

Document Type:	Study Protocol
Official Title:	A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase III study to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease
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Cover page of the integrated protocol

A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase III study to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease

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

- **Original protocol**, Version 1.0, dated 10 JUN 2015
- **Amendment 03**, (global amendment described in Section [15.1](#)) forming integrated protocol Version 2.0, dated 02 MAY 2017
- **Amendment 04**, (global amendment, refer to the "[Protocol amendment summary of changes](#)" section) forming integrated protocol Version 3.0, dated 26 FEB 2019

Local amendments not forming part of this integrated global protocol:

- **Amendment 01**, (dated 18 AUG 2015)
(local amendment, valid for Japan only)
- **Amendment 02**, (dated 29 JUL 2016)
(local amendment, valid for Turkey only)

1. Title page - amended

Study title

A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase III study to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease

Short title: Efficacy and safety of finerenone in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease

Acronym: **FIDELIO-DKD (FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease)**

Test drug: Finerenone / BAY 94-8862

Study purpose: Efficacy and safety

Clinical study phase: III Date: 26 FEB 2019

Registration: EudraCT: 2015-000990-11 Version no.: 3.0

Sponsor's study no.: 16244

Sponsor: Non- US territory: Bayer AG, D-51368 Leverkusen, Germany
US territory: Bayer Healthcare Pharmaceuticals Inc.,
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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: PPD 

Role: Global Clinical Leader

Date: 27 FEB 2019

Signature:

PPD 

Signature of principal investigator

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

Name:

Affiliation:

Date:

Signature:

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

2. Synopsis - amended

This section was changed in Amendment 3, see Section 15.1.2.2.

Title	A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase III study to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease
Short title	Efficacy and safety of finerenone in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease
Acronym	FIDELIO-DKD (F inerenone in reducing kiDnEy faiLure and d isease prO gression in D abetic K idney D isease)
Clinical study phase	III
Study objectives	<p>The primary objective of this study is to:</p> <ul style="list-style-type: none"> • Demonstrate whether, in addition to standard of care (SoC), finerenone is superior to placebo in delaying the progression of kidney disease, as measured by the composite endpoint of time to first occurrence of kidney failure, a sustained decrease of eGFR $\geq 40\%$ from baseline over at least 4 weeks or renal death <p>The secondary objectives of this study are to determine whether, in addition to SoC, finerenone compared to placebo:</p> <ul style="list-style-type: none"> • Delays the time to first occurrence of the following composite endpoint: cardiovascular (CV) death or non-fatal CV events (i.e. non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure [HF]) • Delays the time to all-cause mortality • Delays the time to all-cause hospitalizations • Change in UACR from baseline to Month 4 • Delays the time to first occurrence of the following composite endpoint: onset of kidney failure, a sustained decrease in eGFR of $\geq 57\%$ from baseline over at least 4 weeks or renal death.
Test drugs	
Name of active ingredient	Finerenone
Doses	<ul style="list-style-type: none"> • 10 mg finerenone tablet once daily in the morning OR • 20 mg finerenone tablet once daily in the morning
Route of administration	Oral
Duration of treatment	As an event-driven trial, the actual length of the treatment will depend on the observed event rate, the patient recruitment rate, and length of the recruitment period and will be approximately 3.5 years.

Reference drug Name of active ingredient Dose Route of administration Duration of treatment	Placebo <ul style="list-style-type: none"> • Placebo tablet once daily in the morning Oral As an event-driven trial, the actual length of the treatment will depend on the observed event rate, the patient recruitment rate, and length of the recruitment period and will be approximately 3.5 years.
Background treatment	Standard of care (SoC) therapy
Indication	Diabetic kidney disease (DKD)
Diagnosis and main criteria for inclusion /exclusion	<u>Key inclusion criteria:</u> <ul style="list-style-type: none"> • Men or women ≥ 18 years of age • T2DM as defined by the American Diabetes Association • Diagnosis of DKD with at least one of the following criteria at Run-in and Screening visits: <ul style="list-style-type: none"> – persistent high albuminuria ¹ and presence of diabetic retinopathy OR – persistent very high albuminuria ². • Pretreated for at least 4 weeks prior to the Screening Visit with <u>either</u> ACEI <u>or</u> ARB at maximal tolerated labeled dose, preferably without adjustments to dose or choice of agent or other treatment • Serum potassium ≤ 4.8 mmol/L. <u>Key exclusion criteria:</u> <ul style="list-style-type: none"> • Confirmed significant non-diabetic renal disease, including clinically relevant renal artery stenosis • Uncontrolled arterial hypertension (ie, mean sitting SBP ≥ 170 mmHg, sitting DBP ≥ 110 mmHg at run-in visit, or mean sitting SBP ≥ 160 mmHg, sitting DBP ≥ 100 mmHg at screening) • Clinical diagnosis of chronic HFrEF and persistent symptoms (NYHA class II – IV) at run-in visit (class 1A recommendation for MRAs) • Dialysis for acute renal failure within 12 weeks of run-in visit • Renal allograft in place or scheduled within next 12 months • HbA1c $> 12\%$.
Study design	Randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven
Methodology	Randomized subjects will be treated with finerenone or placebo OD in a blinded fashion. The starting dose of study drug will depend on the subject's eGFR level at the Screening Visit: a lower dose of 10 mg OD if eGFR was

¹ **High albuminuria** (previously known as 'micro-albuminuria') is defined as 300 mg/g $>$ UACR ≥ 30 mg/g in 2 out of 3 first morning void samples.

² **Very high albuminuria** (previously known as 'macro-albuminuria') is defined as UACR ≥ 300 mg/g in 2 out of 3 first morning void samples.

	between 25 to < 60 mL/min/1.73m ² , or the higher (target) dose of 20 mg OD if eGFR was \geq 60 mL/min/1.73m ² . Study drug may be up-titrated from Visit 2 (Month1) onwards provided potassium is \leq 4.8 mmol/L and eGFR decrease is less than 30% below the value last measured. Down-titration or interruption of study drug is permitted at any time during the study for safety reasons.
Type of control	Placebo
Data Monitoring Committee	Yes
Number of subjects	Planned 9600 subjects screened, 4800 subjects randomized to achieve approximately 1068 primary efficacy events
Primary variable	Time to first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR \geq 40% from baseline over at least 4 weeks, or renal death
Time point/frame of measurement for primary variables	Events for inclusion in the primary variable (above) will be counted from the day of randomization (Visit 1) onwards until the End-of-Study (EOS) visit following the study termination decision. In the case of premature termination from the study with no subsequent follow-up information, events will be counted up to the day of premature termination
Plan for statistical analysis	The log-rank test for the difference of the survival function of finerenone compared to placebo, stratified by the stratification factors region, type of albuminuria and eGFR category will be used, an overall two-sided significance level of 5.0% or 3.333% if the CV composite endpoint is not statistically significant according to the weighted Bonferoni-Holm procedure, with a small adjustment for an interim analysis

Protocol amendment summary of changes**Amendment 4 (26 FEB 2019)**

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

This amendment summarizes minor changes in the conduct of the study and planned analyses.

The main change is that the PT Visit will be performed as a telephone contact for all patients except those participating in the iohexol clearance sub-study. The PT Visit is to be performed within 4 weeks + 5 days after last study drug intake for those patients still on treatment at the EOS Visit (Sections 9.1, 9.2.10, and 9.2.11). The rationale for the change is that a telephone call is considered adequate to inquire about possible AEs and concomitant medication usage. This change neither compromises patient safety nor scientific value. The performance as a telephone contact will minimize the burden on patients, sites, and the sponsor. Procedures that would require the presence of the patient at the study site have been adapted accordingly. The following activities will no longer be performed: physical examination, ECG, recording of body weight and vital signs, and laboratory sampling.

All other minor changes with their brief rationale are summarized in the table below.

Table 1 Protocol amendment summary of minor changes

Section number and name	Description of change	Brief rationale
10.1 General considerations 10.3.2 Treatment duration, extent of exposure, up-titration status and compliance	Specification of baseline values.	This was added to clarify the handling of subjects who did not immediately start with study drug treatment at randomization, because all analyses follow the intent-to-treat principle.
10.1 General considerations 10.3.3.2 Primary efficacy variable: supportive	For on-treatment efficacy analyses, the time window after last study drug administration is increased from 3 to 30 days.	The time window was increased to better reflect the more protracted nature of the development and diagnosis of clinical outcome events of interest in relation to treatment exposure.

continued

Section number and name	Description of change	Brief rationale
10.3.4	Provision of more precise wording about the type of discontinuation.	Considering the nature of the underlying disease and the long duration of the study, it is the impact of permanent discontinuation of the study drug that is of particular interest.
10.3.4.1 Adverse events	New definition of treatment-emergent AEs.	The definition of TEAEs was specified to account for permitted study drug interruptions (i.e. temporary discontinuations) which may occur over extended periods.
10.3.4.2 Laboratory data	Specification regarding interruption of study treatment.	This was updated to consider treatment interruptions in a similar manner as done for the AE presentation.
10.3.3.5.2 Decrease in eGFR 10.3.4.2 Laboratory data	Deletion of the following analyses: <ul style="list-style-type: none"> • Absolute value of serum potassium >5.0 mmol/L • Relative decrease from baseline in eGFR of ≥25% • Increase from baseline in serum creatinine >0.3 mg/dL and >0.5 mg/dL 	Patients remain on study drug treatment with potassium values up to 5.5 mmol/L. Safety specific information will be obtained by analyzing the remaining thresholds of >5.5 mmol/L (moderate hyperkalemia) and >6.0 mmol/L (severe hyperkalemia) for serum potassium. In this long-term trial relative eGFR decrease from baseline ≥ 25% does not provide clinically relevant information. The same applies to analyses of change in serum creatinine, which is already incorporated in the currently planned analyses of change in eGFR.
Throughout Section 10 Statistical methods and determination of sample size	More precise wording.	Specifications changed for correctness.
Where applicable	Minor editorial and typographical errors, updated information on responsible persons.	Unsubstantial changes for correctness.

Abbreviations: AE = adverse event; eGFR = estimated glomerular filtration rate; TEAE = treatment-emergent adverse event

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List of abbreviations

AASK	African-American Study of Kidney disease and hypertension
ACEI(s)	angiotensin-converting enzyme inhibitor(s)
AE	adverse event
ANCOVA	analysis of covariance
ALT	alanine aminotransferase
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints
AP	alkaline phosphatase
ARB(s)	angiotensin receptor blocker(s)
ARTS	Mineralocorticoid Receptor Antagonist Tolerability Study
ARTS-DN	Mineralocorticoid Receptor Antagonist Tolerability Study - Diabetic Nephropathy
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
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
BSA	body surface area
CEC	Clinical Event Committee
C _{max}	maximum total (bound and unbound) drug concentration in plasma after single dose administration
CK	creatinine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRO	contract research organization
CV	Cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
CYP3A4	cytochrome P450 isoenzyme 3A4
DBP	diastolic blood pressure
DKD	diabetic kidney disease
DMC	Data Monitoring Committee
DN	diabetic nephropathy
ECG	electrocardiogram
eCRF	electronic case report form
EED	end expiratory diameter
eGFR	estimated glomerular filtration rate
EOS	End-of-Study (visit)
EQ-5D-5L	EuroQol Group 5-dimension, 5-level questionnaire
ESRD	end-stage renal disease
EU	European Union
EWDT	E-wave deceleration time
FAS	full analysis set

FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transpeptidase
GMP	Good Manufacturing Practice
HbA _{1c}	glycated hemoglobin
HDL	high density lipoprotein
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HOPE	H eat O utcomes P revention E valuation
HRQoL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
Hs-TnT	high-sensitivity troponin T
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDNT	I rbesartan D iabetic N ephropathy T rial
IEC	Independent Ethics Committee
IR	immediate release
IRB	Institutional Review Board
IVCD	inferior vena cava diameter
IVSd	inter-ventricular septum diameter
IxRS	Interactive Voice / Web Response System
KDQOL	Kidney Disease Quality of Life
KDIGO	Kidney Disease: Improving Global Outcomes
LA	left atrial
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LOS	listing only set
LVED	left ventricular end-diastolic
LVEDD	left ventricular end-diastolic dimension
LVEDV	left ventricular end-diastolic volume
LVEDVi	left ventricular end-diastolic volume index
LVESV	left ventricular end-systolic volume
LVESVi	left ventricular end-systolic volume index
LVEF	left ventricular ejection fraction
LVM	left ventricular mass
LVMi	left ventricular mass index
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
M.D.	doctor of medicine

MedDRA	Medical Dictionary for Regulatory Activities
MICRO-HOPE	M icroalbuminuria, C ardiovascular, and R enal O utcomes (substudy of the HOPE trial)
MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
NGAL	neutrophil gelatinase-associated lipocalin
NIDDM	non-insulin dependent diabetes mellitus
NONMEM	non-linear mixed effect modeling
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OD	once daily
OPN	osteopontin
PD	premature discontinuation
PGTV	pressure gradient of tricuspid valve
PIIINP	N-terminal pro-peptide of collagen III
PK	pharmacokinetic(s)
PKS	pharmacokinetic analysis set
PP	polypropylene
PPS	per-protocol analysis set
PR	PR interval in ECG
PT	Post-Treatment (visit)
PWd	posterior wall diameter
QA	quality assurance
RA(A)S	renin-angiotensin(-aldosterone) system
RAP	right atrial pressure
RAVE	electronic data capturing system
RBC	red blood cells
RENAAL	R eduction in E ndpoints in N IDDM (non-insulin-dependent diabetes mellitus) with the A ngiotensin II A ntagonist L osartan
RWT	relative wall thickness
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SAS	Statistical Analysis System
SAVOR-TIMI 53	S axagliptin A ssessment of V ascular O utcomes R ecorded in Patients with D iabetes Mellitus – T hrombolysis in M yocardial I nfarction 53
SBP	systolic blood pressure
SD	study drug
SDv	standard deviation
SID	subject identification
SMQ	Standardized MedDRA Queries
SoC	standard of care
sST2	soluble suppression of tumorigenicity 2
SUSAR	suspected, unexpected serious adverse reaction

T2DM	type 2 diabetes mellitus
TAPSE	tricuspid annular plane systolic excursion
t_{\max}	time to reach C_{\max} in plasma after single (first) dose
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
UACR	urinary albumin-to-creatinine ratio
UAE	urinary albumin excretion
US	United States (of America)
VTR	velocity of tricuspid regurgitation
WBC	white blood cells
WHO	World Health Organization

3. Introduction

3.1 Background

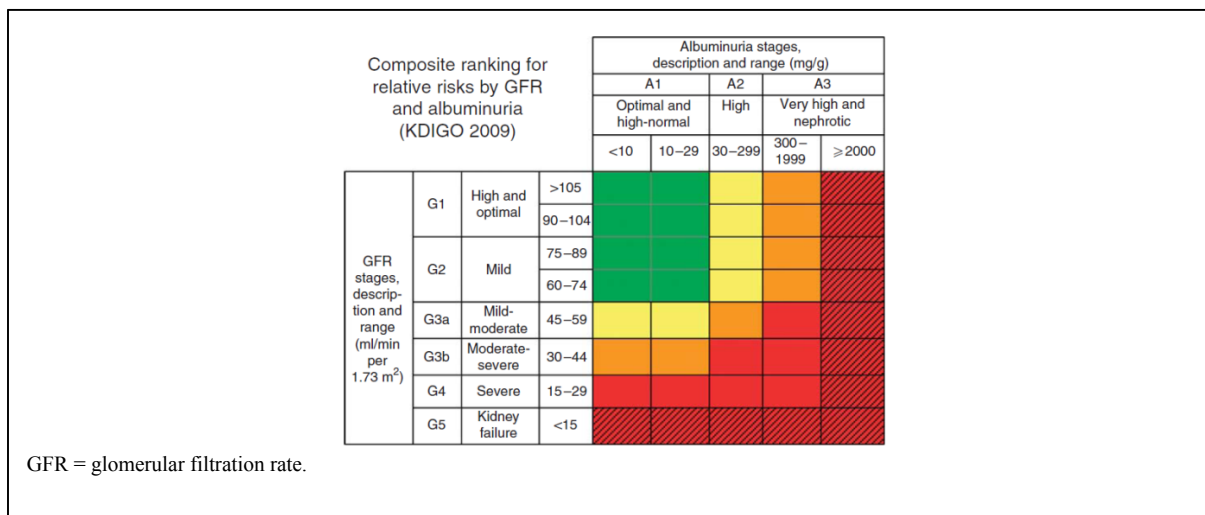
Diabetic kidney disease (DKD) is the most frequent cause of end-stage renal disease (ESRD) in western countries (1). In addition, the risk of cardiovascular (CV) disease and death increases in patients with DKD with decreasing glomerular filtration rate (GFR) and increasing albuminuria levels (2, 3).

As the type 2 diabetes mellitus (T2DM) population rapidly grows throughout the world within the next years (4), and with it the DKD population, there is an increasing need for new therapeutic agents that effectively target underlying disease mechanisms and slow or halt the progression of kidney disease, whilst also addressing the high CV morbidity and mortality in this population.

DKD is a clinical syndrome affecting individuals with diabetes that is characterized by albuminuria on at least 2 occasions separated by 3 to 6 months (5). DKD is usually accompanied by hypertension, progressive rise in proteinuria, and decline in renal function (3). DKD is categorized based on the level of urinary albumin excretion (UAE), either **high albuminuria** (formerly micro-albuminuria, urinary albumin-to-creatinine ratio [UACR] 30 to < 300 mg/g) or **very high albuminuria** (formerly macro-albuminuria, UACR ≥ 300 mg/g).

As indicated in Figure 3–1, increased UAE and decreased GFR are both associated with a worse prognosis, with an increase in all-cause and CV mortality. Additionally, increased UAE and decreased GFR are also risk factors for ESRD, acute kidney injury and progressive CKD, independent of each other and of other cardiovascular disease (CVD) risk factors in general as well as in high-risk populations (2, 6, 7).

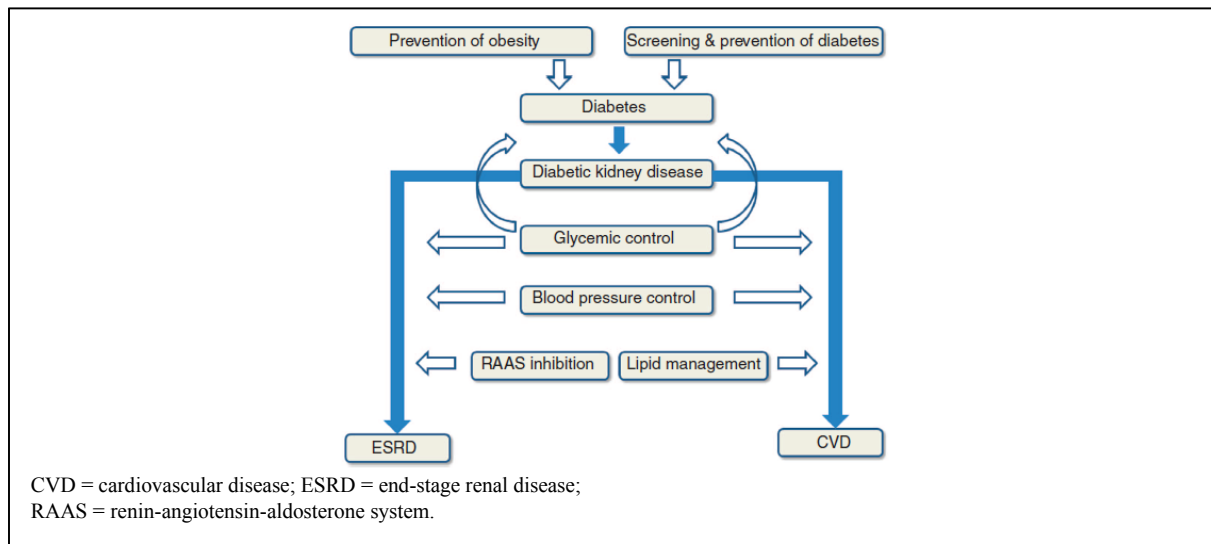
Figure 3–1 Prognosis of CKD by GFR and albuminuria category (3)



Interventions to improve outcomes related to DKD focus on reducing risk (Figure 3–2), including counseling on lifestyle modifications (i.e. smoking cessation and dietary

modifications to reduce proteinuria and aid in weight loss) and interventions aimed at glycemic control, dyslipidemia, and hypertension (8).

Figure 3–2 Approaches to improving outcomes related to DKD (8)



Treatment with renin-angiotensin system (RAS) inhibitors has been of particular interest given the ability of these drugs to reduce the rate of progression of renal disease, independently and in addition to their antihypertensive effects, as evidenced in the Heart Outcomes Prevention Evaluation (HOPE) trial (9), the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial (10), and the Irbesartan DN Trial (IDNT) (11).

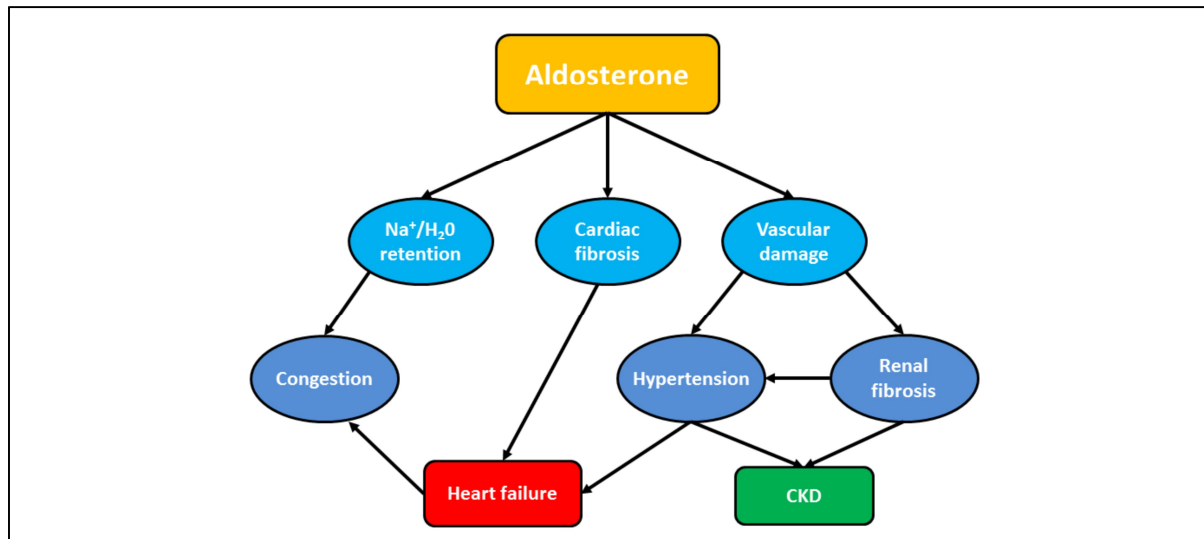
Therefore, angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) can be considered as standard of care (SoC) therapy in patients with DKD and are often prescribed to patients with DKD at early stages (8). However, they slow but neither halt nor reverse kidney disease progression (12).

In addition, in placebo controlled studies in patients with early DKD (i.e. patients with high albuminuria at baseline), only ACEIs were found to significantly reduce the risk of all-cause and CV mortality and morbidity (9). In patients with advanced DKD (i.e. patients with decreased kidney function and very high albuminuria at baseline) an impact on overall survival has not yet been demonstrated with ARBs (10, 11). ACEIs have not been investigated in outcome studies in the advanced DKD population yet.

Animal studies have shown that aldosterone has an independent role in the development of hypertensive kidney disease and vascular injury resulting in myocardial and renal fibrosis (Figure 3–3) and its blockade reduces proteinuria (13-16). Long-term RAS blockade with ACEIs and ARBs results in incomplete suppression of serum aldosterone levels and is known as the ‘aldosterone escape’ phenomenon (17). Exploratory clinical studies in adults have shown that in adults with CKD exhibiting the ‘aldosterone escape’ phenomenon, treatment with mineralocorticoid-receptor antagonists (MRAs) improves kidney outcomes such as proteinuria (18). However, there is also evidence for possible therapeutic utility of

mineralocorticoid receptor (MR) blockade in conditions of tissue and organ damage with normal aldosterone levels (19).

Figure 3–3 Mechanisms of cardiac and renal damage induced by aldosterone excess (20)



The results of several short-term studies support the proposal of Shavit et al. that aldosterone should be considered a novel therapeutic renal target in CKD patients with the added potential ‘off-target’ effects on heart and vasculature (21). Nevertheless, large-scale, long-term outcome trials examining whether MRAs can slow progression of kidney disease or prevent CV events in this population are missing.

Moreover, the use of currently available steroidal MRAs is known to increase the risk of hyperkalemia, particularly in patients with T2DM and decreased kidney function (20, 22).

Finerenone (BAY 94-8862) is a next-generation, oral, selective, non-steroidal MRA. In animal models, finerenone reduced cardiac and renal hypertrophy, plasma prohormone of brain natriuretic peptide (BNP) and proteinuria more efficiently than in those treated with the steroidal MRA eplerenone, when comparing equi-natriuretic doses. Finerenone’s tissue distribution pattern in rats was found to differ from the steroidal MRAs, i.e. spironolactone and eplerenone, which showed a higher accumulation of the drug equivalent concentration in kidney than in heart tissue, in contrast to finerenone which was found to be equally distributed in both the kidney and heart tissue (23). Steroidal MRAs are known to interfere with the steroid hormone receptor, which can cause sexual side effects such as gynecomastia in men. However, finerenone is a non-steroidal and selective MRA *in vitro*, without any detectable affinity for the related androgen receptor; sexual side effects are therefore not expected to occur with finerenone at therapeutic dose levels. These characteristics may translate to a drug with a positive benefit-risk ratio in patients with DKD.

In a Phase IIa study, finerenone was studied in individuals with stable HFrEF and mild (eGFR 60 to < 90 mL/min/1.73 m²) -to-moderate (30–60 mL/min/ 1.73 m²) CKD. In this

minerAlocorticoid Receptor Antagonist Tolerability Study (**ARTS**; IMPACT No. 14563, NCT01345656), finerenone doses of 2.5 to 10 mg/day safely reduced albuminuria and doses of 5.0–10.0 mg/day reduced plasma natriuretic peptides levels to the same magnitude as spironolactone 25–50 mg/day. All doses of finerenone were associated with a statistically significantly smaller mean increase in serum potassium concentration and clinically significantly smaller decreases in eGFR compared to spironolactone (24).

The MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (**ARTS-DN**; IMPACT No. 16243; NCT01874431) was a multicentre, randomized, double-blind, placebo-controlled, parallel-group, Phase IIb study investigating the safety and efficacy of several oral doses of finerenone in patients with T2DM and a clinical diagnosis of DKD, based on either high albuminuria (UACR 30 to 299 mg/g) or very high albuminuria (UACR 300 to 3000 mg/g), and with an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m² or more. Finerenone doses of 1.25 mg up to 20 mg once daily (OD) were investigated in 823 randomized patients over 90 days of treatment compared to placebo in addition to SoC, including a RAS-inhibitor. Finerenone statistically significantly reduced albuminuria by 21 to 38%, compared to placebo, at doses of 7.5 mg to 20 mg OD when added to RAS blockade. All doses of finerenone were safe and well-tolerated. Incidences of treatment-emergent adverse events (TEAEs) were similar between placebo and all finerenone dose groups.

Based on the aforementioned properties and initial results of finerenone in Phase II clinical trials, finerenone has the potential to address the unmet medical needs in patients with the clinical diagnosis of DKD. When added to SoC therapy including a RAS blocker, 10 or 20mg finerenone given OD might demonstrate a reduction of CV mortality and morbidity and also delay the progression of renal disease compared to placebo in addition to SoC.

Further details can be found in the latest available version of the Investigator's Brochure (IB), which contains comprehensive information on the study drug.

In this study (16244), finerenone will be investigated in patients at high risk of progressing to kidney failure and at high risk of CV events. A second study of the Phase III program of finerenone in DKD, Study 17530, will investigate finerenone in patients at lower risk of progressing to kidney failure but still at a high-risk of developing a first or recurrent CV event. Accordingly, in Study 16244, the primary endpoint will focus on renal outcomes whereas in Study 17530, the primary endpoint will focus on CV outcomes.

3.2 Rationale of the study

Study 16244 will be the first large-scale, long-term outcome trial examining whether the non-steroidal MRA finerenone can slow the progression of kidney disease in patients with the clinical diagnosis of DKD. Secondary endpoints will focus on CV outcomes, all-cause mortality, all-cause hospitalizations and change in UACR.

The risk for CKD progression and ESRD is elevated in this population of patients with advanced DKD, with lower eGFR and higher levels of albuminuria being independent risk factors (6).

Together with Study 17530, which will be the first large-scale, long-term outcome trial examining whether the non-steroidal MRA finerenone can decrease CV mortality and morbidity in patients with the clinical diagnosis of DKD, Study 16244 is part of the Phase III trial program to evaluate if finerenone in addition to SoC can reduce the incidence of important clinical outcomes in patients with the clinical diagnosis of DKD.

An inappropriate release of aldosterone contributes to target organ damage found in heart failure, myocardial infarction, chronic renal failure and hypertension. The extensive expression of the MR in the CV system including the heart, endothelial cells, vascular smooth muscle cells and kidney mesangial cells gives further evidence for the role of aldosterone in CV and renal injury.

Blockade of the action of aldosterone and potentially other MR ligands such as cortisol has been demonstrated to be of benefit in different forms of CVD (25-27). Results from several short-term studies show that treatment with MRAs in addition to RAS blockade with an ACEI or ARB improves albuminuria; however, long-term outcome trials examining whether MRAs can prevent CV events or slow progression of kidney disease in a diabetic or non-diabetic CKD population are still lacking. The Phase III program with finerenone in DKD will be the first program addressing both questions: Study 16244 will investigate the effects of the non-steroidal MRA finerenone on renal outcomes and Study 17530 will investigate the effects of finerenone on CV outcomes.

The actual mechanisms behind the pathological effects of aldosterone in DKD have not yet been fully elucidated; however, aldosterone seems to be a key player in the progression of kidney disease, and also contributes to the accompanying high CV morbidity and mortality of these patients. Potent and selective MR blockade with finerenone may therefore provide protection against the burden of CVD and also slow or halt the progression of kidney disease in the targeted DKD population.

3.3 Benefit-risk assessment

Among patients with diabetes, those with kidney disease are consistently observed to have substantially elevated mortality rates. Much of this mortality is due to CVD, although non-CV mortality is also increased. Albuminuria and eGFR are independently and additively associated with increased risks of CV events, CV mortality, and all-cause mortality (28). There is a high unmet medical need for treatments that can reduce the extensive burden of CV mortality and morbidity and the progression of kidney disease in patients with DKD.

The population for Study 16244 has been chosen to adequately define a study population at high risk of developing renal events. Meta-analyses have shown that very high albuminuria is associated with a 3- to 5-fold increased risk for the development of ESRD compared with those with normal levels of albuminuria (29, 30). Another analysis of > 10000 individuals with T2DM have shown that patients with very high albuminuria and an eGFR < 60 mL/min/1.73 m² had a 16-fold higher risk for renal events compared to patients with neither of these risk factors (31). Patients with very high albuminuria and reduced eGFR have a substantially increased risk of subsequent renal events and rapidly progress to ESRD (6). In patients with high albuminuria, the presence of diabetic retinopathy may indicate rapid loss of renal function and thus may be an additional predictive prognostic factor for the progression of CKD secondary to diabetes (32).

Therefore, Study 16244 will include a majority of patients with very high albuminuria and an eGFR < 60 mL/min/1.73 m². However, there are patients with advanced renal disease with very high albuminuria and an eGFR up to 75 mL/min/1.73m² who may also benefit. Patients with high albuminuria and a history of diabetic retinopathy have a higher risk within the patient population of high albuminuric patients to progress to ESRD and have therefore also been chosen as part of the target population for this study.

The presence of albuminuria in an individual is highly predictive of CV events and progression of kidney disease. In ARTS-DN (study 16243) in patients with T2DM and DKD treated with finerenone in combination with SoC therapy using a RAS inhibitor, a dose-dependent reduction in UACR from baseline to Day 90 was demonstrated. Statistically significant reductions in UACR of 21%, 25%, 33% and 38% at Day 90 compared to baseline were observed for the 4 highest doses of finerenone (7.5, 10 mg, 15 mg, and 20 mg od, respectively) compared to placebo. In a post hoc analysis, UACR decreases of ≥ 30% from baseline to Day 90 in the placebo, 7.5 mg, 10 mg, 15 mg and 20 mg groups were seen for 23.9%, 40.2%, 46.0%, 51.3% and 62.5% of subjects, respectively, and UACR decreases of ≥ 50% in the same groups were seen for 13.6%, 17.2%, 17.2%, 33.6% and 40.2% of subjects, respectively. Post-hoc analyses of randomized clinical trials (33, 34) suggest that a meaningful reduction in albuminuria may translate to protection from CV events and declining renal function in patients with diabetic and non-diabetic renal disease with albuminuria. For every 30% reduction in albuminuria, the risk of ESRD decreased by 23.7% (95% confidence interval, 11.4% to 34.2%; p=0.001) (33); there was an 18% reduction in CV risk and 27% reduction in HF risk for every 50% reduction in albuminuria (34).

Due to finerenone's mode of action, hyperkalemia is an important identified risk which was also identified from previous studies with finerenone. Patients with pre-existing impairment of their renal function are likely to have a greater risk of experiencing clinically significant hyperkalemia. A greater risk for hyperkalemia may also occur if drugs which raise the potassium concentration (e.g. ACEI, ARBs or potassium-sparing diuretics) are used concomitantly.

Worsening of renal function has been shown to occur with the steroidal MRAs, i.e. spironolactone and eplerenone, as well as RAS blocker in general.

The risk for such adverse events with finerenone is not ruled out. However, in ARTS-DN, the incidence of hyperkalemia was low, and the incidence of eGFR decline ≥ 30% relative to

baseline was similar between placebo and finerenone groups, with no imbalance in reported AEs related to the MedDRA primary system organ class '*Renal and urinary disorders*'. In ARTS (study 14563), all doses of finerenone resulted in significantly lower potassium increase and less eGFR reduction compared to spironolactone.

Thus, potassium levels and renal function will be closely monitored in this study. To minimize safety risks to the patient, starting doses of study medication will be chosen according to baseline renal function, and subsequent dose up-titration will be performed on the basis of measured potassium and eGFR values. A 2-step up-titration is consistent with current clinical practice to initiate treatment with a RAS blocker at a low dose, and to up-titrate the drug only if tolerated in order to avoid adverse effects on potassium and renal parameters. Stopping rules for temporary and permanent discontinuation or dose reduction of study drug based on potassium values will minimize the risk of hyperkalemia. At any time during the study, the investigator has the option to also down-titrate the study drug, depending on serum potassium and the progression of the underlying disease.

All protocol-related procedures, including vital signs measurements, 12-lead electrocardiograms (ECGs), echocardiography and blood and urine sampling, are non-invasive or established routine assessments in the management of patients with DKD with or without CVD.

The high risk for progression of kidney disease and fatal and non-fatal CV events in the study population of Study 16244, taken together with the beneficial results of MRAs on CVD in previous clinical trials and the results of finerenone in the Phase II studies all point towards a positive risk-benefit assessment that is in favor of the participation of subjects in this study.

4. Study objectives

The **primary objective** of this study is to:

- Demonstrate whether, in addition to standard of care (SoC), finerenone is superior to placebo in delaying the progression of kidney disease, as measured by the composite endpoint of time to first occurrence of kidney failure, a sustained decrease of eGFR $\geq 40\%$ from baseline over at least 4 weeks, or renal death.

The **secondary objectives** of this study are to determine whether, in addition to SoC, finerenone compared to placebo:

- Delays the time to first occurrence of the following composite endpoint: CV death or non-fatal CV events (i.e. non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure [HF])
- Delays the time to all-cause mortality
- Delays the time to all-cause hospitalization
- Change in UACR from baseline to Month 4
- Delays the time to first occurrence of the following composite endpoint: onset of kidney failure, a sustained decrease of eGFR $\geq 57\%$ from baseline over at least 4 weeks, or renal death.

5. Study design - amended

This section was changed in Amendment 3, see Section 15.1.2.3.

Design overview

Study 16244 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase III study. [Figure 5–1](#) displays the overall study design.

Patients from approximately 900 study centers worldwide will be randomized in a 1:1 ratio to either finerenone or placebo in addition to SoC therapy. Assuming a screening failure rate of approximately 50%, 9600 patients will have to be screened to randomize approximately 4800 patients.

The anticipated duration of the study is approximately 4 years: this includes an anticipated recruitment period of 2.75 years followed by a study drug treatment period of 1 year after the enrolment of the last patient into the trial and a maximum of 4.5 months for the run-in and screening period and 1 month for the follow-up period. However, as an event-driven trial, the actual length of the trial will depend on the observed event rates, the patient recruitment rate, and length of the recruitment period.

Since all randomized subjects belong to the Full Analysis Set (FAS) on which the efficacy analyses are based, it is important to avoid randomization of non-eligible subjects into the study.

Run-in Period (4 up to 16 weeks)

Subjects with written informed consent who complete the Run-in Visit and meet all eligibility³ criteria will be enrolled into a mandatory Run-in Period, the purpose of which is to ensure that the subject's SoC therapy including treatment with ACEIs or ARBs is optimized and that all inclusion and exclusion criteria are met at the Screening Visit. The Run-in Period will last for a minimum of 4 weeks and a maximum of 16 weeks.

In the absence of documentation of diagnosis of high or very high albuminuria (see [Section 3.1](#) for definition), the subject may still be enrolled into the study as albuminuria will be measured at the Run-in Visit; in this case, the Run-in Period must last for a minimum of 12 weeks and a maximum of 16 weeks.

Screening Period (up to 2 weeks)

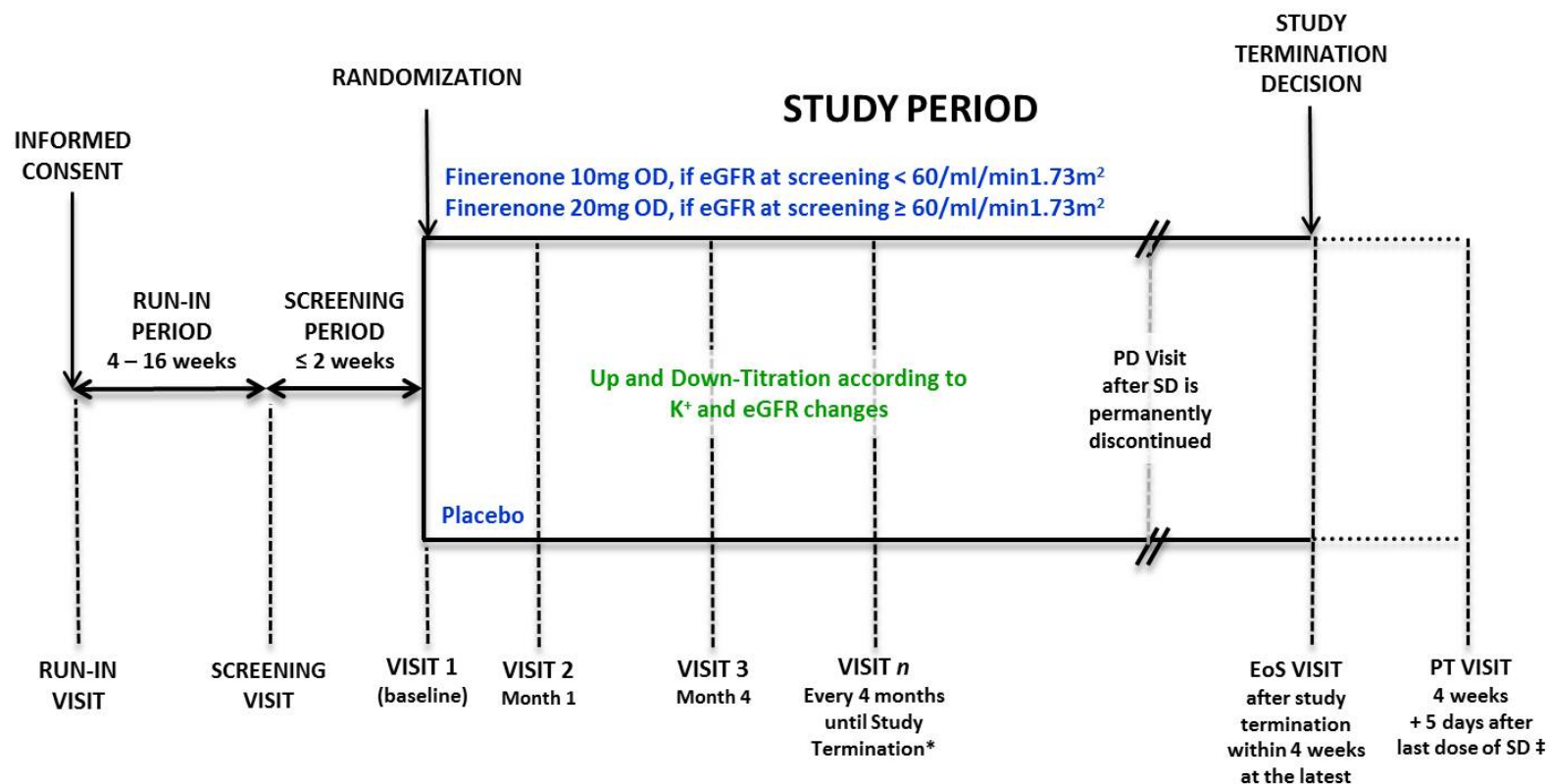
At the end of the Run-in Period, a Screening Visit to confirm the subject's eligibility will take place within ≤ 2 weeks prior to the planned randomization. At this visit, it will be assessed whether the subject still meets all the inclusion and none of the exclusion criteria.³

For those subjects without a prior documented diagnosis of high or very high albuminuria, the Screening Visit must be performed at least 12 weeks after the Run-in Visit, and albuminuria should then be re-evaluated. If the subject still suffers from high or very high albuminuria

³ Eligibility criteria related to central laboratory evaluation will be assessed once results are available.

whilst on SoC treatment, and fulfills all other eligibility criteria, she/he can be randomized into the study.

Figure 5-1 Overall study design - amended



* Scheduled visits will continue even if treatment with SD is discontinued

‡ For all subjects still on treatment with SD at the EoS Visit

K⁺ = Blood Potassium
 SD = Study Drug

OD = once daily
 PD = Premature Discontinuation

EoS = End of Study
 PT = Post-treatment

Treatment Period

Eligible subjects will be randomized to receive once daily (OD) oral doses of finerenone (10 mg or 20 mg) or placebo in addition to their SoC therapy.

There will be up to 4 planned visits (including randomization at Visit 1) in the first 4 months; thereafter visits will take place every 4 months until the end of the study. Study drug dose can be up-titrated from Visit 2 (Month 1) onwards or down-titrated at any point (even between scheduled visits); guidance on dose adjustment is provided in Section 7.4. Subjects may be seen at any time throughout the study, in addition to scheduled visits, at the discretion of the investigator.

It is planned that all randomized subjects will remain in the trial until either:

- a. the projected number of primary endpoints (see Sections 9.4.1 and 10.4) is reached, or
- b. the trial is terminated prematurely at the recommendation of the independent Data Monitoring Committee (DMC) (see Section 13.1.3).

All randomized subjects, including any subject who experienced a health event considered for the pre-specified primary or secondary endpoints, should continue to receive study drug until the trial is completed (see definition for end of study below) provided there are no safety grounds for discontinuing treatment.

Discontinuation of study drug (for any reason) does not constitute the subject's withdrawal from the study, except if the investigator believes that it is in the best interest of the subject or if the subject withdraws consent (see Section 6.4.1 for details).

Details on procedures that are important to ensure the safety of the individual study subject are provided in the relevant sections of this protocol (i.e. *medical management, control of blood pressure and use of potassium supplements/lowering agents* in Section 8.1, and *monitoring blood potassium* in Section 9.7.1).

Follow-up Period

The period between the subject's last intake of study drug and last visit in the study is referred to as the '*Follow-up Period*'. If a subject withdraws from study drug permanently but does not withdraw from the study, this would apply to the period between the Premature Discontinuation (PD) Visit, which should take place as soon as possible following permanent discontinuation of study drug, and the EOS Visit. In the case where a subject discontinues treatment at the EOS Visit, the Follow-up Period applies to the period between the EOS visit and PT visit.

All subjects who had withdrawn consent can be followed up for vital status if they do not sign the '*Declaration of Objection*' form. In addition, vital status can be obtained by the investigator from publicly available data sources. The collection of vital status must be obtained within the timelines provided by Bayer.

End of study

The end of the study as a whole will be reached as soon as the last visit of the last subject of Study 16244 has been reached in all centers in all participating countries (EU and non-EU).

The study will terminate either when:

- (1) the targeted number of primary efficacy endpoint events have been positively adjudicated
- OR
- (2) at a recommendation of the DMC, whichever is earlier.

After notification of study termination, for all subjects still participating in the study, an End-of-Study (EOS) Visit should be scheduled as soon as possible (within 4 weeks of notification at the latest) to determine whether the subject had an event for inclusion in the primary or secondary endpoints.

Subjects who are still on treatment will discontinue study drug treatment at the EOS Visit and must perform the Post-Treatment (PT) Visit (4 weeks + 5 days) after their last dose of study drug.

The primary completion event for this study is the last visit for the last subject.

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

6. Study population

Subjects with T2DM and a clinical diagnosis of DKD treated with the individual maximum tolerated labeled dose of either an ACEI or an ARB (but not both), who meet all the inclusion criteria and none of the exclusion criteria will be eligible for enrollment in this study. Subjects switching over from Study 17530 to this study at the Screening Visit must only meet all the inclusion criteria and none of the exclusion criteria at the Screening Visit to be eligible for enrollment in this study (16244).

6.1 Inclusion criteria

Subjects must meet all of the following inclusion criteria to be included in the study:

1. Written informed consent signed before any study-specific procedure
2. Men or women aged 18 years and older. The lower age limit may be higher if legally required in the participating country.
3. Women of childbearing potential can only be included in the study if a pregnancy test is negative at the Screening Visit and if they agree to use adequate contraception. 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). Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate) or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [for US only: FSH levels > 40 mIU/mL and estradiol < 20 pg/mL] or have had surgical treatment such as bilateral tubal ligation, bilateral ovariectomy, or hysterectomy.
4. Subjects with **type 2 diabetes mellitus** as defined by the American Diabetes Association (35)
5. Subjects with a clinical diagnosis of DKD based on either of the following criteria at the Run-in and Screening Visit:
 - Persistent **high albuminuria** defined as UACR of ≥ 30 mg/g (≥ 3.4 mg/mmol) but < 300 mg/g (< 33.9 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥ 25 but < 60 mL/min/1.73 m² (CKD-EPI) (36, 37) and presence of **diabetic retinopathy** in the medical history ⁴OR
 - Persistent **very high albuminuria** defined as UACR of ≥ 300 mg/g (≥ 33.9 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥ 25 but < 75 mL/min/1.73 m² (CKD-EPI) (36, 37) ⁵

Note: One re-assessment of eGFR and UACR is allowed at the Run-in Visit and the Screening Visit. If one of the 3 UACR measurements is missing but the other 2 are valid, these values can be used to assess subject's eligibility for this study.

⁴ **Note:** The number of subjects with high albuminuria and presence of diabetic retinopathy in the medical history will be capped at approximately 10% of the total population at screening.

⁵ **Note:** The number of subjects with eGFR ≥ 60 to 75 mL/min/1.73m² and very high albuminuria will be capped at approximately 10% of the total population with very high albuminuria at screening.

6. Prior treatment with ACEIs and ARBs as follows:
 - For at least 4 weeks prior to the Run-in Visit, subjects should be treated with **either** an ACEI or ARB, **or** both
 - Starting with the Run-in Visit, subjects should be treated with only an ACEI or ARB
 - For at least 4 weeks prior to the Screening Visit, subjects should be treated with the maximum tolerated labeled dose (but not below the minimal labeled dose) of **only** an ACEI or an ARB (not both) preferably without any adjustments to dose or choice of agent or to any other antihypertensive or antiglycemic treatment (see Section 8.1).
7. Serum potassium ≤ 4.8 mmol/L at both the Run-in and the Screening Visit
Note: One re-assessment of potassium is allowed at the Run-in and the Screening Visit.
8. Ability to understand and follow study-related instructions.

6.2 Exclusion criteria - amended

This section was changed in Amendment 3, see Section 15.1.2.5.

Subjects who meet any of the following criteria will be excluded from the study:

Medical and surgical history

1. Known significant non-diabetic renal disease, including clinically relevant renal artery stenosis
2. UACR > 5000 mg/g (> 565 mg/mmol) at the Run-in Visit or Screening Visit
Note: One re-assessment is allowed in case UACR is > 5000 mg/g in one of the three urine samples collected at the Run-in Visit and the Screening Visit.
3. HbA1c $> 12\%$ (> 108 mmol/mol) at the Run-in Visit or Screening Visit
4. Uncontrolled arterial hypertension with mean sitting systolic blood pressure (SBP) ≥ 170 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
5. Mean SBP < 90 mmHg at the Run-in Visit or at the Screening Visit
6. Subjects with a clinical diagnosis of chronic heart failure with reduced ejection fraction (HFrEF) and persistent symptoms (New York Heart Association class II - IV) at the Run-in Visit (class 1A recommendation for MRAs)
7. Stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening heart failure, in the last 30 days prior to the Screening Visit
8. Dialysis for acute renal failure within 12 weeks prior to the Run-in Visit
9. Renal allograft in place or a scheduled kidney transplant within the next 12 months from the Run-in Visit
10. Known hypersensitivity to the study treatment (active substance or excipients)

11. Addison's disease
12. Hepatic insufficiency classified as Child-Pugh C (see Section 16.2).

Medication and drug use

13. Concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued at least 4 weeks prior to the Screening Visit
14. Concomitant therapy with both ACEI and ARBs which cannot be discontinued for the purpose of the study
15. Concomitant therapy with potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors or inducers (to be stopped at least 7 days before randomization) (see Section 16.1).

Other

16. 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 (e.g. active malignancy or other condition limiting life expectancy to less than 12 months)
17. Pregnant or breast-feeding or intention to become pregnant during the study
18. Previous assignment to treatment during this study or Study 17530
19. Previous (within 30 days prior to randomization) or concomitant participation in another clinical study (i.e. Phase I-III clinical studies) with investigational medicinal product(s), except for participation in the Run-in and Screening period of Study 17530 (see also details on switch over in Section 6.4.2.2)
20. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site).

6.3 Justification of selection criteria

The selection criteria were chosen to adequately define a DKD study population at high risk of progressing with their CKD towards ESRD or developing CV events, and to exclude subjects from the study who may potentially be exposed to particular risks after study drug administration and subjects with conditions that may have an impact on the aims of the study.

6.4 Withdrawal of subjects from study

6.4.1 Withdrawal

6.4.1.1 Discontinuation of study drug - *amended*

This section was changed in Amendment 3, see Section 15.1.2.6.

After randomization, discontinuation of **study drug** (for any reason) does not constitute the subject's withdrawal from the **study** (see also Section 6.4.1.2).

Study drug *must* be permanently discontinued if any of the following occurs:

- Pregnancy of the study subject (see also Section 9.6.2)
- The investigator is of the opinion that continuation of treatment with study drug is harmful to the subject's well-being
- The randomization code is broken by the investigator, or other responsible person, when knowledge of the subject's treatment is required
- Any investigational drug other than the study drug is used.

Study drug *may* be permanently discontinued if any of the following occurs:

- Any suspected drug-related AE or SAE
- If any exclusion criterion applies during treatment
- If a significant violation of the protocol occurs, as defined by the sponsor and the coordinating investigator.

In general, subjects who permanently discontinue study drug are expected to continue in the follow-up period and to attend all protocol-specified study visits, and should be encouraged to perform all assessments described in the visit schedule (see Section 9.2).

If a subject no longer on study drug is unable to attend the clinic for a study visit, a telephone consultation may be performed to determine if relevant health events /endpoints (e.g. development of CV or renal complications) have occurred. Ideally, a face-to-face visit should be performed at least once a year. Expected frequency of telephone contacts should be in line with the standard visit schedule, and therefore performed every 4 months. Ad hoc additional telephone contacts may also be requested (e.g. prior to the interim analysis) and made to the subject themselves or to other contact as provided by the patient, e.g. a next of kin, primary physician (or local equivalent).

Note that study drug may be temporarily discontinued (i.e. interrupted), as described in Section 7.4.

6.4.1.2 Discontinuation of study

Subjects *must* be withdrawn from the study if the following occurs:

- 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 (see also Section 13.4).

Subjects *may* be withdrawn from the study if either of the following occurs:

- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being
- At the specific request of the sponsor and in liaison with the investigator.

Should a subject withdraw consent to participate in the study, he/she may either:

- Agree to continue releasing information for the study (for details, see Section 9.1), or
- Refuse to allow further release of information.

Depending on the time point of withdrawal:

- A subject who discontinues study participation prematurely for any reason is defined as '*dropout*' if the subject has already been randomized
- A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before randomization is regarded as a '*screening failure*'.

General procedures

In all cases, the reason for withdrawal of study drug and/or of study participation must be recorded in the eCRF and in the subject's medical records.

As specified in Section 13.4, the subject may object to the generation and processing of post-withdrawal data.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12.

6.4.2 Replacement

Randomized subjects who withdraw prematurely will not be replaced.

If applicable, a subject who is not eligible at the Run-in or Screening Visit may be re-screened at a later time (see Section 6.4.2.1) or switch over to Study 17530 (see Section 6.4.2.2) provided the pre-requisites are met.

6.4.2.1 Re-screening - *amended*

This section was changed in Amendment 3, see Section 15.1.2.7.

If a subject is not eligible at the Run-in or Screening Visit for either this study (16244) or Study 17530, the subject may be re-screened at a later time.

The following conditions are pre-requisites of re-screening:

- Before re-screening, new written informed consent must be obtained
- Allocation of a new subject identification number
- All assessments for the study must be repeated
- A minimum of 3 months between the initial Run-in Visit and re-screening.

A subject may be re-screened only once and after being declared as a screening failure. During re-screening, a switch over between studies is allowed (see Section 6.4.2.2).

6.4.2.2 Switch over between studies

DKD is a disease continuum characterized by 2 highly variable parameters, eGFR and UACR. The thresholds of these parameters for these studies (16244 and 17530) were chosen in order to define a high risk population. It should be noted these parameters may vary in daily life making the patient eligible for one or the other study. Nevertheless, these variations still reflect the disease continuum and do not alter the high risk. The reason for allowing switch over is to account for these intrinsic variations. In addition, it also serves the purpose of reducing the burden on the subjects due to not needing to repeat the run-in and screening assessments.

Subjects are permitted to switch from Study 16244 to Study 17530, or vice versa.

A switch over from either study is permitted only once and should take place during the respective Run-in and Screening periods.

An example is as follows:

- If a subject initially enrolled in Study 16244 is found to be not eligible during the Run-in or Screening Period of Study 16244, the investigator may consider enrolling this subject into Study 17530 if the subject meets the eligibility criteria at run-in or screening for Study 17530. Prior to the subject being enrolled in Study 17530, the subject must provide written informed consent.

The subject will be transferred to Study 17530 in the IxRS system as outlined in the Investigator Guide. The subject will continue with their originally assigned subject identification (SID) into Study 17530. Within the SID, the study identifier will indicate the subject has switched from Study 16244 to Study 17530 (see Section 6.5). The procedures and assessments from the Run-in and/or Screening Visit(s) of Study 16244 do not have to be repeated for Study 17530; the data, including laboratory data, will be transferred from Study 16244 to Study 17530.

- If a subject switches from Study 16244 to Study 17530 in the Run-in period but is found not to meet the in- and exclusion criteria of Study 17530 at the end of the Screening Period,

this subject is not permitted to switch back into Study 16244 and must be registered as a screening failure of study 17530. If this is the case, the subject may still be re-screened for either of the studies if he or she fulfills the criteria mentioned in Section 6.4.2.1.

6.5 Subject identification

Upon signing the informed consent form and registering the subject in IxRS, each subject will automatically be assigned a unique 9 digit subject identification (SID) number by the IxRS for unambiguous identification throughout the study. The SID number is constructed as follows:

Digits 1 - 2: Unique country number

Digits 3 - 5: Study center number, unique within any country

Digit 6: Study-specific identifier

Digits 7 - 9: Subject number, unique within any study center of a given country for the study.

7. Treatment(s)

7.1 Treatments to be administered

Finerenone immediate-release (IR) tablets are light orange film-coated tablets, oval (modified oblong), containing 10 mg or 20 mg finerenone (Table 7-1). Matching placebo tablets will be supplied.

Following a Screening Visit, eligible subjects will be randomized 1:1 to either finerenone or placebo, and study drug will be dispensed according to the visit schedule (see Section 9.1).

The subject will receive the following:

- Finerenone
 - 10 mg finerenone tablet once daily (OD)
(starting dose for subjects with an eGFR between 25 to < 60 mL/min/1.73m² at the Screening Visit)
 - 20 mg finerenone tablet OD
(starting dose for subjects with an eGFR ≥ 60 mL/min/1.73m² at the Screening Visit)

or

- Placebo tablet OD.

Following randomization of the subject, the IxRS will determine the bottle number for the study site investigator or designee to select for the subject. The investigator at the study site is to instruct subjects to take 1 tablet OD, preferably in the morning. The first dose of study drug should be taken at the site on the same day as Visit 1 (Day 1), preferably in the morning.

7.2 Identity of study treatment

Details (e.g. composition, formulation) of the study drug are provided in [Table 7-1](#).

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 batch 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 treatment as well as the labels will be maintained in the sponsor's study file.

Table 7-1 Identity of test drug / finerenone and matching placebo

Sponsor's substance code	BAY 94-8862
Generic name / brand name	Finerenone
Sponsor's material name and number	finerenone TABL 10 MG 450 COAT finerenone TABL 20 MG 850 COAT finerenone PLAC TABL 002 COAT
Formulation	Film-coated tablet
Tablet strength	10 mg and 20 mg or placebo
Composition	<u>Active ingredient:</u> finerenone micronized <u>Other ingredients:</u> Cellulose microcrystalline, croscarmellose sodium, hypromellose 5 cP, lactose monohydrate, magnesium stearate, sodium laurilsulfate, talc, titanium dioxide, ferric oxide <u>Placebo</u> 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	Not applicable

7.3 Treatment assignment

Eligible subjects will be randomized within ≤ 2 weeks after the Screening Visit. The randomization will be stratified by region (North America, Europe, Asia, Latin America and others), type of albuminuria at screening (high or very high albuminuria) and eGFR at screening (25 to <45 , 45 to <60 , ≥ 60 mL/min/1.73m²). The eGFR will be calculated by the Central Laboratory applying the CKD-EPI formula (36).

The number of subjects with eGFR ≥ 60 to <75 mL/min/1.73 m² and very high albuminuria will be capped at approximately 10% of the total population with very high albuminuria at screening. The number of subjects with high albuminuria and presence of diabetic retinopathy in the medical history will be capped at approximately 10% of the total population at screening.

7.4 Dosage and administration - amended

This section was changed in Amendment 3, see Section 15.1.2.8.

As shown in Table 7–2, the starting dose of finerenone will depend on the eGFR value at the Screening Visit.

Thus, at randomization, subjects with an eGFR between 25 to < 60 mL/min/1.73m² at the Screening Visit (central laboratory results) will be assigned to the lower dose of finerenone (10 mg) or placebo in addition to SoC, whilst subjects with an eGFR ≥ 60 mL/min/1.73m² will be assigned to the higher dose of finerenone (20 mg) or placebo in addition to SoC.

Table 7–2 Dosage of study drug for administration

eGFR value at the Screening Visit, based on central laboratory results:	25 to < 60 mL/min/1.73m ²		≥ 60 mL/min/1.73m ²	
Subject randomized to group: Receives	Finerenone 10 mg finerenone OD + SoC	Placebo Placebo OD + SoC	Finerenone 20 mg finerenone OD + SoC	Placebo Placebo OD + SoC
Study drug intake	One tablet of SD once daily, preferably in the morning at approximately the same time each day.			
Missed intake	<ul style="list-style-type: none"> • If >8 hours before the next scheduled dose, the subject should take one tablet of SD as soon as possible. • If ≤8 hours of the next scheduled dose, the subject should wait and take the next tablet of SD at the usual time. 			
Up-titration of dose Allowed from Visit 2 (Month 1) onwards provided that: <ul style="list-style-type: none"> • Potassium is ≤4.8 mmol/L ^a • eGFR decrease is less than 30% below the value measured at the last scheduled visit ^a • Must be documented in eCRF 	20 mg finerenone OD, maintain SoC	Sham-titrate, maintain SoC	Not applicable	Not applicable
Down-titration of dose <ul style="list-style-type: none"> • Only for safety reasons (for guidance, see Section 9.7.1) • Allowed any time during the study (e.g. between scheduled visits) • Must be documented in eCRF • An unscheduled safety visit is performed within an adequate timeframe proposed by the investigator 	<ul style="list-style-type: none"> • If at higher dose of SD, down-titrate to lower dose of SD, maintain SoC • If at lower dose of SD, interrupt SD, maintain SoC 			

Abbreviations: eGFR = estimated glomerular filtration rate; SD = study drug; SoC = standard of care

^a Potassium and eGFR according to local laboratory values

Intake of study drug

Subjects will be instructed to take one tablet of study drug, preferably in the morning, at approximately the same time each day. The study drug can be taken with a glass of water, with or without food.

Missed intake of study drug

If the subject misses his/her scheduled daily intake of study drug, he/she should consider the following 2 options before continuing study drug intake:

- (1) If intake of the missed tablet is discovered >8 hours before the next scheduled dose, the subject should take the study drug as soon as possible
- (2) If the missed intake is discovered within 8 hours of the next scheduled dose, the subject should wait and take the next tablet at the usual time.

Up- and down-titration of study drug

The investigator is encouraged to up-titrate the dose of study drug at any time once the patient has been on a stable dose for 4 weeks (± 7 days) (e.g. from Visit 2 onwards for patient starting study drug on the lower dose) either at a regular visit or an Up-titration Visit. Up-titration can be performed provided:

- the potassium concentration (local laboratory value) is ≤ 4.8 mmol/L,

AND

- eGFR decrease (local laboratory value) is less than 30% below the value measured at the last regular visit.

Subjects who started with or were up-titrated to the target dose (20 mg OD) of the study drug but who do not tolerate this dose may be down-titrated at any point during the study, including between-scheduled visits if required for safety reasons. These subjects may be up-titrated again based on the rules provided above. If the subject is already at the lower dose, the study drug can be interrupted at the investigator's discretion (refer to Section 9.7.1 for guidance). If the study drug is interrupted for more than 7 days, the study drug should be re-started at the lower dose (10 mg OD).

Subsequent to an up-titration or re-start of study drug after interruption of study drug intake for more than 7 days, the investigator should perform an Up-titration Visit 4 weeks (± 7 days) after titration or restart, in order to monitor potassium levels and renal function (see Table 9-1). If a regular study visit will be scheduled to take place 4 weeks (± 7 days) after up-titration, the monitoring of potassium and renal function is assured and no Up-titration Visit has to be performed in addition. With down-titrations, the unscheduled safety visit may need a smaller time window and should be performed at the investigator's discretion.

At any point during study drug treatment, if blood potassium is found to be elevated, study drug treatment should be adjusted according to guidance provided in Section 9.7.1.

Both up- and down-titrations will be at the investigator's discretion and will depend on the general clinical condition of the individual subject. The investigator should attempt to reach the maximum (target) dose of study drug as long as safety is not compromised.

All titrations, including the reasons for down-titration or for not dispensing the 20 mg dose, must be documented in the eCRF.

7.5 Blinding

7.5.1 Blinding measures

Finerenone IR tablets (10 mg and 20 mg) 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 the subjects. The study data will remain blinded 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.

7.5.2 Unblinding - amended

This section was changed in Amendment 3, see Section 15.1.2.9.

In compliance with applicable regulations, in the event of a SUSAR (see Section 9.6.1.4) related to the blinded treatment, the subject's treatment code will usually be unblinded before reporting to the health authorities and ethic committees.

In order to maintain the integrity of the study, SUSARs will be waived from unblinding and expedited safety reporting if it represents one of the pre-specified disease-related efficacy endpoints (see also Section 9.6.1.4).

7.5.3 Emergency unblinding by the investigator

In the event of an emergency or any finding that requires unblinding, the investigator may break the blind for an individual subject via the IxRS according to the unblinding procedure outlined in the Investigator's Guide. This system allows the investigator, or other responsible person, to identify the study drug if there is 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. 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 for unblinding are to be recorded on 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 [SAE]) of the study drug, and study drug must be discontinued permanently.

7.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/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-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study drug via IxRS. The personnel 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.

7.7 Treatment compliance

To monitor compliance, the investigator will be required to complete a drug dispensing log for each subject. The date of dispensing the study drug to the subject will be documented.

Study drug will be dispensed at each scheduled visit starting from Visit 1 (Day 1), as applicable. Subjects will be instructed to return all of the study drug packaging including unused study drug and empty packaging. Accountability must be performed at each visit (if applicable).

Any discrepancies between actual and expected amount of returned study medication must be discussed with the subject at the time of the visit, and any explanation must be documented in the source records.

8. Non-study therapy

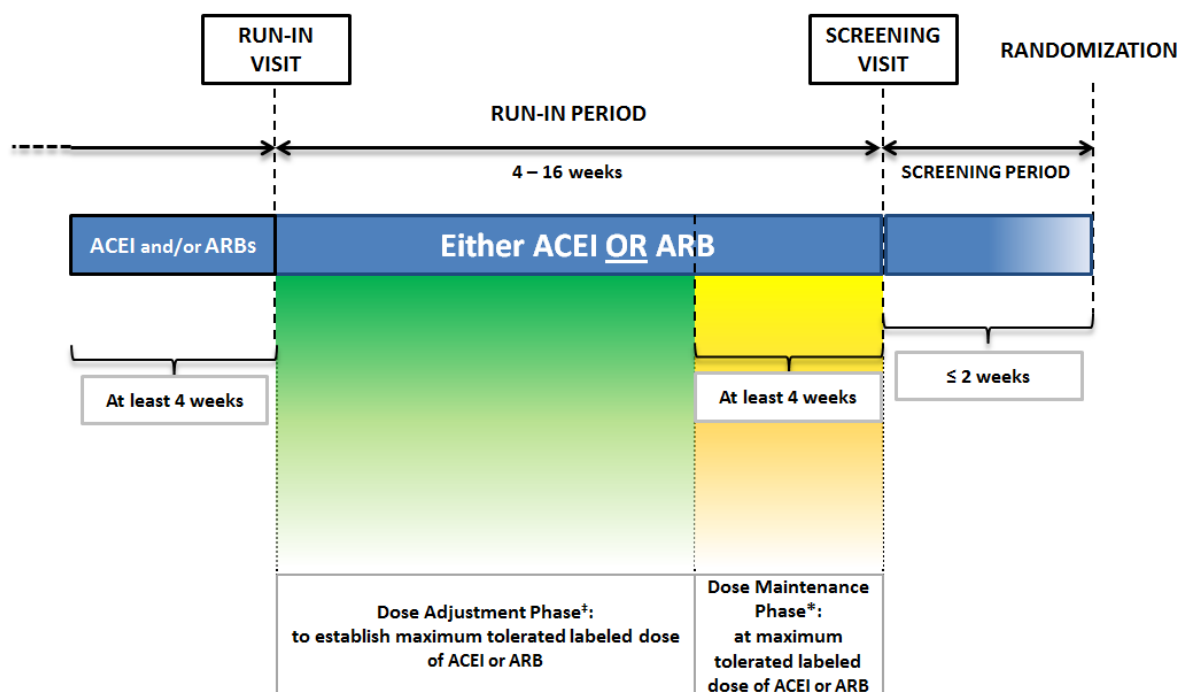
8.1 Prior and concomitant therapy

8.1.1 General considerations for prior and concomitant therapy

Figure 8–1 depicts the conditions of prior therapy on ACEIs and ARBs during the time leading up to the Screening Visit.

- For at least 4 weeks prior to the Run-in Visit, all subjects must be treated with *either* an ACEI or ARB, *or* both
- Starting with the Run-in Visit, subjects should be treated with *only* an ACEI or ARB
- For at least 4 weeks prior to the Screening Visit, subjects should be treated with the maximum tolerated labeled dose (but not below the minimal labeled dose) of *only* an ACEI or an ARB (not both), preferably without any adjustments to dose or choice of agent or to any other antihypertensive or antiglycemic treatment.

Figure 8–1 Background therapy with RAS blockade



‡ If applicable

* During the maintenance phase, there should preferably be no adjustments to dose of ACEI or ARB or to any other antihypertensive or antiglycemic treatment

The maximum tolerated labeled dose for ACEIs or ARBs should be the highest dose within the ranges shown in [Table 8–1](#) or according to local labels, as applicable, which the subject can safely tolerate. This dose should not be below the minimum labeled dose in order to maximize therapeutic benefit of background SoC.

Table 8–1 Dose ranges of ACEIs and ARBs for adults

Angiotensin-converting enzyme inhibitors		Angiotensin receptor blockers	
Generic name	Dose Range (mg/day)*	Generic name	Dose Range (mg/day)*
Benazepril	20 – 40	Candesartan	16 – 32
Captopril	50 – 450	Eprosartan	400 – 800
Cilazapril	1 – 5	Irbesartan	150 – 300
Enalapril	10 – 40	Losartan	50 – 100
Fosinopril	20 – 80	Olmesartan	20 – 40
Lisinopril	20 – 40	Telmisartan	40 – 80
Moexipril	7.5 – 30	Valsartan	80 – 320
Perindopril	4 – 16		
Quinapril	20 – 80		
Ramipril	2.5 – 20		
Trandolapril	2 – 4		

Source: Adapted from Table 28 of reference (38)

Variations to these recommended dose ranges may exist in local clinical guidelines or labels. If the maximum labeled dose cannot be reached, the reason(s) should be documented in the eCRF. Antihypertensive therapy for renal and CVD protection will be administered according to local guidelines (see also Section 8.1.2 on medical management).

Depending on blood pressure, serum creatinine or eGFR, subjects may need to have their study drug dose or the dose of another concomitant medication reduced or discontinued. The dosage of SoC therapies should not be reduced in order to solely facilitate maintenance of study drug.

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

All concomitant medication including therapy for T2DM and DKD until the PT Visit will be recorded in the eCRF.

The following therapies are NOT permitted:

- Concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued at least 4 weeks prior to the Screening Visit and during study drug treatment
- Concomitant therapy with both an ACEI **and** an ARB during the Run-in and Screening periods, and during study drug treatment
- Concomitant therapy with potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors or inducers must be stopped at least 7 days before randomization and is not allowed to be started during study drug treatment

A list of the most common medication regarded as potent CYP3A4 inhibitors or inducers is provided in Section 16.1.

Caution: Increases in finerenone 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. Caution should also be exercised with concomitant use of high-dose acetylsalicylic acid (>500 mg/day), non-steroidal anti-inflammatory agents or trimethoprim or trimethoprim / sulfamethoxazole.

8.1.2 Medical management

ACEs and ARBs are considered as SoC therapy in patients with DKD and often prescribed to patients with DKD at early stages (8).

It is advisable to follow the recommendations of local guidelines for the management of CVD and CKD, the use of statins, anti-platelets and beta-blockers, and for glycemic control.

8.1.3 Control of blood pressure - amended

This section was changed in Amendment 3, see Section 15.1.2.10.

According to international guidelines, the recommended target blood pressure for subjects with T2DM and albuminuria, who are at increased risk of CVD and CKD progression, is <130/80 mmHg (39-41). However, this value may vary for the individual subject depending on concomitant diseases and well-being.

If blood pressure is considered uncontrolled by the investigator during the study period, non-potassium-sparing diuretics may be added as first choice to the treatment regimen if this was not already done. Thereafter, the addition of antihypertensive medication can be performed according to local guideline recommendations.

All concomitant medication added to the treatment regimen during the course of the study must be recorded in the eCRF.

8.1.4 Use of potassium supplements and lowering agents

If needed, potassium supplementation can be prescribed during the course of the study. Investigators are advised to monitor potassium carefully at each visit and to adapt the dose of any 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 (e.g. sodium polystyrene sulfonate, calcium polystyrene sulfonate) are allowed to be started during treatment with study drug.

Any use of potassium supplementation and potassium-lowering agents must be documented in the eCRF.

8.2 Post-study therapy

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.

9. Procedures and variables

9.1 Tabular schedule of evaluations - *amended*

This section was changed in Amendment 3, see Section 15.1.2.11 and Section 15.1.2.12.

Table 9–1 depicts the schedule of activities and evaluations for this study (16244).

An overview of the procedures for sub-studies of 16244 is provided in Table 9–2.

All randomized subjects will remain in the study until its termination, either:

- (1) after positive adjudication of the targeted number of primary efficacy endpoint events,
or
- (2) at a recommendation of the DMC.

Thus, all subjects, including those who stopped taking study drug, should be asked to attend all the protocol-specified study visits in order to perform all assessments as stipulated in the visit schedule (Table 9–1).

If any subject refuses to return for the defined assessments or is unable to do so, every effort should be made to contact him/her or a knowledgeable informant by telephone to ask if any of the primary, secondary, or other endpoints have been reached at the scheduled visits for the remaining duration of the study (see Section 6.4.1.1 for details). Attempts to contact the subject should be documented in the subject's records. If any subject refuses to be contacted by telephone (e.g. the subject withdrew consent to release further information), every effort should be made to obtain vital status (alive or dead) information through consultation of public databases, wherever allowed by local regulations.

Table 9–1 Study 16244: schedule of activities and evaluations - amended

Visit	Run-in	Screening	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4, 6, 7, 9, etc ^h	Visit 5, 8, 11, etc	Up-titration Visit ^j	PD Visit	EOS Visit ^k	PT Visit ^m
Day / Month	4 to 16 weeks pre-screening	≤ 2 weeks	Day 1	Month 1	Month 4	(every 4 months, i.e. Month 8, 16, 20, 28, etc)	(every 12 months, i.e. Month 12, 24, 36, etc)	For up-titration/restart after interruption, and for safety check 4 weeks ± 7 days after any up-titration (see also footnote j)	As soon as possible but within 7 days after SD is permanently discontinued	After study termination	4 weeks + 5 days after last SD intake
Informed consent	X										
In- and exclusion criteria	X	X	X								
Demographic data	X										
Smoking status	X										
Alcohol consumption	X										
Medical history	X										
Prior medication	X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Randomization			X								
Drug accountability				X	X	X	X	X	X	X	
Study drug dispense			X	X	X	X	X				
Study drug administration			X		X						
KDQOL-36, EQ-5D-5L			X				X		X	X	
Physical examination	X	X					X		X	X	
Weight, height, waist and hip circumference ^a	X	X	X	X	X	X	X	X	X	X	
Vital signs ^b	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (local)	X	X	X				X		X	X	
PK blood sample					X ⁿ		X ^o				
Full central laboratory	X	X	X		X	X	X		X	X	
Limited chemistry (central)				X				X			
Urinalysis (central) ^c	X	X	X		X		X			X	
Safety laboratory (local) ^d			X	X	X	X	X	X			
Endpoint assessment ^e				X	X	X	X	X	X	X	
AE assessment ^f	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^g		X					X				

Table 9–1 Study 16244: schedule of activities and evaluations - amended**NOTE:**

One month corresponds to 30 days

A time frame of ± 7 days is allowed for Visit 2 (Month 1), and for the Up-titration Visit(s).

A time frame of ± 12 days is allowed for all regular visits from Visit 3 (Month 4) onwards.

Abbreviations: ECG = electrocardiogram; EOS = end of study; EQ-5D-5L = EuroQol Group 5 dimension, 5 level questionnaire; KDQOL = Kidney Disease Quality of Life; PD = premature discontinuation; PT = post-treatment; (S)AE = (serious) adverse event; SD = study drug

- ^a Height, waist and hip circumference to be assessed at Run-in Visit only.
- ^b After resting for at least 5 minutes, 3 measurements to be taken with at least 1-minute interval in a sitting position (all 3 readings within a maximum of 20 minutes).
- ^c At Visit 1, first morning void urine samples to be preferably collected on three consecutive days at the subject's home within 7 days before scheduled visit and before any intake of study drug. At the other visits the 3 consecutive samples can be collected ± 7 days from the visit date.
- ^d Blood samples (for potassium and creatinine) for measurement in the local laboratory may be obtained up to 72 hours before a scheduled visit. Samples to be taken only if the subject is still taking study drug,
- ^e Categorical renal endpoints, $\geq 40\%$ or $\geq 57\%$ decrease in eGFR compared to baseline and an eGFR decrease to less than 15 mL/min/1.73 m², have to be confirmed by at least one additional standardized serum creatinine measurement. This confirmation should be done at least 4 weeks after the initial measurement as an unscheduled assessment.
- ^f AEs related to study procedures occurring after signing the informed consent as well as all other AEs starting after randomization will be documented on the respective eCRF pages.
- ^g Female subjects of childbearing potential must have a negative serum or urine pregnancy test at screening and yearly thereafter (to be performed at the local laboratory). If required by national / institutional regulations, a serum or urine pregnancy test in subjects of childbearing potential should be performed more often (e.g. at every visit, see Section 9.7.2).
- ^h Every 4 months until study termination, excluding the yearly visits (i.e. Visits 5, 8, 11, etc., at Months 12, 24, 36, etc.).
- ^j The "Up-titration Visit" should be performed for up-titration (at any time after Visit 2), after restart of SD after an interruption for >7 days, and for safety check 4 weeks ± 7 days after any up-titration.
- ^k After the study site is notified about study termination, an EOS Visit must be performed for all the subjects as soon as possible and within 4 weeks at the latest.
- ^m For all the subjects still on treatment with study drug at the EOS Visit, the PT Visit has to be performed 4 weeks + 5 days after last intake of study drug and will be performed by a telephone contact (except for subjects participating in the iohexol sub-study).
- ⁿ A trough PK sample will be drawn before study drug is administered at the study center by study personnel. The exact time of study drug intake on the day before the visit and on the day of the visit and the exact sampling time will have to be recorded in the eCRF. If the trough sample was not taken at Visit 3 it should be obtained at Visit 4 (see Section 9.5).
- ^o Study drug will be taken as usual, ideally in the morning at home. One PK sample will be drawn during the visit. The exact time of study drug intake and the exact sampling times will have to be recorded in the eCRF.

Table 9–2 Sub-studies of Study 16244: schedule of procedures – amended

Visit	Run-in	Screening	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4, 6, 7, 9, etc	Visit 5, 8, 11, etc	Up-titration Visit	PD Visit	EOS Visit	PT Visit ^c
Day / Month	4 to 16 weeks pre-screening	≤ 2 weeks	Day 1	Month 1	Month 4	(every 4 months, i.e. Month 8, 16, 20, 28, etc)	(every 12 months, i.e. Month 12, 24, 36, etc)	For up-titration/ restart after interruption, and for safety check 4 weeks ± 7 days after any up-titration	As soon as possible but within 7 days after SD is permanently discontinued	After study termination	4 weeks + 5 days after last SD intake
Informed consent ^a			X								
Echocardiography ^f			X				X		X ^e	X ^e	
Sampling for biomarkers			X		X		X		X ^e	X ^e	
Iohexol clearance ^b			X		X	X ^d	X ^d		X ^e	X ^e	X

NOTE:

One month corresponds to 30 days.

A time frame of ± 7 days is allowed for Visit 2 (Month 1).

A time frame of ± 12 days is allowed all regular visits from Visit 3 (Month 4) onwards.

Abbreviations: EOS = end of study; PD = premature discontinuation PK = Pharmacokinetics; PT = post-treatment; SD = study drug

^a Separate informed consent for each sub-study is required.

^b Sites in Italy only.

^c For all the subjects still on treatment with study drug at the EOS Visit, the PT Visit has to be performed 4 weeks + 5 days after last intake of study drug.

^d Every other visit (every 8 months) , i.e. Visit 5, Visit 7, Visit 9, Visit 11, etc.

^e Assessment at the end of the study, either at the PD Visit or the EOS Visit.

^f Time window for the assessment at Visit 1 is -14/+7 days, at other visits +/-30 days. Each time an echocardiography is performed, one blood sample should be drawn to assess the echo biomarkers

9.2 Visit description - amended

This section was changed in Amendment 3, see Section 15.1.2.13.

One month in the study schedule corresponds to 30 days. Although study visits should occur as close as possible to the time points specified in the protocol, a time frame of ± 7 days is allowed for Visit 2 (Month 1), and for the Up-titration Visit(s). Starting from Visit 3 (Month 4), a time frame of ± 12 days is allowed for all regular visits.

All procedures and assessments should preferably be conducted on the day of the visit; however, if this is not possible for logistical reasons, the following time windows are allowed:

Blood sampling, ECG and recording of vital signs:

- Screening Visit and all the visits starting from Visit 2: Visit date ± 7 days
- Run-In, PD and EOS Visit: Visit date ± 3 days

Sub-studies / iohexol and biomarker samples:

- all visits starting from Visit 3: Visit date ± 7 days
- PD and EOS Visit: Visit date ± 3 days

Sub-study / echocardiography (note that each time an echocardiography is performed, one blood sample should be drawn to assess the echo biomarkers):

- at Visit 1: Visit date -14 / +7 days
- Other visits: Visit date ± 30 days

NOTE: If applicable, a subject who is not eligible at the Run-in or Screening Visit may be re-screened at a later time (see Section 6.4.2.1) or switch over to Study 17530 (see Section 6.4.2.2) provided the pre-requisites are met.

9.2.1 Run-in Visit (4 to 16 weeks prior to the Screening Visit) - amended

This section was changed in Amendment 3, see Section 15.1.2.14.

The following procedures and assessments will be performed at the Run-in Visit:

- Obtain signed informed consent (may be done earlier).
NOTE: any study-specific procedure can be performed only if written informed consent is **available**
- Check inclusion and exclusion criteria (see Sections 6.1 and 6.2)
- Collect demographic data, smoking status and alcohol consumption (see Section 9.3.1)
- Record medical history (see Section 9.3.2)
- Record use of prior and concomitant medication (see Section 8.1)
- Perform physical examination (see Section 9.7.3)
- Record body weight, height, waist and hip circumference (see Section 9.7.4)

- Record vital signs (see Section 9.7.5)
- Perform 12-lead ECG (see Section 9.7.6)
- Take samples (hematology, HbA_{1c}, chemistry and urinalysis) for central laboratory evaluations (see Section 9.7.2.1).
Note: If HbA_{1c} cannot be analyzed by the central laboratory due to technical reasons, subject can be considered suitable for randomization with one result only (Run-In or Screening).
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3)

9.2.2 Screening Visit (≤ 2 weeks prior to Visit 1) - *amended*

This section was changed in Amendment 3, see Section 15.1.2.15.

The following procedures and assessments will be performed at the Screening Visit:

- Check inclusion and exclusion criteria (see Sections 6.1 and 6.2)
- Record use of concomitant medication (see Section 8.1)
- Perform physical examination (see Section 9.7.3)
- Record body weight (see Section 9.7.4)
- Record vital signs (see Section 9.7.5)
- Perform 12-lead ECG (see Section 9.7.6)
- Take samples (hematology, HbA_{1c}, chemistry, urinalysis) for central laboratory evaluations (see Section 9.7.2.1)
Note: If HbA_{1c} cannot be analyzed by the central laboratory due to technical reasons, subject can be considered suitable for randomization with one result only (Run-In or Screening).
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3)
- Perform pregnancy test (see Section 9.6.2).

9.2.3 Visit 1 (randomization; Day 1 and baseline) - *amended*

This section was changed in Amendment 3, see Section 15.1.2.16.

All measurements on Visit 1 are to be performed on the day of the visit before first study drug intake. The following procedures and assessments will be performed at Visit 1:

- Instruct the subject on how to complete KDQOL-36 and EQ-5D-5L questionnaires; the subject completes the questionnaires (see Section 9.7.7).
- Obtain informed consent for sub-studies (see Section 9.7.8.1)
- Check inclusion and exclusion criteria (see Sections 6.1 and 6.2)

- Record use of concomitant medication (see Section 8.1)
- Record body weight (see Section 9.7.4)
- Record vital signs (see Section 9.7.5)
- Perform 12-lead ECG (see Section 9.7.6)
- Take samples (hematology, HbA_{1c}, chemistry, urinalysis) for central laboratory evaluations (see Section 9.7.2.1)
- Take samples (potassium, creatinine) for local safety laboratory evaluations (see Section 9.7.2.2)
- Optional: if the subject had signed informed consent for the sub-study, obtain respective samples for biomarkers (see Section 9.7.8.1.2) and/or iohexol clearance (see Section 9.7.8.1.3), perform echocardiography (see Section 9.7.8.1.1)
Note: Time window for the echocardiography at Visit 1 is -14/+7 days. On the day the echocardiography is performed, a blood sample should also be drawn to assess the echo biomarkers.
- Randomization to finerenone or placebo once daily (see Section 7.1)
- Dispense the study drug (see Section 7.2)
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3)
- First administration of study drug.

9.2.4 Visit 2 (Month 1)

The following procedures and assessments will be performed at Visit 2:

- Record use of concomitant medication (see Section 8.1)
- Collect unused study drug and perform accountability to assess compliance (see Section 7.6)
- Dispense the study drug (see Section 7.2)
- Record body weight (see Section 9.7.4)
- Record vital signs (see Section 9.7.5)
- Take samples (limited chemistry) central laboratory evaluations (see Section 9.7.2.1)
- Take samples (potassium, creatinine) for local safety laboratory evaluations (see Section 9.7.2.2)
- Assess if the subject has any endpoint event(s) (see Table 13–1 and Section 9.6.1.3.1)
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3).

9.2.5 Visit 3 (Month 4) - amended

This section was changed in Amendment 3, see Section 15.1.2.17.

Ideally, the study personnel should contact the subject prior to Visit 3 to remind them not to take the study drug as usual in the morning at home. The following procedures and assessments will be performed at Visit 3:

- Record use of concomitant medication (see Section 8.1)
- Collect unused study drug and perform accountability to assess compliance (see Section 7.6)
- Dispense the study drug (see Section 7.2)
- Record body weight (see Section 9.7.4)
- Record vital signs (see Section 9.7.5)
- Take samples (hematology, HbA1c, chemistry, urinalysis) for central laboratory evaluations (see Section 9.7.2.1)
- Take samples (potassium, creatinine) for local safety laboratory evaluations (see Section 9.7.2.2)
- Obtain pre-dose sample for PK (see Section 9.5)
- Administer study drug after PK sample has been obtained (see Section 9.5)
- Optional: if the subject had signed informed consent for the sub-study, obtain respective samples for biomarkers (see Section 9.7.8.1.2) and/or iohexol clearance (see Section 9.7.8.1.3)
- Assess if the subject has any endpoint event(s) (see Table 13–1 and Section 9.6.1.3.1)
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3).

9.2.6 Visit 4, 6, 7, 9, etc. (every 4 months; Month 8, 16, 20, 28, etc., excluding yearly visits) - amended

This section was changed in Amendment 3, see Section 15.1.2.18.

The following procedures and assessments will be performed at Visit 4, 6, 7, 9, etc.:

- Record use of concomitant medication (see Section 8.1)
- Collect unused study drug and perform accountability to assess compliance (see Section 7.6)
- Dispense the study drug (see Section 7.2)
- Record body weight (see Section 9.7.4)
- Record vital signs (see Section 9.7.5)

- Take samples (hematology, HbA_{1c}, chemistry) for central laboratory evaluations (see Section 9.7.2.1)
- Take samples (potassium, creatinine) for local safety laboratory evaluations (see Section 9.7.2.2)
- **Visit 4 only:** Obtain pre-dose sample for PK if no PK sample was taken at Visit 3 (see Section 9.5)
- Optional: if the subject had signed informed consent for the sub-study, obtain samples for iohexol clearance (see Section 9.7.8.1.3)
Note: Iohexol clearance should be performed every 8 months only (Visit 7, Visit 9, etc.)
- Assess if the subject has any endpoint event(s) (see Table 13–1 and Section 9.6.1.3.1)
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3).

9.2.7 Visit 5, 8, 11, etc. (every 12 months; Month 12, 24, 36, etc) - *amended*

This section was changed in Amendment 3, see Section 15.1.2.19.

The following procedures and assessments will be performed at Visit 5, 8, 11, etc.:

- Subject to complete KDQOL-36 and EQ-5D-5L questionnaires (see Section 9.7.7).
- Record use of concomitant medication (see Section 8.1)
- Collect unused study drug and perform accountability to assess compliance (see Section 7.6)
- Dispense the study drug (see Section 7.2)
- Perform physical examination (see Section 9.7.3)
- Record body weight (see Section 9.7.4)
- Record vital signs (see Section 9.7.5)
- Perform 12-lead ECG (see Section 9.7.6)
- Take samples (hematology, HbA_{1c}, chemistry, urinalysis) for central laboratory evaluations (see Section 9.7.2.1)
- Take samples (potassium, creatinine) for local safety laboratory evaluations (see Section 9.7.2.2)
- Obtain sample for PK (see Section 9.5)
- Optional: if the subject had signed informed consent for the sub-study, obtain samples for biomarkers (see Section 9.7.8.1.2), perform echocardiography (see Section 9.7.8.1.1)

- Optional: if the subject had signed informed consent for the sub-study, obtain samples for iohexol clearance (see Section 9.7.8.1.3).
Note: Iohexol clearance should be performed every 8 months only (Visit 5, Visit 11, etc.)
- Assess if the subject has any endpoint event(s) (see Table 13–1 and Section 9.6.1.3.1)
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3)
- Perform pregnancy test (see Section 9.6.2).

9.2.8 Up-titration Visit (4 weeks ± 7 days after up-titration or restart of study drug and for up-titration of study drug) - amended

This section was changed in Amendment 3, see Section 15.1.2.20.

The following procedures and assessments will be performed at the Up-titration Visit (see Section 7.4 for details):

- Record use of concomitant medication (see Section 8.1)
- Collect unused study drug and perform accountability to assess compliance, if applicable (see Section 7.6)
- Record body weight (see Section 9.7.4)
- Record vital signs (see Section 9.7.5)
- Take samples (limited chemistry) central laboratory evaluations (see Section 9.7.2.1)
- Take samples (potassium, creatinine) for local safety laboratory evaluations (see Section 9.7.2.2)
- Assess if the subject has any endpoint event(s) (see Table 13–1 and Section 9.6.1.3.1)
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3).

9.2.9 Premature Discontinuation (PD) Visit (as soon as possible but within 7 days after study drug is permanently discontinued) - amended

The section title was changed in Amendment 3, see Section 15.1.2.21.

If the PD visit cannot be performed within the timeframe specified, no PD visit is required. The following procedures and assessments will be performed at the PD Visit:

- The subject completes KDQOL-36 and EQ-5D-5L questionnaires (see Section 9.7.7)
- Record use of concomitant medication (see Section 8.1)
- Collect unused study drug and perform accountability to assess compliance (see Section 7.6)

- Perform physical examination (see Section 9.7.3)
- Record body weight (see Section 9.7.4)
- Record vital signs (see Section 9.7.5)
- Perform 12-lead ECG (see Section 9.7.6)
- Take samples (hematology, HbA_{1c}, chemistry) for central laboratory evaluations (see Section 9.7.2.1)
- Optional: if the subject had signed informed consent for the sub-study, obtain respective samples for biomarkers (see Section 9.7.8.1.2) and/or for iohexol clearance (see Section 9.7.8.1.3), perform echocardiography (see Section 9.7.8.1.1)
- Assess if the subject has any endpoint event(s) (see Table 13–1 and Section 9.6.1.3.1)
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3).

9.2.10 End of study (EOS) visit - *amended*

This section was changed in Amendment 3, see Section 15.1.2.22.

The following procedures and assessments will be performed at the EOS Visit:

- The subject completes KDQOL-36 and EQ-5D-5L questionnaires (see Section 9.7.7)
- Record use of concomitant medication (see Section 8.1)
- Collect unused study drug and perform accountability to assess compliance (see Section 7.6)
- Perform physical examination (see Section 9.7.3)
- Record body weight (see Section 9.7.4)
- Record vital signs (see Section 9.7.5)
- Perform 12-lead ECG (see Section 9.7.6)
- Take samples (hematology, HbA_{1c}, chemistry, urinalysis) for central laboratory evaluations (see Section 9.7.2.1)
- Optional: if the subject had signed informed consent for the sub-study, obtain respective samples for biomarkers (see Section 9.7.8.1.2) and/or for iohexol clearance (see Section 9.7.8.1.3), perform echocardiography (see Section 9.7.8.1.1)
- Assess if the subject has any endpoint event(s) (see Table 13–1 and Section 9.6.1.3.1)
 - Any eGFR declines that meet endpoint criteria that are identified at the EOS Visit, or that cannot be confirmed by the time of the EOS Visit, should be confirmed 4 weeks after the initial decline

- In exceptional circumstances only, if the subject is unable to attend this visit during the given timeframe, the subject (or primary physician/ next of kin) should be contacted to obtain survival status.
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3).

9.2.11 Post-Treatment (PT) Visit - *amended*

This section was changed in Amendment 3, see Section 15.1.2.23.

For all subjects (except those who participate in the iohexol clearance study) who are still on treatment with study drug at the end of study visit, this will be performed by telephone contact within 4 weeks + 5 days after last study drug intake. The following will be performed at the PT Visit:

- Record use of concomitant medication (see Section 8.1)
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3).

For subjects who signed informed consent for the iohexol clearance sub-study, the PT Visit will be performed as an on-site visit with the following procedures and assessments:

- Record use of concomitant medication (see Section 8.1)
- Obtain samples for iohexol clearance (see Section 9.7.8.1.3)
- Record adverse events (see Section 9.6.1), accounting for the rules of assessment and documentation (see Section 9.6.1.3).

9.3 Population characteristics

9.3.1 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.

9.3.2 Medical history - amended

This section was changed in Amendment 3, see Section 15.1.2.24.

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

- Pertaining to the study indication or CVD history
- Start before randomization
- Considered relevant to the study (e.g. CV and metabolic diseases, periodontal disease)
- Medical history related to concomitant medication.

Detailed instructions on the differentiation between (1) medical history and (2) adverse events can be found in Section 9.6.1.1.

9.4 Efficacy- amended

This section was changed in Amendment 3, see Section 15.1.2.25.

The parameters in Section 9.4.1 (primary), Section 9.4.2 (secondary) and Section 9.4.3 (exploratory) will be used to assess the efficacy of the study drug.

Efficacy endpoints will be evaluated by a Clinical Event Committee (CEC) (see Section 13.1.2).

Kidney failure is defined as either the occurrence of ESRD or an eGFR of less than 15 mL/min/1.73 m², confirmed by a second measurement at the earliest 4 weeks after the initial measurement. ESRD is defined as the initiation of chronic dialysis (haemo- or peritoneal-dialysis) for at least 90 days or renal transplantation. In addition, the eGFR threshold of 15 mL/min/1.73 m² is consistent with the definition of kidney failure from KDIGO (Kidney Disease: Improving Global Outcomes)(3) and was chosen in order to include an objective component to the endpoint because the decision to initiate dialysis therapy or kidney transplantation may be affected by factors other than the eGFR. All other definitions of individual endpoints (e.g. CV death) will be provided in the Endpoint Manual.

9.4.1 Primary efficacy variable

The primary efficacy variable will be the time to the first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR \geq 40% from baseline over at least 4 weeks, or renal death.

9.4.2 Secondary efficacy variables

Secondary efficacy variables will be as follows:

- Time to first occurrence of the following composite endpoint: cardiovascular (CV) death or non-fatal CV events (i.e. non-fatal myocardial infarction, non-fatal stroke, or hospitalization for HF)
- Time to all-cause mortality
- Time to all-cause hospitalization

- Change in UACR from baseline to Month 4
- Time to the first occurrence of the following composite endpoint: onset of kidney failure, a sustained decrease of eGFR $\geq 57\%$ from baseline over at least 4 weeks, or renal death.

9.4.3 Other exploratory efficacy variables - *amended*

This section was changed in Amendment 3, see Section 15.1.2.26.

Other exploratory efficacy variables will be as follows:

- Time to onset of ESRD
- Time to onset of eGFR decrease of $\geq 40\%$ from baseline sustained over at least 4 weeks
- Time to onset of eGFR decrease of $\geq 57\%$ from baseline sustained over at least 4 weeks
- Time to CV death
- Time to first CV hospitalization
- Time to first non-fatal CV event (e.g. myocardial infarction, stroke, hospitalization for HF)
- Number of subjects with new diagnosis of atrial fibrillation or atrial flutter
- Number of subjects with new diagnosis of HF
- Change in UACR from baseline
- Change in eGFR from baseline
- Regression from very high to high albuminuria and high albuminuria to albuminuria accompanied by a decrease in UACR of at least 30% from baseline
- Number of subjects with UACR decrease of at least 30% from baseline at any time post-baseline
- Number of subjects with UACR decrease of at least 50% from baseline at any time post-baseline
- Change in QoL summary scores measured by the following health-related quality of life (HRQoL) questionnaires: Kidney Disease Quality of Life (KDQOL-36) and EuroQol Group 5-dimension, 5-level questionnaire (EQ-5D-5L), see Section 9.7.7 for details.

9.5 Pharmacokinetics / pharmacodynamics - amended

This section was changed in Amendment 3, see Section 15.1.2.27.

For the investigation of systemic exposure to finerenone and its relationship with treatment effects, the plasma concentrations of finerenone will be determined at different time points using a sparse sampling approach in all participating subjects. Details about the collection, processing, storage and shipment of samples will be provided separately (Laboratory Manual).

The plasma concentration versus time data of Visit 3 (Month 4) and at subsequent yearly visits will be evaluated descriptively, separated by dose. Plots will be prepared of all individual plasma concentrations vs. actual relative study times (time of sample collection after time of study drug administration).

The PK data will be evaluated using non-linear mixed effect modeling (NONMEM). In addition, attempts will be made to identify whether the PK of finerenone is influenced by covariates and to explore exposure-response relationships. This evaluation will be described in a separate analysis plan and will be reported separately.

At Visit 3 (Month 4), a trough sample for the determination of finerenone plasma concentrations will be drawn before intake of study drug (if the sample could not be obtained at Visit 3, it can be drawn at Visit 4). At this visit, study drug will be administered at the study center by study personnel and the exact time of study drug intake on the day before the visit and on the day of the visit and the exact sampling time will be recorded in the eCRF. Ideally, the study personnel should contact the subject prior to Visit 3 to remind them not to take the study drug as usual in the morning at home.

At each of the yearly visits, one blood sample for the determination of finerenone plasma concentrations will be drawn during the visit after intake of study drug at home. The subjects should be advised to take their drug as usual in the morning at home and recall the time of drug intake. The exact time of study drug intake and the exact sampling times will be recorded in the eCRF.

PK sampling is not necessary if the study treatment was temporarily interrupted or permanently discontinued at the time of the visit.

The PK bioanalysis will be performed under the responsibility of Bayer Bioanalytics Laboratory, Bayer AG, PPD [REDACTED], 42096 Wuppertal, Germany. Study responsible bioanalytical personnel will remain unblinded during the study.

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions - *amended*

This section was changed in Amendment 3, see Section 15.1.2.28.

Definition of adverse event (AE)

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. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

All diagnoses, symptom(s), sign(s) or finding(s) with a start date **from randomization onwards** must be recorded as (S)AEs, except those related to study procedure. The latter have to be recorded as (S)AEs **after informed consent** has been obtained (see also end of this section for definition of SAE).

A surgical procedure that was planned prior to randomization by any physician treating the subject should not be recorded as an 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 were present before randomization and for which no symptoms or treatment are present until randomization are recorded as medical history (e.g. seasonal allergy without acute complaints)
- Conditions that started before randomization and for which symptoms or treatment are present after randomization, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis)
- Conditions that started or deteriorated after randomization will be documented as (S)AEs
- Conditions assessed as related to study procedure (such as invasive procedures and adjustment of SoC therapy [see Section 8.1.1 for guidance]) that start or deteriorate after signed informed consent must be documented as (S)AEs.

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 subject 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 12 hours
- The admission is pre-planned
(e.g. elective or scheduled surgery arranged prior to the first dose of study drug; admission is part of the study procedures as described in Section 9.2)
- 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 serious or important medical event as judged by the investigator.

9.6.1.2 Classifications for adverse event assessment

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

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.2.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

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

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of 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 highly likely 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 that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include the following:

- 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 re-challenge should be considered in 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 might have caused 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.
- The assessment is not possible.

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'.

9.6.1.2.4 Action taken with study treatment

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

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown.

9.6.1.2.5 Other specific treatment(s) of adverse events

Specific treatment of AE(s), if given, is to be documented follows:

- None
- Remedial drug therapy
- Other.

9.6.1.2.6 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.

9.6.1.3 Assessments and documentation of adverse events (AEs) - *amended*

This section was changed in Amendment 3, see Section 15.1.2.29.

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

AEs observed, mentioned upon open questioning by a member of the investigator's team or spontaneously reported by the patient will be documented. The observation period for AEs will start with randomization and will end with the last visit of follow-up **except** for AEs related to study procedures; the observation period for the latter AEs will start with signed informed consent and will end with the last visit of follow-up. In the event of ongoing study-related AEs and medically relevant AEs at the end of the study, the investigator is urged to monitor the subject and document the outcome on the subject's source document. After the end of the follow-up phase, there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

See also Section 9.6.1.1 above for the differentiation between medical history and AEs.

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. SAEs will be recorded on the AE page of the eCRF.

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 for that treatment period.

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

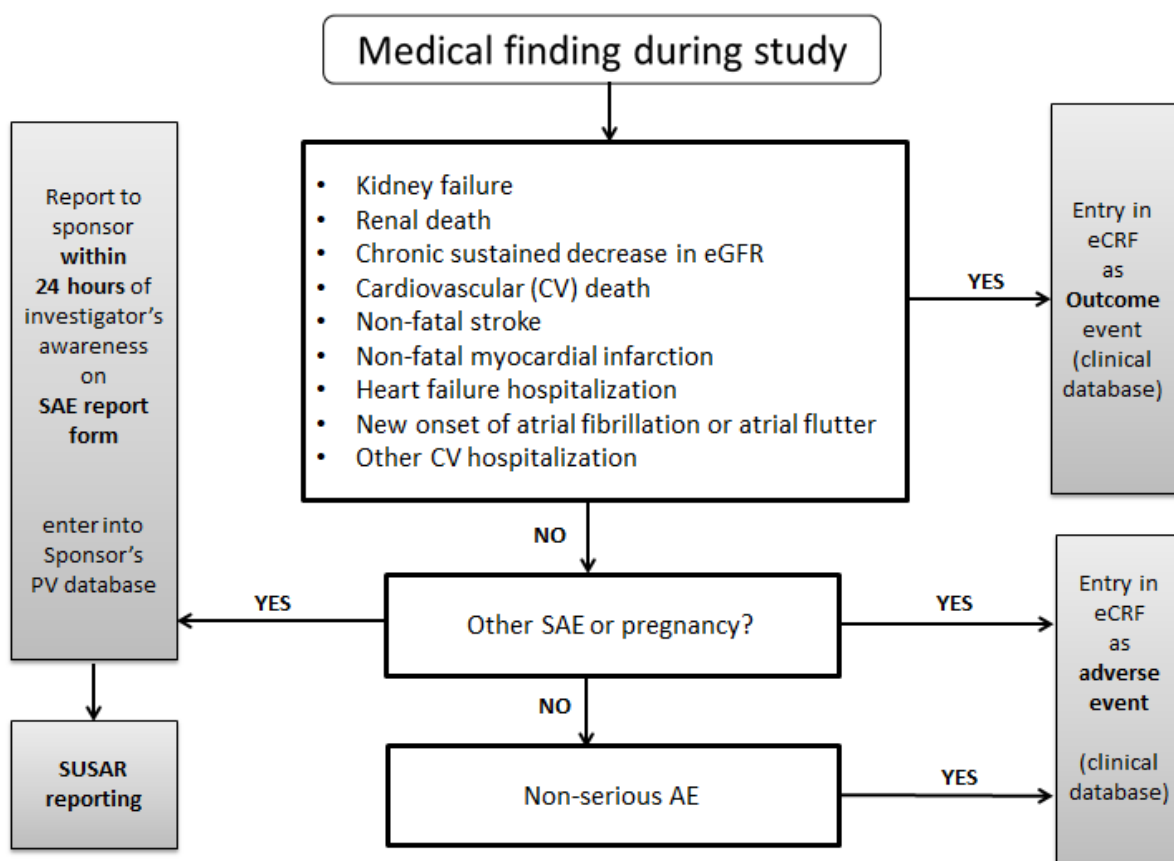
For all serious adverse events (SAEs), the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

9.6.1.3.1 Event versus outcome

The efficacy and pre-defined disease-related outcome events specified in Figure 9–1 will not be documented as (S)AEs. Instead, these events will be documented only on the Outcome Event pages of the eCRF. In addition, they will not be reported as SAEs and will neither be unblinded, nor reported to regulatory authorities, IECs, or investigators (see also Section 9.6.1.4 for details).

However, they will be collected in the eCRF, monitored by the DMC during the study and analyzed in the clinical report after study termination. If unexpected safety issues are identified, specific amendments will be implemented.

Figure 9–1 Medical finding during the study: event versus outcome



9.6.1.4 Reporting of serious adverse events (SAEs) - amended

This section was changed in Amendment 3, see Section 15.1.2.30.

The definition of SAEs is provided in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

The pre-defined disease-related efficacy events (see Table 13–1) will not be subject to AE documentation and expedited reporting as SAE because they are not unexpected in this study population. Thus, they will not be recorded as SAEs on the AE page and will not be sent to

Sponsor's Pharmacovigilance department. Instead, these events will be recorded on the eCRF as outcome events. Consequently, they will neither be unblinded, nor reported to regulatory authorities, IECs or investigators. However, they will be collected in the eCRF, evaluated by the CEC, monitored by the independent DMC during the study and analyzed in the clinical study report after termination of the study. The independent DMC will periodically review and assess all safety data for imbalances in safety outcomes. It is believed that in this way, patient safety can continue to be monitored throughout the duration of the trial, without affecting the integrity of the study. Should unexpected safety issues be identified, specific amendments will be implemented.

All other SAEs that fulfill the seriousness criteria provided in Section 9.6.1.1 must be collected on the AE page of the eCRF and reported as SAEs to the Sponsor's Pharmacovigilance department. All SAEs that fulfill SUSAR criteria as defined by the ICH E2A Guideline will be reported to the concerned authorities by expedited means (see details below).

The investigator is responsible for continuing to follow-up on all SAE reports (whether or not the event is related to study drug) until resolution of the event, or until the event is considered chronic and/or stable by the investigator and/or other physician who is responsible for the subject's medical care. Follow-up SAE reports will be reported according to the same timelines as initial reports, as soon as new significant information becomes available.

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, will be summarized in the investigator site file and updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs that are not exempted from SAE reporting occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File.

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.

The efficacy and pre-defined disease-related outcome events as described in Section 9.6.1.3.1 will not be subject to AE documentation. Thus they will neither be unblinded, nor reported to regulatory authorities, IECs, or investigators in the event of fulfilling criteria for a SUSAR.

Notification of the IECs / IRBs

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

In compliance with applicable regulations, in the event of a SUSAR, the subject's treatment code will usually be unblinded before reporting to the competent authorities, IECs/IRBs. For reporting to investigators the treatment blind will be kept.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, 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.

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the IB for finerenone.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

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

9.6.2 Pregnancies

Female subjects of childbearing potential must have a negative serum or urine pregnancy test at screening and at yearly-intervals during study participation. If required by national/institutional regulations, a serological or urine pregnancy test in subjects of childbearing potential should be performed more often (e.g. at every visit).

The investigator must report to the sponsor any pregnancy occurring in a female study subject during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

The child's health should be followed up until birth.

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

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE, i.e. within 24 hours of his/her awareness.

9.7 Other procedures and variables

9.7.1 Monitoring of potassium - *amended*

This section was changed in Amendment 3, see Section 15.1.2.31.

Hyperkalemia is a frequent event in subjects with DKD progressing to ESRD and one of the main risks identified from previous studies with MRAs including finerenone. Potassium will be monitored closely during this study, with assessments of potassium concentration scheduled at all visits (see [Table 9–1](#) for schedule).

During treatment with study drug, all assessments of potassium, including re-tests, will be performed at both local and central laboratories. Due to sample handling and extended transportation time to the central laboratory, falsely elevated serum potassium values in centrally (but not locally) analyzed samples have been observed in previous studies with finerenone. Since the value of potassium in the local sample is usually not affected by this and results from the local laboratory are available earlier, local samples will be taken not only for safety purposes but also for dose adjustments.

Re-checking of potassium values must be done at the latest within 72 hours of the investigator being aware of results that need confirmation. The investigator can perform a re-test at any time if they consider it necessary to confirm the potassium concentration of the local or the central sample.

Adjustment of dose after start of study drug intake based on blood potassium levels is provided in [Table 9–3](#).

Table 9–3 Blood potassium: guidance for dose adjustment at Visit 2 and subsequent visits

Blood potassium (mmol/L)	Action
First sample:	
≤4.8	If on lower dose of study drug, up-titrate to higher dose. If on higher dose of study drug, continue on the same dose.
4.9 to 5.5	Continue on the same dose.
>5.5	Withhold study drug and re-check potassium within 72 hours.
Second and subsequent samples:	
≤5.0	Re-start study drug at lower dose.
>5.0	Continue to withhold study drug; continue to monitor potassium and restart study drug at the lower dose only if potassium is ≤5.0

NOTE: lower dose = 10 mg once daily; higher dose = 20 mg once daily.

The following aspects have also to be taken into consideration:

- Blood potassium should be measured 4 weeks (\pm 7 days) after re-starting treatment or dose adjustment, especially after up-titration
- If central laboratory results for blood potassium differ from local laboratory results to such an extent that the investigator is uncomfortable with the dose adjustment guidance shown in [Table 9–3](#) , blood sampling may be repeated at the investigator’s discretion
- If the subject is already on the lower dose of study drug but hyperkalemia recurs soon after a previous event of hyperkalemia with interruption of study drug, and there is no explanation for the recurring hyperkalemia event other than intake of study drug, permanent discontinuation of study drug is recommended
- If blood potassium is > 6.5 mmol/L, an ECG should be obtained
- Subjects will maintain their normal diet throughout the study and will not be given any specific advice on dietary potassium restrictions.

9.7.2 Laboratory assessments

9.7.2.1 Central laboratory

The name and the address for the central laboratory service provider can be found in the documentation supplied by the vendor. Only centrally analyzed blood samples will be considered for statistical analysis, unless otherwise specified. Details of the collections, shipment of samples and reporting of results by the central laboratory will be provided to the investigators in the Laboratory Manual.

Laboratory evaluations (*hematology, HbA_{1c}, clinical chemistry and urinalysis* parameters) are shown in [Table 9–4](#). Hematology, HbA_{1c} and (full) clinical chemistry are considered as ‘*Full central laboratory*’ assessments.

Laboratory evaluations will be performed according to the visit schedule (see [Table 9–1](#)).

Table 9–4 Central laboratory parameters

Parameter	Component
Hematology	White blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), platelets
Glycated hemoglobin (HbA1c)	HbA1c only
Clinical chemistry (full)	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), blood urea nitrogen, uric acid, bilirubin, sodium, serum potassium, magnesium, total protein, albumin, high-sensitivity C-reactive protein (hs-CRP)
Clinical chemistry (limited)	Serum creatinine, eGFR (CKD-EPI), sodium, serum potassium
Urinalysis	Urine albumin-to-creatinine ratio (UACR) will be measured in the first morning void urine samples collected at the subject's home on 3 consecutive days

9.7.2.2 Local laboratory - amended

This section was changed in Amendment 3, see Section 15.1.2.32.

In addition to samples for the central laboratory, other blood **safety samples** will be taken from Visit 1 (Day 1; baseline) onwards (see Table 9–1) for analysis at the local laboratory. These samples may be obtained up to 72 hours before a scheduled visit.

The following clinical chemistry parameters must be measured for as long as subject is not prematurely discontinued from the study drug:

- Blood potassium
- Blood creatinine (eGFR will be calculated automatically in the eCRF using the CKD-EPI formula (36)).

Up-titration of the study drug will be based on local potassium and eGFR values and must be documented in the eCRF. Down-titration of the study drug will occur for safety reasons only (for guidance, see Section 9.7.1 and Table 7–2).

Potassium values should be recorded using a single decimal point (e.g. 4.5 mmol/L or mEq/L). In the event of hyperkalemia, please see Section 9.7.1 for guidance on treatment.

In women of childbearing potential, a **pregnancy test** will be performed locally, at the Screening Visit and following randomization at yearly visits as long as the subject is not permanently discontinued from the study drug (since more than 7 days). However, pregnancy tests in subjects of childbearing potential should be performed more frequently (e.g. at every visit) if this is required by national / institutional regulations. Both serological and urine tests are acceptable.

9.7.3 Physical examination

Abnormal physical examination findings are recorded either as medical history or as an AE (see Section 9.6.1.1).

A complete physical examination will be performed at the Run-In and Screening Visits, at the yearly visits and again at the PD and EOS Visits (see Table 9–1).

9.7.4 Weight and height

Body weight (to the nearest 0.1 kg in indoor clothing without shoes) will be measured at all scheduled visits except the PT Visit (see Table 9–1). Height as well as hip and waist circumference in centimeters will be only measured at the Run-in Visit.

9.7.5 Measurement of vital signs

Vital signs will be assessed at all scheduled visits except the PT Visit (see Table 9–1). This will include blood pressure (BP) and pulse measurements.

BP will be measured by using a standard sphygmomanometer with an appropriate size cuff in the sitting position after 5 minutes of rest.

There must be 3 consecutive BP readings with at least a 1-minute interval between each reading (all 3 readings should be obtained within a maximum of 20 minutes).

The same arm and the appropriate size cuff should be used for measurements at each visit.

9.7.6 Electrocardiogram (ECG) - *amended*

This section was changed in Amendment 3, see Section 15.1.2.33.

A standard 12-lead ECG will be performed locally at the Run-In Visit, Screening Visit, at Visit 1 (Day 1; baseline), at the yearly visits, and again at the PD and EOS Visits (see Table 9–1). If there is any clinical indication, unscheduled 12-lead ECGs can be performed at any point during the study.

In addition, an ECG should be obtained if potassium >6.5 mmol/L.

The interpretation of the tracing must be made locally by a qualified physician.

The date of the recording must be documented on the ECG section of the eCRF. Each ECG tracing should be labeled with the study number, subject number, and date and kept in the source documents at the study site.

Clinically significant abnormalities should be reported as AEs or outcome event as appropriate (e.g. new onset atrial fibrillation) when not already reported in the medical history or in one of the previous recordings and in case of worsening of previous findings.

9.7.7 Health-related quality of life (HRQoL) questionnaires

HRQoL questionnaires will be completed by the subject at Visit 1 (Day 1; baseline), the yearly visits and at the PD and EOS Visits (see Table 9–1). The following HRQoL questionnaires will be used: ▪ Kidney Disease Quality of Life (KDQOL-36) and ▪ EuroQol

Group 5-dimension, 5-level questionnaire (EQ-5D-5L). A general description of these questionnaires is provided in Section 16.3.

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.

9.7.8 Planned optional sub-studies

9.7.8.1 Sub-studies

The results of the sub-studies for Study 16244 will not be presented in its main clinical study report (CSR) but will be provided as separate reports.

9.7.8.1.1 Echocardiography sub-study - *amended*

This section was changed in Amendment 3, see Section 15.1.2.34.

At selected centers, approximately 500 subjects per study consenting to participate in Studies 16244 and 17530 will be invited to take part in an echocardiography sub-study. Subjects will be asked to sign a separate informed consent to participate in this sub-study.

Diabetes mellitus, hypertension and dyslipidemia are CV risk factors which contribute to the CVD continuum and potentially results in a sequence of CV events. The development of HF in subjects with DKD is the most common CV complication and imposes significant morbidity and mortality (42, 43). Patients with symptomatic HFrEF are excluded from the Phase III program of finerenone in DKD. However, before becoming symptomatic, sub-clinical cardiac dysfunction and abnormal leftventricular structure including leftventricular hypertrophy can be demonstrated in the majority of subjects with moderate CKD. Imaging plays a central role in the diagnosis of structural heart disease. Of the various imaging modalities available, for reasons of accuracy, availability, safety and cost, echocardiography is the method of choice in subjects with suspected or the beginnings of structural heart disease.

In all participating sites, echocardiography will be performed according to a study-specific protocol at Visit 1 (Day 1; baseline), at yearly visits and at the end of the study (either at the PD Visit or the EOS Visit). If a baseline assessment is not available or analysable, the subject will not continue in to undergo echocardiography assessments due to inability to perform a comparison against baseline.

Echocardiography examinations, data collection and procedures for central blinded adjudication in the echo core laboratory are given in the Echocardiography Manual. In addition, each time an echocardiography is performed, one blood sample should be drawn to assess the following biomarkers shown in Table 9-5.

Table 9–5 Echocardiography sub-study: biomarkers for evaluation

Biomarker	Mechanism	Rationale for assessing this biomarker
NT-proBNP	myocardial pressure-volume overload	NT-proBNP is typically increased in patients with asymptomatic or symptomatic left ventricular dysfunction and is associated with coronary artery disease and myocardial ischemia.
Galectin-3	(Cardiac) fibroblast / cardiomyocyte stress	Gal-3 is barely detectable in cardiomyocytes but cardiac fibroblasts express high levels of this protein Serum Gal-3 predicts short-, mid- and long-term mortality and HF-associated hospitalization in early and late stage HFpEF and HFrEF
sST2	Myocardial stress	In HF, ST2 mRNA and protein are upregulated and protein becomes detectable in serum. In severe chronic HF, change in serum sST2 independently predicts mortality or transplant.
PIIINP	Tissue remodeling / collagen synthesis	PIIINP is produced and secreted into the circulation upon collagen synthesis Increased baseline PIIINP levels are associated with increased risk of death in CHF patients and decreased in response to spironolactone or eplerenone
OPN	Inflammation / tissue remodelling	OPN mRNA and protein are hardly detectable in healthy myocardium, but becomes detectable upon cardiomyocyte and fibroblast injury.

Abbreviations: CHF = chronic heart failure; CRT = cardiac resynchronization therapy; HFp/rEF = heart failure with preserved/reduced ejection fraction; NT-proBNP = N-terminal pro-peptide of brain natriuretic peptide; OPN = osteopontin; PIIINP = N-terminal pro-peptide of collagen III

Local echocardiography examinations will be performed to capture at least all of the variables listed in [Table 9–6](#). The recordings of echocardiography examinations will be digitally transferred to the vendor / echo core laboratory (ECL) for centralized interpretation and reporting. Echocardiography from videotape will be digitized, and analyses will be performed on an offline analysis workstation. Quantitative measures on all study echocardiographies will be performed by dedicated analysts at the core laboratory, who will be blinded to clinical information and randomized treatment assignment. The echocardiography results will not be provided to sites.

Table 9–6 Echocardiography sub-study: variables for evaluation

Variables	Details
LV structure, systolic function and geometry	<ul style="list-style-type: none"> • Left ventricular ejection fraction (LVEF %) using modified Simpson's biplane method • LV end-diastolic volume (LVEDV, ml), LVED volume index (LVEDVi [=LVEDV /body surface area (BSA)], mL/m²) • LV end-systolic volume (LVESV, ml), LVES volume index (LVESVi [=LVESV /BSA], mL/m²) • LV end-diastolic dimension (LVEDD, cm) and LV end-systolic diameter (LVESD, cm) • LV mass (LVM, g) and LV mass index (LVMI [LVM/BSA], g/m²) • Wall thicknesses, including inter-ventricular septum diameter (IVSd, cm) and LV posterior wall diameter (PWd, cm) in diastole • Relative wall thickness (RWT) defined as [2 x PWd] / LVEDD • LV geometry based on RWT and LVMI (normal, concentric remodeling, concentric hypertrophy or eccentric hypertrophy)
LV diastolic function	<ul style="list-style-type: none"> • Left atrial size (LA diameter, cm; LA area, cm²), LA volume index (LAVi [=LA/BSA], mL/m²) • Early diastolic mitral annular velocity (e', cm/s), using average calculated from: <ul style="list-style-type: none"> ○ Lateral e' (early diastolic mitral annular relaxation velocity at lateral border of mitral annulus [by Tissue Doppler], cm/s) and ○ Septal e' (early diastolic mitral annular relaxation velocity at septal border of mitral annulus [by Tissue Doppler], cm/s) • E wave (mitral peak early diastolic transmitral flow velocity, m/s) • A wave (mitral peak late diastolic transmitral flow velocity, m/s) • Ratio of E/A • Ratio of E/e' (using lateral e', septal e' and average e') • E-wave deceleration time (EWDt, ms)
Right heart function	<ul style="list-style-type: none"> • Pulmonary artery systolic pressure estimated by pressure gradient of tricuspid valve (PGTV) + estimated right atrial pressure (RAP) <ul style="list-style-type: none"> ○ PGTV [equivalent to peak RV-to-RA systolic gradient] = 4 x [tricuspid regurgitation velocity (VTR, m/s)]² ○ Estimated RAP depends on inferior vena cava diameter (IVCD, mm) and its respiratory collapsibility / change with respiration (end expiratory diameter [EED] - end inspiratory diameter / EED x 100, %) as well as the ratio of systolic to diastolic flow signals in the hepatic veins • Right heart function (using tricuspid annular plane systolic excursion [TAPSE], mm)
Other	<ul style="list-style-type: none"> • Assessment of aortic and mitral valves for stenosis or regurgitation, using color or continuous wave Doppler

9.7.8.1.2 Biomarker sub-study

At selected centers, the first approximately 500 subjects per study who consent to participate in Studies 16244 and 17530 will be invited to take part in a biomarker sub-study. Subject will be asked to sign a separate informed consent to participate in this sub-study.

For participating sites, samples for biomarkers will be drawn at Visit 1 (Day 1; baseline), at Visit 3 (Month 4), at yearly visits and at the end of the study (either at the PD Visit or the EOS Visit). The selected biomarkers studied are the ones believed to be relevant to the pathophysiology of the disease processes of CV and renal disease progression. The biomarkers studied are shown in [Table 9–7](#).

Table 9–7 Biomarker sub-study: variables for evaluation

Biomarker	Mechanism	Rationale for assessing this biomarker
NT-proBNP	Cardiomyocyte pressure-volume overload	NT-proBNP is typically increased in subjects with asymptomatic or symptomatic left ventricular dysfunction and is associated with coronary artery disease and myocardial ischemia.
High sensitivity troponin T (hs-TnT)	Cardiomyocyte injury	Cardiac troponin T is independently associated with cardiovascular events and mortality in patients with CKD. Serum levels of hs-TnT reflect subclinical myocardial injury in ambulatory patients.
Cystatin C		Cystatin C level to have an important association with mortality across the GFR range
Neutrophil Gelatinase-Associated Lipocalin (NGAL)	Renal tubular cells injury	Increased NGAL levels are an indicator of progression of renal damage in CKD patients even after adjustment for eGFR

9.7.8.1.3 Iohexol clearance sub-study - amended

This section was changed in Amendment 3, see Section [15.1.2.35](#).

At selected centers in Italy, at least 50 subjects per study consenting to participate in Studies 16244 and 17530 will be invited to take part in an iohexol clearance sub-study. Subjects will be asked to sign a separate informed consent to participate in this sub-study.

Subjects who are included in this sub-study will have their GFR directly measured by the iohexol plasma clearance technique (44).

Iohexol plasma clearance will be assessed at Visit 1 (Day 1, baseline), at Visit 3 (Month 4) and thereafter at every other visit (i.e. every 8 months) until the end of the study (either at the PD Visit or the EOS Visit) plus an additional assessment at the PT Visit (recovery). The Iohexol results will not be provided to the sites.

The variables for evaluation in this sub-study are as follows:

- Primary variable:
Chronic GFR slope, i.e. the rate of GFR decline from Visit 3 (Month 4) after randomization to the end of the treatment period.

As previously addressed in the AASK trial, this approach is needed to address the biphasic change in GFR decline that is expected after exposure to the study drug. The GFR slope will be determined separately during the first 4 months following randomization (acute slope) and after 4 months (chronic slope). The acute and chronic phases are differentiated because the study treatment might have acute effects on GFR that may differ from its long term effects on disease progression (45, 46) (an approach approved by the U.S. National Institute of Diabetes and Digestive and Kidney Diseases (47)).
- Exploratory variable:
 - Change in GFR from Visit 1 (baseline) and at the PT Visit (recovery)
 - Acute GFR changes from baseline to Visit 3 (Month 4)
 - Acute GFR changes from the end of the treatment period until the end of the recovery period
 - Correlation analyses between short term GFR changes between Visit 1 (baseline) and Visit 3 (Month 4) after randomization, and long term GFR decline (chronic slope).

An ANCOVA model will be fitted to the GFR efficacy variables including the factors treatment group, the stratification factors (type of albuminuria, eGFR category) and the baseline GFR as covariate. Corresponding two-sided 95% confidence intervals will be computed. In addition, correlation analyses between short term GFR changes between Visit 1 (baseline) and Visit 3 (Month 4) after randomization, and long term GFR decline (chronic slope).

9.8 Appropriateness of procedures / measurements

All parameters and their methods of measurement are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analysis will be performed using SAS; the version used will be specified in the statistical analysis plan (SAP).

A log-normal distribution is assumed for serum creatinine and UACR. For all other metric variables, a normal distribution is assumed. The distributional assumptions will be investigated and if necessary, nonparametric methods or transformation of the data will be considered.

All variables will be analyzed by descriptive statistical methods. The number of data available, mean, standard deviation (SDv), minimum, median, and maximum will be calculated for metric data. The geometric mean and SDv will be provided instead of the arithmetic mean and SDv for the variables where lognormal distributions are assumed. Frequency tables will be generated for categorical data.

Baseline values will be defined as the last non-missing measurement before randomization (Visit 1). If the last observation available prior to randomization is the measurement from the Screening Visit, this would be used as the baseline value. This also includes assessments from a local laboratory, in case that prior to randomization, no assessment from the central laboratory is available. Otherwise baseline will be missing. The measurement from the Run-in Visit will not be used as a baseline value. If more than one measurement was planned for a scheduled time point, for example blood pressure measurements and heart rate, the mean value of the last set of measurements per time point prior to randomization will be used as the baseline value.

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.

In the event of repeated measurements for Pre-treatment Visits and the Visit 1 (Day 1; baseline), the closest measurement prior to randomization will be used for analysis instead of the scheduled measurements. At all visits post-randomization and unless stated otherwise, only the values at scheduled measurements will be used for analysis.

The derived visit '*Any time post baseline*' (applicable for efficacy) will include any measurement after randomization, including unscheduled assessments. For the derived visit '*Any time on treatment*', only assessments up to 30 days after last study drug administration, including unscheduled assessments, will be considered (applicable for efficacy; for safety assessments within 3 days after last study drug administration will be considered).

Further details on the statistical analyses will be provided in the SAP that will be approved before database release.

10.2 Analysis sets - amended

This section was changed in Amendment 3, see Section 15.1.2.36.

Safety analysis set (SAF):	All randomized subjects who have taken at least 1 dose of study drug
Full analysis set (FAS):	All randomized subjects
Per-protocol analysis set (PPS):	All subjects of the FAS without any validity findings
Pharmacokinetic analysis set (PKS):	All finerenone-treated subjects with at least 1 valid finerenone plasma concentration and without protocol deviation, which would interfere with the evaluation of the PK data.
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.

All subjects will be analyzed according to the planned treatment in FAS (the intent-to-treat or ITT principle). All subjects will be analyzed according to the actual treatment in SAF and PPS. If a subject receives both treatments due to a bottle error, the treatment actually received for the majority of the time in the study will be used in SAF and PPS.

The stratum variable type of albuminuria and eGFR category used in the statistical analysis will be derived based on the screening UACR and eGFR assessment, respectively. All subjects will be analyzed according to their correct stratification category. In the event of stratification errors, the primary analysis will also be repeated based on the stratification category used in the randomization as a sensitivity analysis.

10.3 Variables and planned statistical analyses

10.3.1 Disposition, baseline, history, demography and medication

The analyses of disposition, baseline, history and demography are described below:

10.3.1.1 Disposition - amended

This section was changed in Amendment 3, see Section 15.1.2.37.

The number of subjects enrolled, randomized and valid for the SAF, FAS, PPS and PKS will be summarized overall and by treatment group, country and investigator. The number of subjects discontinuing the treatment and follow-up epochs, together with the primary reason for discontinuation will be presented by treatment group and overall in separate tables. In addition, the number of subjects with important deviations and validity findings will be presented overall, by investigator and country for each treatment group, and in total. The frequencies of each important deviation and validity finding will be presented by treatment group and in total.

10.3.1.2 Population characteristics

Population characteristics analyses, except for subject disposition, will be performed for the FAS, if not stated otherwise.

10.3.1.3 Demography and other baseline characteristics - *amended*

This section was changed in Amendment 3, see Section 15.1.2.38.

Demography includes age, sex, race, ethnicity, region (North America, Europe, Asia, Latin America and others), body weight, body height, BMI, hip and waist circumference, smoking history (never, former, current smoker) and alcohol consumption. Other baseline characteristics include baseline UACR, serum potassium, categories for serum potassium (≤ 4.5 mmol and > 4.5 mmol), eGFR (calculated by CKD-EPI formula), serum creatinine, HbA1c, values for vital signs parameters (i.e. systolic blood pressure, diastolic blood pressure and heart rate).

All demographic data and baseline characteristics will be tabulated by treatment group and overall. The demographic and other baseline characteristics table will also be presented, separated by each level of the stratification factors type of albuminuria, region and eGFR category.

The non-stratified demographic and other baseline characteristics table will be repeated for all other analysis sets if they differ in sample size from the FAS.

Demographics and other baseline characteristics will be presented for the FAS separately for the subjects belonging to PPS or not (only overall, not by treatment group).

10.3.1.4 Medical history

Medical history will be coded using the MedDRA dictionary. Medical history will be presented for each MedDRA Primary System Organ Class and Preferred Term by treatment group and overall in a summary table. Additional medical history terms by Standardized MedDRA Queries (SMQ) will also be presented.

10.3.1.5 Concomitant medication

Concomitant medication will be coded using 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. These tables will be repeated, summarizing the number of subjects with medication in the Bayer drug groups of interest (including ACEI, ARBs, beta-blocker, diuretics, potassium supplements, potassium lowering agents, alpha blocking agents, calcium channel blockers, centrally acting antihypertensives and strong, moderate and weak CYP3A4 inhibitors and CYP3A4 inducers). A subject will be counted only once within each ATC class / subclass or Bayer drug group, respectively.

A listing will be provided including all medication classified as a weak, moderate or strong CYP3A4 inhibitor according to the Bayer drug groupings together with the respective classification information.

10.3.2 Treatment duration, extent of exposure, up-titration status and compliance - amended

This section was changed in Amendment 3, see Section 15.1.2.39.

The analyses described in this section will be repeated for the SAF and PPS if they differ in sample size from the FAS.

Treatment duration (number of months with study drug intake) will be summarized using descriptive statistics by treatment group and overall. In addition, treatment duration will be categorized and presented with the corresponding number and percentage of subjects by treatment group and overall. Further specification of the categories will be provided in the SAP.

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 grams) will be summarized using descriptive statistics by treatment group.

The up-titration status (yes/no), regardless of actual or sham up-titration, will be summarized with absolute and relative frequencies per treatment group for each visit as well as subjects never up-titrated, up-titrated once, and up-titrated more than once. Compliance (as a percentage) will be calculated as follows:

$$100 * \text{Number of taken tablets} / \text{Number of planned tablets}.$$

The number of planned tablets will be calculated as follows:

$$(\text{Days from randomization to last intake of study drug} + 1) * \text{Number of planned tablets per day}.$$

All tablets, including the dummy placebo tablets, will be counted. For subjects who withdraw prematurely from the study drug, compliance will be calculated up to the time of last dose.

The compliance will be summarized descriptively by treatment group and overall. In addition, percent of compliance will be categorized into three groups, <80%, ≥80 to ≤120% and >120%, and the categories will be summarized by treatment group and overall.

10.3.3 Efficacy variables

The primary and secondary variables of efficacy are defined in Section 9.4.

10.3.3.1 Primary efficacy variable: primary analysis

The primary analysis of the primary efficacy variable will be performed in FAS.

Randomized subjects without an event of the primary composite endpoint at the time of analysis will be censored at the date of their last visit or date of non-renal death. Subjects without information about the primary composite endpoint after baseline will be censored at Day 1.

The weighted Bonferroni-Holm procedure will be used for the hierarchical testing of the primary and secondary efficacy endpoints.

- If the primary renal composite endpoint achieves statistical significance at a two-sided p-value ≤ 0.03333 ($z_{0.9833} = 2.128$), the secondary CV endpoint will be tested at the two-sided 0.05 level.
- Alternatively, if the secondary CV endpoint achieves statistical significance at a two-sided p-value ≤ 0.01667 ($z_{0.99167} = 2.394$), the primary renal composite endpoint will be tested at the two-sided 0.05 level.
- Only if both the renal and CV endpoints achieve formal statistical significance, can further secondary endpoints be tested.

In order to evaluate whether finerenone is superior to placebo in prolonging the time to the first event of the primary composite endpoint, the following null hypothesis will be tested using the log-rank test at the significance level given above:

$$H_0: S_{\text{finerenone}}(t) = S_{\text{placebo}}(t) \text{ for all time points } t \geq 0$$

The alternative hypothesis will be:

$$H_1: S_{\text{finerenone}}(t) > S_{\text{placebo}}(t) \text{ for at least one time point } t \geq 0 \text{ and} \\ S_{\text{finerenone}}(t) \geq S_{\text{placebo}}(t) \text{ for all time points } t \geq 0,$$

where $S_{\text{finerenone}}$ denotes the ‘survival’ function of the finerenone treatment group and S_{placebo} denotes the ‘survival’ function of the placebo treatment group. ‘Survival’ means ‘no event of the primary composite endpoint’ in this context.

The following decision rule to test the null hypothesis will be applied:

According to the size of this study it is justified to assume under H_0 a sufficiently close approximation of the log-rank test (48) to the normal distribution. If the z-value from the log-rank test (for the difference $S_{\text{finerenone}} - S_{\text{placebo}}$), stratified by the stratification factors (type of albuminuria, region, eGFR category) is larger than the critical quantile from the normal distribution ($z_{0.975} = 1.960$ or $z_{0.9833} = 2.128$), the null hypothesis will be rejected in favor of the alternative hypothesis.

The nominal significance levels and the critical values at the final analysis will be adjusted to account for the interim analysis, see Section 10.5 for more details.

In order to provide a point estimate of the hazard ratio and a corresponding two-sided 95% or 96.67% confidence interval, a stratified Cox proportional regression model will be used. Kaplan-Meier curves will be provided for the cumulative proportions of events by treatment groups.

10.3.3.2 Primary efficacy variable: supportive analyses

The primary analysis of the primary efficacy variable will be repeated in the PPS as a supportive analysis. Further supportive analyses of the primary efficacy variable will be performed in the FAS and PPS.

The absolute and relative frequency of subjects with an event of the primary composite endpoint until 6, 12, 18, 24, 30 and 36 months will be displayed overall and by treatment group. The number of individual events of the primary composite endpoint until 6, 12, 18, 24, 30 and 36 months will be displayed overall and by treatment group. Frequencies will be calculated for the number of individual events of the primary composite endpoint per subject until 6, 12, 18, 24, 30 and 36 months overall and by treatment group.

Kaplan-Meier estimates (the 25th, 50th and 75th percentile) of the time to the first event of the primary composite endpoint (including 95% or 96.67% confidence interval), overall 'survival' rates at 6, 12, 18, 24, 30 and 36 months and Kaplan-Meier curves will be presented for each treatment group. These analyses will be presented in total and for each level of the stratification factors (type of albuminuria, region, eGFR category).

The censoring mechanism of subjects without an event of the primary composite endpoint at the time of analysis is assumed to be non-informative for the primary efficacy analysis. Sensitivity analyses will be performed, assessing the impact of potential informative censoring of such subjects. These will include the use of different imputation rules for considering subjects without an event of the primary composite endpoint as having an event or being censored, and will be further outlined in the SAP.

For the individual events of the primary composite endpoint, the number of events per patient year will be presented overall and by treatment group. The frequency of events per patient year for a treatment group will be calculated as the number of events observed for a treatment group (counting all events, not only the first one) divided by the sum of the days from first intake of study drug for all subjects within a treatment group and multiplied by 365.25.

An 'on-treatment' analysis will be performed, including only events occurring while taking study drug or until 30 days after stop of study drug. This analysis will be performed in the FAS.

10.3.3.3 Secondary efficacy variables: primary analysis

The primary analysis of the secondary efficacy variables will be analyzed in FAS.

The testing procedure for the secondary CV composite endpoint is described in Section 10.3.3.1. If the null hypothesis of both the primary renal composite endpoint analysis and the secondary CV composite endpoint analysis are rejected using the Bonferroni-Holm procedure as described in Section 10.3.3.1, the further secondary efficacy variables will be tested hierarchically in the order as they are listed in Section 9.4.2, while keeping the two-sided significance level of 5.0%. Otherwise, the testing of the secondary efficacy variables will be performed in an explorative manner only.

The primary analysis of the secondary time-to-event endpoints will be analyzed analogously to the primary analysis of the primary composite endpoint.

An ANCOVA model will be fitted to the logarithmized ratios of UACR at Month 4 to UACR at baseline including the factors treatment group, the stratification factors (type of albuminuria, region, eGFR category) and the logarithmized baseline UACR as covariate. Corresponding two-sided 95% confidence intervals will be computed. This is consistent with the primary analysis of the Phase II Study 16243.

10.3.3.4 Secondary efficacy variables: supportive analyses

The primary analysis of the secondary efficacy variables will be repeated in the PPS as a supportive analysis. Further supportive analyses of the secondary efficacy variables will be performed in FAS and PPS.

The supportive analysis of the secondary time-to-event endpoints will be analyzed in the same way as that for the primary composite endpoint, UACR at Month 4 will be analyzed using an ANCOVA as described above.

10.3.3.5 Analysis of other exploratory efficacy variables

All other efficacy variables will be analyzed in FAS and PPS in an explorative manner.

10.3.3.5.1 UACR and albuminuria - amended

This section was changed in Amendment 3, see Section 15.1.2.40.

UACR during the study 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 (type of albuminuria, region and eGFR category).

The log-transformed ratio of UACR to baseline at each visit up to Month 24 will be analyzed by a mixed model with the factors treatment group, visit, treatment by visit interaction, factors for the stratification levels (type of albuminuria, region and eGFR category), log-transformed baseline value as covariate nested within type of albuminuria and log-transformed baseline value by visit interaction. Pairwise ratios between the finerenone and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

Frequency tables will be generated for the number of subjects with a relative decrease and increase in UACR of $\geq 30\%$, $\geq 40\%$ and $\geq 50\%$ from baseline UACR. The analysis will be performed for each visit and for any time post baseline. The analysis will also be performed stratified for each level of the stratification factors (type of albuminuria, region and eGFR category).

A shift table will be provided displaying the number of subjects who changed from baseline to each visit from very high albuminuria to high albuminuria, from very high albuminuria to UACR < 30mg/g, from high albuminuria to UACR < 30mg/g, from high albuminuria to very high albuminuria and from UACR < 30mg/g 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 decrease of at least 30% from baseline to each visit.

The additional categorical UACR efficacy variables listed in Section 9.4.3 will be summarized for presence or absence of the event using logistic regression with the factors treatment group

and stratification levels (type of albuminuria, region and eGFR category). Pairwise differences between the finerenone and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

10.3.3.5.2 Decrease in eGFR

eGFR will be summarized descriptively by treatment group and visit including absolute and relative changes to baseline. These analyses will be performed overall and separated by the stratification factors (type of albuminuria, region and eGFR category).

The absolute change of eGFR to baseline at each visit until Month 24 will be analyzed by a mixed model with the factors treatment group, visit, treatment by visit interaction, factors for the stratification levels (type of albuminuria, region and eGFR category), baseline value as covariate nested within eGFR category and baseline by visit interaction. Pairwise differences between the finerenone and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

Frequency tables will be generated for the number of subjects with a relative decrease in eGFR of $\geq 30\%$, $\geq 40\%$, $\geq 50\%$ and $\geq 57\%$ from baseline eGFR. The analysis will be performed for each visit and for any time post baseline. In addition, for each patient, the annual change in eGFR will be calculated by fitting the patient's eGFR assessments into a linear regression model with time as the independent variable. The derived annual change will be analyzed using an ANCOVA model including baseline, treatment group and stratification factors as fixed-effects.

10.3.3.5.3 Health-related quality of life (HR-QoL)

Domain scores for each of the 5 domains (PCS, MCS, Burden of Kidney Disease, Symptoms / Problems, and Effects of Kidney Disease) will be calculated according to the KDQOL scoring instruction (http://www.rand.org/health/surveys_tools/kdqol.html [6th September 2013]). The KDQOL-36 domain scores will be presented by visit and treatment group by means of number of observations, number of missing values, minimum, first quartile, mean, SD, median, third quartile, and maximum, including the changes from baseline.

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-5L User Guide (49) and to the EQ-5D Value Sets (50)]. The values and the changes from baseline of the summary scores and the EQ Visual Analogue scale (VAS) will be summarized by treatment group and visit using the same descriptive statistics as for KDQOL.

For details on HR-QoL questionnaires, see Section 16.3.

10.3.3.5.4 New diagnosis of atrial fibrillation, new diagnosis of heart failure and regression of albuminuria

These other exploratory efficacy variables will be summarized for presence or absence of the event using logistic regression with the factors treatment group and stratification levels (type of albuminuria, region and eGFR category). Pairwise differences between the finerenone and the placebo treatment group will be calculated and corresponding two-sided 95% confidence intervals will be computed.

10.3.3.6 Subgroup analyses

Exploratory subgroup analyses are planned for the primary efficacy variable, also the secondary efficacy variables. This will include descriptive statistics and a statistical test for interaction.

The following subgroups will be considered for exploratory subgroup analyses:

- Region (North America, Latin America, Europe, Asia, Others)
- eGFR category at screening and baseline (eGFR 25 to < 45, 45 to < 60 and ≥ 60 mL/min/1.73m²)
- Type of albuminuria at screening and baseline (high albuminuria vs very high albuminuria)
- History of CVD (present, absent)
- Baseline serum potassium (≤ 4.5 vs. > 4.5 mmol/L)
- Systolic blood pressure at baseline (90 to <130 , 130 to <160 and ≥ 160 mmHg).

It is anticipated that in these proposed subgroups for analysis, differences in treatment effects may be observed according to the screening or baseline characteristics defined, due in part to the differences in the risk of clinical events expected in the different subgroups.

Furthermore, subgroup analysis usually required will be performed, including the following subgroups:

- Race
- Gender
- Age group.

10.3.4 Safety variables

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

The following safety variables will be assessed during the study:

- SAEs and AEs leading to discontinuation of treatment with study drug
- Change in body weight
- Change in serum potassium from baseline
- Number of subjects with hyperkalemia (serum potassium > 5.5 mmol/L)
- Number of subjects with severe hyperkalemia (serum potassium > 6.0 mmol/L)
- Number of subjects with hospitalization for hyperkalemia
- Number of subjects discontinuing study drug permanently due to hyperkalemia
- Change in vital signs from baseline

- Change in renal function measured by eGFR (CKD-EPI) change from baseline
- Number of subjects with hospitalization for worsening of renal function
- Number of subjects discontinuing study drug permanently due to worsening of renal function
- Changes in laboratory values.

10.3.4.1 Adverse events

Adverse events (AEs) 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 will also be presented grouped by SMQs.

AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug will be considered as treatment emergent AEs (TEAEs).

An overall summary of all AEs and TEAEs will be generated by treatment group.

The number of subjects with TEAEs, post-treatment AEs occurring more than 3 days after stop of study drug, treatment-emergent SAEs, treatment-emergent study drug-related AEs, treatment-emergent study drug-related SAEs, TEAEs causing permanent discontinuation of study drug, treatment-emergent non-serious AEs, non-serious AEs, TEAEs by maximum intensity, treatment-emergent SAEs 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 using MedDRA terms grouped by Primary System Organ Class and Preferred Term.

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. 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.

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 permanent study drug discontinuation will be listed separately.

10.3.4.2 Laboratory data

The number of subjects with treatment emergent (until 3 days after any temporary or permanent interruption of study drug) abnormal laboratory values above or below the normal range will be tabulated by the laboratory parameter and treatment group.

Summary statistics including changes to baseline will be calculated by treatment group and visit for all quantitative laboratory parameters, e.g. for hematology, HbA1c, clinical chemistry and urinalysis. Geometric statistics and ratios to baseline will be presented for creatinine

instead of arithmetic statistics with changes from baseline. For 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 level of the stratification factors (type of albuminuria, region and eGFR category).

The following special safety parameters will be further assessed by displaying the number of subjects with safety events as described below by treatment group, visit and for any time on treatment (including unscheduled assessments) and up to 3 days after last study drug administration. This will also be performed by stratification factors. The summaries will be performed for the number of subjects with

- Absolute value of serum potassium >5.5 mmol/L and >6 mmol/L
- Relative decrease from baseline in eGFR of $\geq 30\%$, $\geq 40\%$, $\geq 50\%$ and $\geq 57\%$, also sustained decrease over 4 weeks
- Absolute value of eGFR < 30 mL/min/1.73m²

The percentage of subjects with the respective events (non-stratified) at any time post-baseline (including unscheduled assessments) and within 3 days after last study drug administration will be compared between the finerenone and the placebo treatment group by applying separate explorative χ^2 tests with continuity correction. If the expected number of subjects in at least 1 cell of the 2x2 contingency table is <5 (51), Fisher's exact test will be applied instead of the χ^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.

10.3.4.3 Vital signs

At the corresponding visits, 3 measurements of vital signs parameters will be taken in sitting position with at least a 1-minute interval between each reading. 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 baseline SBP >90 to <130 mmHg, 130 to <160 mmHg and ≥ 160 mmHg.

10.3.4.4 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.

10.3.4.5 Further safety variables

All safety variables are listed at the start of this section. Not covered in the above sections is the presence or absence of events associated with hyperkalemia and renal failure. These will be summarized by treatment group using frequency counts.

10.3.5 Missing data / drop outs

A subject who has been randomized and discontinues study participation prematurely for any reason, either from study treatment or from follow-up, is defined as a 'dropout', 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.

All missing or partial data will be presented in the subject data listing as they are recorded on the electronic eCRF.

Sensitivity analyses using other imputation methods will be performed for the primary endpoint.

For further information on missing data, please refer to Section 11.4.

10.4 Determination of sample size - amended

This section was changed in Amendment 3, see Section 15.1.2.41.

This is an event-driven study. A total of 1068 primary efficacy endpoint events will have a minimum 90% power to demonstrate superiority of finerenone to placebo using a logrank test at a two-sided significance level of 3.3333%, assuming a 20% relative risk reduction, i.e. a true hazard ratio of 0.80 (the hazard ratio that will be observed in the study will be different, i.e. closer to 1 due to treatment discontinuations). The study will stop when at least 1068 primary efficacy endpoints accrue across both treatment arms.

With an assumed treatment duration of 44 months (duration of recruitment period: 33 months, equal recruitment pattern during the accrual period, maximum treatment period of the last subject recruited: 11 months), the planned total number of subjects to be randomized is estimated to be 4690 subjects, assuming an annual placebo event rate of 12%, a common annual lost-to-follow-up rate of 0.7% in both treatment groups, an annual finerenone discontinuation rate of 5% and assuming that placebo discontinuation will not change the hazard. 4800 subjects are planned to be randomized taking a certain ramp-up during recruitment into account. Assuming a screening failure rate of 50%, 9600 subjects are planned to be screened.

Due to the minimal effect of the interim analysis on the overall power of the study, an adjustment of sample size would be negligible.

The assumption of the annual placebo event rate of 12% is based on a recent analysis of the results from the IDNT and RENAAL trials using alternative endpoints defined by smaller declines in eGFR, similar to those proposed in Study 16244. Event rates were obtained from the respective studies in the arms where treatment would more closely resemble that in the placebo population of study 16244 who will be on standard of care treatment for DKD. Annual event rates for the composite renal endpoint range from 11-16% for these studies. The planned population of study 16244 will have some differences compared to IDNT and RENAAL, with a likely lower median UACR value but comparable mean eGFR. The comorbidity of diabetic retinopathy in subjects with high albuminuria may predict a higher

rate of renal events. Consequently, the assumed annual placebo event rate of 12% is assumed to be appropriate for this Phase III setting (10, 11).

The calculations of the required total number of events and subjects to be randomized were performed using PASS 11 (52).

10.5 Planned interim analyses - amended

This section was changed in Amendment 3, see Section 15.1.2.42.

One formal interim analysis is planned when 2/3 of the required total number of primary efficacy endpoint events have been observed. Based on the assumptions from sample size determination the interim analysis will take place about 34 months after start of study treatment. As an event-driven trial, the actual timing of the interim analysis will depend on the observed event rate, the patient recruitment rate, and length of the recruitment period.

If the interim analysis shows clear and consistent benefit in the finerenone treatment group, the DMC may recommend early study termination. The Haybittle-Peto rule will be used to guide the decision regarding early stopping of the study for success: a reduction of 3 standard deviations in the analysis of the primary efficacy endpoint and the secondary CV composite endpoint at the interim analysis (two-sided p-value < 0.00270).

If the decision will be to stop the study early for success, the final primary analyses, both for the primary and secondary efficacy endpoints, will be performed at an overall two-sided significance level of 0.270%. A group sequential design with a single interim analysis when 2/3 of the information is available with a stopping rule of two-sided $p < 0.00270$ would require a final $p < 0.04967$ ($p < 0.03283$, $p < 0.01576$) to maintain the overall significance level at 5% (3.333%, 1.667%). Consequently, if the decision will be to continue the study without stopping early for success, the following testing procedure at the final analysis will control the overall familywise error rate at 5% according to Tang and Geller (1999) (53).

- If the primary renal composite endpoint achieves statistical significance at a two-sided p value ≤ 0.03283 ($z_{0.9836} = 2.134$), the secondary CV endpoint will be tested at the two sided level of 0.04967 ($z_{0.9752} = 1.963$)
- Alternatively, if the secondary CV endpoint achieves statistical significance at a two sided p value ≤ 0.01576 ($z_{0.9921} = 2.414$), the primary renal composite endpoint will be tested at the two-sided level of 0.04967 ($z_{0.9752} = 1.963$)
- Only if both the renal and CV endpoints achieve formal statistical significance, the remaining secondary endpoints will be tested hierarchically at a two-sided level of 0.04967 ($z_{0.9752} = 1.963$).

For a lack of efficacy, a non-binding futility approach will be utilized at the time of the planned interim analysis. If the conditional probability of rejecting the null hypothesis for the primary comparison, given the assumed and current event rates, falls to an unacceptably low level (as will be specified in the DMC Charter), the DMC may consider recommending early termination of the study.

The Executive Committee will oversee overall blinded event rates to ensure that they meet protocol projections. If overall event rates are lower than expected, consideration will be given to altering the trial design, such as increasing the sample size or extending the study duration without knowledge of any treatment effect.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be a validated electronic data capture system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system.

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

It is the expectation of the sponsor that key data entered into the eCRF has source documentation available at the site.

Study-specific data (race and ethnic group) may be entered directly into the CRF, without availability of corresponding source documentation. For all other data, source documentation must be available at the site.

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

Data recorded from screening failures

Data of ‘*only screened subjects*’ will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, the following data should be recorded in the eCRF:

- Demographic information (subject number; year of birth / age; sex; if applicable race / ethnicity)
- Date of informed consent
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

11.2 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 treatment 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.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor’s/CRO’s standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. IxRS, laboratory, adjudication committees).

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

11.4 Missing data

All efforts will be made to collect complete data for all subjects randomized in this study. Subjects will be followed until the end of the study, and all required data will be collected, regardless of their compliance with study medication use or visit schedule.

After randomization, study drug discontinuation for any reason does not constitute withdrawal from the study and should not lead to the subject being withdrawn from the study. On the contrary, even subjects who have stopped taking study drug are expected to attend all the protocol specified study visits and will be encouraged to perform all assessments as stipulated in the visit schedule.

If it is not possible for a subject who has withdrawn from study drug to attend any visit(s) in person, the site staff will keep in touch with the subject by means of phone contact to the subject himself/herself, or to a person pre-designated by the subject, in accordance with the subject's study visit schedule. Data will continue to be collected about the subject's health status, including information on developing of renal or CV complications and vital status. This information may be provided either by the subject himself/herself, his/her general practitioner or a family relative (if allowed in the respective country). Data, such as information on survival and potential protocol-specified endpoints, might be also collected from a healthcare provider, from public or medical records, or other sources as available according to local guidelines and as allowed by local regulations. These data will be collected until the study is concluded, even if the subject no longer attends study visits in person, unless the subject withdrew consent and did not agree to release further information.

When an event date is not known, the site investigator will be asked to provide a best-estimate as to when the event occurred. Even though the exact date of an event is unknown, the investigator often has some information that would give an approximate date (e.g. the first week of a month, the fall of a year, or the middle of a particular year) or at least the date when the subject was last seen or contacted. This information can be meaningfully incorporated into the estimated date recorded, as this is likely to be closer to the true date than any produced by an uninformed computer algorithm. This estimated date should be the middle date within the period that the event is known to have occurred. If the event is known to have occurred in the first week of a month, then the date in the middle of that week should be recorded as the estimate. If it occurred in the fall of a year, then the middle date in the fall is the appropriate estimate. If no information is known, then the date in the middle of the plausible time period should be given, based on the last contact with the subject prior to the event and the date of contact when information about the event was known.

Data from subjects who prematurely terminate the study will be used to the maximum extent possible. All missing or partial data will be presented in the subject data listing as they are recorded on the eCRF. Data are collected primarily through an EDC system, which allows ongoing data entry and monitoring.

For those subjects who withdraw consent, sensitivity analyses will be performed to assess the impact of potential informative censoring of such subjects. These will include the use of different imputation rules for considering subjects without an event of the primary composite endpoint as having an event or being censored.

11.5 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.

11.6 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 contract with the investigator/institution will contain all regulations relevant for the study site.

12. Premature termination of the study

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

- If 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; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial 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. Final decision on the closure must be in writing.
- 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 is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing subjects must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section [6.4.1](#).

13. Ethical and legal aspects

13.1 Investigator(s) 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.

Whenever the term '*investigator*' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor)

before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals 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's 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 investigators for this study are:

PPD

ASH Comprehensive Hypertension Center,
The University of Chicago Medicine & Biological Sciences
5841 S. Maryland Avenue; MC 1027, Chicago, IL 60637

and

PPD

University of Athens, University Hospital Attikon
Department of Cardiology, Heart Failure Unit
28 Doukissis Plakentias; 11523 Athens; Greece

13.1.1 Executive Committee

The Executive Committee, which consists of external experts in the area of nephrology, diabetology and cardiology, will ensure the overarching integrity of the study.

The Executive Committee will be established for Study 16244 and Study 17530. The committee's responsibilities include the following:

- Review feedback from the independent DMC
- Input into the Clinical Event Committee (CEC) charter
- Provision of recommendations regarding sub-studies and amendments to the protocol
- Contribution to and oversight of publications and communication of study results
- Projecting study termination, and other study-related activities as appropriate
- Overseeing overall blinded event rates to ensure that they meet protocol projections.

Decisions will be made by consensus; in the absence of consensus, the co-Chairs of the Executive Committee will provide their recommendation to the Sponsor for final determination.

13.1.2 Clinical Event Committee (CEC)

A Clinical Event Committee (CEC), blinded to study treatment assignment, will adjudicate all events that could potentially fulfill the criteria for the primary, secondary or other endpoints during the study.

The CEC Charter will describe the roles and responsibilities of the CEC and define the events to be adjudicated and the manner in which they will be adjudicated. The CEC will judge whether an event meets the predetermined definitions. The co-Chairs of the CEC will be members of the Executive Committee established for Study 16244 and Study 17530.

All of the endpoint events shown in [Table 13–1](#) will be reported to the CEC.

Table 13–1 Endpoint events to be reported to the Clinical Event Committee (CEC)

-
- Kidney failure
 - Decrease of eGFR of $\geq 40\%$ from baseline, confirmed by at least one additional standardized measurement at least 4 weeks after the initial measurement
 - Decrease of eGFR of $\geq 57\%$ from baseline, confirmed by at least one additional standardized measurement at least 4 weeks after the initial measurement
 - Decrease of eGFR to less than 15 mL/min/1.73m², confirmed by at least one additional standardized measurement at least 4 weeks after the initial measurement
 - CV and renal death events
 - Non-fatal myocardial infarction
 - Non-fatal stroke
 - Hospitalization for heart failure
 - Other CV hospitalization
 - New onset of atrial fibrillation or atrial flutter
-

Note: Other endpoints of interest may be added. These will be specified in the CEC Charter.

The CEC will be responsible for classifying all death and hospitalization events and for determining whether pre-specified endpoint criteria were met for CV, renal or other fatal and non-fatal events. Sites are instructed to take a conservative approach when reporting endpoints; if the investigator suspects an endpoint may have occurred, it is best to report the event to the CEC for a final determination.

Reporting guidelines for AEs and SAEs as outlined in Sections 9.6.1.1 and 9.6.1.4 must be followed if the event is not a defined endpoint (see [Table 13–1](#)).

13.1.3 Data Monitoring Committee (DMC)

Ongoing safety monitoring during the conduct of the study will be performed by an external and independent DMC. An independent statistical analysis center (SAC) will be involved in processing unblinded safety data for the DMC. Analysis periods and procedures will be defined in an operational charter (DMC charter) filed in the study file.

Outcome events as defined in Section 9.6.1.3.1 will not be reported as AEs or SAEs by the investigators; however, they will be collected in the eCRF. The independent DMC will periodically review and assess all outcome events as well as safety data from the study for imbalances in safety outcomes in an unblinded manner. It is believed that in this way, patient safety can continue to be monitored throughout the duration of the trial, and the integrity of the study maintained. If unexpected safety issues are identified, specific amendments will be implemented based on the recommendation of the DMC.

Following data review, the DMC will provide written recommendations that will be transferred to the chairmen of the Executive Committee and Bayer. DMC opinions and recommendations will be notified by Bayer as soon as possible to the competent authorities and the IECs where they qualify for expedited reporting.

13.1.4 Steering Committee

The Steering Committee will consist of country representative(s) and will be led by the Executive Committee. The Steering Committee will be blinded to the study data while the trial is ongoing. Their main responsibilities are as follows:

- Provide input to protocol-related issues and protocol amendments that may arise during the course of the study
- Oversee study progress and provide recommendations to Executive Committee in regards to any necessary modifications that may be required in study conduct or study monitoring
- Transmission of information to individual investigators
- Serve as resource for scientific review of sub-studies, publications, presentations and/or educational material as applicable.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 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 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)/IRBs 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 EC/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 of, the protocol to eliminate an immediate hazard(s) to the trial 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 12.

13.4 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 will be 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 consentor (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 IRB/IEC has been obtained.

Each subject / legal representative or proxy consentor will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit description described in Section 9.2 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The subject has the right to object to the generation and processing of this post-withdrawal data. For this, he/she needs to sign a corresponding declaration of objection; alternatively, the subject's oral objection may be documented in the subject's source data.

Each subject / legal representative or proxy consentor will have ample time and opportunity to ask questions.

Only if the subject / legal representative or proxy consentor voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The subject / legal representative or proxy consentor 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 adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consentors 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 consenters of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB's approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

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

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 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.

13.7 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.

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56. Barotfi S, Molnar MZ, Almasi C, Kovacs AZ, Rempert A, Szeifert L, et al. Validation of the Kidney Disease Quality of Life-Short Form questionnaire in kidney transplant patients. *J Psychosom Res.* 2006;60(5):495-504.
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15. Protocol amendments

15.1 Amendment 3

Amendment 3 is the first global amendment dated 02 MAY 2017. The following is an overview of the changes made to the original Protocol Version 1.0.

15.1.1 Overview of changes to the study

The original protocol for this study was amended for the following reasons:

- 1) To account for the lower than expected recruitment rate, the duration of study and the number of sites required worldwide were increased.
- 2) To allow re-screening at an earlier stage and even if the reason for initial screen failure was an elevated blood potassium value, the re-screening rules were amended.
- 3) To allow randomization of patients with a recent CVD episode (i.e. those suffering from stroke, transient ischemic cerebral attack, acute coronary syndrome or hospitalization for worsening heart failure in the last 30 days prior to the Screening visit), the respective Exclusion criterion (#7) was modified.
- 4) In order to allow up-titration of study drug at any time during the study (from Visit 2 onwards), the instructions for up-titration were modified. Additionally, a requirement to specify the reason for not dispensing the 20 mg dose in the eCRF was added.
- 5) The recommended blood pressure targets after randomization were updated according to the most recent literature.
- 6) The definition of the endpoint “kidney failure” was added.
- 7) Administrative changes:
Sponsor name was updated (Bayer AG became the sponsor for ongoing Bayer HealthCare AG sponsored studies on 1st July 2016), Sponsor for US territory was added, contact details for Sponsor’s medical expert were updated, and terminology changes due to updated Operating Instructions (“protocol deviation” was replaced by “validity finding”) were made.
- 8) To improve clarity and correct typographical errors or inconsistencies.

Sections affected include:

- [Section 1 Title page](#)
- [Section 2 Synopsis](#)
- [Section 5 Study design](#)
- [Figure 5-1 Overall study design](#)
- [Section 6.2 Exclusion criteria](#)
- [Section 6.4.1.1 Discontinuation of study drug](#)

- Section 6.4.2.1 Re-screening
- Section 7.4 Dosage and administration
- Section 7.5.2 Unblinding
- Section 8.1.3 Control of blood pressure
- Table 9-1 Study 16244: schedule of activities and evaluations
- Table 9-2 Sub-studies of Study 16244: schedule of procedures
- Section 9.2 Visit description
- Section 9.2.1 Run-in Visit (4 to 16 weeks prior to the Screening Visit)
- Section 9.2.2 Screening Visit (≤ 2 weeks prior to Visit 1)
- Section 9.2.3 Visit 1 (randomization; Day 1 and baseline)
- Section 9.2.5 Visit 3 (Month 4)
- Section 9.2.6 Visit 4, 6, 7, 9, etc. (every 4 months; Month 8, 16, 20, 28, etc., excluding yearly visits)
- Section 9.2.7 Visit 5, 8, 11, etc. (every 12 months; Month 12, 24, 36, etc.)
- Section 9.2.8 Up-titration Visit (unscheduled; from 4 weeks \pm 7 days post-titration)
- Section 9.2.9 Premature Discontinuation (PD) Visit
- Section 9.2.10 End of study (EOS) visit
- Section 9.2.11 Post-Treatment (PT) Visit
- Section 9.3.2 Medical history
- Section 9.4 Efficacy
- Section 9.4.3 Other exploratory efficacy variables
- Section 9.5 Pharmacokinetics / pharmacodynamics
- Section 9.6.1.1 Definitions
- Section 9.6.1.3 Assessments and documentation of adverse events (AEs)
- Section 9.6.1.4 Reporting of serious adverse events (SAEs)
- Section 9.7.1 Monitoring of blood potassium
- Section 9.7.2.2 Local laboratory
- Section 9.7.6 Electrocardiogram (ECG)
- Section 9.7.8.1.1 Echocardiography sub-study
- Section 9.7.8.1.3 Iohexol clearance sub-study
- Section 10.2 Analysis sets
- Section 10.3.1.1 Disposition
- Section 10.3.1.3 Demography and other baseline characteristics
- Section 10.3.2 Treatment duration, extent of exposure, up-titration status and compliance

- [Section 10.3.3.5.1 UACR and albuminuria](#)
- [Section 10.4 Determination of sample size](#)
- [Section 10.5 Planned interim analyses](#)

15.1.2 Changes to the protocol text

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version. As applicable, changes to the protocol text are highlighted as follows:

- **Addition of a whole new portion** Brief identification of the new portion
- **Removal of a whole portion** Complete display of the removed portion, formatted as ~~crossed-out~~
- **Editing of an existing portion** Comparative presentation of “old text” versus “new text”, with “old text” referring to the most recent previous protocol version. Deletions are ~~crossed-out~~ in the “old text”. Additions are underlined in the “new text”.
- **Tables / figures** The term “amended” is added to the caption.
- **Terminological changes** Brief specification of the terminological change
Thus, in this section, a terminological change (e.g. “period” versus “epoch”) is defined only once, without displaying “old text” versus “new text” for each appearance.

Corrections of typos or omissions are not highlighted in this section.

15.1.2.1 Section 1 Title page**Old text:**Sponsor: **Bayer HealthCare AG, D-51368 Leverkusen, Germany**Sponsor's medical expert: PPD
Study Medical Expert
Bayer S.A.
Bayer HealthCare
~~04779-900 São Paulo, Brazil.~~
Phone no.: PPD**New text:**Sponsor: Non-US territory: Bayer AG, D-51368 Leverkusen, Germany
US territory: Bayer Healthcare Pharmaceuticals Inc.,
100 Bayer Boulevard, P.O. Box 915, Whippany
NJ 07981-0915, USASponsor's medical expert: PPD
Study Medical Expert
Bayer AG
Aprather Weg 18a
42113 Wuppertal, Germany
Phone no.: PPD**15.1.2.2 Section 2 Synopsis****Old text:**

Test drugs	
Name of active ingredient	Finerenone
Doses	<ul style="list-style-type: none"> • 10 mg finerenone tablet once daily in the morning OR • 20 mg finerenone tablet once daily in the morning
Route of administration	Oral
Duration of treatment	Approximately 3.25 years (i.e. an anticipated 2-year recruitment period plus a study drug treatment period of 1.25 year after enrolment of the last patient into the trial)

Reference drug	
Name of active ingredient	Placebo
Dose	<ul style="list-style-type: none"> • Placebo tablet once daily in the morning
Route of administration	Oral
Duration of treatment	Approximately 3.25 years (i.e. an anticipated 2 year recruitment period plus a study drug treatment period of 1.25 year after enrolment of the last patient into the trial)
New text:	
Test drugs	
Name of active ingredient	Finerenone
Doses	<ul style="list-style-type: none"> • 10 mg finerenone tablet once daily in the morning OR • 20 mg finerenone tablet once daily in the morning
Route of administration	Oral
Duration of treatment	<u>As an event-driven trial, the actual length of the treatment will depend on the observed event rate, the patient recruitment rate, and length of the recruitment period and will be approximately 3.5 years.</u>
Reference drug	
Name of active ingredient	Placebo
Dose	<ul style="list-style-type: none"> • Placebo tablet once daily in the morning
Route of administration	Oral
Duration of treatment	<u>As an event-driven trial, the actual length of the treatment will depend on the observed event rate, the patient recruitment rate, and length of the recruitment period and will be approximately 3.5 years.</u>

15.1.2.3 Section 5 Study design

Old text:

[...]

Patients from approximately 650 study centers worldwide will be randomized in a 1:1 ratio to either finerenone or placebo in addition to SoC therapy. Assuming a screening failure rate of approximately 50%, 9600 patients will have to be screened to randomize approximately 4800 patients.

The anticipated duration of the study is approximately 3.25 years: this includes an anticipated recruitment period of 2 years followed by a study drug treatment period of 1.25 years after the enrolment of the last patient into the trial. However, as an event-driven trial, the actual length of the trial will depend on the observed event rates, the patient recruitment rate, and length of the recruitment period.

[...]

Run-in Period (4 up to 16 weeks)

Subjects with written informed consent who complete the Run-in Visit and meet all eligibility criteria will be enrolled into a mandatory Run-in Period, the purpose of which is to ensure that the subject's SoC therapy including treatment with ACEIs or ARBs is optimized and that all inclusion and exclusion criteria are met at the Screening Visit.

[...]

Screening Period (up to 2 weeks)

At the end of the Run-in Period, a Screening Visit to confirm the subject's eligibility will take place within ≤ 2 weeks 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.

[...]

Treatment Period

[...]

There will be up to 4 planned visits (including randomization at Visit 1) in the first 4 months; thereafter visits will take place every 4 months until the end of the study. Study drug dose can be up-titrated ~~at scheduled visits starting from~~ Visit 2 (Month 1) onwards or down-titrated at any point (even between scheduled visits); guidance on dose adjustment is provided in Section 7.4. Subjects may be seen at any time throughout the study, in addition to scheduled visits, at the discretion of the investigator.

[...]

End of study

[...]

~~All subjects who had withdrawn consent can be followed up for vital status if they do not sign the 'Declaration of Objection' form. In addition, vital status can be obtained by the investigator from publicly available data sources. The collection of vital status must be obtained within the timelines provided by Bayer.~~

[...]

New text:

[...]

Patients from approximately 900 study centers worldwide will be randomized in a 1:1 ratio to either finerenone or placebo in addition to SoC therapy. Assuming a screening failure rate of approximately 50%, 9600 patients will have to be screened to randomize approximately 4800 patients.

The anticipated duration of the study is approximately 4 years: this includes an anticipated recruitment period of 2.75 years followed by a study drug treatment period of 1 year after the enrolment of the last patient into the trial and a maximum of 4.5 months for the run-in and screening period and 1 month for the follow-up period. However, as an event-driven trial, the actual length of the trial will depend on the observed event rates, the patient recruitment rate, and length of the recruitment period.

[...]

Run-in Period (4 up to 16 weeks)

Subjects with written informed consent who complete the Run-in Visit and meet all eligibility³ criteria will be enrolled into a mandatory Run-in Period, the purpose of which is to ensure that the subject's SoC therapy including treatment with ACEIs or ARBs is optimized and that all inclusion and exclusion criteria are met at the Screening Visit.

³ Eligibility criteria related to central laboratory evaluation will be assessed once results are available.

[...]

Screening Period (up to 2 weeks)

At the end of the Run-in Period, a Screening Visit to confirm the subject's eligibility will take place within ≤ 2 weeks 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.³

³ Eligibility criteria related to central laboratory evaluation will be assessed once results are available.

[...]

Treatment Period

[...]

There will be up to 4 planned visits (including randomization at Visit 1) in the first 4 months; thereafter visits will take place every 4 months until the end of the study. Study drug dose can be up-titrated from Visit 2 (Month 1) onwards or down-titrated at any point (even between scheduled visits); guidance on dose adjustment is provided in Section 7.4. Subjects may be seen at any time throughout the study, in addition to scheduled visits, at the discretion of the investigator.

[...]

Follow-up period

All subjects who had withdrawn consent can be followed up for vital status if they do not sign the '*Declaration of Objection*' form. In addition, vital status can be obtained by the investigator from publicly available data sources. The collection of vital status must be obtained within the timelines provided by Bayer.

[...]

15.1.2.4 Figure 5-1 Overall study design

Old text:

‡ For all subjects ~~who have received SD. Subjects who continued taking study drug until the EOS visit and consent to the LTE study will not have to undergo this visit.~~

New text:

‡ For all subjects still on treatment with SD at the EoS Visit

15.1.2.5 Section 6.2 Exclusion criteria

Old text:

2. UACR > 5000 mg/g (> 565 mg/mmol) at the Run-in Visit or Screening Visit

[...]

5. SBP < 90 mmHg at the Run-in Visit or at the Screening Visit

[...]

7. 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

[...]

18. Previous assignment to treatment during this study or Studies 17530 or ~~16275~~

New text:

2. UACR > 5000 mg/g (> 565 mg/mmol) at the Run-in Visit or Screening Visit

Note: One re-assessment is allowed in case UACR is > 5000 mg/g in one of the three urine samples collected at the Run-in Visit and the Screening Visit.

[...]

5. Mean SBP < 90 mmHg at the Run-in Visit or at the Screening Visit

[...]

7. Stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening heart failure, in the last 30 days prior to the Screening Visit

[...]

18. Previous assignment to treatment during this study or Study 17530

15.1.2.6 Section 6.4.1.1 Discontinuation of study drug

Old text:

- The randomization code is broken ~~for any reason~~

[...]

If a subject no longer on study drug is unable to attend the clinic for a study visit, a telephone consultation may be performed to determine if relevant health events / endpoints (e.g. development of CV or renal complications) have occurred. Ideally, a face-to-face visit should be performed at least once a year.

New text:

- The randomization code is broken by the investigator, or other responsible person, when knowledge of the subject's treatment is required

[...]

If a subject no longer on study drug is unable to attend the clinic for a study visit, a telephone consultation may be performed to determine if relevant health events / endpoints (e.g. development of CV or renal complications) have occurred. Ideally, a face-to-face visit should be performed at least once a year. Expected frequency of telephone contacts should be in line with the standard visit schedule, and therefore performed every 4 months. Ad hoc additional telephone contacts may also be requested (e.g. prior to the interim analysis) and made to the subject themselves, a next of kin or primary physician (or local equivalent).

15.1.2.7 Section 6.4.2.1 Re-screening**Old text:**

If a subject is not eligible at the Run-in or Screening Visit for either this study (16244) or Study 17530, the subject may be re-screened at a later time ~~provided the investigator believes that a change in the subject's condition will make the subject potentially eligible at a later time point.~~

[...]

- A minimum of ~~6~~ months between the initial Run-in Visit and re-screening.

~~Re-screening of the subject is not allowed if elevated blood potassium was the reason for the subject's non-eligibility.~~

~~A subject may be re-screened only once. During re-screening, a switch over between studies is allowed (see Section 6.4.2.2).~~

New text:

If a subject is not eligible at the Run-in or Screening Visit for either this study (16244) or Study 17530, the subject may be re-screened at a later time.

[...]

- A minimum of 3 months between the initial Run-in Visit and re-screening.

A subject may be re-screened only once and after being declared as a screening failure. During re-screening, a switch over between studies is allowed (see Section 6.4.2.2).

15.1.2.8 Section 7.4 Dosage and administration**Old text:**

Up- and down-titration of study drug

~~If a subject started with the lower dose of finerenone, the investigator may up-titrate the dose of study drug. Up-titration can be performed at any scheduled visit from Visit 2 (Month 1) onwards provided:~~

[...]

~~Subjects who started with or were up-titrated to the target dose (20 mg OD) of the study drug but who do not tolerate this dose may be down-titrated at any point during the study, including between-scheduled visits if required for safety reasons. These subjects may be up-titrated at any scheduled visit based on the rules provided above. [...]~~

~~Subsequent to any up-titration or re-start of study drug after interruption of study drug intake, the investigator should perform an unscheduled visit within 4 weeks (± 7 days) of titration or restart, in order to monitor potassium levels and renal function. [...]~~

~~All titrations, including the reasons for down-titration, must be documented in the eCRF.~~

New text:

Up- and down-titration of study drug

The investigator is encouraged to up-titrate the dose of study drug at any time once the patient has been on a stable dose for 4 weeks (± 7 days) (e.g. from Visit 2 onwards for patient starting study drug on the lower dose) either at a regular visit or an Up-titration Visit. Up-titration can be performed provided:

[...]

Subjects who started with or were up-titrated to the target dose (20 mg OD) of the study drug but who do not tolerate this dose may be down-titrated at any point during the study, including between-scheduled visits if required for safety reasons. These subjects may be up-titrated again based on the rules provided above. [...]

Subsequent to an up-titration or re-start of study drug after interruption of study drug intake for more than 7 days, the investigator should perform an Up-titration Visit 4 weeks (± 7 days) after titration or restart, in order to monitor potassium levels and renal function (see Table 9-1). If a regular study visit will be scheduled to take place 4 weeks (± 7 days) after up-titration, the monitoring of potassium and renal function is assured and no Up-titration Visit has to be performed in addition. [...]

All titrations, including the reasons for down-titration or for not dispensing the 20 mg dose, must be documented in the eCRF.

15.1.2.9 Section 7.5.2 Unblinding

Old text:

In compliance with applicable regulations, in the event of a SUSAR (see Section 9.6.1.4) related to the blinded treatment, the subject's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators.

New text:

In compliance with applicable regulations, in the event of a SUSAR (see Section 9.6.1.4) related to the blinded treatment, the subject's treatment code will usually be unblinded before reporting to the health authorities and ethic committees.

15.1.2.10 Section 8.1.3 Control of blood pressure**Old text:**

According to international guidelines, the target blood pressure for subjects with T2DM is <140/90 mmHg (39,40). [...]

New text:

According to international guidelines, the recommended target blood pressure for subjects with T2DM and albuminuria, who are at increased risk of CVD and CKD progression, is <130/80 mmHg (39-41). [...]

15.1.2.11 Table 9-1 Study 16244: schedule of activities and evaluations

Old text:

Table 9-1 Study 16244: schedule of activities and evaluations

Visit	Run-in	Screening	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4, 6, 7, 9, etc ^h (every 4 months)	Visit 5, 8, 11, etc (every 12 months)	Up-titration visit ^j (from 4 weeks ± 7 days post-titration)	PD visit	EOS visit ^k	PT visit ^m
Day / Month	4 to 16 weeks pre-screening	≤ 2 weeks	Day 1	Month 1	Month 4	Month 8, 16, 20, 28, etc	Month 12, 24, 36, etc	Unscheduled	After SD is permanently discontinued	After study termination	4 weeks + 5 days after last SD intake

[...]

NOTE:

One month corresponds to 30 days

A time frame of ± 7 days is allowed for Visit 2 (Month 1), and for the ~~unscheduled~~ Up-titration Visit(s).

A time frame of ± 12 days is allowed for all regular visits from Visit 3 (Month 4) onwards.

[...]

^c ~~First morning void urine samples to be collected at the subject's home on 2 consecutive days before scheduled visit and on the day of the visit. At the Run in visit, the 3 samples can be collected the 3 days after the visit.~~

^d Blood samples (for potassium and creatinine) for measurement in the local laboratory. Samples to be taken only if the subject is still taking study drug.

[...]

^f AEs related to study procedures occurring after signing the informed consent as well as all other AEs starting after ~~the first dose of study drug~~ will be documented on the respective eCRF pages.

[...]

^j ~~These procedures also apply for a re-start of study drug after interruption of study drug intake.~~

^m For all the subjects ~~who have taken any study drug~~, the PT Visit has to be performed 4 weeks + 5 days after last intake of study drug.

ⁿ A trough PK sample will be drawn before study drug is administered at the study center by study personnel. The exact time of study drug intake on the day before the visit and on the day of the visit and the exact sampling time will have to be recorded in the eCRF.

^o Study drug will be taken as usual in the morning at home. One PK sample will be drawn during the visit. The exact time of study drug intake and the exact sampling times will have to be recorded in the eCRF.

New text:

Table 9-1 Study 16244: schedule of activities and evaluations

Visit	Run-in	Screening	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4, 6, 7, 9, etc ^h	Visit 5, 8, 11, etc	Up-titration Visit ^j	PD Visit	EOS Visit ^k	PT Visit ^m
Day / Month	4 to 16 weeks pre-screening	≤ 2 weeks	Day 1	Month 1	Month 4	(every 4 months, i.e. Month 8, 16, 20, 28, etc)	(every 12 months, i.e. Month 12, 24, 36, etc)	<u>For up-titration/restart after interruption, and for safety check 4 weeks ± 7 days after any up-titration (see also footnote j)</u>	<u>As soon as possible but within 7 days after SD is permanently discontinued</u>	After study termination	4 weeks + 5 days after last SD intake

[...]

NOTE:

One month corresponds to 30 days
 A time frame of ± 7 days is allowed for Visit 2 (Month 1), and for the Up-titration Visit(s).
 A time frame of ± 12 days is allowed for all regular visits from Visit 3 (Month 4) onwards.

[...]

^c At Visit 1, first morning void urine samples to be preferably collected on three consecutive days at the subject's home within 7 days before scheduled visit and before any intake of study drug. At the other visits the 3 consecutive samples can be collected ± 7 days from the visit date.

^d Blood samples (for potassium and creatinine) for measurement in the local laboratory may be obtained up to 72 hours before a scheduled visit. Samples to be taken only if the subject is still taking study drug.

[...]

^f AEs related to study procedures occurring after signing the informed consent as well as all other AEs starting after randomization will be documented on the respective eCRF pages.

[...]

^j The "Up-titration Visit" should be performed for up-titration (at any time after Visit 2), after restart of SD after an interruption for >7 days, and for safety check 4 weeks ± 7days after any up-titration.

^m For all the subjects still on treatment with study drug at the EOS Visit, the PT Visit has to be performed 4 weeks + 5 days after last intake of study drug.

ⁿ A trough PK sample will be drawn before study drug is administered at the study center by study personnel. The exact time of study drug intake on the day before the visit and on the day of the visit and the exact sampling time will have to be recorded in the eCRF. If the trough sample was not taken at Visit 3 it should be obtained at Visit 4 (see Section 9.5).

^o Study drug will be taken as usual, ideally in the morning at home. One PK sample will be drawn during the visit. The exact time of study drug intake and the exact sampling times will have to be recorded in the eCRF.

15.1.2.12 Table 9-2 Sub-studies of Study 16244: schedule of procedures

Old text:

Table 9-2 Sub-studies of Study 16244: schedule of procedures

Visit	Run-in	Screening	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4, 6, 7, 9, etc (every 4 months)	Visit 5, 8, 11, etc (every 12 months)	Up-titration visit <i>(from 4 weeks ± 7 days post-titration)</i>	PD visit	EOS visit ^k	PT visit ^m
Day / Month	4 to 16 weeks pre-screening	≤ 2 weeks	Day 1	Month 1	Month 4	Month 8, 16, 20, 28 etc	Month 12, 24, 36 etc	Unscheduled	After SD is permanently discontinued	After study termination	4 weeks + 5 days after last SD intake
Informed consent ^a			X								
Echocardiography			X				X		X ^e	X ^e	
Sampling for biomarkers			X		X		X		X ^e	X ^e	
Iohexol clearance ^b			X		X	X ^d			X ^e	X ^e	X

[...]

^c For all the subjects who have taken any study drug, the PT Visit has to be performed 4 weeks + 5 days after last intake of study drug.^d Every other visit (i.e. every 8 months)

[...]

New text:**Table 9-2 Sub-studies of Study 16244: schedule of procedures**

Visit	Run-in	Screening	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4, 6, 7, 9, etc	Visit 5, 8, 11, etc	Up-titration visit	PD visit	EOS visit	PT visit ^c
Day / Month	4 to 16 weeks pre-screening	≤ 2 weeks	Day 1	Month 1	Month 4	(every 4 months, i.e. Month 8, 16, 20, 28, etc)	(every 12 months, i.e. Month 12, 24, 36, etc)	<u>For up-titration/ restart after interruption, and for safety check 4 weeks ± 7 days after any up-titration</u>	<u>As soon as possible but within 7 days after</u> SD is permanently discontinued	After study termination	4 weeks + 5 days after last SD intake
Informed consent ^a			X								
Echocardiography ^f			X				X		X ^e	X ^e	
Sampling for biomarkers			X		X		X		X ^e	X ^e	
Iohexol clearance ^b			X		X	X ^d	X ^d		X ^e	X ^e	X

[...]

^c For all the subjects still on treatment with study drug at the EOS Visit, the PT Visit has to be performed 4 weeks + 5 days after last intake of study drug.^d Every other visit (every 8 months) , i.e. Visit 5, Visit 7, Visit 9, Visit 11, etc.

[...]

^f Time window for the assessment at Visit 1 is -14/+7 days, at other visits +/-30 days. Each time an echocardiography is performed, one blood sample should be drawn to assess the echo biomarkers

15.1.2.13 Section 9.2 Visit description**Old text:**

One month in the study schedule corresponds to 30 days. Although study visits should occur as close as possible to the time points specified in the protocol, a time frame of ± 7 days is allowed for Visit 2 (Month 1), and for the ~~unscheduled~~ Up-titration Visit(s). Starting from Visit 3 (Month 4), a time frame of ± 12 days is allowed for all regular visits.

[...]

New text:

One month in the study schedule corresponds to 30 days. Although study visits should occur as close as possible to the time points specified in the protocol, a time frame of ± 7 days is allowed for Visit 2 (Month 1), and for the Up-titration Visit(s). Starting from Visit 3 (Month 4), a time frame of ± 12 days is allowed for all regular visits.

All procedures and assessments should preferably be conducted **on the day of the visit**; however, if this is not possible for logistical reasons, the following time windows are allowed:

Blood sampling, ECG and recording of vital signs:

- Screening Visit and all visits starting from Visit 2: Visit date ± 7 days
- Run-In, PD and EOS Visit: Visit date ± 3 days

Sub-studies / iohexol and biomarker samples:

- all visits starting from Visit 3: Visit date ± 7 days
- PD and EOS Visit: Visit date ± 3 days

Sub-study / echocardiography (note that each time an echocardiography is performed, one blood sample should be drawn to assess the echo biomarkers):

- at Visit 1: Visit date -14 / +7 days
- Other visits: Visit date ± 30 days

[...]

15.1.2.14 Section 9.2.1 Run-in Visit (4 to 16 weeks prior to the Screening Visit)**Old text:**

- Take samples (hematology, HbA_{1c}, chemistry and urinalysis) for central laboratory evaluations (see Section 9.7.2.1).

New text:

- Take samples (hematology, HbA_{1c}, chemistry, urinalysis) for central laboratory evaluations (see Section 9.7.2.1)
Note: If HbA_{1c} cannot be analyzed by the central laboratory due to technical reasons,

subject can be considered suitable for randomization with one result only (Run-In or Screening).

15.1.2.15 Section 9.2.2 Screening Visit (≤ 2 weeks prior to Visit 1)

Old text:

- Take samples (hematology, HbA_{1c}, chemistry and urinalysis) for central laboratory evaluations (see Section 9.7.2.1).

New text:

- Take samples (hematology, HbA_{1c}, chemistry, urinalysis) for central laboratory evaluations (see Section 9.7.2.1)
Note: If HbA_{1c} cannot be analyzed by the central laboratory due to technical reasons, subject can be considered suitable for randomization with one result only (Run-In or Screening).

15.1.2.16 Section 9.2.3 Visit 1 (randomization; Day 1 and baseline)

Old text:

All measurements on Visit 1 are to be performed before first study drug intake. The following procedures and assessments will be performed at Visit 1:

[...]

- Optional: if the subject had signed informed consent for the sub-study, obtain respective samples for biomarkers (see Section 9.7.8.1.2) and/or iohexol clearance (see Section 9.7.8.1.3), perform echocardiography (see Section 9.7.8.1.1)

New text:

All measurements on Visit 1 are to be performed on the day of the visit before first study drug intake. The following procedures and assessments will be performed at Visit 1:

[...]

- Optional: if the subject had signed informed consent for the sub-study, obtain respective samples for biomarkers (see Section 9.7.8.1.2) and/or iohexol clearance (see Section 9.7.8.1.3), perform echocardiography (see Section 9.7.8.1.1)
Note: Time window for the echocardiography at Visit 1 is -14/+7 days. On the day the echocardiography is performed, a blood sample should also be drawn to assess the echo biomarkers.

15.1.2.17 Section 9.2.5 Visit 3 (Month 4)**Old text:**

- Obtain sample for PK (see Section 9.5)

New text:

- Obtain pre-dose sample for PK (see Section 9.5)

15.1.2.18 Section 9.2.6 Visit 4, 6, 7, 9, etc. (every 4 months; Month 8, 16, 20, 28, etc., excluding yearly visits)**Old text:**

- Take samples (potassium, creatinine) for local safety laboratory evaluations (see Section 9.7.2.2)
- Optional: if the subject had signed informed consent for the sub-study, obtain samples for iohexol clearance (see Section 9.7.8.1.3).
Note: Iohexol clearance should be performed every 8 months only

New text:

- Take samples (potassium, creatinine) for local safety laboratory evaluations (see Section 9.7.2.2)
- **Visit 4 only:** Obtain pre-dose sample for PK if no PK sample was taken at Visit 3 (see Section 9.5)
- Optional: if the subject had signed informed consent for the sub-study, obtain samples for iohexol clearance (see Section 9.7.8.1.3).
Note: Iohexol clearance should be performed every 8 months only (Visit 7, Visit 9, etc.)

15.1.2.19 Section 9.2.7 Visit 5, 8, 11, etc. (every 12 months; Month 12, 24, 36, etc.)**Added text:**

- Optional: if the subject had signed informed consent for the sub-study, obtain samples for iohexol clearance (see Section 9.7.8.1.3).
Note: Iohexol clearance should be performed every 8 months only (Visit 5, Visit 11, etc.)

15.1.2.20 Section 9.2.8 Up-titration Visit (unscheduled; from 4 weeks \pm 7 days post-titration)**Old text:****9.2.8 Up-titration Visit (unscheduled; from 4 weeks \pm 7 days post-titration)**

The following procedures and assessments will be performed at the Up-titration Visit. ~~These procedures also apply for a re-start of study drug after interruption of study drug intake.~~

- Record use of concomitant medication (see Section 8.1)
- Collect unused study drug and perform accountability to assess compliance (see Section 7.6)

New text:**9.2.8 Up-titration Visit (4 weeks \pm 7 days after up-titration or restart of study drug, and for up-titration of study drug)**

The following procedures and assessments will be performed at the Up-titration Visit (see Section 7.4 for details).

- Record use of concomitant medication (see Section 8.1)
- Collect unused study drug and perform accountability to assess compliance, if applicable (see Section 7.6)

15.1.2.21 Section 9.2.9 Premature Discontinuation (PD) Visit**Old text:****9.2.9 Premature Discontinuation (PD) Visit**

The following procedures and assessments will be performed at the PD Visit:

New text:**9.2.9 Premature Discontinuation (PD) Visit (as soon as possible but within 7 days after study drug is permanently discontinued)**

If the PD visit cannot be performed within the timeframe specified, no PD visit is required.

The following procedures and assessments will be performed at the PD Visit:

15.1.2.22 Section 9.2.10 End of study (EOS) visit**Added text:**

- In exceptional circumstances only, if the subject is unable to attend this visit during the given timeframe, the subject (or primary physician / next of kin) should be contacted to obtain survival status.

15.1.2.23 Section 9.2.11 Post-Treatment (PT) Visit**Old text:**

The following procedures and assessments will be performed at the PT Visit:

New text:

For all subjects who are still on treatment with study drug at the end of study visit, the following procedures and assessments will be performed at the PT Visit:

15.1.2.24 Section 9.3.2 Medical history**Old text:**

- Start before ~~first dose of study drug~~

New text:

- Start before randomization

15.1.2.25 Section 9.4 Efficacy**Old text:**

Definitions of individual endpoints (e.g. CV death) will be provided in the Endpoint Manual.

New text:

Kidney failure is defined as either the occurrence of ESRD or an eGFR of less than 15 mL/min/1.73 m², confirmed by a second measurement at the earliest 4 weeks after the initial measurement. ESRD is defined as the initiation of chronic dialysis (haemo- or peritoneal-dialysis) for at least 90 days or renal transplantation. In addition, the eGFR threshold of 15 mL/min/1.73 m² is consistent with the definition of kidney failure from KDIGO (Kidney Disease: Improving Global Outcomes)(3) and was chosen in order to include an objective component to the endpoint because the decision to initiate dialysis therapy or kidney transplantation may be affected by factors other than the eGFR. All other definitions of individual endpoints (e.g. CV death) will be provided in the Endpoint Manual.

15.1.2.26 Section 9.4.3 Other exploratory efficacy variables**Old text:**

- Time to ~~confirmed decrease~~ of eGFR $\geq 40\%$ from baseline sustained over at least 4 weeks
- Time to ~~confirmed decrease~~ of eGFR $\geq 57\%$ from baseline sustained over at least 4 weeks

[...]

- Number of subjects with UACR decrease of ~~more than~~ 30% from baseline at any time post-baseline
- Number of subjects with UACR decrease of ~~more than~~ 50% from baseline at any time post-baseline

New text:

- Time to onset of eGFR decrease of $\geq 40\%$ from baseline sustained over at least 4 weeks
- Time to onset of eGFR decrease of $\geq 57\%$ from baseline sustained over at least 4 weeks

[...]

- Number of subjects with UACR decrease of at least 30% from baseline at any time post-baseline
- Number of subjects with UACR decrease of at least 50% from baseline at any time post-baseline

15.1.2.27 Section 9.5 Pharmacokinetics / pharmacodynamics**Old text:**

At Visit 3 (Month 4), a trough sample for the determination of finerenone plasma concentrations will be drawn before intake of study drug. [...]

The PK bioanalysis will be performed under the responsibility of Bayer HealthCare Bioanalytics Laboratory, Bayer Pharma AG, ^{PPD} [REDACTED], 42096 Wuppertal, Germany.

New text:

At Visit 3 (Month 4), a trough sample for the determination of finerenone plasma concentrations will be drawn before intake of study drug (if the sample could not be obtained at Visit 3, it can be drawn at Visit 4). [...]

PK sampling is not necessary if the study treatment was temporarily interrupted or permanently discontinued at the time of the visit.

The PK bioanalysis will be performed under the responsibility of Bayer Bioanalytics Laboratory, Bayer AG, ^{PPD} [REDACTED], 42096 Wuppertal, Germany. Study responsible bioanalytical personnel will remain unblinded during the study.

15.1.2.28 Section 9.6.1.1 Definitions

Old text:

All diagnoses, symptom(s), sign(s) or finding(s) with a start date ~~after first dose of study drug~~ must be recorded as (S)AEs, except those related to study procedure. [...]

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

[...]

- Conditions that were present before first dose of study drug and for which no symptoms or treatment are present until administration of study drug are recorded as medical history (e.g. seasonal allergy without acute complaints)
- Conditions that started before first dose of study drug and for which symptoms or treatment are present after first dose of study drug, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis)
- Conditions that started or deteriorated after first dose of study drug will be documented as (S)Aes

New text:

All diagnoses, symptom(s), sign(s) or finding(s) with a start date **from randomization onwards** must be recorded as (S)AEs, except those related to study procedure. [...]

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

[...]

- Conditions that were present before randomization and for which no symptoms or treatment are present until randomization are recorded as medical history (e.g. seasonal allergy without acute complaints)
- Conditions that started before randomization and for which symptoms or treatment are present after randomization, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis)
- Conditions that started or deteriorated after randomization will be documented as (S)AEs

15.1.2.29 Section 9.6.1.3 Assessments and documentation of adverse events (AEs)

Old text:

AEs observed, mentioned upon open questioning by a member of the investigator's team or spontaneously reported by the patient will be documented. The observation period for AEs

will start with ~~administration of first dose of study drug~~ and will end with the last visit of follow-up except for AEs related to study procedures; the observation period for the latter AEs will start with signed informed consent and will end with the last visit of follow-up.

New text:

AEs observed, mentioned upon open questioning by a member of the investigator's team or spontaneously reported by the patient will be documented. The observation period for AEs will start with randomization and will end with the last visit of follow-up except for AEs related to study procedures; the observation period for the latter AEs will start with signed informed consent and will end with the last visit of follow-up.

15.1.2.30 Section 9.6.1.4 Reporting of serious adverse events (SAEs)**Old text:**

In compliance with applicable regulations, in the event of a SUSAR, the subject's treatment code will usually be unblinded before reporting to the competent authorities, IECs/IRBs. For reporting to investigators the treatment blind, ~~if possible~~, will be kept.

New text:

In compliance with applicable regulations, in the event of a SUSAR, the subject's treatment code will usually be unblinded before reporting to the competent authorities, IECs/IRBs. For reporting to investigators the treatment blind will be kept.

15.1.2.31 Section 9.7.1 Monitoring of blood potassium**Old text:**

- Blood potassium should be measured ~~within the first month~~ (4 weeks \pm 7 days) after re-starting treatment or dose adjustment, especially after up-titration

New text:

- Blood potassium should be measured 4 weeks (\pm 7 days) after re-starting treatment or dose adjustment, especially after up-titration

15.1.2.32 Section 9.7.2.2 Local laboratory

Old text:

In addition to samples for the central laboratory, other blood **safety samples** will be taken from Visit 1 (Day 1; baseline) onwards (see Table 9-1) for analysis at the local laboratory. These samples ~~will be taken only while the subject is treated with the study drug.~~

The following *clinical chemistry* parameters must be measured for as long as subject is ~~treated with~~ the study drug:

- Blood potassium
- ~~Serum~~ creatinine (eGFR will be calculated automatically in the eCRF using the CKD-EPI formula (36)).

[...]

In women of childbearing potential, a **pregnancy test** will be performed locally, at the Screening Visit and following randomization at yearly visits. [...]

New text:

In addition to samples for the central laboratory, other blood **safety samples** will be taken from Visit 1 (Day 1; baseline) onwards (see Table 9-1) for analysis at the local laboratory. These samples may be obtained up to 72 hours before a scheduled visit.

The following *clinical chemistry* parameters must be measured for as long as subject is not prematurely discontinued from the study drug:

- Blood potassium
- Blood creatinine (eGFR will be calculated automatically in the eCRF using the CKD-EPI formula (36)).

[...]

In women of childbearing potential, a **pregnancy test** will be performed locally, at the Screening Visit and following randomization at yearly visits as long as the subject is not permanently discontinued from the study drug (since more than 7 days). [...]

15.1.2.33 Section 9.7.6 Electrocardiogram (ECG)

Old text:

A standard 12-lead ECG will be performed locally at the Run-In Visit, Screening Visit, at Visit 1 (Day 1; baseline), at the yearly visits, and again at the PD, EOS and PT Visits (see Table 9-1).

New text:

A standard 12-lead ECG will be performed locally at the Run-In Visit, Screening Visit, at Visit 1 (Day 1; baseline), at the yearly visits, and again at the PD, EOS and PT Visits (see

Table 9-1). If there is any clinical indication, unscheduled 12-lead ECGs can be performed at any point during the study.

15.1.2.34 Section 9.7.8.1.1 Echocardiography sub-study

Old text:

In all participating sites, echocardiography will be performed according to a study-specific protocol at Visit 1 (Day 1; baseline), at yearly visits and at the end of the study (either at the PD Visit or the EOS Visit).

Echocardiography examinations, data collection and procedures for central blinded adjudication in the echo core laboratory are given in the Echocardiography Manual. ~~Vital signs (i.e. systolic and diastolic BP and heart rate) should be measured during echocardiography in addition to acquisition of echo data.~~ In addition, each time an echocardiography is performed, one blood sample should be drawn to assess the following biomarkers shown in Table 9-5.

[...] Quantitative measures on all study echocardiographies will be performed by dedicated analysts at the core laboratory, who will be blinded to clinical information and randomized treatment assignment.

New text:

In all participating sites, echocardiography will be performed according to a study-specific protocol at Visit 1 (Day 1; baseline), at yearly visits and at the end of the study (either at the PD Visit or the EOS Visit). If a baseline assessment is not available or analysable, the subject will not continue to undergo echocardiography assessments due to the inability to perform a comparison against baseline.

Echocardiography examinations, data collection and procedures for central blinded adjudication in the echo core laboratory are given in the Echocardiography Manual. In addition, each time an echocardiography is performed, one blood sample should be drawn to assess the following biomarkers shown in Table 9-5.

[...] Quantitative measures on all study echocardiographies will be performed by dedicated analysts at the core laboratory, who will be blinded to clinical information and randomized treatment assignment. The echocardiography results will not be provided to sites.

15.1.2.35 Section 9.7.8.1.3 Iohexol clearance sub-study

Old text:

Iohexol plasma clearance will be assessed at Visit 1 (Day 1, baseline), at Visit 3 (Month 4) and thereafter at every other visit (i.e. every 8 months) until the end of the study (either at the PD Visit or the EOS Visit) plus an additional assessment at the PT Visit (recovery).

New text:

Iohexol plasma clearance will be assessed at Visit 1 (Day 1, baseline), at Visit 3 (Month 4) and thereafter at every other visit (i.e. every 8 months) until the end of the study (either at the PD Visit or the EOS Visit) plus an additional assessment at the PT Visit (recovery). The Iohexol results will not be provided to the sites.

15.1.2.36 Section 10.2 Analysis sets**Old text:**

Per-protocol analysis set (PPS): All subjects of the FAS without ~~major protocol deviations~~
[...]

All subjects will be analyzed according to the planned treatment in FAS (the intent-to-treat or ITT principle). All subjects will be analyzed according to the actual treatment in SAF and PPS.

New text:

Per-protocol analysis set (PPS): All subjects of the FAS without any validity findings
[...]

All subjects will be analyzed according to the planned treatment in FAS (the intent-to-treat or ITT principle). All subjects will be analyzed according to the actual treatment in SAF and PPS. If a subject receives both treatments due to a bottle error, the treatment actually received for the majority of the time in the study will be used in SAF and PPS.

15.1.2.37 Section 10.3.1.1 Disposition**Old text:**

[...] In addition, the number of subjects with ~~major and minor protocol deviations~~ will be presented overall, 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 in total.

New text:

[...] In addition, the number of subjects with important deviations and validity findings will be presented overall, by investigator and country for each treatment group, and in total. The frequencies of each important deviation and validity finding will be presented by treatment group and in total.

15.1.2.38 Section 10.3.1.3 Demography and other baseline characteristics**Old text:**

[...] Other baseline characteristics include baseline UACR, serum potassium, categories for serum potassium (≤ 4.5 mmol and ≥ 4.5 mmol), eGFR (calculated by CKD-EPI formula), serum creatinine, HbA1c, values for vital signs parameters (i.e. systolic blood pressure, diastolic blood pressure and heart rate).

New text:

[...] Other baseline characteristics include baseline UACR, serum potassium, categories for serum potassium (≤ 4.5 mmol and > 4.5 mmol), eGFR (calculated by CKD-EPI formula), serum creatinine, HbA1c, values for vital signs parameters (i.e. systolic blood pressure, diastolic blood pressure and heart rate).

15.1.2.39 Section 10.3.2 Treatment duration, extent of exposure, up-titration status and compliance**Old text:**

Treatment duration (number of months with study drug intake, ~~excluding any gaps~~) will be summarized using descriptive statistics by treatment group and overall. [...]

New text:

Treatment duration (number of months with study drug intake) will be summarized using descriptive statistics by treatment group and overall. [...]

15.1.2.40 Section 10.3.3.5.1 UACR and albuminuria**Old text:**

[...] 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 each visit.

New text:

[...] The albuminuria category changes will only be considered as shifts, if they are accompanied by a UACR change of at least 30% from baseline to each visit.

15.1.2.41 Section 10.4 Determination of sample size

Old text:

This is an event-driven study. A total of ~~1061~~ primary efficacy endpoint events will have 90% power to demonstrate superiority of finerenone to placebo using a logrank test at a two-sided significance level of 3.3333%, assuming a 20% relative risk reduction, i.e. a true hazard ratio of 0.80 (the hazard ratio that will be observed in the study will be different, i.e. closer to 1 due to treatment discontinuations). The study will stop when at least ~~1061~~ primary efficacy endpoints accrue across both treatment arms.

With an assumed ~~study~~ duration of ~~39~~ months (duration of recruitment period: ~~24~~ months, equal recruitment pattern during the accrual period, maximum treatment period of the last subject recruited: ~~15~~ months), the planned total number of subjects to be randomized is estimated to be ~~4701~~ subjects, assuming an annual placebo event rate of 12%, a common annual lost-to-follow-up rate of 0.7% in both treatment groups, an annual finerenone discontinuation rate of 5% and assuming that placebo discontinuation will not change the hazard. [...]

The assumption of the annual placebo event rate of 12% is based on ~~the results from the MICRO-HOPE, RENAAL, IDNT, ALTITUDE and SAVOR-TIMI 53 trials. The latter 2 are more recent studies.~~ Event rates were obtained from the respective studies in the arms where treatment would more closely resemble that in the placebo population of ~~the CV-DKD study who will be on standard of care treatment for DKD.~~ Annual event rates for the composite ~~CV~~ endpoint range from ~~7-10%~~ for ~~older studies~~ and ~~5-6%~~ for ~~more recent studies~~. ~~As the anticipated population of Study 16244 will be more enriched for CV outcomes than ALTITUDE and SAVOR-TIMI 53 with regard to the requirement for CV history or CV risk factors for subjects with high albuminuria, a likely lower mean eGFR and higher median UACR value,~~ the assumed annual placebo event rate of 12% is assumed to be appropriate for this Phase III setting.

New text:

This is an event-driven study. A total of 1068 primary efficacy endpoint events will have a minimum 90% power to demonstrate superiority of finerenone to placebo using a logrank test at a two-sided significance level of 3.3333%, assuming a 20% relative risk reduction, i.e. a true hazard ratio of 0.80 (the hazard ratio that will be observed in the study will be different, i.e. closer to 1 due to treatment discontinuations). The study will stop when at least 1068 primary efficacy endpoints accrue across both treatment arms.

With an assumed treatment duration of 44 months (duration of recruitment period: 33 months, equal recruitment pattern during the accrual period, maximum treatment period of the last subject recruited: 11 months), the planned total number of subjects to be randomized is estimated to be 4690 subjects, assuming an annual placebo event rate of 12%, a common annual lost-to-follow-up rate of 0.7% in both treatment groups, an annual finerenone discontinuation rate of 5% and assuming that placebo discontinuation will not change the hazard. [...]

The assumption of the annual placebo event rate of 12% is based on a recent analysis of the results from the IDNT and RENAAL trials using alternative endpoints defined by smaller declines in eGFR, similar to those proposed in Study 16244. Event rates were obtained from the respective studies in the arms where treatment would more closely resemble that in the placebo population of study 16244 who will be on standard of care treatment for DKD. Annual event rates for the composite renal endpoint range from 11-16% for these studies. The planned population of study 16244 will have some differences compared to IDNT and RENAAL, with a likely lower median UACR value but comparable mean eGFR. The comorbidity of diabetic retinopathy in subjects with high albuminuria may predict a higher rate of renal events. Consequently, the assumed annual placebo event rate of 12% is assumed to be appropriate for this Phase III setting

15.1.2.42 Section 10.5 Planned interim analyses

Old text:

One formal interim analysis is planned when $2/3$ (~~707~~) of the required total number of primary efficacy endpoint events have been observed. Based on the assumptions from sample size determination the interim analysis will take place about ~~30~~ months after ~~study initiation~~.

New text:

One formal interim analysis is planned when $2/3$ of the required total number of primary efficacy endpoint events have been observed. Based on the assumptions from sample size determination the interim analysis will take place about 34 months after start of study treatment. As an event-driven trial, the actual timing of the interim analysis will depend on the observed event rate, the patient recruitment rate, and length of the recruitment period.

15.2 Amendment 4

Amendment 4 is presented using a different approach compared with the previous amendment to this protocol (Amendment 3, Section 15.1). The rationale for this amendment and all affected sections are provided in the “[Protocol amendment summary of changes](#)” section directly before the “Table of contents” in this document. Changes are made directly in the protocol body without annotations. A separate file with tracked changes against the last integrated protocol version is available upon request.

16. Appendices

16.1 Guidance on use of common CYP inhibitors or inducers

Table 16–1 lists the most common medication regarded as potent CYP3A4 inhibitors or inducers.

Table 16–1 Cytochrome P450: list of concomitant medication

Excluded CYP3A4 inducers	Excluded CYP3A4 inhibitors	Allowed CYP3A4 inhibitors
<ul style="list-style-type: none"> ▪ avasimibe ▪ bosentan 	<ul style="list-style-type: none"> ▪ amprenavir ▪ atazanavir and other inhibitors of human HIV protease 	<ul style="list-style-type: none"> ▪ amiodarone ▪ aprepitant
<ul style="list-style-type: none"> ▪ carbamazepin ▪ efavirenz 	<ul style="list-style-type: none"> ▪ boceprevir ▪ clarithromycin 	<ul style="list-style-type: none"> ▪ bicalutamide ▪ chloramphenicol
<ul style="list-style-type: none"> ▪ enzalutamide ▪ etravirine ▪ fosphenytoin ▪ hypericum perforatum / St John's wort 	<ul style="list-style-type: none"> ▪ cobicistat ▪ conivaptan > 20 mg ▪ crizotinib ▪ danoprevir 	<ul style="list-style-type: none"> ▪ conivaptan ≤ 20 mg ▪ fluconazole ≤ 200 mg ▪ imatinib ▪ mifepristone
<ul style="list-style-type: none"> ▪ lersivirine ▪ mephenytoin ▪ methylphenobarbital ▪ mitotane 	<ul style="list-style-type: none"> ▪ darunavir ▪ delavirdine ▪ diltiazem ▪ dronedarone 	<ul style="list-style-type: none"> ▪ norfloxacin ▪ tacrolimus ▪ verapamil ▪ lapatinib
<ul style="list-style-type: none"> ▪ modafinil ▪ nafcillin ▪ nevirapine ▪ oxcarbazepine 	<ul style="list-style-type: none"> ▪ elvitegravir ▪ erythromycin ▪ fluconazole > 200 mg ▪ fosamprenavir 	<ul style="list-style-type: none"> ▪ dasatinib ▪ nilotinib
<ul style="list-style-type: none"> ▪ phenobarbital ▪ phenytoin ▪ primidone ▪ rifabutin 	<ul style="list-style-type: none"> ▪ grapefruit ▪ idealisib ▪ indinavir ▪ itraconazole 	
<ul style="list-style-type: none"> ▪ rifampicin ▪ semagacestat ▪ talviraline ▪ thioridazine 	<ul style="list-style-type: none"> ▪ ketoconazole ▪ lopinavir ▪ miconazole ▪ nefazodone 	
<ul style="list-style-type: none"> ▪ troglitazone ▪ vemurafenib 	<ul style="list-style-type: none"> ▪ nelfinavir ▪ posaconazole ▪ ritonavir ▪ saquinavir 	
	<ul style="list-style-type: none"> ▪ telaprevir ▪ telithromycin ▪ tipranavir ▪ troleandomycin 	
	<ul style="list-style-type: none"> ▪ voriconazole 	

16.2 Calculating the Child Pugh score

The severity of liver disease ([Table 16–2](#)) will determine the Child Pugh score ([Table 16–3](#)).

Table 16–2 Grading of severity of liver disease (adapted from (54))

Factor	+1	+2	+3
Bilirubin (mg/dL)	< 2	2 – 3	> 3
Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
International Normalized Ratio	< 1.7	1.7 – 2.3	> 2.3
Ascites	None	Mild	Moderate / Severe
Encephalopathy	None	Grade I - II	Grade III – IV

Table 16–3 Classification using the added score from [Table 16–2](#) (adapted from (54))

Child-Pugh Class	A	B	C
Points	5 – 6	7 – 9	10 – 15

16.3 HR-QoL questionnaires

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.

Two forms of the KDQOL exist: the KDQOL-SF and the KDQOL-36. Both were developed 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 (55). 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 (56). 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 (57). 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 shown in Table 16–4.

The **EQ-5D-5L** was introduced in 2005. The EQ-5D-5L still consists of 2 pages: the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS).

The descriptive system comprises the same 5 dimensions as the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

Table 16–4 KDQOL-36: grouping of items and description

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