stratification levels. However, a ratio of approximately 50:50 for high and very high albuminuria is planned to be reached with an imbalance of up to 65:35 being considered as acceptable. In order to achieve a proportion of at least 35% of subjects with very high albuminuria, single centers or countries predominantly recruiting subjects with high albuminuria may be closed during the course of the study. In case that less than 35% of subjects randomized were diagnosed with very high albuminuria, the sample size may be increased to approximately 90 subjects in each treatment group (in case it can be reduced to 75 subjects per treatment arm after the dose decision meeting) in order to increase the amount of available safety data per treatment arm for the subjects with very high albuminuria.
13.1.2.6 Section 6.9 Prior concomitant therapy

Old:
Subjects must be on an ACEI or ARB for at least 3 months and treated with at least the minimal recommended dose of that ACEI or ARB, but not both, for at least 4 weeks prior to the screening visit. Subjects with an eGFR of 30 - 45 mL/min/1.73 m² (CKD-EPI)(50) must also be treated with a non-potassium sparing diuretic at randomization. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. At the screening visit, subject’s treatment should be stable and without any adjustments for at least 4 weeks as documented in the subject’s medical records.

Prior and concomitant medications not allowed during the study include:

- Concomitant treatment with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued for the run-in and the treatment periods

Note: Any potassium supplementation should be stopped at randomization if serum potassium levels are within the normal range. If serum potassium levels are low at randomization or at any of the following visits, potassium supplementation can be continued or re-started until serum potassium values are within the normal range again.

New:
Subjects must be on an ACEI and/or ARB for at least 3 months and treated with at least the minimal recommended dose of that ACEI or ARB, but not both for at least 4 weeks prior to the screening visit. Subjects with an eGFR of 30 - 45 mL/min/1.73 m² (CKD-EPI)(50) must also be treated with a non-potassium sparing diuretic at screening. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. At the screening visit, subject’s treatment should be stable and without any adjustments for at least 4 weeks as documented in the subject’s medical records.

Prior medication that was discontinued to comply with the eligibility criteria of the study should also be recorded in the eCRF.

[...]
Prior and concomitant medications not allowed during the study include:

- Concomitant treatment with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued for the run-in and the treatment periods

**Note:** Any potassium supplementation should be stopped at randomization if potassium levels are within the normal range. If potassium levels are low at randomization or at any of the following visits, potassium supplementation can be continued or re-started until potassium values are within the normal range again
### 13.1.2.7 Section 7.1.1 Tabulated overview

**Old:**

```
[...]
```

#### Table 7-1: Schedule of procedures

<table>
<thead>
<tr>
<th></th>
<th>Run-in visit ≤ -12 weeks</th>
<th>Screening visit ≤ -14 days</th>
<th>Visit 1 * (Baseline) (Day 1)</th>
<th>Visit 2 (Day 7±2)</th>
<th>Visit 3 (Day 30±2)</th>
<th>Visit 4 (Day 60±2)</th>
<th>Visit 5 (Day 90±2)</th>
<th>PD visit</th>
<th>FU visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK blood sample (study drug intake at study center)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Urine sample (central lab)</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>Blood samples for iohexol plasma clearance</td>
<td>X</td>
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<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

FU = follow-up; PD = premature discontinuation; PK = pharmacokinetic

- **d** The signed written informed consent must be available before any study procedures are conducted.
- **e** Smoking status and alcohol consumption to be recorded at run-in visit. Smoking status to be checked at all visits.
- **f** Height as well as waist and hip circumference will only be measured once at the run-in visit.

---

**n** At selected sites only (see Section 7.6.5)

**o** In all Italian centers, subjects who are not sensitive to iodine or other iodinated contrast agents can be included in this sub-study, if they consent.
Table 7-1: Schedule of procedures

<table>
<thead>
<tr>
<th></th>
<th>Run-in visit ≤ -12 weeks</th>
<th>Screening visit ≤ -14 days</th>
<th>Visit 1* (Baseline) (Day 1)</th>
<th>Visit 2 (Day 7±2)</th>
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<th>Visit 5 (Day 90±2)</th>
<th>PD visit b</th>
<th>FU visit c</th>
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</thead>
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<td>PK blood sample (study drug intake at study center) d</td>
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<tr>
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<tr>
<td>Ambulatory blood pressure monitoring g</td>
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<td></td>
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</tr>
<tr>
<td>Pregnancy test i</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FU = follow-up; PD = premature discontinuation; PK = pharmacokinetic

[...]

d The signed written informed consent must be available before any study procedures are conducted.

e Smoking status and alcohol consumption to be recorded at run in visit. Smoking status to be checked at all visits, except at Follow up visit.

f Height as well as waist and hip circumference will only be measured once at the run-in visit.

[...]

n At selected sites only (see Section 7.6.5)

o In all Italian centers, subjects who are not sensitive to iodine or other iodinated contrast agents can be included in this sub-study, if they consent.

p All 3 urine samples should be taken before first intake of study drug

q All 3 urine samples should be taken before last intake of study drug
13.1.2.8 Section 7.1.4 Run-in visit

Old:

[...]

- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

- Assess inclusion and exclusion criteria (see Section 5.1)

- In all subjects, 1 re-assessment of eGFR and serum-potassium is allowed at the run-in visit. If 1 of the 3 UACR measurements is missing, but the other 2 are consistent, these values can be used to assess subject’s eligibility for this study.

- Schedule the screening visit for ≤12 weeks after the run-in visit

Note: At the end of this run-in period, each subject should receive at least the minimal recommended dose of conventional therapy according to local guidelines which consists either of an ACEI or ARB, but not both. Subjects with an eGFR of 30-45 mL/min/1.73 m² (CKD-EPI) must also be treated with a non-potassium-sparing diuretic at randomization. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. The treatment should be stable and without any adjustments for at least 4 weeks before the screening visit.

New:

[...]

- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

- Pregnancy test (to be performed at local laboratory, see Section 7.6.1.2)

- Assess inclusion and exclusion criteria (see Section 5.1)

- In all subjects, 1 re-assessment of eGFR and serum potassium is allowed at the run-in visit. If 1 of the 3 UACR measurements is missing, but the other 2 are consistent, these values can be used to assess subject’s eligibility for this study.

- Schedule the screening visit if applicable

Note: At the end of this run-in period, each subject should receive at least the minimal recommended dose of conventional therapy according to local guidelines which consists either of an ACEI or ARB, but not both. Subjects with an eGFR of
30 - 45 mL/min/1.73 m² (CKD-EPI)\(^{50}\) must also be treated with a non-potassium-sparing diuretic at screening. Treatment can be commenced during the run-in period if the subject was not treated with a non-potassium-sparing diuretic at the run-in visit. The treatment should be stable and without any adjustments for at least 4 weeks before the screening visit.

### 13.1.2.9 Section 7.1.5 Screening visit

**Old:**

The following procedures and assessments will be performed within ≤14 days prior to randomization but after the run-in visit (for a subject who is already treated with an ACEI or ARB for at least 3 months and on at least the minimal recommended dose of that ACEI or ARB and without any adjustments for at least 4 weeks, the run-in visit will be considered as screening visit and the subject can be randomized within the next 14 days if she / he meets all the inclusion and none of the exclusion criteria):

[...]

- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)
- Adverse events (see Section 7.5)
- In all subjects, 1 re-assessment of eGFR and serum-potassium is allowed at the screening visit. If 1 of the 3 UACR measurements is missing, but the other 2 are consistent, these values can be used to assess subject’s eligibility for this study.

[...]

**New:**

The following procedures and assessments will be performed within ≤14 days prior to randomization but after the run-in visit (for a subject who is already treated with an ACEI and/or ARB for at least 3 months and on at least the minimal recommended dose of that ACEI or ARB and without any adjustments for at least 4 weeks, the run-in visit may be considered as screening visit and the subject can be randomized within the next 14 days if she / he meets all the inclusion and none of the exclusion criteria):

[...]

- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)
- Pregnancy test (to be analyzed at the local laboratory, see Section 7.6.1.2)
- Adverse events (see Section 7.5)
In all subjects, 1 re-assessment of eGFR and serum potassium is allowed at the screening visit. If 1 of the 3 UACR measurements is missing, but the other 2 are consistent, these values can be used to assess subject’s eligibility for this study.

13.1.2.10 Section 7.1.6 Visit 1 (Baseline and randomization) - Day 1

Old:

[...]

Laboratory examinations in blood including hematology and clinical chemistry (full central lab) (to be analyzed at central laboratory, see Section 7.6.1)

Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)

Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

[...]

New:

[...]

Laboratory examinations in blood including hematology and clinical chemistry (full central lab) (to be analyzed at central laboratory, see Section 7.6.1)

Urinalysis (to be analyzed at central laboratory, see Section 7.6.1). All 3 urine samples for this visit should be collected before first study drug intake.

Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

[...]

13.1.2.11 Section 7.1.7 Visit 2– Day 7±2

Old:

The following procedures and assessments will be performed during this visit:

Concomitant medications (see Section 6.9)

[...]

[...]

[...]

[...]

[...]

[...]

[...]

[...]
New:

The following procedures and assessments will be performed during this visit:

- Smoking status
- Concomitant medications (see Section 6.9)

13.1.2.12 Section 7.1.10 Visit 5 – Day 90±2

Old:

[...]

- Iohexol plasma clearance (at selected sites only, see Section 7.6.5)
- Urinalysis (to be analyzed at central laboratory, see Section 7.6.1)
- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

[...]

New:

[...]  

- Iohexol plasma clearance (at selected sites only, see Section 7.6.5)
- Urinalysis (to be analyzed at central laboratory, see Section 7.6.1). All 3 urine samples for this visit should be collected before last study drug intake.
- Urinalysis (to be analyzed at local laboratory, see Section 7.6.1.2)

[...]

13.1.2.13 Section 7.3.3 Health-related quality of life

Old:

[...]

- Items 17-28: Symptoms / Problems (12); general health, activity limits, ability to accomplish desired tasks, depression/anxiety, energy level, social activities

[...]
New:

[…]

- Items 17-28: Symptoms / Problems (12); general health, activity limits, ability to accomplish desired tasks, depression/anxiety, energy level, social activities (item 28 not applicable in this study)

[…]

13.1.2.14 Section 7.5.1.6 Adverse events of special safety interest

Old:
A confirmed increase in serum potassium ≥5.6 mmol/L and subsequent discontinuation of study treatment is considered an adverse event of special interest and has to be reported to the sponsor according to the timelines set for SAEs, i.e. within 24 hours of the investigator’s awareness as described in Section 7.5.1.4. In any case, adverse events of special interest fulfilling the seriousness criteria, should be reported as SAE (see also Section 7.5.1.1).

New:
An increase in potassium ≥5.6 mmol/L and subsequent discontinuation of study treatment is considered an adverse event of special interest and has to be reported to the sponsor as SAE, i.e. within 24 hours of the investigator’s awareness as described in Section 7.5.1.4.

13.1.2.15 Section 7.6.1.1 Central laboratory

Old:
[…]

Clinical chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), cholesterol [high density lipoprotein (HDL), low density lipoprotein (LDL), total], triglycerides, creatinine, eGFR (CKD-EPI(50)), blood urea nitrogen, uric acid, bilirubin, sodium, potassium, magnesium, total protein, albumin, and high-sensitivity C-reactive protein (hs-CRP) will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit.

[…]

Blood sample for biomarkers: NT-proBNP, BNP, troponin T, aldosterone, cystatin C, and galectin-3 will be performed at Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or the premature discontinuation visit as well as at the follow-up visit.
If the blood sample for the central laboratory taken at any visit is hemolytic or not evaluable, the measurements have to be repeated as soon as possible.

**Urinalysis:** urine albumin-to-creatinine ratio (measured in first morning void urine samples collected at the subject’s home on 3 consecutive days) and urinary sodium-potassium ratio will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit.

**Albuminuria**

The determination of albuminuria will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit.

For the determination of albuminuria, first morning void urine collections will be used which can be collected at the subject’s home on 3 consecutive days. Subjects must use the first morning urine after getting up for these first morning void urine samples.

If one of the following cases is reported, the subject will be asked to repeat urine sampling as soon as practical and come again to the study center: febrile illness, flu, urinary tract infection, menstruation, or unusual physical exercises.

[...]

**New:**

[...]

**Clinical chemistry:** aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl trasnpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), cholesterol [high density lipoprotein (HDL), low density lipoprotein (LDL), total], triglycerides, creatinine, eGFR (CKD-EPI[50]), blood urea nitrogen, uric acid, bilirubin, sodium, serum potassium, magnesium, total protein, albumin, and high-sensitivity C-reactive protein (hs-CRP) will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit.

[...]

**Blood sample for biomarkers:** NT-proBNP, BNP, troponin T, aldosterone, cystatin C, and galectin-3 will be performed at Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or the premature discontinuation visit as well as at the follow-up visit.

If the blood sample for the central laboratory taken at any visit is missing or not evaluable, the measurements have to be repeated as soon as possible.
Urinalysis: urine albumin-to-creatinine ratio and urinary sodium-potassium ratio will be performed at the run-in visit and screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2), or at the premature discontinuation visit as well as at the follow-up visit and will be measured in the first morning void urine samples collected at the subject’s home on 3 consecutive days.

Subjects must use the first morning urine after getting up for these first morning void urine samples.

If one of the following cases is reported, the subject will be asked to repeat urine sampling as soon as practical and come again to the study center: febrile illness, flu, urinary tract infection, menstruation, or unusual physical exercises.

All 3 urine samples on Visit 1 (Day 1) and Visit 5 (Day 90±2) should be collected before the respective study drug intake.

[...]

13.1.2.16 Section 7.6.1.2 Local laboratory

Old:

[...]

It is expected that the local lab results will be available earlier than the central lab results allowing the investigator to take any required action as soon as possible. Regarding withdrawal of subjects because of increase in serum potassium, Table 4-2 outlines how to manage differences in results between the central and local labs. Local urinalysis using a dipstick will also be conducted.

Clinical chemistry [from Visit 1 (Day 1) to Visit 5 (Day 90±2)]

- Potassium
- Creatinine

Urinalysis [at the run-in visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), Visit 5 (Day 90±2) or the premature discontinuation visit, and the follow-up visit]

- Dipstick (to confirm sample validity for analysis)
New:

[...]

It is expected that the local lab results will be available earlier than the central lab results allowing the investigator to take any required action as soon as possible. Regarding withdrawal of subjects because of increase in potassium, Table 4-2 outlines how to manage differences in results between the central and local labs. Local urinalysis using a dipstick will also be conducted.

Clinical chemistry [from Visit 1 (Day 1) to Visit 5 (Day 90±2)]

- Potassium
- Creatinine

Urinalysis [at the run-in visit, screening visit, Visit 1 (Day 1), Visit 3 (Day 30±2), Visit 4 (Day 60±2), Visit 5 (Day 90±2) or the premature discontinuation visit, and the follow-up visit]

- Dipstick (to confirm sample validity for analysis). Results of the dipstick and confirmation about samples validity should be recorded in the source notes only. If more than 1 of the 3 UACR measurements is missing or invalid urine sample collection should be repeated (3 first morning void samples taken on 3 consecutive days).

Pregnancy test [at the run-in visit and the screening visit]

- Both serological as well as urine test is acceptable
- In case the run-in visit is regarded as screening visit it is sufficient to perform the pregnancy test at the run-in visit only

13.1.2.17 Section 8.1 General considerations

Old:

[...]

Doses which will be closed prematurely due to safety concerns will not be included in the primary analysis and in the ANCOVA models.

In case of any unexpected finding, further exploratory analyses might be performed.
New:

[...]

Doses which will be closed prematurely due to safety concerns will not be included in the primary analysis and in the ANCOVA models.

Baseline values will be defined as the last non-missing measurement before the first intake of study treatment. In case the last observation available prior to treatment is the measurement from the screening visit, this would be used as the baseline value. If the last observation prior to treatment is the measurement from the run-in visit, this value will only be used in case the run-in visit is the same visit as the screening visit. Otherwise baseline will be missing.

In case of any unexpected finding, further exploratory analyses might be performed.

13.1.2.18 Section 8.2 Analysis sets

Old:

Safety analysis set (SAF): All randomized subjects who have taken at least 1 dose of study drug.

[...]

New:

Safety analysis set (SAF): All randomized subjects who have taken at least 1 dose of study drug and with data after beginning of treatment.

[...]

13.1.2.19 Section 8.4.2 Analysis of primary efficacy variable

Old:

[...]

The UACR will be determined 3 times at each visit from first morning void urine samples collected on 3 consecutive days. For all analyses of UACR, the 3 measurements at 1 visit will be combined as follows: First, the coefficient of variation will be calculated for the 3 values. If the coefficient of variation exceeds 25%, the median from the measurements will be used for the analyses. The median in case of an even number of values will be defined as the geometric mean from the 2 middle values. If the coefficient of variation is 25% at the most, the geometric mean will be used.

In order to describe the course of UACR and the ratio of UACR to baseline for all visits, descriptive statistics will be provided including the geometric means, geometric standard deviations (SDs), and geometric coefficients of variation by treatment group and time point.
This will be done overall and separately for all subgroups defined in Section 8.4.6. Graphs displaying the geometric group means and SDs of the ratios vs. time will be generated.

Primarily, the aim is to demonstrate a dose-dependent effect of BAY 94-8862 with respect to the primary variable. For this purpose, an ANCOVA model will be fitted to the logarithmized ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline including a factor for treatment group, factors to adjust for the stratification factors (type of albuminuria and region) and the logarithmized baseline UACR as covariate. The UACR values and ratios will be transformed since the primary variable is considered to be approximately log-normally distributed, i.e. the log-values are considered to be normally distributed. In the event of a region with a relatively small number of subjects, this region might be pooled with another region for this analysis. The decision will be made during the blind data review meeting and documented in the Validity Report.

The primary hypothesis $H_0$: $L' \cdot \mu = 0$ will be tested by means of the F-test with a 1-sided significance level of 5%, where $\mu = (\mu_1, \ldots, \mu_k)'$ with $\mu_i =$ expected value for $\ln(UACR$ at Visit 5 (Day 90±2)) – $\ln(UACR$ at baseline) adjusted for baseline log-UACR and the stratification factors (type of albuminuria and region), where $i = 1, \ldots, k$ means the different $k$ dose groups. The alternative hypothesis $H_1$: $L' \cdot \mu > 0$ which shall demonstrate a linear trend in the group means will be tested by applying the linear contrast $L_k'$ which reflects the intervals between the dose groups.

[...]

If the primary hypothesis could be rejected, the single dose groups will be compared to placebo by a hierarchical procedure starting with the highest dose of BAY 94-8862 vs. placebo within the same ANCOVA model in order to investigate the dose-response relationship further. The 1-sided significance level of 40% will be kept for each pairwise comparison and the procedure will stop when the first hypothesis could not be rejected.

[...]

New:

[...]

The UACR will be determined 3 times at each visit from first morning void urine samples collected on 3 consecutive days. For all analyses of UACR, the 3 measurements at 1 visit will be combined as follows: First, the coefficient of variation will be calculated for the 3 values. If the coefficient of variation exceeds 25%, the median from the measurements will be used for the analyses. The median in case of an even number of values will be defined as the geometric mean from the 2 middle values. If the coefficient of variation is 25% at the most, the geometric mean will be used. If a scheduled measurement is missing or invalid and an additional unscheduled measurement was performed instead, this unscheduled measurement should be used to determine the UACR if the measurement was within two days after the last
scheduled measurement. If all three assessments have been repeated, then these will be used for analysis. For Visit 1 (Day 1), only measurements taken prior to the first intake of study drug will be used to determine the respective visit assessment. If only one UACR measurement at a visit is available, then this measurement will not be used for analysis.

In order to describe the course of UACR and the ratio of UACR to baseline for all visits, descriptive statistics will be provided including the geometric means, geometric standard deviations (SDs), and geometric coefficients of variation by treatment group and time point. This will be done overall and separately for all subgroups defined in Section 8.4.6. Graphs displaying the geometric group means and SDs of the ratios vs. time will be generated.

Primarily, the aim is to demonstrate a dose-dependent effect of BAY 94-8862 with respect to the primary variable. For this purpose, an ANCOVA model will be fitted to the logarithmized ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline including a factor for treatment group, factors to adjust for the stratification factors (type of albuminuria and region) and the logarithmized baseline UACR as covariate nested within type of albuminuria. The UACR values and ratios will be transformed since the primary variable is considered to be approximately log-normally distributed, i.e. the log-values are considered to be normally distributed. In the event of a region with a relatively small number of subjects, this region might be pooled with another region for this analysis. The decision will be made during the blind data review meeting and documented in the Validity Report.

The primary hypothesis $H_0$: $L_k' \mu = 0$ will be tested by means of the F-test with a 1-sided significance level of 5%, where $\mu = (\mu_1, \ldots, \mu_k)'$ with $\mu_i = \text{expected value for ln(UACR at Visit 5 (Day 90±2))} - \text{ln(UACR at baseline)}$ adjusted for baseline log-UACR and the stratification factors (type of albuminuria and region), where $i = 1, \ldots, k$ means the different k dose groups. The alternative hypothesis $H_1$: $L_k' \mu > 0$ which shall demonstrate a linear trend in the group means will be tested by applying the linear contrast $L_k'$ which reflects the intervals between the dose groups.

If the primary hypothesis could be rejected, the single dose groups will be compared to placebo by a hierarchical procedure starting with the highest dose of BAY 94-8862 vs. placebo within the same ANCOVA model in order to investigate the dose-response relationship further. The 1-sided significance level of 5% will be kept for each pairwise comparison and the procedure will stop when the first hypothesis could not be rejected.
13.1.2.20 Section 8.4.3.1 Ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline

Old:

The logarithmized ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline will be analyzed by a mixed-effects repeated measures model with treatment group as the main effect, factors for the stratification levels (type of albuminuria and region), a factor for time, the interaction factor between treatment and time and the logarithmized baseline value as covariate.

[...]

New:

[...]

The logarithmized ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline will be analyzed by a mixed-effects repeated measures model with treatment group as the main effect, factors for the stratification levels (type of albuminuria and region), a factor for time, the interaction factor between treatment and time and the logarithmized baseline value as covariate nested within type of albuminuria.

[...]

13.1.2.21 Section 8.4.3.5 Health-related quality of life

Old:

[...]

The frequencies of changes from baseline at Visit 3 (Day 30±2), Visit 5 (Day 90±2), and the follow-up visit will be presented regarding the categories improvement / no change / worsening for the summary scores and single items. Incidences of improvement and improvement / no change will be compared between the BAY 94-8862 treatment groups and the placebo treatment group by means of the $\chi^2$ test.

With regard to the EQ-5D-3L, the summary score and the scores for each dimension including changes from baseline will be described by treatment group and overall by visit using number of observations, minimum, first quartile, median, third quartile, and maximum, including the changes from baseline. The above specified statistics plus the arithmetic mean and standard deviations will be provided for the EQ VAS and its changes to baseline. Furthermore, the frequencies of answers to all individual questions will be provided by treatment group and overall by visit. The frequencies of changes from baseline at Visit 3 (Day 30±2), Visit 5 (Day 90±2), and the follow-up visit will be presented regarding the categories improvement /
no change / worsening for the summary score, each dimension and the EQ VAS. Incidences of improvement and improvement/no change in the summary scores and the EQ VAS will be compared between the BAY 94-8862 treatment groups and the placebo treatment group by means of the $\chi^2$ test.

New:

[...]

The frequencies of changes from baseline at Visit 3 (Day 30±2), Visit 5 (Day 90±2), and the follow-up visit will be presented regarding the categories improvement / no change / worsening for the single items.

With regard to the EQ-5D-3L, the summary score including changes from baseline will be described by treatment group and overall by visit using number of observations, minimum, first quartile, median, third quartile, and maximum, including the changes from baseline. The above specified statistics plus the arithmetic mean and standard deviations will be provided for the EQ VAS and its changes to baseline. Furthermore, the frequencies of answers to all individual questions will be provided by treatment group and overall by visit. The frequencies of changes from baseline at Visit 3 (Day 30±2), Visit 5 (Day 90±2), and the follow-up visit will be presented regarding the categories improvement / no change / worsening for each dimension.

13.1.2.22 Section 8.4.5.1 Adverse events

Old:

[...]

AEs that occurred or worsened on or after the date of the first dose of study drug up to 3 days after the date of the last dose of study drug will be considered as TEAEs.

An overall summary of all TEAEs will be generated.

The number and incidence of non-treatment-emergent (pre-treatment) AEs, TEAEs, treatment-emergent SAEs, treatment-emergent study drug-related AEs, treatment-emergent study drug-related SAEs, treatment-emergent AEs causing discontinuation of study drug and treatment-emergent non-serious AEs will be summarized by treatment group and overall in total and using MedDRA terms grouped by system organ class and preferred terms.

[...]

New:

[...]

AEs that occurred or worsened on or after the first dose of study drug up to 3 days after the date of the last dose of study drug will be considered as TEAEs.
An overall summary of all TEAEs will be generated.

The number and incidence of subjects with non-treatment-emergent (pre-treatment) AEs, TEAEs, treatment-emergent SAEs, treatment-emergent study drug-related AEs, treatment-emergent study drug-related SAEs, treatment-emergent AEs causing discontinuation of study drug and treatment-emergent non-serious AEs will be summarized by treatment group and overall in total and using MedDRA terms grouped by system organ class and preferred terms.

[...]

13.1.2.23 Section 8.4.5.2 Laboratory data

Old:

[...]

Serum potassium will be further assessed by displaying the number and incidence of serum potassium values \( \geq 5.6 \text{ mmol/L} \) and \( >6 \text{ mmol/L} \) by treatment, visit, and overall. This will also be done stratified by the subgroups, specified in Section 8.4.6.

[...]

New:

[...]

Serum potassium will be further assessed by displaying the number and incidence of subjects with serum potassium values \( \geq 5.6 \text{ mmol/L} \) and \( >6 \text{ mmol/L} \) by treatment, visit, and overall. This will also be done stratified by the subgroups, specified in Section 8.4.6.

[...]

13.1.2.24 Section 8.5 Planned interim analyses

Old:

No interim analysis is planned. However, data will be reviewed for safety and tolerability by an independent DMC.

New:

No formal interim analysis is planned. However, data will be reviewed for safety and tolerability by an independent DMC.
### 13.1.2.25 Section 8.6 Determination of sample size

*Old:*

With the primary analysis, dose-dependent effects on the primary variable, the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline, shall be demonstrated. Considering the method to detect an overall effect described in Section 8.4.2 (without covariate and adjustment for stratification factors), we estimated the power in 4 different scenarios for 6 treatment groups, as well as for 7 treatment groups (for the case of the addition of the 15 mg BAY 94-8862 once daily treatment group) with several sample sizes of subjects valid for FAS per treatment group. We simplified the planned ANCOVA to an analysis of variance (ANOVA) for the determination of sample size. We consider this approach as valid because the inclusion of the baseline log-UACR as a covariate will rather increase the power to detect a dose-dependent effect. For sample size calculations, the software nQuery Advisor® 7.0 was used.

The 4 scenarios used for the power calculations were designed based on the geometric means and geometric standard deviations of the UACR ratios from Study 14563 (ARTS) in subjects with high or very high albuminuria at baseline.

The results of the power estimations for 6 treatment groups (5 BAY 94-8862 groups and 1 placebo group) for sample sizes between 70 and 120 subjects per treatment group are summarized in Table 8-1.

#### Table 13-1: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862

<table>
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<tr>
<th>Sample size per treatment group</th>
<th>Total sample size</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
<th>SD of difference on log scale a</th>
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</tr>
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</table>

a Standard deviation of ln (UACR at Visit 5 (Day 90±2)) - ln (UACR at baseline)

The different assumed scenarios are (expected values of the logarithmized UACR ratios for the different treatments placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862):

- Scenario 1: ln(0.91), ln(0.87), ln(0.82), ln(0.74), ln(0.66), ln(0.59)
- Scenario 2: ln(0.91), ln(0.87), ln(0.82), ln(0.69), ln(0.60), ln(0.55)
- Scenario 3: ln(0.91), ln(0.82), ln(0.73), ln(0.58), ln(0.56), ln(0.55)
- Scenario 4: ln(0.91), ln(0.73), ln(0.64), ln(0.60), ln(0.57), ln(0.55)
A sample size of 90 subjects valid for FAS per treatment group would lead to 88% power in the worst case. For the best case assumed, the primary analysis would demonstrate a power of 96%.

With 90 evaluable subjects per treatment group, a total of 540 evaluable subjects are needed. Considering an assumed screening failure rate of up to 50% and an assumed dropout rate of 10%, 100 subjects per treatment group should be randomized and approximately 1200 subjects need to be enrolled.

The results of the power estimations in the case that 1 treatment group with 15 mg BAY 94-8862 will be added after the DMC decision, i.e. for 6 BAY 94-8862 treatment groups and 1 placebo group, are summarized in Table 8-2 for sample sizes between 70 and 80 subjects per treatment group (fewer subjects than in Table 8-1 are considered here since the additional dose leads to an increase in power).

<table>
<thead>
<tr>
<th>Sample size per treatment group</th>
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<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
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<th>SD of difference on log scale a</th>
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<tr>
<td>70</td>
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a Standard deviation of ln (UACR at Visit 5 (Day 90±2)) - ln (UACR at baseline)
The different assumed scenarios are (expected values of the logarithmized UACR ratios for the different treatments placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, and 15 mg BAY 94-8862):
- Scenario 1: ln(0.91), ln(0.87), ln(0.82), ln(0.74), ln(0.66), ln(0.59), ln(0.46)
- Scenario 2: ln(0.91), ln(0.87), ln(0.82), ln(0.69), ln(0.60), ln(0.55), ln(0.48)
- Scenario 3: ln(0.91), ln(0.82), ln(0.73), ln(0.58), ln(0.56), ln(0.55), ln(0.54)
- Scenario 4: ln(0.91), ln(0.73), ln(0.64), ln(0.60), ln(0.57), ln(0.55), ln(0.52)

A sample size of 75 subjects valid for FAS per treatment group would lead to a power between 87% (worst case scenario) and 99% (best case scenario).

With the same assumptions on screening failure and dropout rate, a total of 83 subjects per treatment group should be randomized. The approximate number of enrolled subjects would not exceed 1200 subjects, as calculated for 6 treatment groups.

Sample size considerations for adding the 20 mg BAY 94-8862 treatment group as well are not considered here since reliable assumptions can hardly be made and it is expected that the power will even increase with 75 additional subjects valid for FAS for 20 mg BAY 94-8862.

Sample size considerations for adding the 20 mg BAY 94-8862 treatment group are not considered here. It is expected that the power will increase even in case a plateau will be reached with 75 additional subjects valid for FAS for 20 mg BAY 94-8862.
New:

With the primary analysis, dose-dependent effects on the primary variable, the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline, shall be demonstrated. Considering the method to detect an overall effect described in Section 8.4.2 (without covariate and adjustment for stratification factors), we estimated the power in 5 different scenarios for 6 treatment groups, as well as for 7 treatment groups (for the case of the addition of the 15 mg BAY 94-8862 once daily treatment group) with several sample sizes of subjects valid for FAS per treatment group. We simplified the planned ANCOVA to an analysis of variance (ANOVA) for the determination of sample size. We consider this approach as valid because the inclusion of the baseline log-UACR as a covariate will rather increase the power to detect a dose-dependent effect. For sample size calculations, the software nQuery Advisor® 7.0 was used.

The 5 scenarios used for the power calculations were designed based on the geometric means and geometric standard deviations of the UACR ratios from Study 14563 (ARTS) in subjects with high or very high albuminuria at baseline, where the fifth scenario should reflect a reduced effect in case of a much higher rate of high albuminuria subjects compared to very high albuminuria subjects.

The results of the power estimations for 6 treatment groups (5 BAY 94-8862 groups and 1 placebo group) for sample sizes between 70 and 120 subjects per treatment group are summarized in Table 8-1.

<table>
<thead>
<tr>
<th>Sample size per treatment group</th>
<th>Total sample size</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
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<th>SD of difference on log scale a</th>
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<td>89</td>
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</tbody>
</table>

a Standard deviation of ln (UACR at Visit 5 (Day 90±2)) - ln (UACR at baseline)

The different assumed scenarios are (expected values of the logarithmized UACR ratios for the different treatments placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862):

- Scenario 1: ln(0.91), ln(0.87), ln(0.82), ln(0.74), ln(0.66), ln(0.59)
- Scenario 2: ln(0.91), ln(0.87), ln(0.82), ln(0.69), ln(0.60), ln(0.55)
- Scenario 3: ln(0.91), ln(0.82), ln(0.73), ln(0.58), ln(0.56), ln(0.55)
- Scenario 4: ln(0.91), ln(0.73), ln(0.64), ln(0.60), ln(0.57), ln(0.55)
- Scenario 5: ln(0.95), ln(0.91), ln(0.86), ln(0.79), ln(0.71), ln(0.65)

A sample size of 90 subjects valid for FAS per treatment group would lead to 88% power in the worst case among scenarios 1 to 4 and still to a power of 80% for Scenario 5. For the best case assumed, the primary analysis would demonstrate a power of 96%.
With 90 evaluable subjects per treatment group, a total of 540 evaluable subjects are needed. Considering an assumed screening failure rate of up to 50% and an assumed dropout rate of 10%, 100 subjects per treatment group should be randomized and approximately 1200 subjects need to be enrolled.

The results of the power estimations in the case that 1 treatment group with 15 mg BAY 94-8862 will be added after the DMC decision, i.e. for 6 BAY 94-8862 treatment groups and 1 placebo group, are summarized in Table 8-2 for sample sizes between 70 and 90 subjects per treatment group (fewer subjects than in Table 8-1 are considered here since the additional dose leads to an increase in power).

Table 13-4: Power [%] to demonstrate dose-dependent effects for given sample sizes valid for the full analysis set, significance level: 0.05 (1-sided), treatments: placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg BAY 94-8862

<table>
<thead>
<tr>
<th>Sample size per treatment group</th>
<th>Total sample size</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
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<td>88</td>
</tr>
</tbody>
</table>

a Standard deviation of ln (UACR at Visit 5 (Day 90±2)) - ln (UACR at baseline)  
The different assumed scenarios are (expected values of the logarithmized UACR ratios for the different treatments placebo, 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, and 15 mg BAY 94-8862):  
Scenario 1: ln(0.91), ln(0.87), ln(0.82), ln(0.74), ln(0.66), ln(0.59), ln(0.46)  
Scenario 2: ln(0.91), ln(0.87), ln(0.82), ln(0.69), ln(0.60), ln(0.55), ln(0.48)  
Scenario 3: ln(0.91), ln(0.82), ln(0.73), ln(0.58), ln(0.56), ln(0.55), ln(0.54)  
Scenario 4: ln(0.91), ln(0.73), ln(0.64), ln(0.60), ln(0.57), ln(0.55), ln(0.52)  
Scenario 5: ln(0.95), ln(0.91), ln(0.86), ln(0.79), ln(0.71), ln(0.65), ln(0.64)

A sample size of 75 subjects valid for FAS per treatment group would lead to a power among scenarios 1 to 4 between 87% (worst case scenario) and 99% (best case scenario) and for scenario 5 to a power of 83%.

With the same assumptions on screening failure and dropout rate, a total of 83 subjects per treatment group should be randomized. The approximate number of enrolled subjects would not exceed 1200 subjects, as calculated for 6 treatment groups.

Sample size considerations for adding the 20 mg BAY 94-8862 treatment group are not considered here. It is expected that the power will increase even in case a plateau will be reached with 75 additional subjects valid for FAS for 20 mg BAY 94-8862.

14. Appendices

Not applicable.
A randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy

Short title: Safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy (ARTS-DN)

Test drug: BAY 94-8862

Study purpose: Safety and efficacy

Clinical study phase: IIb

Date: 20-SEP-2013

Study No.: 16243

Version: 1.0

Author: Alexander Pieper

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This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.
# Table of Contents

1. Introduction ........................................................................................................... 5
2. Study Objectives .................................................................................................... 6
3. Study Design ......................................................................................................... 7
4. General Statistical Considerations ......................................................................... 9
   4.1 General Principles .......................................................................................... 9
   4.2 Handling of Dropouts .................................................................................. 10
   4.3 Handling of Missing Data .............................................................................. 10
   4.4 Interim Analyses and Data Monitoring ......................................................... 10
   4.5 Data Rules ..................................................................................................... 11
       4.5.1 Screening ................................................................................................ 11
       4.5.2 Baseline values ..................................................................................... 11
       4.5.3 Change from baseline .......................................................................... 12
       4.5.4 Other data handling ............................................................................. 12
       4.5.5 Subgroup analyses ............................................................................... 13
   4.6 Validity Review ............................................................................................... 14
5. Analysis Sets ......................................................................................................... 14
   5.1 Safety analysis set (SAF) .............................................................................. 14
   5.2 Full analysis set (FAS) ................................................................................ 14
   5.3 Per-protocol analysis set (PPS) ..................................................................... 14
   5.4 Listing only set (LOS) ................................................................................ 15
   5.5 Pharmacokinetic analysis set (PKS) ............................................................. 15
6. Statistical Methodology ....................................................................................... 15
   6.1 Population characteristics ............................................................................ 15
       6.1.1 Disposition ............................................................................................ 15
       6.1.2 Demography and other baseline characteristics .................................. 15
       6.1.3 Medical History ................................................................................... 16
       6.1.4 Concomitant Medications .................................................................... 16
       6.1.5 Treatment duration, extent of exposure and compliance ..................... 17
       6.1.6 Smoking status ..................................................................................... 17
   6.2 Efficacy ........................................................................................................... 17
       6.2.1 Analysis of primary efficacy variable ................................................... 17
           6.2.1.1 Primary analysis .......................................................................... 18
           6.2.1.2 Supportive analyses for the primary endpoint ............................ 20
           6.2.1.3 Mixed model for ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline .......................... 21
           6.2.1.4 Changes in albuminuria .................................................................. 22
       6.2.2 Analysis of further exploratory efficacy variables ................................. 22
           6.2.2.1 Decrease in eGFR ......................................................................... 22
           6.2.2.2 Efficacy biomarkers ...................................................................... 23
           6.2.2.3 Health-related quality of life .......................................................... 23
   6.3 Pharmacokinetics / pharmacodynamics ....................................................... 24
       6.3.1 Pharmacokinetics .................................................................................. 24
6.3.2 Pharmacodynamics ................................................................. 25
6.4 Safety ......................................................................................... 25
6.4.1 Adverse events ............................................................... 25
6.4.2 Laboratory parameters .................................................. 26
6.4.3 Other additional safety variables .................................. 28
   6.4.3.1 Safety Biomarkers ................................................... 28
   6.4.3.2 Vital Signs ............................................................. 28
   6.4.3.3 Weight and BMI ..................................................... 29
   6.4.3.4 ECG ................................................................. 29
   6.4.3.5 Ambulatory blood pressure monitoring (ABPM) ..... 29
   6.4.3.6 Iohexol plasma clearance ...................................... 29
7. Document history and changes in the planned statistical analysis .................. 30
   7.1 Changes to planned analysis ........................................... 30
   7.2 Document history ............................................................ 31
8. References ................................................................................. 31
### Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<td>ABPM</td>
<td>Ambulatory blood pressure monitoring</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
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<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACEIs</td>
<td>angiotensin-converting enzyme inhibitors</td>
</tr>
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<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blockers</td>
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<td>AUC</td>
<td>Area under the curve</td>
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<td>Body Mass Index</td>
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<tr>
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<td>EQ-5D-3L</td>
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</tr>
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<td>HF</td>
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<td>heart failure with reduced ejection fraction</td>
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<td>L</td>
<td>Liter</td>
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<tr>
<td>LLOQ</td>
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<td>Last Observation Carried Forward</td>
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<td>Least square means</td>
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<td>Modification of Diet in Renal Disease</td>
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<td>mg</td>
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<td>μg</td>
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<td>myocardial infarction</td>
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1. Introduction

According to the World Health Organization (WHO), diabetes mellitus currently affects more than 240 million people worldwide, and the number is predicted to rise to more than 360 million by 2030. Diabetic nephropathy (DN) represents the most common cause of end-stage renal failure in the United States (US) and accounts for approximately 40% of all new patients entering end-stage renal disease (ESRD) programs and approximately 45% of patients receiving renal replacement therapy.

Overall approximately 20 to 30% of patients with type 1 or type 2 diabetes mellitus develop evidence of nephropathy although there is considerable variability by type in terms of disease progression.
Until recently, DN was very much a disease of Western countries, but in the future, Asian countries are likely to represent the bulk of the DN population, due to their size but also to the predilection of Asian diabetic patients to develop renal complications.

In patients with DN, albuminuria at baseline is an important factor to predict ESRD in addition to lowering albuminuria, and it is now clearly demonstrated that interruption of the renin-angiotensin system (RAS) reduces the risk of progression to ESRD. However, an impact on overall survival has not yet been demonstrated.

Despite significant progress over the last decade, the ultimate goal of preventing the development of ESRD in DN is still far from being reached. Without therapy, the average time from diagnosed chronic kidney disease (CKD) to ESRD is about 4 to 5 years. On therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), this time is extended by 1 to 2 years only. DN remains the primary diagnosis leading to ESRD in the US and 1 of the top 2 or 3 in most other countries.

Current therapies for DN rely on the control of albuminuria through inhibition of the RAS with ACEIs or ARBs. Despite initial down-regulation of the release of aldosterone by the adrenal glands, up to 50% of the patients treated with a RAS blocker develop an increase in plasma aldosterone within 6 to 12 months after the initiation of treatment. Several studies have shown a direct relationship between increases in plasma aldosterone after ACEI treatment and increases in albuminuria and decreases in kidney function. Explorative clinical studies in adults have shown a potential role for mineralocorticoid receptor antagonists (MRAs), when added to RAS blockers, to delay the development of ESRD further.

In this situation BAY 94-8862 is a novel non-steroidal MRA. In vitro investigations have demonstrated superior selectivity vs. spironolactone and improved potency vs. eplerenone. These properties have also been demonstrated in a number of nonclinical in vivo investigations, which showed BAY 94-8862 to be effective in reducing mortality in models of heart failure and stroke; and in reducing cardiac remodeling and end-organ lesions.

This study (Study 16243) will investigate short-term efficacy and safety of different oral doses of BAY 94-8862 given once daily over 90 days in comparison to placebo in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN.

This SAP is based on the study protocol (Version 1.0 approved on 04 March 2013) and describes the final analysis of the study.

2. **Study Objectives**

Primary objective of the study is

- To investigate the change of urinary albumin-to-creatinine ratio (UACR) after treatment with different oral doses of BAY 94-8862 given once daily from baseline to Visit 5 (Day 90±2)
Further exploratory objectives of the study are

- To assess safety and tolerability of these doses by assessing the effects on serum potassium and renal function
- To assess change in health-related quality of life (HRQoL) from baseline to 90 days of treatment assessed by the Kidney Disease Quality of Life (KDQOL 36) and EuroQol Group 5 dimension, 3 level (EQ-5D-3L) questionnaires

3. **Study Design**

This study will be conducted in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN using a multi-center, randomized, adaptive, double-blind, placebo-controlled, parallel-group design.

Planned number of subjects valid for the full analysis set: approximately 90 subjects in each treatment group in case that no additional treatment group will be added, and approximately 75 subjects in each treatment group if at least one of the additional treatment groups will be added and not closed due to safety reasons during the further course of the study.

Following an open-label run-in and screening period of up to 12 weeks in total, eligible subjects will be randomized to 1 of up to 7 doses of BAY 94-8862 or placebo on top of standard of care treatment to receive a 90-day study drug treatment. Initially, the following 5 doses of BAY 94-8862 will be compared to placebo in a double-blind manner: 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg once daily. Subjects will be assigned to the treatment groups with balanced samples sizes by a stratified randomization with stratification factors region (Europe, North America, Asia, others), and type of albuminuria (very high albuminuria or high albuminuria at baseline). After safety and tolerability of the initial doses have been assessed by an independent DMC, none or up to 2 further doses of BAY 94-8862 may be introduced: 15 mg and 20 mg once daily. After the DMC decision, the randomization will be adapted in order to obtain approximately equally balanced sample sizes across all treatment groups at the end of the study. Dose arms may be closed prematurely due to safety concerns at any DMC Meeting.

If serum potassium is ≥5.6 and ≤6.0 mmol/L measured in the central or local laboratory, a second blood sample has to be taken as soon as possible but at the latest within 48 hours. If serum potassium is again ≥5.6 mmol/L in the locally or centrally analyzed blood sample, study drug has to be discontinued permanently for the respective subject.

If serum potassium is >6.0 mmol/L in the centrally analyzed blood sample but <5.6 mmol/L in the locally analyzed sample, treatment with study drug can be continued. If serum potassium is >6.0 mmol/L in the centrally analyzed blood sample and ≥5.6 mmol/L in the locally analyzed sample, study drug has to be discontinued permanently.
If serum potassium is >6.0 mmol/L in the locally analyzed blood sample, study drug has to be discontinued permanently.

The premature discontinuation visit will take place as soon as possible after premature discontinuation of study drug due to any reason except death or lost to follow-up.

If the locally analyzed blood sample is missing or the result is inconclusive and the central laboratory result is not available, another blood sample must be taken as soon as possible but at the latest within 48 hours. The assessment of serum potassium during the course of the study is also presented in Table 3–1.

### Table 3–1 Monitoring of serum potassium during the treatment period

<table>
<thead>
<tr>
<th>Result of first serum potassium measurement</th>
<th>&lt;5.6 mmol/L</th>
<th>5.6 - 6.0 mmol/L</th>
<th>&gt;6.0 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central lab</td>
<td>Continue study drug</td>
<td>Repeat serum potassium measurement within 48 hours&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Check serum potassium in locally analyzed sample&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Local lab</td>
<td>Continue study drug</td>
<td>Repeat serum potassium measurement within 48 hours&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Discontinue study drug permanently</td>
</tr>
</tbody>
</table>

<sup>a</sup> If serum potassium is again <5.6 mmol/L in the repeat blood sample, discontinue study drug permanently.

If serum potassium is <5.6 mmol/L in the repeat blood sample, continue study drug.

<sup>b</sup> If serum potassium is ≥5.6 mmol/L in the (first) locally analyzed blood sample, discontinue study drug permanently.

If serum potassium is <5.6 mmol/L in the (first) locally analyzed blood sample, continue study drug.

### Figure 3–1 Study design of study 16243

FU = follow-up; OD = once daily; DMC = Data Monitoring Committee

Reference Number: BPD-SOP-060
Supplement Version: 5
4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

The analysis will be based on the Global Standard Tables (Version 2.0) and the Clinical Pharmacology Standards (CLIPS) (Version 1.2) where appropriate.

The validity of subjects for allocation to various analysis sets will be assessed in an ongoing manner in several validity review meetings and decisions will be documented in the validity review reports prior to unblinding (conditional validity for PK analysis set). This SAP might be updated based on the results of the validity review meetings.

All variables will be analyzed by descriptive statistical methods. The number of data available, mean, standard deviation (SD), minimum, median, and maximum will be calculated for metric data. The geometric mean, SD and coefficient of variation (CV) will be provided instead of the arithmetic mean and SD for the variables where lognormal distributions are assumed. Frequency tables will be generated for categorical data.

All subjects will be analyzed according to the actual treatment group.

For log-transformed UACR, safety and efficacy biomarkers, scores of questionnaires and the safety parameters serum potassium, estimated Glomerular Filtration Rate (eGFR) and serum creatinine normally distributed data are assumed and ANCOVA models are planned as statistical analyses. In case of signs for not approximately normally distributed data (e.g. identified by graphical illustration in combination with test for normality), either nonparametric methods instead of ANCOVA models or transformation methods (e.g. log transformation) will be applied and summary statistics for lognormally distributed variables will include geometric means, SDs and CVs. If applicable, these methods will be described in a SAP amendment prior to unblinding of the study.

The laboratory parameter eGFR will be calculated based on the CKD-EPI formula for all analyses specified in this SAP.

Descriptive summary statistics for safety and efficacy variables stratified by the stratification factors or by the subgroups defined in Section 4.5.5 will only include baseline and the scheduled Visits 3 (Day 30±2), 4 (Day 60±2) and 5 (Day 90±2).

Dose arms which were closed prematurely due to safety concerns will not be included in the primary analysis and in the ANCOVA models or \( \chi^2 \) test procedures.

In case of any unexpected finding, further exploratory analyses might be performed.
4.2 Handling of Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a “dropout” if the subject has been randomized (even if no study drug has been taken). Dropouts will not be replaced. Data from subjects who prematurely terminated the study will be used to the maximum extent possible. The number and percentage of subjects who did not complete the treatment epoch or the follow-up epoch, as well as the primary reason for discontinuation, will be displayed by treatment group and overall as described in Section 6.1.1.

In the 90-day treatment period of this study, a dropout rate of approximately 30% is expected, i.e. there will be a high number of missing UACR values at Visit 5 (Day 90±2). 10% of the subjects are expected to drop out during the first month and another 20% during the following 2 months. Dropouts after the first month are expected to be due to worsening renal function or uncontrolled hypertension. The remaining dropouts are expected to be due to clinical outcomes or hyperkalemia. While albuminuria might not be influenced in subjects with clinical outcomes or hyperkalemia, a worsening albuminuria is expected in cases of worsening renal function or uncontrolled hypertension.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the electronic Case Report Form (eCRF).

Analyses focusing on the exploration of any potential missing data pattern are described in Section 6.1.1, 6.1.2 and 6.1.5.

For the primary analyses of the primary endpoint [the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline] described in Section 6.2.1.1 a last observation carried forward (LOCF) approach will be used to impute missing data. Thereby, the higher UACR value from the premature discontinuation measurement and follow-up measurement will be used for subjects who prematurely terminated the study (worst case imputation on subject level).

Sensitivity analyses using other imputation methods will be performed for the primary endpoint and are described in Section 6.2.1.2.

4.4 Interim Analyses and Data Monitoring

No formal interim analysis is planned. Data will be reviewed for safety and tolerability by an independent data monitoring committee (DMC). One DMC has been established for this study and the parallel Phase IIb study of BAY 94-8862 in worsening chronic heart failure and left ventricular systolic dysfunction and either type 2 diabetes mellitus with or without chronic kidney disease or moderate chronic kidney disease alone (study 14564). The first DMC meeting will take place when a combined total number of 30 subjects has been randomized in both BAY 94-8862 Phase IIb studies. Thereafter, DMC meetings will take
place approximately every other month. In addition, an overview regarding SAEs reported in the 2 studies will be sent to the DMC chair on a weekly basis. When a minimum of 150 subjects have been randomized in this study, a dose decision meeting will take place. During this meeting, the 5 initial treatment groups of BAY 94-8862 will be assessed for safety and tolerability (in particular changes in serum potassium, e.g. number of subjects with hyperkalemia, and changes in eGFR, e.g. number of subjects with an eGFR decrease ≥30%) by the independent DMC. Based on this assessment, none or up to 2 of the additional treatment groups will be introduced into the study. The detailed plan for these assessments will be covered in the DMC charter (Version 1.0 approved on 6 June 2013), the analysis planned to be provided to the DMC is described in a separate statistical analysis plan for the DMC (Version 1.0 approved on 25 June 2013) and a DMC specific specification of tables, listings and figures (Version 1.0 approved on 25 June 2013). The statistical analysis for the DMC Meetings will be performed by an independent statistical analysis center.

The DMC will review the data in a semi-blinded manner (treatment arms coded by A, B, C, D etc.) and in an unblinded manner for the dose decision meeting. There are no predefined stopping conditions for the ongoing safety monitoring of this trial. However, the DMC may recommend termination, temporary suspension of the study, and intervention of treatment arm or modification of the study.

4.5 Data Rules

General data rules are described in this section, further data rules for specific parameters or analyses are specified in the respective subsections of Section 6.

4.5.1 Screening

For a subject who is already treated with an ACEI or ARB for at least 3 months and on at least the minimal recommended dose of that ACEI or ARB, without any adjustments in her or his medical treatment for at least 4 weeks, and fulfilling all the inclusion and none of the exclusion criteria, the run-in visit will be considered as screening visit.

In case that the run-in visit will be considered as screening visit for a subject, all assessments performed on the run-in visit for the respective subject will be analyzed only for the screening visit.

4.5.2 Baseline values

Baseline values will be defined as the last non-missing measurement before the first intake of study treatment. In case the last observation available prior to treatment is the measurement from the screening visit, this would be used as the baseline value. If the last observation prior to treatment is the measurement from the run-in visit, this value will only be used in case the run-in visit is as well the screening visit. Otherwise baseline will be missing.
If more than one measurement was planned for a scheduled time point (i.e. blood pressure measurements and heart rate), the average value of the last set of measurements per time point prior to treatment will be used as the baseline value.

4.5.3 Change from baseline

Change from baseline will in general be displayed as absolute change from baseline defined as the difference to baseline, i.e.:

\[
\text{Absolute change} = \text{Post baseline value} - \text{baseline value}.
\]

Some parameters will be additionally analyzed as relative change defined as

\[
\text{Relative change} = 100 \times \left(\frac{\text{post baseline value} - \text{baseline value}}{\text{baseline value}}\right).
\]

For specific analyses, the relative decrease of a variable will be analyzed instead of the relative change. The relative decrease is equivalent to the negative of the relative change and defined as

\[
\text{Relative decrease} = 100 \times \left(\frac{\text{baseline value} - \text{post baseline value}}{\text{baseline value}}\right).
\]

4.5.4 Other data handling

In case of repeated measurements for pre-treatment visits and the baseline visit, the closest measurement prior to the treatment start will be used for analysis instead of the scheduled measurements. At all post-treatment visits and if not stated otherwise, only the values at scheduled measurements will be used for analysis.

For values which are < LLOQ (Lower limit of quantification), half the value of the LLOQ will be used for analysis. Differences between two values < LLOQ will be assigned values of 0.

In case of log-normally distributed data, descriptive statistics other than minimum, maximum and median will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification. In tables showing descriptive statistics, where values below LLOQ are included, these descriptive statistics will be marked.

Only the data provided by the central laboratory will be used for analysis, values from local laboratories will not be used in the statistical analysis and listed only.

Serum potassium values >6.0 mmol/L in the centrally analyzed blood sample which cannot be confirmed by the locally analyzed sample (serum potassium locally <5.6 mmol/L) will not be considered for analysis.

For serum potassium values only, in the cases in which samples are repeated, the following approach will be used. If the potassium value from the repeated sample is \( \geq 5.6 \text{ mmol/l} \), the
higher of the two values (value from the original and repeated sample) will be used. If the value from the repeated sample is < 5.6 mmol/l, this value will be used for analysis. However, all available potassium values will be listed.

4.5.5 Subgroup analyses

The following subgroup factors (including the stratification factors region and type of albuminurira) will be considered for descriptive and explorative analyses:

- Age (18 to ≤45 years, >45 to ≤65 years, >65 to ≤75 years, and >75 years)
- Age (≤ median and > median)
- Region (Europe, North America, Asia, others [Australia, Israel and South Africa])
- Gender (male, female)
- Race (white, black, Asian, other)
- Baseline BMI (≤30, >30)
- Baseline serum potassium value (≤ median and > median)
- eGFR values (CKD-EPI) (≤ median and > median)
- eGFR values (CKD-EPI) (30-45, 45-60, and > 60 ml/min/1.73m² )
- Baseline eGFR (CKD-EPI formula) between 30 and 45 ml/min/1.73m² and baseline serum potassium ≥ 4.5 mmol/L (yes, no)
- Concomitant medication (ACEI or ARB)
- Type of albuminuria: Very high albuminuria (UACR ≥300 mg/g) vs. high albuminuria (UACR ≥30 mg/g but <300 mg/g) at screening
- Very high albuminuria (UACR ≥300 mg/g) vs. high albuminuria (UACR ≥30 mg/g but <300 mg/g) at baseline [present only if different from type of albuminuria at screening]
- Systolic blood pressure at baseline (>90 to <140 mmHg, ≥140 to <180 mmHg, and ≥180 mmHg; ≤ median and > median)
- Concomitant medication (beta-blocker vs. no beta-blocker at baseline, diuretic vs. no diuretic at baseline)

- Potassium supplementation vs. no potassium supplementation at any time during the study

- Allowed CYP3A4 inhibitors vs. no CYP3A4 inhibitor as concomitant medication (Note: Subjects taking non-allowed CYP3A4 inhibitors will not be considered for this subgroup analysis)

However, if the total number of subjects in a subgroup category is <15, the analysis for that level of the subgroup will not be performed.

4.6 Validity Review

The results of the validity review meetings will be documented in the validity review reports and may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the validity review meetings will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

Assignment of analysis set

The allocation of each subject to analysis sets will be documented before the database lock (conditional validity for PK analysis set).

Final decisions regarding the assignment of subjects to analysis sets will be made during the validity review meetings and documented in the validity review reports (see Section 4.6).

5.1 Safety analysis set (SAF)

All randomized subjects who have taken at least 1 dose of study drug and with data after beginning of treatment.

5.2 Full analysis set (FAS)

All subjects of the SAF who have baseline and at least 1 post-baseline UACR value.

5.3 Per-protocol analysis set (PPS)

All subjects of the FAS who have valid UACR data at Visit 5 (Day 90±2) and have no major protocol deviations (defined in the protocol deviation document). Major protocol deviations are for example:
- Intake of any prohibited concomitant medication
- Overall compliance with study drug intake of <80% or >120%

5.4 Listing only set (LOS)

The LOS will not be used as an analysis set and accordingly, subjects will not be assigned explicitly to this set during the validity review meetings. The LOS consists of all other subjects screened who did not receive any dose of study drug or for whom no data after beginning of treatment are available. Their data will be presented in the individual subject data listings but will not be included in any statistical analysis.

5.5 Pharmacokinetic analysis set (PKS)

All BAY 94-8862-treated subjects with at least 1 valid BAY 94-8862 plasma concentration and without protocol deviation, which would interfere with the evaluation of the PK data.

6. Statistical Methodology

6.1 Population characteristics

Population characteristic analyses, except for subject disposition, will be performed in SAF, if not stated otherwise.

6.1.1 Disposition

The number of subjects enrolled, randomized and valid for the safety analysis set, full analysis set, per protocol analysis set and pharmacokinetic analysis set will be summarized overall and by treatment groups, country and investigator in a table. The number of subjects discontinuing the run-in/screening epoch together with the primary reason for discontinuation will be presented overall. The number of subjects discontinuing the treatment and follow-up epoch together with the primary reason for discontinuation will be presented by treatment groups and overall in separate tables. In addition, the number of subjects with major and minor protocol deviations will be presented overall and by investigator and country for each treatment group and in total. The frequencies of each major protocol deviation will be presented by treatment group and total.

6.1.2 Demography and other baseline characteristics

All demographic data and baseline characteristics will be tabulated by treatment group and overall.
Demography includes age, sex, race, ethnicity, region (North America, Europe, Asia and others), body weight, categories for body weight, body height, BMI, hip and waist circumference, smoking history (never, former, current smoker) and alcohol consumption, while other baseline characteristics include baseline UACR, baseline NT-proBNP, baseline BNP, baseline galectin-3, baseline aldosterone, baseline serum potassium, categories for baseline serum potassium, baseline eGFR (calculated by CKD-EPI formula), baseline serum creatinine, baseline HbA1c, baseline troponin T, baseline cystatin C, baseline values for vital signs parameters (i.e. systolic blood pressure, diastolic blood pressure and heart rate) and the subgroup categories described in Section 4.5.5.

Weight will be summarized as a continuous variable, as well as categorized to >50 kg and ≤50 kg. Serum potassium will be analyzed as a continuous and a categorical variable with categories <4.5 mmol and ≥4.5 mmol.

The demographic table will also be presented by type of albuminuria (very high albuminuria or high albuminuria at baseline) and region (Europe, North America, Asia, others).

The description of demographic data (non-stratified) and other baseline characteristics will be repeated for all other analysis sets if they differ from the SAF.

Demographics and other baseline characteristics will be presented for the FAS separately for the subjects belonging to PPS or not (only for the overall treatment group).

6.1.3 Medical History

Medical history will be coded using MedDRA dictionary. Medical history will be presented for each MedDRA Primary System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall in a summary table.

6.1.4 Concomitant Medications

Concomitant medications will be coded using the most recent version of the WHO Drug Dictionary (WHO-DD). The number of subjects who took at least one concomitant medication, the number of subjects who took at least one medication that started and ended before administration of study drug and the number of subjects who took at least one concomitant medication that started after start of study drug will be presented by treatment group and overall using ATC classes and subclasses. Additionally, the above described tables will be repeated summarizing the number and incidence of subjects with medications in the drug groups of interest (ACEi, ARBs, β-blocker, diuretics, potassium supplements and allowed vs. non-allowed CYP3A4 inhibitors, CYP3A4 inducers and CYP2C8 inhibitors). A subject will be counted only once within each ATC class / subclass or drug group, respectively.
6.1.5  Treatment duration, extent of exposure and compliance

The analyses described in this section will be repeated for FAS and PPS if they differ from the SAF.

For subjects who withdraw prematurely from the study drug, compliance will be calculated up to the time of last dose.

Treatment duration (number of days with study drug intake, not including any gaps) will be summarized using descriptive statistics by treatment group and overall. In addition, treatment duration will be categorized to \( \leq 32 \) days, \( >32 - \leq 62 \) days and \( >62 \) days, and presented with the corresponding number and percentage of subjects by treatment group and overall.

A table will be presented with the absolute and relative frequencies of subjects still in the study at each visit. Kaplan-Meier plots for “Time to end of study treatment” will be provided.

The extent of exposure to study drug (total amount of intake in mg) will be summarized using descriptive statistics by treatment group and overall.

The compliance (as percentage) is calculated as:

\[
100 \times \frac{\text{Number of taken tablets}}{\text{Number of planned tablets}}.
\]

The number of planned tablets is calculated as: Treatment duration (days) \* Number of planned tablets per day. All tablets, including the dummy placebo tablets, are to be counted.

The compliance will be summarized descriptively by treatment group and overall. In addition, percent of compliance will be categorized into three groups, less than 80%, 80 to 120% and greater than 120%, and the categories will be summarized by treatment group and overall.

6.1.6  Smoking status

Changes in the smoking status will be summarized with number and percentage of subjects by treatment group.

6.2  Efficacy

6.2.1  Analysis of primary efficacy variable

The primary efficacy variable, the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline, will be analyzed for FAS (primary analysis) and PPS (supportive analysis). Further supportive analyses described in Section 6.2.1.2, Section 6.2.1.3, and Section 6.2.1.4 will be performed in FAS and PPS.
The primary analysis will focus on the on-treatment data (i.e. the actual treatment groups will be used).

The UACR will be determined 3 times at each visit from first morning void urine samples collected on 3 consecutive days. For all analyses of UACR, the 3 measurements at one visit will be combined as follows: First, the coefficient of variation will be calculated for the 3 values. If the coefficient of variation exceeds 25%, the median from the measurements will be used for the analyses. The median in case of an even number of values will be defined as the geometric mean from the 2 middle values. If the coefficient of variation is 25% at the most, the geometric mean will be used. If a scheduled measurement is missing or invalid and an additional unscheduled measurement was performed instead, this unscheduled measurement should be used to determine the UACR if the measurement was within two days after the last scheduled measurement. If all three assessments have been repeated, then these will be used for analysis. If only one UACR measurement at a visit is available, then this measurement will not be used for analysis. For Visit 1 (Day 1), only measurements taken prior to the first intake of study drug will be used to determine the respective visit assessment.

Imputation methods for missing Visit 5 (Day 90±2) data are described in Section 4.3 and Section 6.2.1.2.

### 6.2.1.1 Primary analysis

The analyses described in the following will be performed in FAS.

In the primary analyses described in the following, the LOCF approach in combination with an additional imputation rule for subjects who prematurely terminated the study (see Section 4.3) will be applied for missing Visit 5 (Day 90±2) of the primary endpoint. Sensitivity analyses on the imputation method are described in Section 6.2.1.2.

Primarily, the aim of the study is to demonstrate a dose-dependent effect of BAY 94-8862 with respect to the primary variable. For this purpose, an analysis of covariance (ANCOVA) model

\[ Y_{ijlm} = \eta + \alpha_i + \beta_j + \gamma_l + \zeta_l X_{ijlm} + \epsilon_{ijlm} \]

with

- \( Y_{ijlm} \) = Log-transformed ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline for Subject \( m \) \((m=1,\ldots,n)\), with \( n \) = Number of subjects valid for the analysis
- \( \eta \) = Overall mean
- \( \alpha_i \) = i-th treatment effect \((i=1,\ldots,k)\)
- \( \beta_j \) = j-th region effect \((j=1,\ldots,4)\)
- \( \gamma_l \) = l-th type of albuminuria effect \((l=1,2)\)
\[ \zeta_l = \text{effect of log-transformed baseline UACR within } l\text{-th type of albuminuria } (l=1,2) \]

\[ X_{ijlm} = \text{Log-transformed UACR at baseline of subject } m \text{ (m=1,\ldots,n)} \]

\[ \varepsilon_{ijlm} = \text{Random error of subject } m \text{ (m=1,\ldots,n)} \]

will be fitted to the log-transformed ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline including a factor for treatment group, factors to adjust for the stratification factors (type of albuminuria and region) and the log-transformed baseline UACR as covariate. As the baseline UACR defines the type of albuminuria, the log-transformed baseline UACR will be nested as covariate in type of albuminuria. The UACR values and ratios will be log-transformed since the primary variable is considered to be approximately log-normally distributed, i.e. the log-values are considered to be normally distributed.

The distributional model assumptions will be checked by inspection of residual plots of studentized residuals vs. normal order scores to check normality, and studentized residuals vs. predicted values to check homogeneity of variance.

The primary hypothesis

\[ H_0: L_k' \cdot \mu = 0 \]

will be tested by means of the F-test with a 1-sided significance level of 5%, where

\[ \mu = (\mu_1, \ldots, \mu_k) \text{' with } \mu_i = \text{expected value for log(UACR at Visit 5 (Day 90±2)) – log(UACR at baseline) adjusted for baseline log-UACR and the stratification factors (type of albuminuria and region)}, \]

\[ i=1,\ldots,k, \text{with } k = \text{number of treatment groups in analysis and} \]

\[ L_k' = \text{linear contrast reflecting the intervals between the dose groups (i.e. a difference of 1 between the weights of the contrast reflecting an amount of 1.25mg).} \]

The alternative hypothesis \[ H_1: L_k' \cdot \mu > 0 \] shall demonstrate a linear trend in the group means. The signs of the contrast were chosen according to this one-sided hypothesis.

The linear contrast \[ L_k' \] depends on the number of treatment groups. In case that the dose groups will be placebo (= 0 mg), 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862 (k=6), the linear contrast will be

\[ L_6' = (3.5, 2.5, 1.5, -0.5, -2.5, -4.5). \]

If 15 mg BAY 94-8862 will be added (k=7), the linear contrast will be

\[ L_7' = (4.714, 3.714, 2.714, 0.716, -1.286, -3.286, -7.286). \]
If both additional treatment groups, 15 mg and 20 mg BAY 94-8862, will be added, the linear contrast will be

\[ L_8' = (6.125, 5.125, 4.125, 2.125, 0.125, -1.875, -5.875, -9.875). \]

If doses were closed prematurely due to safety concerns, the linear contrast for the primary analysis reflecting the intervals between the remaining treatment groups will be defined in a SAP amendment.

The determination of the sample size (see Section 8.6 of the study protocol) was based on the primary hypothesis testing procedure described above.

If the primary hypothesis could be rejected, the single dose groups will be compared to placebo by a hierarchical procedure starting with the highest dose of BAY 94-8862 vs. placebo within the same ANCOVA model in order to investigate the dose-response relationship further. The one-sided significance level of 5% will be kept for each pairwise comparison and the procedure will stop when the first hypothesis could not be rejected.

Based on these analyses point estimates (LS-Means) and two-sided 90% confidence intervals of the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline will be calculated by re-transformation of the logarithmic results for each treatment group and for the treatment ratios (each BAY 94-8862 treatment group vs. placebo). In addition, the LS means for each treatment group and for the treatment ratios vs. placebo will be presented for each category of the stratification factors region and type of albuminuria.

The point estimates and two-sided 90% confidence intervals of the ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline will be plotted vs. the treatment groups.

### 6.2.1.2 Supportive analyses for the primary endpoint

Sensitivity analyses on the imputation method which will be performed in FAS only. The repetition of the primary analyses described in Section 6.2.1.1 will be performed in PPS. All other supportive analyses for the primary efficacy variable will be performed in FAS and PPS.

The primary LOCF approach will not be applied for the supportive analyses in FAS and PPS.

The analysis described in Section 6.2.1.1 will be repeated for the PPS.

Sensitivity analyses for the primary imputation method (LOCF), will be performed by repeating the primary analyses for several other imputation methods including:

- an observed case analysis (only subjects with a UACR value at Visit 5 (Day 90±2) available)
- an on-treatment LOCF approach (as for the primary analysis, but only including data until the premature discontinuation visit)
- a baseline observation carried forward analysis (BOCF, impute the baseline value for missing data, i.e. include all subjects of the FAS with missing Visit 5 (Day 90±2) data with a value of 1 for the primary efficacy variable)

- a mean value imputation (impute the value of the primary efficacy variable by the mean value of all non-missing values of the primary efficacy variable of the respective treatment group)

- a random imputation (impute the value of the primary efficacy variable by a random number from a normal distribution with mean and variance from the respective treatment group of the primary analysis. For reproducibility, the SAS seed number for creating the random numbers will be set to 1984).

Further analyses might be performed in case that these imputation methods seem to have a major impact on the results.

To investigate the relationship between treatment groups and stratification factors further, the primary analysis model described in Section 6.2.1.1 will be repeated with additional interaction terms for treatment group and region, as well as for treatment group and type of albuminuria. LS means and two-sided 90% confidence intervals of the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline will be calculated by re-transformation of the logarithmic results for each treatment group and for the treatment ratios (each BAY 94-8862 treatment group vs. placebo) for the overall treatment effect and on each category of the stratification factors (region and type of albuminuria).

In order to describe the course of UACR and the ratio of UACR to baseline for all visits, descriptive statistics will be provided including the geometric means, geometric standard deviations, and geometric coefficients of variation by treatment group and visit. This will be done overall and separately for all subgroups defined in Section 4.5.5.

Graphs displaying the geometric group means and SDs (non-stratified) of UACR values and the ratios to baseline vs. time will be generated.

Furthermore, it is intended to analyze which treatment group means of the log-transformed ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline are different from each other as an exploratory analysis. Therefore, the REGWQ (Ryan-Einot-Gabriel-Welsch Q) option of the SAS GLM (generalized linear model) procedure will be applied with a 2-sided significance level of 10%. The option performs a Ryan-Einot-Gabriel-Welsch multiple range test, which tests subsets of the group means for equality. This option is only available for unadjusted means.

### 6.2.1.3 Mixed model for ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline

The analysis will be performed in the FAS and PPS.
The log-transformed ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline will be analyzed within one model by a mixed-effects repeated measures model with treatment group as the main effect, factors for the stratification levels (type of albuminuria and region), a factor for time, the interaction factor between treatment and time and the log-transformed baseline value as covariate nested within type of albuminuria. The overall treatment effect will be tested (exploratively) at a two-sided significance level of 5%. Based on this analysis point estimates (LS-Means) and two-sided 95% confidence intervals of the overall treatment effect (across Visit 3 (Day 30±2), Visit 4 (Day 60±2) and Visit 5 (Day 90±2)) and of the ratio of UACR at each visit to UACR at baseline will be calculated by re-transformation of the logarithmic results for each treatment group and for the treatment ratios (each BAY 94-8862 treatment group vs. placebo). The SAS Procedure Proc Mixed will be used estimating covariance patterns within subjects to adjust for the within subject variance. For each treatment group a separate covariance pattern will be estimated based on an unstructured covariance.

6.2.1.4 Changes in albuminuria

A shift table will be provided displaying the number and incidence of subjects who changed from baseline to Visit 5 (Day 90±2) from very high albuminuria to high albuminuria, from very high albuminuria to albuminuria, from high albuminuria to albuminuria and from high albuminuria to very high albuminuria by treatment group and overall. The albuminuria category changes will only be considered as shifts, if they are accompanied by a UACR change of more than 30% from baseline to Visit 5 (Day 90±2).

6.2.2 Analysis of further exploratory efficacy variables

All exploratory efficacy variables will be analyzed in the FAS and PPS.

6.2.2.1 Decrease in eGFR

eGFR values will be summarized descriptively by treatment group and visit including relative changes to baseline.

Frequency tables will be generated for the number and incidence of subjects with a relative decrease in eGFR of ≥25% from baseline eGFR, with a decrease in eGFR of ≥30% from baseline eGFR, of ≥40% from baseline eGFR, and of ≥57% from baseline eGFR. The analysis will be performed for each visit and overall (subjects with at least 1 event in the respective category after start of study drug administration). The analyses will also be performed stratified by the subgroups, specified in Section 4.5.5.

Further analyses will be performed for eGFR in SAF as described in Section 6.4.2.
6.2.2.2 Efficacy biomarkers

Efficacy biomarkers, i.e. NT-proBNP, BNP, aldosterone and galectin-3, will be summarized descriptively by treatment group and visit including absolute changes to baseline. These analyses will be performed overall and separated by the stratification factors (type of albuminuria and region). Group means and standard deviations of efficacy biomarker values and changes to baseline (non-stratified) will be plotted versus time.

The change in efficacy biomarkers from baseline to Visit 3 (Day 30±2), Visit 4 (Day 60±2) and Visit 5 (Day 90±2) will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (region and type of albuminuria), and baseline value as covariate. The treatment effect will be tested at a two-sided significance level of 5%. Pairwise differences between each BAY 94-8862 treatment group and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

6.2.2.3 Health-related quality of life

The items of the KDQOL-36 are grouped as follows:

- Items 1-12: Physical Component Summary (PCS) / SF-12 physical health composite on physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health
- Items 1-12: Mental Component Summary (MCS) / SF-12 mental health composite on physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health (including a different weighting than the PCS)
- Items 13-16: Burden of Kidney Disease; interference with daily life, time to deal with kidney disease, frustration, feeling like a burden
- Items 17-27: Symptoms / Problems; general health, activity limits, ability to accomplish desired tasks, depression/anxiety, energy level, social activities
- Items 29-36: Effects of Kidney Disease; impact of fluid & diet limits, ability to work around the house and to travel, feeling depending on medical team, stress or worries, sex life, personal appearance

With regard to the KDQOL-36, the frequencies of answers to single items will be displayed by treatment group and overall by visit. In addition, domain scores for the 5 above defined domains will be calculated according to the KDQOL scoring instruction.1

The KDQOL-36 results will be described by visit and treatment group by presenting the domain scores (PCS, MCS, Burden of Kidney Disease, Symptoms / Problems, and Effects of...
Kidney Disease) by means of number of observations, minimum, first quartile, mean, SD, median, third quartile, and maximum, including the changes from baseline. It is not sensible to calculate an overall summary score.

In addition, the frequencies of changes from baseline at Visit 3 (Day 30±2), Visit 5 (Day 90±2) and the follow-up visit will be presented regarding the categories improvement / no change / worsening for the single items.

The change from baseline to Visit 3 (Day 30±2), Visit 5 (Day 90±2) and the follow-up visit in the 5 domain scores will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (region, type of albuminuria), and baseline value as covariate. The treatment effect will be tested at a two-sided significance level of 5%. Pairwise differences between each BAY 94-8862 treatment group and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

The EQ-5D-3L will be analyzed similarly. Summary scores will be calculated out of the 5 dimensions according to the scoring instructions from Europe and the US (refer to the EQ-5D-3L User Guide² and to the EQ-5D Value Sets³). The values and the changes from baseline of the summary scores and the EQ VAS will be summarized by treatment group and visit using the same descriptive statistics as for KCCQ. Furthermore, the frequencies of answers to all single items will be provided by treatment group and overall by visit as well as the frequencies of improvement, no change, and worsening for single items. The change from baseline to Visit 3 (Day 30±2), Visit 5 (Day 90±2) and the follow-up visit in the summary scores and the EQ VAS will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (region, type of albuminuria), and baseline value as covariate. The treatment effect will be tested at a two-sided significance level of 5%. Pairwise differences between each BAY 94-8862 treatment group and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

### 6.3 Pharmacokinetics / pharmacodynamics

#### 6.3.1 Pharmacokinetics

The pharmacokinetic analysis will be performed in the pharmacokinetic analysis set.

The plasma concentration vs. time data of BAY 94-8862 at Visit 3 (Day 30±2) and Visit 5 (Day 90±2) will be sorted in categories (depending on the distribution of data: e.g. 60 - 90, >90 - 120, 240 - 270 and >270 - 300 minutes or 60 - 75, >75 - 90, > 90 - 105, >105 - 120, 240 - 255, >255 - 270, >270 - 285 and >285 - 300 minutes for Visit 3 (Day 30±2), pre-dose, 30 - 60, >60 - 90, 180 - 210, and >210 - 240 minutes or pre-dose, 30 - 45, >45 - 60, >60 - 75, >75 - 90, 180 - 195, >195 - 210, >210 - 225, and >225 - 240 minutes for Visit 5 (Day 90±2)) and the following statistics will be calculated separated by dose, visit and category: geometric mean, standard deviation (re-transformed standard deviation of the logarithms) and coefficient
of variation (CV), arithmetic mean, standard deviation and CV, minimum, median, maximum value and the number of measurements.

Descriptive statistics other than minimum and maximum at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the descriptive statistics, a data point below LLOQ will be substituted by one half of this limit. In tables showing descriptive statistics, where values below LLOQ are included, these descriptive statistics will be marked.

Plots will be prepared separately by dose pooling all individual plasma concentrations (naive pooling) vs. actual relative study times (time of sample collection after time of study drug administration).

Measurements that were not taken within the pre-defined time windows for Visit 3 (Day 30±2) and Visit 5 (Day 90±2) [60 to 120 minutes and 240 to 300 minutes after study drug administration for Visit 3 (Day 30±2); pre-administration, 30 to 90 minutes and 180 to 240 minutes after drug administration for Visit 5 (Day 90±2)] will be excluded from the descriptive statistics and plots.

Further evaluation of the concentration data will be performed using Population PK methods, followed by PK/PD analyses. These analyses will be described in a separate SAP outside of this document and will be reported under separate cover.

### 6.3.2 Pharmacodynamics

Not applicable.

### 6.4 Safety

Safety analyses will be performed in SAF.

The analysis of the treatment duration, extent of exposure and compliance are described in Section 6.1.5.

#### 6.4.1 Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, latest version available prior to data base freeze). A listing will be provided linking the original investigator terms and the coded terms.

Adverse Events (AEs) that occurred or worsened on or after the first dose of study drug up to 3 days after the date of the last dose of study drug will be considered as treatment emergent AEs (TEAEs).
A confirmed increase in serum potassium ≥5.6 mmol/L and subsequent discontinuation of study drug is considered an adverse event of special interest.

An overall summary of all AEs and TEAEs will be generated by treatment group and overall.

The number and incidence of subjects with non-treatment-emergent (pre-treatment) AEs, TEAEs, treatment-emergent SAEs, treatment-emergent study drug-related AEs, treatment-emergent study drug-related SAEs, TEAEs causing discontinuation of study drug, TEAEs of special interest, treatment-emergent non-serious AEs, non-serious AEs, TEAEs by maximum intensity, treatment-emergent serious AEs by maximum intensity, drug-related TEAEs by maximum intensity, TEAEs by worst outcome and treatment-emergent SAEs by worst outcome will be summarized by treatment group and overall using MedDRA terms grouped by Primary System Organ Class (SOC) and Preferred Term (PT).

In case of events with different intensity within a subject, the maximum reported intensity will be used. If intensity is missing, the event will be considered as severe. Similarly, if the same event is reported as both unrelated and related to the study drug within a subject, the event will be reported as related to study drug. If the drug relationship is missing, the event will be considered as being related to the study drug.

The number and incidence of subjects with treatment emergent study drug related AEs will in addition be displayed by treatment group and overall for the subgroup categories of allowed CYP3A4 inhibitors vs. no CYP3A4 inhibitor as concomitant medication (Section 4.5.5) using MedDRA terms grouped by SOC and PT.

Separate tables summarizing TEAEs, treatment-emergent study drug-related AEs, and SAEs that occurred in more than 5% of the subjects will be provided.

Deaths, SAEs and AEs leading to study drug discontinuation will be listed separately.

6.4.2 Laboratory parameters

The laboratory parameter UACR will not be included in any of the analyses described in this section. UACR analysis will only be presented for efficacy analyses as described in Section 6.2.1.

Summary statistics including changes to baseline will be calculated by treatment group and visit for all quantitative laboratory parameters, e.g. for hematology, clinical chemistry and urinalysis.

For the eGFR the relative change will be displayed in addition to the absolute change from baseline.

Summary statistics for serum potassium, eGFR and serum creatinine will also be repeated by treatment group and visit separately for each of the stratification levels (region, type of albuminuria).
For log 10(10*urinary sodium / potassium ratio) a normal distribution can be assumed. Therefore, geometric statistics and ratios to baseline will be presented for this parameter.

The number of subjects with transitions from baseline with respect to reference ranges categories (low, normal, high) will be provided by treatment group and visit. In addition, the number of subjects with treatment emergent abnormal laboratory values above or below the normal range will be tabulated by the laboratory parameter and treatment group and overall.

For the special safety parameters serum potassium, eGFR and serum creatinine the means and standard deviations of laboratory values and changes to baseline of the treatment groups will be plotted versus time.

The special safety parameters will be further assessed by displaying the number and incidence of subjects with safety events as described below by treatment group, visit and overall (subjects with at least 1 event in the respective category after start of study drug administration). This will also be performed stratified by the subgroups, specified in Section 4.5.5. The summaries will be performed for the number and incidence of subjects with

- serum potassium ≥5.6 mmol/L and >6 mmol/L
- relative decrease in eGFR of ≥25%, ≥30%, ≥40% and ≥57%
- eGFR < 30 ml/min/1.73m²
- increase in serum creatinine >0.3 mg/dL and >0.5 mg/dL.

The percentage of subjects with the respective events (non-stratified) at any time during the study will be compared between each BAY 94-8862 treatment group and the placebo treatment group by applying separate $\chi^2$ tests with continuity correction. Estimates and two-sided 90% confidence intervals will be provided for each treatment group and the treatment differences. Clopper Pearson confidence intervals will be calculated for each treatment group, while for treatment differences the exact unconditional confidence limits will be calculated.

Subjects with serum potassium ≥5.6 mmol/L or a relative decrease in eGFR ≥30% will be listed with their full profile for the respective parameter.

The absolute change in serum potassium, eGFR and serum creatinine from baseline to Visit 3 (Day 30±2), Visit 4 (Day 60±2) and Visit 5 (Day 90±2) will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (region, and type of albuminuria) and baseline value as covariate. The treatment effect will be tested at a two-sided significance level of 5%. Pairwise differences between each BAY 94-8862 treatment group and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.
6.4.3 Other additional safety variables

6.4.3.1 Safety Biomarkers

Safety biomarkers, i.e. troponin T and cystatin C, will be summarized descriptively by treatment group and visit including absolute changes to baseline. These analyses will be performed overall and separated by the stratification factors (region and type of albuminuria). Group means and standard deviations of safety biomarker values (including a medical threshold of 0.049999 μg/L for Troponin T) and changes to baseline (non-stratified) will be plotted versus time.

The change in safety biomarkers from baseline to Visit 3 (Day 30±2), Visit 4 (Day 60±2) and Visit 5 (Day 90±2) will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (region and type of albuminuria) and baseline value as covariate. The treatment effect will be tested at a two-sided significance level of 5%. Pairwise differences between each BAY 94-8862 treatment group and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

In addition, the laboratory results of the safety biomarker Troponin T will be summarized with the numbers and incidences of subjects with values > 99 percentile of a normal reference population (upper reference limit) and > 5* 99 percentile of a normal reference population by treatment group and visit as well as overall (subjects with at least 1 event in the respective category after start of study drug administration) as described by the Third Universal Definition of Myocardial Infarction \(^4\). The value of the upper reference limit, i.e. the 99 percentile of a normal reference population, as provided by the central laboratory, is 0.049999 μg/L.

6.4.3.2 Vital Signs

At the corresponding visits, three measurements of vital signs parameters will be taken in sitting position at time intervals of about 2 minutes. Averages of non-missing values of these three measurements will be calculated and used for the statistical analysis. If only one of the planned measurements is available, this value will be used.

Vital signs values will be summarized by treatment group and visit using descriptive statistics including absolute changes from baseline. The analysis will be repeated for SBP stratified by the baseline SBP ≤ its median or > its median, as well as stratified by baseline SBP >90 - <130 mmHg, 130 – <160 mmHg and ≥ 160 mmHg.

Group means and standard deviations of vital signs values and changes to baseline (non-stratified) will be plotted versus time.
6.4.3.3  **Weight and BMI**

The values and the changes from baseline will be summarized by treatment group and visit using descriptive statistics for weight and BMI.

6.4.3.4  **ECG**

ECG parameters will be summarized by treatment group and visit using descriptive statistics including absolute changes from baseline.

ECGs considered as invalid will be excluded from the analysis. ECGs considered as invalid for QT analysis will be excluded from the QT analysis.

Group means and standard deviations of ECG values and changes to baseline will be plotted versus time.

The number of subjects with abnormal electrocardiogram findings will be presented by visit.

A summary of QTc interval prolongations will be provided by visit and treatment group.

6.4.3.5  **Ambulatory blood pressure monitoring (ABPM)**

The multiple assessments per visit [screening, Visit 4 (Day 60±2) and Visit 5 (Day 90±2)] will be summarized as averages for night and day time and as minimum and maximum (for day and night time). Day time averages will be calculated based on assessments between 6 am and 10 pm, while night time averages will be calculated for assessments between 10 pm and 6 am.

Invalid measurements (the minimum percentage of successful readings must be ≥ 80% per visit) will be excluded from the statistical analysis.

The day and night time averages, minimums and maximums from the ABPM will be summarized by treatment group and visit using descriptive statistics including absolute changes from baseline.

Group means and standard deviations of the 24-hour profile will be plotted versus time for each visit.

6.4.3.6  **Iohexol plasma clearance**

Summary statistics including changes to baseline will be calculated by treatment group and visit for iohexol plasma clearance.
7. Document history and changes in the planned statistical analysis

7.1 Changes to planned analysis

The protocol defines the SAF as all randomized subjects who have taken at least one dose of study medication. For the LOS the protocol states that it consists of all other subjects screened who did not receive any dose of study drug or for whom no data after beginning of treatment are available. This includes randomized and treated subjects without any further data. As the two specifications overlap it was decided to add to the definition of the SAF the specification “with data after beginning on treatment”.

The ANCOVA model for the primary analysis includes according to the protocol a factor for treatment group, the stratification factors (region and type of albuminuria) and the log-transformed baseline UACR as a covariate. As the baseline UACR defines the type of albuminuria, the covariate log-transformed baseline UACR and the stratification factor “Type of albuminuria” are not independent. To adjust for this, the ANCOVA model was newly specified with a nested effect of log-transformed baseline UACR within “Type of albuminuria” and otherwise as defined in the protocol. This model will estimate for each type of albuminuria a separate slope for the covariate. In addition, the protocol states that a region might be pooled with another region, if the sample size within these region is very small. In order to present the actual stratification within the primary analysis, the pooling of regions will not be performed in any case.

Changes in albuminuria and the mixed model for the ratios of UACR at Visit 3 (Day 30 ±2), Visit 4 (Day 60 ±2) and Visit 5 (Day 90 ±2) to UACR at baseline are described in the protocol as further exploratory efficacy analyses. In order to describe the complete analyses based on UACR within the same subsection, these specific analyses on change in albuminuria and the mixed model for the ratios of UACR at Visit 3 (Day 30 ±2), Visit 4 (Day 60 ±2) and Visit 5 (Day 90 ±2) to UACR at baseline are described in Section 6.2.1 (Analysis of primary efficacy variable) as well. In addition, the protocol describes also the change from albuminuria to high albuminuria, which cannot be presented as subjects with albuminuria at baseline will not be eligible for the study.

The protocol defines UACR not only as an efficacy variable, but also as a safety variable. As UACR is intensively analyzed for FAS and PPS in the efficacy analysis, UACR will not additionally be analyzed for the SAF.

Items 28a and 28b of the KDQOL questionnaire are excluded from this study as these items refer to problems of dialysis which are not relevant to the present study population. Therefore the domain score Symptoms / Problems consists of Items 17-27 instead of 17-28.

The protocol defines separate analyses for scores for each dimension of the EQ-5D. However, a score for each dimension is not meaningful and instead the 5 dimensions can be summarized to a single summary score (see Section 6.2.2.3).
For the KDQOL-Questionnaires scores and the EQ-5D questionnaire scores the protocol defines analyses based on categories improvement / no change / worsening (Frequency tables and a $\chi^2$ Test for treatment comparison). As a clinical meaningful change from baseline could be defined for both questionnaire scores the frequency tables will only be presented for the single items and not for the questionnaire scores. The treatment comparison will be performed based on an ANCOVA model with treatment group as the main effect, factors for the stratification levels (region and type of albuminuria), and the baseline score as covariate.

The protocol states that hemolytic blood samples should not be considered for the statistical analyses. But the central laboratory will already check whether a measured laboratory parameter is valid for further evaluation, if the sample was hemolytic. The central laboratory will only provide data which are valid for evaluation and accordingly, available laboratory assessments from hemolytic blood samples do not need to be excluded from the statistical analyses.

According to the protocol, several descriptive summaries for safety and efficacy variables should be repeated for the stratification factors and the subgroups defined in Section 4.5.5. These summaries will only include baseline and the scheduled Visits 3 (Day 30±2), 4 (Day 60±2) and 5 (Day 90±2) since these are the visits of major interest.

7.2 Document history
- SAP dated 23 AUG 2013 submitted for internal review
- Approval of the SAP dated 20 SEP 2013

8. References
5. 16243 Cytochrome P450 Concomitant Medications List. Version 1.0. (14.02.2013)
A randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy

Short title: Safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy (ARTS-DN)

Test drug: BAY 94-8862

Study purpose: Safety and efficacy

Clinical study phase: IIb

Date: 02-SEP-2014

Study No.: 16243

Version: 3.0

Author: Alexander Pieper

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The approval of the Statistical Analysis Plan is documented in a separate Signature Document.
# Table of Contents

1. Introduction........................................................................................................................................ 5
2. Study Objectives .................................................................................................................................. 6
3. Study Design ........................................................................................................................................ 7
4. General Statistical Considerations .................................................................................................. 9
   4.1 General Principles ............................................................................................................................. 9
   4.2 Handling of Dropouts ...................................................................................................................... 10
   4.3 Handling of Missing Data ............................................................................................................. 11
   4.4 Interim Analyses and Data Monitoring .......................................................................................... 11
   4.5 Data Rules ....................................................................................................................................... 12
       4.5.1 Screening ................................................................................................................................. 12
       4.5.2 Baseline values ....................................................................................................................... 12
       4.5.3 Change from baseline ........................................................................................................... 12
       4.5.4 Other data handling ............................................................................................................. 13
       4.5.5 Subgroup analyses ................................................................................................................ 14
   4.6 Validity Review ............................................................................................................................... 15
5. Analysis Sets ....................................................................................................................................... 15
   5.1 Safety analysis set (SAF) ............................................................................................................... 15
   5.2 Full analysis set (FAS) ................................................................................................................... 15
   5.3 Per-protocol analysis set (PPS) .................................................................................................... 15
   5.4 Listing only set (LOS) .................................................................................................................. 16
   5.5 Pharmacokinetic analysis set (PKS) ............................................................................................. 16
6. Statistical Methodology ...................................................................................................................... 16
   6.1 Population characteristics ............................................................................................................ 16
       6.1.1 Disposition .............................................................................................................................. 16
       6.1.2 Demography and other baseline characteristics ...................................................................... 16
       6.1.3 Medical History .................................................................................................................... 17
       6.1.4 Concomitant Medications .................................................................................................... 17
       6.1.5 Treatment duration, extent of exposure and compliance ...................................................... 18
       6.1.6 Smoking status ..................................................................................................................... 18
   6.2 Efficacy .......................................................................................................................................... 18
       6.2.1 Analysis of primary efficacy variable ....................................................................................... 18
           6.2.1.1 Primary analysis ............................................................................................................... 19
           6.2.1.2 Supportive analyses for the primary endpoint .................................................................. 21
           6.2.1.3 Mixed model for ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline ................................................................. 23
           6.2.1.4 Changes in albuminuria .................................................................................................. 23
       6.2.2 Analysis of further exploratory efficacy variables ................................................................. 24
           6.2.2.1 Decrease in eGFR ............................................................................................................ 24
           6.2.2.2 Efficacy biomarkers ........................................................................................................ 24
           6.2.2.3 Health-related quality of life ............................................................................................ 24
   6.3 Pharmacokinetics / pharmacodynamics ...................................................................................... 26
       6.3.1 Pharmacokinetics .................................................................................................................. 26
6.3.2 Pharmacodynamics ................................................................. 27
6.4 Safety ....................................................................................... 27
  6.4.1 Adverse events ................................................................. 27
  6.4.2 Laboratory parameters ..................................................... 28
  6.4.3 Other additional safety variables ....................................... 30
    6.4.3.1 Safety Biomarkers ..................................................... 30
    6.4.3.2 Vital Signs ................................................................. 30
    6.4.3.3 Weight and BMI ......................................................... 31
    6.4.3.4 ECG .......................................................................... 31
    6.4.3.5 Ambulatory blood pressure monitoring (ABPM) ............. 31
    6.4.3.6 Iohexol plasma clearance ............................................ 32

7. Document history and changes in the planned statistical analysis ...... 32
  7.1 Changes to planned analysis .................................................. 32
  7.2 Document history ................................................................. 33

8. References .................................................................................. 34
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPM</td>
<td>Ambulatory blood pressure monitoring</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACEIs</td>
<td>angiotensin-converting enzyme inhibitors</td>
</tr>
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<td>ANCOVA</td>
<td>Analysis of covariance</td>
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<td>ARB</td>
<td>angiotensin receptor blockers</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BOCF</td>
<td>Baseline observation carried forward</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>Chi-square</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Chronic Kidney Disease Epidemiology Collaboration</td>
</tr>
<tr>
<td>CLIPS</td>
<td>Clinical Pharmacology Standards</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P450</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>cytochrome P450 isoenzyme 2C8</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>cytochrome P450 isoenzyme 3A4</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
</tr>
<tr>
<td>dL</td>
<td>Deciliter</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
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<tr>
<td>DN</td>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
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<tr>
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<td>estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>EOD</td>
<td>Every Other Day</td>
</tr>
<tr>
<td>EQ-5D-3L</td>
<td>EuroQol Group 5 dimension, 3 level</td>
</tr>
<tr>
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<td>End-stage renal disease</td>
</tr>
<tr>
<td>FAS</td>
<td>Full analysis set</td>
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<tr>
<td>FU</td>
<td>Follow Up</td>
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<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
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<tr>
<td>HF</td>
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</tr>
<tr>
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<td>heart failure with reduced ejection fraction</td>
</tr>
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<td>Heart Rate</td>
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<tr>
<td>KDQOL 36</td>
<td>Kidney Disease Quality of Life</td>
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<td>kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>L</td>
<td>Liter</td>
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<tr>
<td>LLOQ</td>
<td>Lower Limit Of Quantification</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
</tr>
<tr>
<td>log</td>
<td>Natural Logarithm</td>
</tr>
<tr>
<td>LOS</td>
<td>Listing only set</td>
</tr>
<tr>
<td>LS means</td>
<td>Least square means</td>
</tr>
<tr>
<td>MCS</td>
<td>Mental Component Summary</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
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1. Introduction

According to the World Health Organization (WHO), diabetes mellitus currently affects more than 240 million people worldwide, and the number is predicted to rise to more than 360 million by 2030. Diabetic nephropathy (DN) represents the most common cause of end-stage renal failure in the United States (US) and accounts for approximately 40% of all new patients entering end-stage renal disease (ESRD) programs and approximately 45% of patients receiving renal replacement therapy.

Overall approximately 20 to 30% of patients with type 1 or type 2 diabetes mellitus develop evidence of nephropathy although there is considerable variability by type in terms of disease progression.
Until recently, DN was very much a disease of Western countries, but in the future, Asian countries are likely to represent the bulk of the DN population, due to their size but also to the predilection of Asian diabetic patients to develop renal complications.

In patients with DN, albuminuria at baseline is an important factor to predict ESRD in addition to lowering albuminuria, and it is now clearly demonstrated that interruption of the renin-angiotensin system (RAS) reduces the risk of progression to ESRD. However, an impact on overall survival has not yet been demonstrated.

Despite significant progress over the last decade, the ultimate goal of preventing the development of ESRD in DN is still far from being reached. Without therapy, the average time from diagnosed chronic kidney disease (CKD) to ESRD is about 4 to 5 years. On therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), this time is extended by 1 to 2 years only. DN remains the primary diagnosis leading to ESRD in the US and 1 of the top 2 or 3 in most other countries.

Current therapies for DN rely on the control of albuminuria through inhibition of the RAS with ACEIs or ARBs. Despite initial down-regulation of the release of aldosterone by the adrenal glands, up to 50% of the patients treated with a RAS blocker develop an increase in plasma aldosterone within 6 to 12 months after the initiation of treatment. Several studies have shown a direct relationship between increases in plasma aldosterone after ACEI treatment and increases in albuminuria and decreases in kidney function. Explorative clinical studies in adults have shown a potential role for mineralocorticoid receptor antagonists (MRAs), when added to RAS blockers, to delay the development of ESRD further.

In this situation BAY 94-8862 is a novel non-steroidal MRA. In vitro investigations have demonstrated superior selectivity vs. spironolactone and improved potency vs. eplerenone. These properties have also been demonstrated in a number of nonclinical in vivo investigations, which showed BAY 94-8862 to be effective in reducing mortality in models of heart failure and stroke; and in reducing cardiac remodeling and end-organ lesions.

This study (Study 16243) will investigate short-term efficacy and safety of different oral doses of BAY 94-8862 given once daily over 90 days in comparison to placebo in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN.

This SAP is based on the integrated study protocol Version 2.0 approved on 04 December 2013 (integrating the study protocol Version 1.0 approved on 04 March 2013 and Amendment 1) and describes the final analysis of the study.

2. **Study Objectives**

Primary objective of the study is
• To investigate the change of urinary albumin-to-creatinine ratio (UACR) after treatment with different oral doses of BAY 94-8862 given once daily from baseline to Visit 5 (Day 90±2)

Further exploratory objectives of the study are

• To assess safety and tolerability of these doses by assessing the effects on serum potassium and renal function

• To assess change in health-related quality of life (HRQoL) from baseline to 90 days of treatment assessed by the Kidney Disease Quality of Life (KDQOL 36) and EuroQol Group 5 dimension, 3 level (EQ-5D-3L) questionnaires

3. Study Design

This study will be conducted in subjects with type 2 diabetes mellitus and the clinical diagnosis of DN using a multi-center, randomized, adaptive, double-blind, placebo-controlled, parallel-group design.

Planned number of subjects valid for the full analysis set: approximately 90 subjects in each treatment group in case that no additional treatment group will be added, and approximately 75 subjects in each treatment group if at least one of the additional treatment groups will be added and not closed due to safety reasons during the further course of the study.

Following an open-label run-in and screening period of up to 12 weeks in total, eligible subjects will be randomized to 1 of up to 7 doses of BAY 94-8862 or placebo on top of standard of care treatment to receive a 90-day study drug treatment. Initially, the following 5 doses of BAY 94-8862 will be compared to placebo in a double-blind manner: 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg once daily. Subjects will be assigned to the treatment groups with balanced sample sizes by a stratified randomization with stratification factors region (Europe, North America, Asia, others), and type of albuminuria (very high albuminuria or high albuminuria at screening). No formal caps will be applied within the stratification levels. However, a ratio of approximately 50:50 for high and very high albuminuria is planned to be reached with an imbalance of up to 65:35 being considered as acceptable. In order to achieve a proportion of at least 35% of subjects with very high albuminuria, single centers or countries predominantly recruiting subjects with high albuminuria may be closed during the course of the study. In case that less than 35% of subjects randomized were diagnosed with very high albuminuria, the sample size may be increased to approximately 90 subjects in each treatment group (in case it can be reduced to 75 subjects per treatment arm after the dose decision meeting) in order to increase the amount of available safety data per treatment arm for the subjects with very high albuminuria. After safety and tolerability of the initial doses have been assessed by an independent DMC, none or up to 2 further doses of BAY 94-8862 may be introduced: 15 mg and 20 mg once daily. After the DMC decision, the randomization will be adapted in order to obtain approximately equally balanced sample sizes across all
treatment groups at the end of the study. Dose arms may be closed prematurely due to safety concerns at any DMC Meeting.

If potassium is ≥5.6 and ≤6.0 mmol/L measured in the central or local laboratory, a second blood sample has to be taken as soon as possible but at the latest within 48 hours. If potassium is again ≥5.6 mmol/L in the locally or centrally analyzed blood sample (considered as second potassium measurement), study drug has to be discontinued permanently for the respective subject.

If potassium is >6.0 mmol/L in the centrally analyzed blood sample but <5.6 mmol/L in the locally analyzed sample, treatment with study drug can be continued. If potassium is >6.0 mmol/L in the centrally analyzed blood sample and ≥5.6 mmol/L in the locally analyzed sample, study drug has to be discontinued permanently.

If potassium is >6.0 mmol/L in the locally analyzed blood sample, study drug has to be discontinued permanently.

The premature discontinuation visit will take place as soon as possible after premature discontinuation of study drug due to any reason except death or lost to follow-up.

If the locally analyzed blood sample is missing or the result is inconclusive and the central laboratory result is not available, another blood sample must be taken as soon as possible but at the latest within 48 hours after becoming aware of the results. The assessment of potassium during the course of the study is also presented in Table 3-1.

Table 3–1 Monitoring of potassium during the treatment period

<table>
<thead>
<tr>
<th>Central lab</th>
<th>Local lab</th>
<th>Result of first potassium measurement</th>
<th>5.6 - 6.0 mmol/L</th>
<th>&gt;6.0 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.6 mmol/L</td>
<td>Continue study drug</td>
<td>Repeat potassium measurement within 48 hours</td>
<td>Check potassium in locally analyzed sample</td>
<td>Discontinue study drug permanently</td>
</tr>
<tr>
<td></td>
<td>Continue study drug</td>
<td>Repeat potassium measurement within 48 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a If potassium is again ≥5.6 mmol/L in the repeat blood sample, discontinue study drug permanently.
If potassium is <5.6 mmol/L in the repeat blood sample, continue study drug.

b If potassium is ≥5.6 mmol/L in the (first) locally analyzed blood sample, discontinue study drug permanently.
If potassium is <5.6 mmol/L in the (first) locally analyzed blood sample, continue study drug.
4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

The analysis will be based on the Global Standard Tables (Version 2.0) and the Clinical Pharmacology Standards (CLIPS) (Version 1.2) where appropriate.

The validity of subjects for allocation to various analysis sets will be assessed on an ongoing basis in several validity review meetings and decisions will be documented in the validity review reports prior to unblinding (conditional validity for PK analysis set). This SAP might be updated based on the results of the validity review meetings.

All variables will be analyzed by descriptive statistical methods. The number of data available, mean, standard deviation (SD), minimum, median, and maximum will be calculated for metric data. The geometric mean, SD and coefficient of variation (CV) will be provided instead of the arithmetic mean and SD for the variables where lognormal distributions are assumed. Frequency tables will be generated for categorical data.

All subjects will be analyzed according to the actual treatment group.

For log-transformed UACR, safety and efficacy biomarkers, scores of questionnaires, vital signs (including systolic and diastolic blood pressure and heart rate) and the safety parameters
serum potassium, estimated Glomerular Filtration Rate (eGFR) and serum creatinine normally distributed data are assumed and ANCOVA models are planned as statistical analyses. After inspection of the pooled baseline data prior to unblinding of the database, a lognormal distribution will be assumed for efficacy biomarkers (NT-proBNP, BNP, Galectin – 3), safety biomarkers (Cystatin C) as well as for serum creatinine. Details to the assessment of normal distribution are attached.

For Troponin T most values were observed as below the lower limit of quantification and no numerical analyses will be performed.

For all other parameters the analyses will be performed as planned assuming a normal distribution.

For aldosterone, which can only be assessed after unblinding of the study, the planned analyses will be amended as for the other efficacy biomarkers and lognormally distributed data are also assumed for aldosterone. In case of a deviation from the assumption of approximately log-normally distributed data, changes to the analyses will be documented in an SAP Supplement.

The laboratory parameter eGFR will be calculated based on the CKD-EPI formula for all analyses specified in this SAP.

Descriptive summary statistics for safety and efficacy variables stratified by the stratification factors or by the subgroups defined in Section 4.5.5 will only include baseline and the scheduled Visits 3 (Day 30±2), 4 (Day 60±2) and 5 (Day 90±2).

Dose arms which were closed prematurely due to safety concerns will not be included in the primary analysis and in the ANCOVA models or \( \chi^2 \) test procedures.

In case of any unexpected finding, further exploratory analyses might be performed.

4.2 Handling of Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has been randomized (even if no study drug has been taken). Dropouts will not be replaced. Data from subjects who prematurely terminated the study will be used to the maximum extent possible. The number and percentage of subjects who did not complete the treatment epoch or the follow-up epoch, as well as the primary reason for discontinuation, will be displayed by treatment group and overall as described in Section 6.1.1.

In the 90-day treatment period of this study, a dropout rate of approximately 30% is expected, i.e. there will be a high number of missing UACR values at Visit 5 (Day 90±2). 10% of the subjects are expected to drop out during the first month and another 20% during the following 2 months. Dropouts after the first month are expected to be due to worsening renal function or uncontrolled hypertension. The remaining dropouts are expected to be due to clinical
outcomes or hyperkalemia. While albuminuria might not be influenced in subjects with clinical outcomes or hyperkalemia, a worsening albuminuria is expected in cases of worsening renal function or uncontrolled hypertension.

### 4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the electronic Case Report Form (eCRF).

Analyses focusing on the exploration of any potential missing data pattern are described in Section 6.1.1, 6.1.2 and 6.1.5.

For the primary analyses of the primary endpoint [the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline] described in Section 6.2.1.1 a last observation carried forward (LOCF) approach will be used to impute missing data. Thereby, the higher UACR value from the premature discontinuation measurement and follow-up measurement will be used for subjects who prematurely terminated the study (worst case imputation on subject level).

Sensitivity analyses using other imputation methods will be performed for the primary endpoint and are described in Section 6.2.1.2.

### 4.4 Interim Analyses and Data Monitoring

No formal interim analysis is planned. Data will be reviewed for safety and tolerability by an independent data monitoring committee (DMC). One DMC has been established for this study and the parallel Phase IIb study of BAY 94-8862 in worsening chronic heart failure and left ventricular systolic dysfunction and either type 2 diabetes mellitus with or without chronic kidney disease or moderate chronic kidney disease alone (study 14564). The first DMC meeting will take place when a combined total number of 30 subjects has been randomized in both BAY 94-8862 Phase IIb studies. Thereafter, DMC meetings will take place approximately every other month. In addition, an overview regarding SAEs reported in the 2 studies will be sent to the DMC chair on a weekly basis. When a minimum of 150 subjects have been randomized in this study, a dose decision meeting will take place. During this meeting, the 5 initial treatment groups of BAY 94-8862 will be assessed for safety and tolerability (in particular changes in serum potassium, e.g. number of subjects with hyperkalemia, and changes in eGFR, e.g. number of subjects with an eGFR decrease ≥30%) by the independent DMC. Based on this assessment, none or up to 2 of the additional treatment groups will be introduced into the study. The detailed plan for these assessments will be covered in the DMC charter (Version 1.0 approved on 6 June 2013), the analysis planned to be provided to the DMC is described in a separate statistical analysis plan for the DMC (Version 1.0 approved on 25 June 2013) and a DMC specific specification of tables, listings and figures (Version 1.0 approved on 25 June 2013). The statistical analysis for the DMC Meetings will be performed by an independent statistical analysis center.
The DMC will review the data in a semi-blinded manner (treatment arms coded by A, B, C, D etc.) and in an unblinded manner for the dose decision meeting. There are no predefined stopping conditions for the ongoing safety monitoring of this trial. However, the DMC may recommend termination, temporary suspension of the study, and intervention of treatment arm or modification of the study.

4.5 Data Rules

General data rules are described in this section, further data rules for specific parameters or analyses are specified in the respective subsections of Section 6.

4.5.1 Screening

For a subject who is already treated with an ACEI and/or ARB for at least 3 months and on at least the minimal recommended dose of that ACEI or ARB, without any adjustments in her or his medical treatment for at least 4 weeks, and fulfilling all the inclusion and none of the exclusion criteria, the run-in visit may be considered as screening visit.

In case that the run-in visit will be considered as screening visit for a subject, all assessments performed on the run-in visit for the respective subject will be analyzed only for the screening visit.

4.5.2 Baseline values

Baseline values will be defined as the last non-missing measurement before the first intake of study treatment. In case the last observation available prior to treatment is the measurement from the screening visit, this would be used as the baseline value. If the last observation prior to treatment is the measurement from the run-in visit, this value will only be used in case the run-in visit is as well the screening visit. Otherwise baseline will be missing.

If more than one measurement was planned for a scheduled time point (i.e. blood pressure measurements and heart rate), the average value of the last set of measurements per time point prior to treatment will be used as the baseline value.

4.5.3 Change from baseline

Change from baseline will in general be displayed as absolute change from baseline defined as the difference to baseline, i.e.:

\[
\text{Absolute change} = \text{Post baseline value} - \text{baseline value}
\]

Some parameters will be additionally analyzed as relative change defined as

\[
\text{Relative change} = 100 \times \left( \frac{\text{post baseline value} - \text{baseline value}}{\text{baseline value}} \right)
\]
For specific analyses, the relative decrease of a variable will be analyzed instead of the relative change. The relative decrease is equivalent to the negative of the relative change and defined as

\[
\text{Relative decrease} = 100 \times \frac{\text{baseline value} - \text{post baseline value}}{\text{baseline value}}.
\]

### 4.5.4 Other data handling

In case of repeated measurements for pre-treatment visits and the baseline visit, the closest measurement prior to the treatment start will be used for analysis instead of the scheduled measurements. At all post-treatment visits and if not stated otherwise, only the values at scheduled measurements will be used for analysis.

For values which are < LLOQ (Lower limit of quantification), half the value of the LLOQ will be used for analysis. Differences between two values < LLOQ will be assigned values of 0.

In case of log-normally distributed data, descriptive statistics other than minimum, maximum and median will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification. In tables showing descriptive statistics, where values below LLOQ are included, these descriptive statistics will be marked.

Only the data provided by the central laboratory will be used for analysis, values from local laboratories will not be used in the statistical analysis and listed only.

Serum potassium values >6.0 mmol/L in the centrally analyzed blood sample which cannot be confirmed by the locally analyzed sample (potassium locally <5.6 mmol/L) will not be considered for analysis.

For potassium values only, in the cases in which samples are repeated and the repeated sample is within 7 days after the scheduled sample, the following approach will be used. If the potassium value from the repeated sample is \(\geq 5.6 \text{ mmol/L}\), the higher of the two values (value from the original and repeated sample) will be used. If the value from the repeated sample is < 5.6 mmol/L, this value will be used for analysis. In case the repeated sample is later than 7 days after the scheduled sample, the original sample will be used for analysis. However, all available potassium values will be listed.

The stratum variable type of albuminuria used in the statistical analysis will be derived based on the screening UACR assessment. The stratum information about the type of albuminuria from the IXRS system will be listed only.

For Visit 5 (Day 90±2) only assessments until 3 days after last intake of study drug will be included in the statistical analysis, while all assessments thereafter will be listed only.

For the derived Visit “Any time post baseline”, only assessments within 3 days after last study drug administration will be considered.
4.5.5 Subgroup analyses

The following subgroup factors (including the stratification factors region and type of albuminuria) will be considered for descriptive and explorative analyses:

- Age (18 to ≤45 years, >45 to ≤65 years, >65 to ≤75 years, and >75 years)
- Age (≤ median and > median)
- Region (Europe, North America, Asia, others [Australia, Israel and South Africa])
- Gender (male, female)
- Race (white, black, Asian, other)
- Baseline BMI (≤30, >30)
- Baseline serum potassium value (≤ median and > median)
- eGFR values (CKD-EPI) (≤ median and > median)
- eGFR values (CKD-EPI) (30-45, 45-60, and > 60 ml/min/1.73m²)
- Baseline eGFR (CKD-EPI formula) between 30 and 45 ml/min/1.73m² and baseline serum potassium ≥ 4.5 mmol/L (yes, no)
- Concomitant medication until 3 days after last study drug administration (ACEI or ARB)
- Type of albuminuria: Very high albuminuria (UACR ≥300 mg/g) vs. high albuminuria (UACR ≥30 mg/g but <300 mg/g) at screening
- Very high albuminuria (UACR ≥300 mg/g) vs. high albuminuria (UACR ≥30 mg/g but <300 mg/g) and UACR <30 g/kg (if applicable) at baseline
- Systolic blood pressure at baseline (>90 to <140 mmHg, ≥140 to <160 mmHg, and ≥160 mmHg; ≤ median and > median)
- Concomitant medication (beta-blocker vs. no beta-blocker at baseline, diuretic vs. no diuretic at baseline)
- Concomitant potassium supplementation until 3 days after last study drug administration (Potassium supplementation vs. no potassium supplementation)
• Concomitant medication with CYP3A4 inhibitors until 3 days after last study drug administration (CYP3A4 inhibitors vs. no CYP3A4 inhibitor as concomitant medication)

• Potency of concomitant CYP3A4 inhibitors until 3 days after last study drug administration (strong CYP3A4 inhibitors vs. only weak or moderate CYP3A4 inhibitors vs. no CYP3A4 inhibitor as concomitant medication)

4.6 Validity Review

The results of the validity review meetings will be documented in the validity review reports and may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the validity review meetings will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

Assignment of analysis set

The allocation of each subject to analysis sets will be documented before the database lock (conditional validity for PK analysis set).

Final decisions regarding the assignment of subjects to analysis sets will be made during the validity review meetings and documented in the validity review reports (see Section 4.6).

5.1 Safety analysis set (SAF)

All randomized subjects who have taken at least 1 dose of study drug and with data after beginning of treatment.

5.2 Full analysis set (FAS)

All subjects of the SAF who have baseline and at least 1 post-baseline UACR value.

5.3 Per-protocol analysis set (PPS)

All subjects of the FAS who have valid UACR data at Visit 5 (Day 90±2) and have no major protocol deviations (defined in the protocol deviation document). Major protocol deviations are for example:

• Intake of any prohibited concomitant medication
• Overall compliance with study drug intake of <80% or >120%

5.4 Listing only set (LOS)

The LOS will not be used as an analysis set and accordingly, subjects will not be assigned explicitly to this set during the validity review meetings. The LOS consists of all other subjects screened who did not receive any dose of study drug or for whom no data after beginning of treatment are available. Their data will be presented in the individual subject data listings but will not be included in any statistical analysis.

5.5 Pharmacokinetic analysis set (PKS)

All BAY 94-8862-treated subjects with at least 1 valid BAY 94-8862 plasma concentration and without protocol deviation, which would interfere with the evaluation of the PK data.

6. Statistical Methodology

6.1 Population characteristics

Population characteristic analyses, except for subject disposition, will be performed in SAF, if not stated otherwise.

6.1.1 Disposition

The number of subjects enrolled, randomized and valid for the safety analysis set, full analysis set, per protocol analysis set and pharmacokinetic analysis set will be summarized overall and by treatment groups, country and investigator in a table. The number of subjects discontinuing the run-in/screening epoch together with the primary reason for discontinuation will be presented overall. The number of subjects discontinuing the treatment and follow-up epoch together with the primary reason for discontinuation will be presented by treatment groups and overall in separate tables. In addition, the number of subjects with major and minor protocol deviations will be presented overall and by investigator and country for each treatment group and in total. The frequencies of each major protocol deviation will be presented by treatment group and total.

6.1.2 Demography and other baseline characteristics

All demographic data and baseline characteristics will be tabulated by treatment group and overall.

Demography includes age, sex, race, ethnicity, region (North America, Europe, Asia and others), body weight, categories for body weight, body height, BMI, hip and waist circumference, smoking history (never, former, current smoker) and alcohol consumption,
while other baseline characteristics include baseline UACR, baseline NT-proBNP, baseline BNP, baseline galectin-3, baseline aldosterone, baseline serum potassium, categories for baseline serum potassium, baseline eGFR (calculated by CKD-EPI formula), baseline serum creatinine, baseline HbA1c, baseline troponin T, baseline cystatin C, baseline values for vital signs parameters (i.e. systolic blood pressure, diastolic blood pressure and heart rate) and the subgroup categories described in Section 4.5.5.

Weight will be summarized as a continuous variable, as well as categorized to >50 kg and ≤50 kg. Serum potassium will be analyzed as a continuous and a categorical variable with categories <4.5 mmol and ≥4.5 mmol.

The demographic table and other baseline characteristics will also be presented by type of albuminuria (very high albuminuria or high albuminuria at screening), eGFR subgroups (30-45, 45-60, and > 60 ml/min/1.73m²) and region (Europe, North America, Asia, others).

The description of demographic data (non-stratified) and other baseline characteristics will be repeated for all other analysis sets if they differ from the SAF.

Demographics and other baseline characteristics will be presented for the FAS separately for the subjects belonging to PPS or not (only for the overall treatment group).

6.1.3 Medical History

Medical history will be coded using MedDRA dictionary. Medical history will be presented for each MedDRA Primary System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall in a summary table.

6.1.4 Concomitant Medications

Concomitant medications will be coded using the most recent version of the WHO Drug Dictionary (WHO-DD). The number of subjects who took at least one concomitant medication, the number of subjects who took at least one medication that started and ended before administration of study drug and the number of subjects who took at least one concomitant medication that started after start of study drug will be presented by treatment group and overall using ATC classes and subclasses. Additionally, the above described tables will be repeated summarizing the number and incidence of subjects with medications in the drug groups of interest (ACEI, ARBs, β-blocker, diuretics, potassium supplements, alpha blocking agents, calcium channel blockers, centrally acting antihypertensives and strong, moderate and weak CYP3A4 inhibitors, CYP3A4 inducers and CYP2C8 inhibitors). A subject will be counted only once within each ATC class / subclass or drug group, respectively.

A listing will be provided including all medications classified as a weak, moderate or strong CYP3A4 inhibitor according to the Bayer drug groupings together with the respective classification information.
6.1.5 Treatment duration, extent of exposure and compliance

The analyses described in this section will be repeated for FAS and PPS if they differ from the SAF.

For subjects who withdraw prematurely from the study drug, compliance will be calculated up to the time of last dose.

Treatment duration (number of days with study drug intake, not including any gaps) will be summarized using descriptive statistics by treatment group and overall. In addition, treatment duration will be categorized to ≤32 days, >32 - ≤62 days and >62 days, and presented with the corresponding number and percentage of subjects by treatment group and overall.

A table will be presented with the absolute and relative frequencies of subjects still in the study at each visit. Kaplan-Meier plots for “Time to end of study treatment” will be provided.

The extent of exposure to study drug (total amount of intake in mg) will be summarized using descriptive statistics by treatment group.

The compliance (as percentage) is calculated as:

\[
100 \times \frac{\text{Number of taken tablets}}{\text{Number of planned tablets}}.
\]

The number of planned tablets is calculated as: Treatment duration (days) * Number of planned tablets per day. All tablets, including the dummy placebo tablets, are to be counted.

The compliance will be summarized descriptively by treatment group and overall. In addition, percent of compliance will be categorized into three groups, less than 80%, 80 to 120% and greater than 120%, and the categories will be summarized by treatment group and overall.

6.1.6 Smoking status

Changes in the smoking status will be summarized with number and percentage of subjects by treatment group.

6.2 Efficacy

6.2.1 Analysis of primary efficacy variable

The primary efficacy variable, the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline, will be analyzed for FAS (primary analysis) and PPS (supportive analysis). Further supportive analyses described in Section 6.2.1.2, Section 6.2.1.3, and Section 6.2.1.4 will be performed in FAS and PPS.
The primary analysis will focus on the on-treatment data (i.e. the actual treatment groups will be used).

The UACR will be determined 3 times at each visit from first morning void urine samples collected on 3 consecutive days. For all analyses of UACR, the 3 measurements at one visit will be combined as follows: First, the coefficient of variation will be calculated for the 3 values. If the geometric coefficient of variation exceeds 25%, the median from the measurements will be used for the analyses. The median in case of an even number of values will be defined as the geometric mean from the 2 middle values. If the geometric coefficient of variation is 25% at the most, the geometric mean will be used. If a scheduled measurement is missing or invalid and an additional unscheduled measurement was performed instead, this unscheduled measurement should be used to determine the UACR if the measurement was within two days after the last scheduled measurement. If all three scheduled assessments have been missing or invalid and unscheduled assessments have been performed, then these will be used for analysis if performed within 7 days before or after the scheduled visit (with an exception for Visit 5, where only assessments until 3 days after last study drug intake will be considered). If only one UACR measurement at a visit is available, then this measurement will not be used for analysis. For Visit 1 (Day 1), only measurements taken prior to the first intake of study drug will be used to determine the respective visit assessment.

Imputation methods for missing Visit 5 (Day 90±2) data are described in Section 4.3 and Section 6.2.1.2.

### 6.2.1.1 Primary analysis

The analyses described in the following will be performed in FAS.

In the primary analyses described in the following, the LOCF approach in combination with an additional imputation rule for subjects who prematurely terminated the study (see Section 4.3) will be applied for missing Visit 5 (Day 90±2) of the primary endpoint. Sensitivity analyses on the imputation method are described in Section 6.2.1.2.

Primarily, the aim of the study is to demonstrate a dose-dependent effect of BAY 94-8862 with respect to the primary variable. For this purpose, an analysis of covariance (ANCOVA) model

\[ Y_{ijlm} = \eta + \alpha_i + \beta_j + \gamma_l + \zeta_l X_{ijlm} + \epsilon_{ijlm} \]

with

- \( Y_{ijlm} = \) Log-transformed ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline for Subject m \( (m=1, \ldots, n) \), with n = Number of subjects valid for the analysis
- \( \eta = \) Overall mean
- \( \alpha_i = i\)-th treatment effect \( (i=1, \ldots, k) \)
- \( \beta_j = j\)-th region effect \( (j=1, \ldots, 4) \)
• $\gamma_l = l$-th type of albuminuria effect ($l=1,2$)
• $\zeta_l = \text{effect of log-transformed baseline UACR within } l\text{-th type of albuminuria} (l=1,2)$
• $X_{ijlm} = \text{log-transformed UACR at baseline of subject } m (m=1,\ldots,n)$
• $\varepsilon_{ijlm} = \text{Random error of subject } m (m=1,\ldots,n)$

will be fitted to the log-transformed ratios of UACR at Visit 5 (Day 90) to UACR at baseline including a factor for treatment group, factors to adjust for the stratification factors (type of albuminuria and region) and the log-transformed baseline UACR as covariate. As the baseline UACR defines the type of albuminuria, the log-transformed baseline UACR will be nested as covariate in type of albuminuria. The UACR values and ratios will be log-transformed since the primary variable is considered to be approximately log-normally distributed, i.e. the log-values are considered to be normally distributed.

The distributional model assumptions will be checked by inspection of residual plots of studentized residuals vs. normal order scores to check normality, and studentized residuals vs. predicted values to check homogeneity of variance.

The primary hypothesis

$$H_0: \mathbf{L}_k' \cdot \mathbf{\mu} = 0$$

will be tested by means of the F-test with a 1-sided significance level of 5%, where

• $\mathbf{\mu} = (\mu_1, \ldots, \mu_k)'$ with $\mu_i = \text{expected value for log(UACR at Visit 5 (Day 90±2))} - \text{log(UACR at baseline)}$ adjusted for baseline log-UACR and the stratification factors (type of albuminuria and region),
• $i=1,\ldots,k$, with $k = \text{number of treatment groups in analysis}$ and
• $\mathbf{L}_k' = \text{linear contrast reflecting the intervals between the dose groups (i.e. a difference of 1 between the weights of the contrast reflecting an amount of 1.25mg)}$.

The alternative hypothesis $H_1: \mathbf{L}_k' \cdot \mathbf{\mu} > 0$ shall demonstrate a linear trend in the group means. The signs of the contrast were chosen according to this one-sided hypothesis.

The linear contrast $\mathbf{L}_k'$ depends on the number of treatment groups. In case that the dose groups will be placebo (= 0 mg), 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg BAY 94-8862 (k=6), the linear contrast will be

$$\mathbf{L}_6' = (3.5, 2.5, 1.5, -0.5, -2.5, -4.5).$$

If 15 mg BAY 94-8862 will be added (k=7), the linear contrast will be
If both additional treatment groups, 15 mg and 20 mg BAY 94-8862, will be added, the linear contrast will be

$$L_8' = (6.125, 5.125, 4.125, 2.125, 0.125, -1.875, -5.875, -9.875).$$

If doses were closed prematurely due to safety concerns, the linear contrast for the primary analysis reflecting the intervals between the remaining treatment groups will be defined in a SAP amendment.

The determination of the sample size (see Section 8.6 of the study protocol) was based on the primary hypothesis testing procedure described above.

If the primary hypothesis could be rejected, the single dose groups will be compared to placebo by a hierarchical procedure starting with the highest dose of BAY 94-8862 vs. placebo within the same ANCOVA model in order to investigate the dose-response relationship further. The one-sided significance level of 5% will be kept for each pairwise comparison and the procedure will stop when the first hypothesis could not be rejected.

Based on these analyses point estimates (LS-Means) and two-sided 90% confidence intervals of the ratio of UACR at Visit 5 (Day 90 ± 2) to UACR at baseline will be calculated by re-transformation of the logarithmic results for each treatment group and for the treatment ratios (each BAY 94-8862 treatment group vs. placebo).

The point estimates and two-sided 90% confidence intervals of the ratios of UACR at Visit 5 (Day 90 ± 2) to UACR at baseline will be plotted vs. the treatment groups.

6.2.1.2 Supportive analyses for the primary endpoint

Sensitivity analyses on the imputation method which will be performed in FAS only. The repetition of the primary analyses described in Section 6.2.1.1 will be performed in PPS. All other supportive analyses for the primary efficacy variable will be performed in FAS and PPS.

The primary LOCF approach will not be applied for the supportive analyses in FAS and PPS, if not stated otherwise.

The analysis described in Section 6.2.1.1 will be repeated for the PPS.

Sensitivity analyses for the primary imputation method (LOCF), will be performed by repeating the primary analyses for several other imputation methods including:

- an observed case analysis (only subjects with a UACR value at Visit 5 (Day 90 ± 2) available)
- an on-treatment LOCF approach (as for the primary analysis, but only including data before the premature discontinuation visit)

- a baseline observation carried forward analysis (BOCF, impute the baseline value for missing data, i.e. include all subjects of the FAS with missing Visit 5 (Day 90±2) data with a value of 1 for the primary efficacy variable)

- a mean value imputation (impute the value of the primary efficacy variable by the ls-mean value of the primary efficacy analysis of the respective treatment group)

- a random imputation (impute the value of the primary efficacy variable by a random number from a normal distribution with ls-mean and variance (from descriptive statistics) from the respective treatment group of the primary efficacy analysis. For reproducibility, the SAS seed number for creating the random numbers will be set to 1984)

Further analyses might be performed in case that these imputation methods seem to have a major impact on the results.

Section 6.2.1 states, that Visits with only one of the three UACR measurements available will not be included in the analysis. In case that this situation occurs at baseline or at the study end point (Visit 5 (Day 90±2) or in case of premature discontinuation the PD Visit or the Follow-up Visit), then a further sensitivity analysis will be performed for the primary ANCOVA model including also visits with only 1 valid UACR assessment.

To investigate the relationship between treatment groups and stratification factors further, the primary analysis model described in Section 6.2.1.1 will be repeated with additional interaction terms for treatment group and region, as well as for treatment group and type of albuminuria. LS means and two-sided 90% confidence intervals of the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline will be calculated by re-transformation of the logarithmic results for each treatment group and for the treatment ratios (each BAY 94-8862 treatment group vs. placebo) for the overall treatment effect and on each category of the stratification factors (region and type of albuminuria). Plots for the LS means and two-sided 90% confidence intervals of the ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline vs. treatment groups will be presented for the overall effect as well as for the different stratum levels.

In order to describe the course of UACR and the ratio of UACR to baseline for all visits, descriptive statistics will be provided including the geometric means, geometric standard deviations, and geometric coefficients of variation by treatment group and visit. This will be done overall and separately for all subgroups defined in Section 4.5.5. Boxplots for the geometric mean ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline will be presented for each treatment group including the overall mean ratio as well as the mean ratios per subgroup level for all subgroups in FAS.
Graphs displaying the geometric group means and SDs (non-stratified) of UACR values and the ratios to baseline vs. time will be generated.

Furthermore, it is intended to analyze which treatment group means of the log-transformed ratios of UACR at Visit 5 (Day 90±2) to UACR at baseline (including the LOCF approach from the primary analysis) are different from each other as an exploratory analysis. Therefore, the REGWQ (Ryan-Einot-Gabriel-Welsch Q) option of the SAS GLM (generalized linear model) procedure will be applied with a 2-sided significance level of 10% in the ANCOVA model specified in the primary analysis. The option performs a Ryan-Einot-Gabriel-Welsch multiple range test, which tests subsets of the group means for equality. This option is only available for unadjusted means.

6.2.1.3 Mixed model for ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline

The analysis will be performed in the FAS and PPS.

The log-transformed ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), and Visit 5 (Day 90±2) to UACR at baseline will be analyzed within one model by a mixed-effects repeated measures model with treatment group as the main effect, factors for the stratification levels (type of albuminuria and region), a factor for time, the interaction factor between treatment and time and the log-transformed baseline value as covariate nested within type of albuminuria. The overall treatment effect will be tested (exploratively) at a two-sided significance level of 5%. Based on this analysis point estimates (LS-Means) and two-sided 95% and 90% confidence intervals of the overall treatment effect (across Visit 3 (Day 30±2), Visit 4 (Day 60±2) and Visit 5 (Day 90±2)) and of the ratio of UACR at each visit to UACR at baseline will be calculated by re-transformation of the logarithmic results for each treatment group and for the treatment ratios (each BAY 94-8862 treatment group vs. placebo). The SAS Procedure Proc Mixed will be used estimating covariance patterns within subjects to adjust for the within subject variance. For each treatment group a separate covariance pattern will be estimated for three covariance structures including compound symmetry, Toeplitz and an unstructured covariance. The best model will be selected for summary tables based on the AIC criterion. Degrees of freedom will be derived using the Kenwards Rodgers method$^5$ as a SAS option in all three models.

The point estimates and two-sided 90% confidence intervals of the ratios of UACR at Visit 3 (Day 30±2), Visit 4 (Day 60±2), Visit 5 (Day 90±2) and overall to UACR at baseline will be plotted vs. the treatment groups.

6.2.1.4 Changes in albuminuria

A shift table will be provided displaying the number and incidence of subjects who changed from baseline to Visit 5 (Day 90±2) from very high albuminuria to high albuminuria, from very high albuminuria to albuminuria, from high albuminuria to albuminuria, from high
albuminuria to very high albuminuria and from albuminuria to high and very high albuminuria by treatment group and overall. The albuminuria category changes will only be considered as shifts, if they are accompanied by a UACR change of more than 30% from baseline to Visit 5 (Day 90±2).

6.2.2 Analysis of further exploratory efficacy variables

All exploratory efficacy variables will be analyzed in the FAS and PPS.

6.2.2.1 Decrease in eGFR

eGFR values will be summarized descriptively by treatment group and visit including relative changes to baseline.

Frequency tables will be generated for the number and incidence of subjects with a relative decrease in eGFR of ≥25% from baseline eGFR, with a decrease in eGFR of ≥30% from baseline eGFR, of ≥40% from baseline eGFR, and of ≥57% from baseline eGFR. The analysis will be performed for each visit and overall (subjects with at least 1 event in the respective category after start of study drug administration). The analyses will also be performed stratified by the subgroups, specified in Section 4.5.5.

Further analyses will be performed for eGFR in SAF as described in Section 6.4.2.

6.2.2.2 Efficacy biomarkers

Efficacy biomarkers, i.e. NT-proBNP, BNP, aldosterone and galectin-3, will be summarized descriptively by treatment group and visit including ratios to baseline. Geometric group means and standard deviations of efficacy biomarker values and ratios to baseline (non-stratified) will be plotted versus time. Boxplots for the ratios to baseline at Visit 5 (Day 90±2) will be presented for each treatment group overall and for each stratum level of type of albuminuria in FAS only.

The log-transformed ratio of efficacy biomarkers to baseline at Visit 3 (Day 30±2), Visit 4 (Day 60±2) and Visit 5 (Day 90±2) will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (region and type of albuminuria), and log-transformed baseline value as covariate. The treatment effect will be tested at a two-sided significance level of 5%. Pairwise ratios between each BAY 94-8862 treatment group and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

6.2.2.3 Health-related quality of life

The items of the KDQOL-36 are grouped as follows:
• Items 1-12: Physical Component Summary (PCS) / SF-12 physical health composite on physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health

• Items 1-12: Mental Component Summary (MCS) / SF-12 mental health composite on physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health (including a different weighting than the PCS)

• Items 13-16: Burden of Kidney Disease; interference with daily life, time to deal with kidney disease, frustration, feeling like a burden

• Items 17-27: Symptoms / Problems; general health, activity limits, ability to accomplish desired tasks, depression/anxiety, energy level, social activities

• Items 29-36: Effects of Kidney Disease; impact of fluid & diet limits, ability to work around the house and to travel, feeling depending on medical team, stress or worries, sex life, personal appearance

With regard to the KDQOL-36, the frequencies of answers to single items will be displayed by treatment group and overall by visit. In addition, domain scores for the 5 above defined domains will be calculated according to the KDQOL scoring instruction1.

The KDQOL-36 results will be described by visit and treatment group by presenting the domain scores (PCS, MCS, Burden of Kidney Disease, Symptoms / Problems, and Effects of Kidney Disease) by means of number of observations, minimum, first quartile, mean, SD, median, third quartile, and maximum, including the changes from baseline. It is not sensible to calculate an overall summary score. Group means and standard deviations of domain scores and changes to baseline will be plotted versus time.

In addition, the frequencies of changes from baseline at Visit 3 (Day 30±2), Visit 5 (Day 90±2) and the follow-up visit will be presented regarding the categories improvement / no change / worsening for the single items.

The change from baseline to Visit 3 (Day 30±2), Visit 5 (Day 90±2) and the follow-up visit in the 5 domain scores will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (region, type of albuminuria), and baseline value as covariate. The treatment effect will be tested at a two-sided significance level of 5%. Pairwise differences between each BAY 94-8862 treatment group and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

The EQ-5D-3L will be analyzed similarly. Summary scores will be calculated out of the 5 dimensions according to the scoring instructions from Europe and the US (refer to the EQ-5D-3L User Guide2 and to the EQ-5D Value Sets3). The values and the changes from baseline
of the summary scores and the EQ VAS will be summarized by treatment group and visit using the same descriptive statistics as for KDQOL. Group means and standard deviations of summary scores and EQ VAS and changes to baseline will be plotted versus time. Furthermore, the frequencies of answers to all single items will be provided by treatment group and overall by visit as well as the frequencies of improvement, no change, and worsening for single items. The change from baseline to Visit 3 (Day 30±2), Visit 5 (Day 90±2) and the follow-up visit in the summary scores and the EQ VAS will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (region, type of albuminuria), and baseline value as covariate. The treatment effect will be tested at a two-sided significance level of 5%. Pairwise differences between each BAY 94-8862 treatment group and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

6.3 Pharmacokinetics / pharmacodynamics

6.3.1 Pharmacokinetics

The pharmacokinetic analysis will be performed in the pharmacokinetic analysis set.

The plasma concentration vs. time data of BAY 94-8862 at Visit 3 (Day 30±2) and Visit 5 (Day 90±2) will be sorted in categories (depending on the distribution of data: e.g. 60 - 90, >90 - 120, 240 - 270 and >270 - 300 minutes or 60 - 75, >75 - 90, > 90 - 105, >105 - 120, 240 - 255, >255 - 270, >270 - 285 and >285 - 300 minutes for Visit 3 (Day 30±2), pre-dose, 30 - 60, >60 - 90, 180 - 210, and >210 - 240 minutes or pre-dose, 30 - 45, >45 - 60, >60 - 75, >75 - 90, 180 - 195, >195 - 210, >210 - 225, and >225 - 240 minutes for Visit 5 (Day 90±2)) and the following statistics will be calculated separated by dose, visit and category: geometric mean, standard deviation (re-transformed standard deviation of the logarithms) and coefficient of variation (CV), arithmetic mean, standard deviation and CV, minimum, median, maximum value and the number of measurements.

Descriptive statistics other than minimum and maximum at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the descriptive statistics, a data point below LLOQ will be substituted by one half of this limit. In tables showing descriptive statistics, where values below LLOQ are included, these descriptive statistics will be marked.

Plots will be prepared separately by dose pooling all individual plasma concentrations (naive pooling) vs. actual relative study times (time of sample collection after time of study drug administration).

Measurements that were not taken within the pre-defined time windows for Visit 3 (Day 30±2) and Visit 5 (Day 90±2) [60 to 120 minutes and 240 to 300 minutes after study drug administration for Visit 3 (Day 30±2); pre-administration, 30 to 90 minutes and 180 to 240 minutes after drug administration for Visit 5 (Day 90±2)] will be excluded from the descriptive statistics and plots.

Reference Number: BPD-SOP-060
Supplement Version: 5
Further evaluation of the concentration data will be performed using Population PK methods, followed by PK/PD analyses. These analyses will be described in a separate SAP outside of this document and will be reported under separate cover.

### 6.3.2 Pharmacodynamics

Not applicable.

### 6.4 Safety

Safety analyses will be performed in SAF.

The analysis of the treatment duration, extent of exposure and compliance are described in Section 6.1.5.

### 6.4.1 Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, latest version available prior to data base freeze). A listing will be provided linking the original investigator terms and the coded terms.

Adverse Events (AEs) that occurred or worsened on or after the first dose of study drug up to 3 days after the date of the last dose of study drug will be considered as treatment emergent AEs (TEAEs).

An increase in potassium $\geq 5.6$ mmol/L and subsequent discontinuation of study drug is considered an adverse event of special interest.

An overall summary of all AEs and TEAEs will be generated by treatment group and overall.

The number and incidence of subjects with non-treatment-emergent (pre-treatment) AEs, TEAEs, treatment-emergent SAEs, treatment-emergent study drug-related AEs, treatment-emergent study drug-related SAEs, TEAEs causing discontinuation of study drug, TEAEs of special interest, treatment-emergent non-serious AEs, non-serious AEs, TEAEs by maximum intensity, treatment-emergent serious AEs by maximum intensity, drug-related TEAEs by maximum intensity, TEAEs by worst outcome and treatment-emergent SAEs by worst outcome will be summarized by treatment group and overall using MedDRA terms grouped by Primary System Organ Class (SOC) and Preferred Term (PT).

In case of events with different intensity within a subject, the maximum reported intensity will be used. If intensity is missing, the event will be considered as severe. Similarly, if the same event is reported as both unrelated and related to the study drug within a subject, the event will be reported as related to study drug. If the drug relationship is missing, the event will be considered as being related to the study drug.
The number and incidence of subjects with treatment emergent study drug related AEs will in addition be displayed by treatment group and overall for the subgroup categories strong CYP3A4 inhibitors vs. only weak or moderate CYP3A4 inhibitors vs. no CYP3A4 inhibitor as concomitant medication (Section 4.5.5) using MedDRA terms grouped by SOC and PT.

Separate tables summarizing TEAEs, treatment-emergent study drug-related AEs, and SAEs that occurred in more than 5% of the subjects will be provided.

Deaths, SAEs and AEs leading to study drug discontinuation will be listed separately.

6.4.2 Laboratory parameters

The laboratory parameter UACR will not be included in any of the analyses described in this section. UACR analysis will only be presented for efficacy analyses as described in Section 6.2.1.

Summary statistics including changes to baseline (ratios to baseline for creatinine) will be calculated by treatment group and visit for all quantitative laboratory parameters, e.g. for hematology, clinical chemistry and urinalysis. Urinalysis is assessed 3 times per visit. As for log 10(10*urinary sodium / potassium ratio) a normal distribution can be assumed, the geometric mean of all non-missing assessments for the sodium to potassium ratio will be calculated to derive a single value per visit. For all other urine parameters arithmetic means will be calculated to derive a single value per visit. In addition, geometric statistics and ratios to baseline will be presented for the urinary sodium / potassium ratio instead of arithmetic statistics with changes from baseline.

For the eGFR the relative change will be displayed in addition to the absolute change from baseline.

Summary statistics for serum potassium, eGFR and serum creatinine will also be repeated by treatment group and visit separately for each of the stratification levels (region, type of albuminuria).

The number of subjects with transitions from baseline with respect to reference ranges categories (low, normal, high) will be provided by treatment group and visit. In addition, the number of subjects with treatment emergent (until 3 days after last study drug administration) abnormal laboratory values above or below the normal range will be tabulated by the laboratory parameter and treatment group and overall.

For the special safety parameters serum potassium, eGFR and serum creatinine the means and standard deviations (geometric means and standard deviations for creatinine) of laboratory values and changes to baseline (ratios to baseline for creatinine) of the treatment groups will be plotted versus time.

The special safety parameters will be further assessed by displaying the number and incidence of subjects with safety events as described below by treatment group, visit and overall.
(subjects with at least 1 event in the respective category after start of study drug administration). This will also be performed stratified by the subgroups, specified in Section 4.5.5. Bar charts for the percentage of subjects at any time post baseline will be presented overall, as well as stratified for type of albuminuria. The summaries will be performed for the number and incidence of subjects with

- serum potassium ≥5.6 mmol/L and >6 mmol/L
- relative decrease in eGFR of ≥25%, ≥30%, ≥40% and ≥57%
- eGFR < 30 ml/min/1.73m²
- increase in serum creatinine >0.3 mg/dL and >0.5 mg/dL.

The percentage of subjects with the respective events (non-stratified) at any time post baseline and within 3 days after last study drug administration will be compared between each BAY 94-8862 treatment group and the placebo treatment group by applying separate $\chi^2$ tests with continuity correction. If the expected number of subjects in at least 1 cell of the 2x2 contingency table is <56, Fisher’s exact test will be applied instead of the $\chi^2$ test. Estimates and two-sided 95% confidence intervals will be provided for each treatment group and the treatment differences. Clopper Pearson confidence intervals will be calculated for each treatment group, while for treatment differences the exact unconditional confidence limits will be calculated.

Subjects with serum potassium ≥5.6 mmol/L or a relative decrease in eGFR ≥30% will be listed with their full profile for the respective parameter.

The absolute change in serum potassium and eGFR from baseline to Visit 3 (Day 30±2), Visit 4 (Day 60±2) and Visit 5 (Day 90±2), as well as the log-transformed ratios of serum creatinine at each of these visits to baseline will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (region, and type of albuminuria) and baseline value (log-transformed for creatinine) as covariate. The treatment effect will be tested at a two-sided significance level of 5%. Pairwise differences (ratios for creatinine) between each BAY 94-8862 treatment group and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

A full profile listing of all serum potassium assessments (including both local and central lab) will be displayed for all subjects with at least one serum potassium assessment ≥5.6 mmol/l. The listing will include in addition the information, whether a subject experienced a treatment emergent event of special interest (an increase in potassium ≥5.6 mmol/L and subsequent discontinuation of study drug).
6.4.3 Other additional safety variables

6.4.3.1 Safety Biomarkers

The safety biomarker cystatin C will be summarized descriptively by treatment group and visit including ratios to baseline. These analyses will be performed overall and separated by the stratification factors (region and type of albuminuria). Geometric group means and standard deviations of Cystatin C values and ratios to baseline (non-stratified) will be plotted versus time. Boxplots for ratios to baseline at Visit 5 (Day 90±2) will be presented for each treatment group overall and for each stratum level of type of albuminuria.

The log-transformed ratio of Cystatin C at Visit 3 (Day 30±2), Visit 4 (Day 60±2) and Visit 5 (Day 90±2) to baseline will be analyzed by separate ANCOVA models with treatment group as the main effect, factors for the stratification levels (region and type of albuminuria) and the log-transformed baseline value as covariate. The treatment effect will be tested at a two-sided significance level of 5%. Pairwise ratios between each BAY 94-8862 treatment group and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

In addition, the laboratory results of the safety biomarker Troponin T will be summarized with the numbers and incidences of subjects with values > 99 percentile of a normal reference population (upper reference limit) and > 5* 99 percentile of a normal reference population by treatment group and visit as well as overall (subjects with at least 1 event in the respective category after start of study drug administration and within 3 days after last study drug administration) as described by the Third Universal Definition of Myocardial Infarction. The value of the upper reference limit, i.e. the 99 percentile of a normal reference population, as provided by the central laboratory, is 0.049999 μg/L. The percentage of subjects with the respective events at any time post baseline and within 3 days after last study drug administration will be compared between each BAY 94-8862 treatment group and the placebo treatment group by applying separate χ² tests with continuity correction as described in Section 6.4.2. 95% confidence intervals will be presented for the percentages per treatment group and the difference to placebo. Absolute and relative frequencies of decreases, no changes and increases will be presented by visit and treatment group for Troponin T.

6.4.3.2 Vital Signs

At the corresponding visits, three measurements of vital signs parameters will be taken in sitting position at time intervals of about 2 minutes. Only assessments in sitting position will be included in the analysis. Averages of non-missing values of these three measurements will be calculated and used for the statistical analysis. If only one of the planned measurements is available, this value will be used.

Vital signs values will be summarized by treatment group and visit using descriptive statistics including absolute changes from baseline. The analysis will be repeated for SBP stratified by
the baseline SBP ≤ its median or > its median, as well as stratified by baseline SBP >90 -
<140 mmHg, 140 – <160 mmHg and ≥ 160 mmHg.

Group means and standard deviations of vital signs values and changes to baseline (non-
stratified) will be plotted versus time.

The change in vital signs parameters from baseline to Visit 3 (Day 30±2), Visit 4 (Day 60±2)
and Visit 5 (Day 90±2) will be analyzed by separate ANCOVA models with treatment group
as the main effect, factors for the stratification levels (region and type of albuminuria) and
baseline value as covariate. The treatment effect will be tested at a two-sided significance
level of 5%. Pairwise differences between each BAY 94-8862 treatment group and the
placebo treatment group will be calculated and corresponding two-sided 95% confidence
intervals will be computed.

6.4.3.3 Weight and BMI

The values and the changes from baseline will be summarized by treatment group and visit
using descriptive statistics for weight and BMI.

6.4.3.4 ECG

ECG parameters will be summarized by treatment group and visit using descriptive statistics
including absolute changes from baseline.

ECGs considered as invalid will be excluded from the analysis. ECGs considered as invalid
for QT analysis will be excluded from the QT analysis.

Group means and standard deviations of ECG values and changes to baseline will be plotted
versus time.

The number of subjects with abnormal electrocardiogram findings will be presented by visit.

A summary of QTc interval prolongations will be provided by visit and treatment group.

6.4.3.5 Ambulatory blood pressure monitoring (ABPM)

The multiple assessments per visit [screening, Visit 4 (Day 60±2) and Visit 5 (Day 90±2)]
will be summarized as averages for night and day time and as minimum and maximum (for
day and night time). Day time averages will be calculated based on assessments between 6 am
and 10 pm, while night time averages will be calculated for assessments between 10 pm and 6
am.

Invalid measurements (the minimum percentage of successful readings must be ≥ 80% per
visit) will be excluded from the statistical analysis.
The day and night time averages, minima and maxima from the ABPM will be summarized by treatment group and visit using descriptive statistics including absolute changes from baseline.

Descriptive statistics will be presented for the time intervals 06:00 a.m. - < 07:00 a.m., 07:00 a.m. - < 08:00 a.m., … , 05:00 a.m. – 06:00 a.m by visit and treatment group. The group means and standard deviations of these time intervals will be plotted versus time for each visit.

6.4.3.6 Iohexol plasma clearance

Summary statistics including changes, as well as relative changes to baseline will be calculated by treatment group and visit for iohexol plasma clearance.

7. Document history and changes in the planned statistical analysis

7.1 Changes to planned analysis

The protocol defines the SAF as all randomized subjects how have taken at least one dose of study medication. For the LOS the protocol states, that it consists of all other subjects screened who did not receive any dose of study drug or for whom no data after beginning of treatment are available. This includes randomized and treated subjects without any further data. As the two specifications overlap it was decided to add to the definition of the SAF the specification “with data after beginning on treatment”.

The ANCOVA model for the primary analysis includes according to the protocol a factor for treatment group, the stratification factors (region and type of albuminuria) and the log-transformed baseline UACR as a covariate. As the baseline UACR defines the type of albuminuria, the covariate log-transformed baseline UACR and the stratification factor “Type of albuminuria” are not independent. To adjust for this, the ANCOVA model was newly specified with a nested effect of log-transformed baseline UACR within “Type of albuminuria” and otherwise as defined in the protocol. This model will estimate for each type of albuminuria a separate slope for the covariate. In addition, the protocol states that a region might be pooled with another region, if the sample size within these region is very small. In order to present the actual stratification within the primary analysis, the pooling of regions will not be performed in any case.

Changes in albuminuria and the mixed model for the ratios of UACR at Visit 3 (Day 30 ±2), Visit 4 (Day 60 ±2) and Visit 5 (Day 90 ±2) to UACR at baseline are described in the protocol as further exploratory efficacy analyses. In order to describe the complete analyses based on UACR within the same subsection, these specific analyses on change in albuminuria and the mixed model for the ratios of UACR at Visit 3 (Day 30 ±2), Visit 4 (Day 60 ±2) and Visit 5 (Day 90 ±2) to UACR at baseline are described in Section 6.2.1 (Analysis of primary efficacy variable) as well.
The protocol defines UACR not only as an efficacy variable, but also as a safety variable. As UACR is intensively analyzed for FAS and PPS in the efficacy analysis, UACR will not additionally be analyzed for the SAF.

Items 28a and 28b of the KDQOL questionnaire are excluded from this study as these items refer to problems of dialysis which are not relevant to the present study population. Therefore the domain score Symptoms / Problems consists of Items 17-27 instead of 17-28.

The protocol defines separate analyses for scores for each dimension of the EQ-5D. However, a score for each dimension is not meaningful and instead the 5 dimensions can be summarized to a single summary score (see Section 6.2.2.3).

For the KDQOL-Questionnaires scores and the EQ-5D questionnaire scores the protocol defines analyses based on categories improvement / no change / worsening (Frequency tables and a $\chi^2$ Test for treatment comparison). As a clinical meaningful change from baseline could not be defined for both questionnaire scores the frequency tables will only be presented for the single items and not for the questionnaire scores. The treatment comparison will be performed based on an ANCOVA model with treatment group as the main effect, factors for the stratification levels (region and type of albuminuria), and the baseline score as covariate instead of the $\chi^2$ Test.

The protocol states that hemolytic blood samples should not be considered for the statistical analyses. But the central laboratory will already check whether a measured laboratory parameter is valid for further evaluation, if the sample was hemolytic. The central laboratory will only provide data which are valid for evaluation and accordingly, available laboratory assessments from hemolytic blood samples do not need to be excluded from the statistical analyses.

According to the protocol, several descriptive summaries for safety and efficacy variables should be repeated for the stratification factors and the subgroups defined in Section 4.5.5. These summaries will only include baseline and the scheduled Visits 3 (Day 30±2), 4 (Day 60±2) and 5 (Day 90±2) since these are the visits of major interest. In addition, the protocol states, if the total number of subjects in a subgroup category is <15, the analysis for that level of the subgroup will not be performed. In order to avoid any post hoc analysis, in case the results of such subgroups become necessary to fully interpret the results, this rule is removed and all subgroups will be presented in any case.

The initial SAP stated that the assumption of a normal distribution will be checked for some parameters. After an assessment of the assumption for normal distribution of the baseline data prior to unblinding, a lognormal distribution will be assumed for efficacy biomarkers NT-proBNP, BNP, Galectin -3, safety biomarker Cystatin C, and for the laboratory parameter serum creatinine. Consequently the analysis was adjusted as described in Amendment 2.

### 7.2 Document history
- SAP dated 23 AUG 2013 submitted for internal review
• Approval of the SAP dated 20 SEP 2013
• SAP Amendment 1 (due to protocol amendment, addition of plots and further clarifications and specifications) leading to SAP version 2.0 dated 06 MAY 2014 submitted for internal review and approved on 25 JUL 2014
• SAP Amendment 2 (due to assessment of the assumption of normal distribution) leading to SAP version 3.0 dated 02 SEP 2014 approved on 02 SEP 2014

8. References


7. 16243_normal_distributions_02_Sept_2014.pdf