Clinical Trial Protocol

	Document Number:	**c35391746-03**
EudraCT No.	Not applicable	
BI Trial No.	1366-0026	
BI Investigational Medicinal Product	Not applicable	
Title	Evaluation of homogeneity between eGFR slopes derived from retrospective clinical practice data and eGFR slopes derived from prospectively collected, protocol-driven data	
Lay Title	A study to examine past estimated Glomerular Filtration Rate (eGFR) slope as a risk marker for rapid kidney function decline in people with chronic kidney disease	
Clinical Phase	Phase II: "Low-interventional" study (collection of serum/capillary creatinine values) in parallel to phase II dose-finding clinical program for BI 685509 (sGC activator) and BI 690517 (AS-inhibitor)	
Clinical Trial Leader	[redacted] Tel.: [redacted]	
Coordinating Investigators	[redacted] Tel: [redacted] [redacted] Tel.: [redacted]	
Version and Date	**Version: 3.0**	**Date: 25 Apr 2022**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	06 Apr 2021
Revision date	25 Apr 2022
BI trial number	1366-0026
Title of trial	Evaluation of homogeneity between eGFR slopes derived from retrospective clinical practice data and eGFR slopes derived from prospectively collected, protocol-driven data.
Coordinating Investigators	[redacted] Tel: [redacted] [redacted] Tel.: [redacted]
Trial sites	Multi-centre trial
Clinical phase	II
Trial rationale	The trial intends to establish the potential role of eGFR slope as a biomarker to determine rapid progression of chronic kidney disease. The eGFR slopes might subsequently be used to enrol patients at high renal risk into phase III trials of BI 685509/BI 690517.
Trial objectives	Main objective: The aim of this trial is to examine homogeneity between eGFR slopes derived via retrospective and prospective eGFR values. [redacted]

	[redacted]
Trial endpoints/outcomes	Primary Outcome: Homogeneity (eGFR slope shift table) between eGFR slopes derived from retrospective and prospective eGFR values. Secondary Outcome: Not applicable.
Trial design	Non-randomized, low-intervention design with no trial drug administration except background therapy. The trial will consist of a retrospective phase of up to 5.5 years prior to Screening visit (i.e. visit 1), and a prospective phase of 48 weeks duration.
Total number of patients enrolled	600 Patients (400 fast progressors with an eGFR slope ≥3ml/min/1.73m²/year and 200 slow progressors with an eGFR slope between 1 and 3ml/min/1.73m²/year)
Number of patients on each treatment	Not applicable.
Diagnosis	Chronic Kidney Disease (CKD)
Main in- and exclusion criteria	Inclusion criteria: • Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial. • Patients with available medical records for data extraction. • Male or female patients aged ≥ 18 years at time of consent. • Clinical diagnosis of CKD. • Retrospective eGFR decline of at least1 ml/min/1.73m²/year. • eGFR 20 – 90 ml/min/1.73m² at Visit 1 calculated from serum creatinine measured by a central laboratory. • Optimal and stable background treatment according to locally applicable guidelines. • At least 4 serum creatinine values in the retrospective phase: - The most recent creatinine value not more than 6 months prior to Visit 1 (Screening Visit). - The most recent and oldest serum creatinine values should be no less than 1 year apart and no greater than 5 years apart - There should be no gap of creatinine values of 2 years or longer. Exclusion criteria: • Changes in CKD or other key background treatments (including dose changes) known to impact eGFR values, over the past 4 to 8 weeks (depending on class of drugs). • Autosomal Dominant Polycystic Kidney Disease (ADPKD), uncontrolled lupus nephritis, in the opinion of the investigator.

	• Any iv immunosuppressive therapy in the last 3 months prior to Visit 1 or treatment with >45 mg prednisolone (or equivalent). • Acute kidney injury (AKI) according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition[2] in the 30 days prior to Visit 1 until the start of trial assessments. • Planned start of chronic renal replacement therapy during the trial or end stage renal disease (i.e < 15 ml/min at 2 measurements 30 days apart) before start of trial. • Medical history of cancer or treatment for cancer in the last two years prior to Visit 1 (except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix, and prostatic cancer of low grade [T1 or T2]). • Major surgery (investigator's judgement) planned during the trial. • Currently enrolled in an investigational device or drug trial, i.e., less than 30 days before Visit 1 since ending another investigational device or drug trial(s) or receiving other investigational treatment(s). • Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial subject or unlikely to complete the trial. • Any medical condition or clinically relevant laboratory value, that will put the patient at increased risk.
Test product	N/AP
Dose	N/AP
mode of administration	N/AP
Comparator product	N/AP
dose	N/AP
mode of administration	N/AP
Duration of treatment	N/AP
Statistical methods	Retrospective and prospective slopes will be derived using a linear random slope model. The prospective eGFR slope for each patient will be derived using eGFR values in the prospective phase as the dependent variable and time in the prospective phase as the continuous independent variable with random intercept and random slope. The trial targets to be included in the linear random slope model and the most appropriate data to be used for this analysis will be determined based on residual variance. Details will be found in the Trial Statistical Analysis Plan (TSAP). The retrospective eGFR slope for each patient will be derived similarly using the data in the retrospective phase. Summary

	statistics (mean, SD, min, median, max) will be provided for the overall population and by patient population (DKD vs. ndCKD). The residual variance (i.e. mean squared error) of the slope estimates will be estimated using the linear random slope model, for both the retro- and prospective slopes, to assess the reliability of slope estimation. Homogeneity will be primarily evaluated via a shift analysis: - A shift table of patients with categories of eGFR slopes of 1 to < 3 (slow progression) and ≥ 3 mL/min/1.73m^2/year (fast progression), in each of the retrospective and prospective phases, will be provided. The shift analysis will be considered as the primary analysis to evaluate homogeneity. Further analyses include: - A categorical analysis of the number and proportion of patients with eGFR slopes >1, > 3 and >5 mL/min/1.73m^2/year will be provided, for both retro- and prospective phases, via tabular and graphical presentations. - Histograms will be plotted for retro- and prospective slopes to evaluate their distributions graphically. - The Pearson's linear correlation coefficient between retro- and prospective slopes will be derived for overall population and by patient population. - A descriptive summary of the proportion of "shifters" and non-"shifters". A "shifter" is defined as a patient whose: Retrospective relative to prospective slope category shifts from slow to fast or fast to slow, respectively and Percent change from retrospective to prospective phase slope exceeds 20%. - McNemar's test will also be conducted to further assess the homogeneity between retro- and prospective slopes for categories of < 3 and ≥ 3 mL/min/1.73m^2. In addition to the above analyses, - A descriptive summary of the percent change in retrospective to prospective slopes will be provided.

	Furthermore, the association between retrospective and prospective slopes will be assessed as a continuous endpoint, the details of which will be provided in the TSAP.
	[redacted]
	Further details of analyses will be provided in the TSAP.

FLOW CHART

Procedures should be performed in the order they appear in this flowchart.

Trial Periods	**Screening**	**Prospective Period**												
Sampling at Home and Clinic visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Weeks	Screening[1] -2 to 0	**Baseline 1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48/ EOT**
Days	-14 to 0	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**
Permitted visit window (days)	-	0	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**
Informed[2] consent	X													
Demographics medical history including historical creatinine data, baseline conditions.	X	X												
Check of in-/exclusion criteria	X													
Background[3] therapies (e.g: ACEis, ARBs and SGLT2)	X	X			X			X			X			X
Height	X													
Weight	X													
Physical examination	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Optional biobanking sampling (serum, plasma, urine)		X												
First Morning Void Urine[4]		X												X

Trial Periods	**Screening**	**Prospective Period**												
Sampling at Home and Clinic visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Weeks	Screening[1] -2 to 0	**Baseline 1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48/ EOT**
Days	-14 to 0	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**
Permitted visit window (days)	-	0	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**
Train patient on Urine and Mitra® sampling[5]	X													
Provide Home sampling kits (for Urine and Mitra® Cartridges)		X			X			X			X			
Mitra® micro sampling at home[6]			X	X		X	X		X	X		X	X	
Mitra® micro sampling at clinic visits		X			X			X			X			X
Provide training on smartphone/ tablet application including provision of app /device[7]		X			X			X			X			
Mitra® micro sampling at Home paper diary handout *(where electronic capture is not used)*		X			X			X			X			
Review of home Mitra® sampling and Urine via application or paper diary (to be collected)					X			X			X			X
eGFR (central laboratory)[8]	X	X			X			X			X			X
Safety laboratory		X			X			X			X			X

Trial Periods	**Screening**	**Prospective Period**												
Sampling at Home and Clinic visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Weeks	Screening[1] -2 to 0	**Baseline 1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48/ EOT**
Days	-14 to 0	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**
Permitted visit window (days)	-	0	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**
All AEs/SAEs	X	X			X			X			X			X
Completion of patient participation														X

1. Screening assessments may be conducted over more than one day. The baseline may start as soon as all screening procedures have been performed and laboratory results have been received and reviewed. Therefore the 14 days prior to enrollment that are indicated in the flow chart may be less. The timepoint of baseline (Visit 2) defines Day 1.

- Screening procedures may be repeated if the patient is not eligible due to a transient medical condition (e.g. elevation of certain lab parameters due to an acute infection).
- If the patient currently does not fulfil all inclusion/exclusion criteria but may in the opinion of the investigator fit the criteria later, the patient can be re-screened once if screening into this trial is still open. Re-screening examinations will only be performed after a written informed consent has been obtained again from the patient and is to be documented in relevant source document.
- If screening is not completed within 14 days, the patient will be a screen failure. If appropriate the patient may be re-screened (see above).
- Once screening assessments have been completed, a member of the trial team will contact the patient by phone to provide confirmation about eligibility.

2. Informed consent does not need to be obtained on the day of the screening visit but must be obtained before the first screening assessment. The consent discussion should include showing the patient the home sampling kits and explaining the procedures involved in the trial.

3. Any changes to the background therapies that could have an impact on eGFR slopes during trial must be captured in the relevant section of eCRF/source doucments.

4. First Morning Void Urine for UACR estimation. Patients are advised to collect their urine 2 times for each visit planned in the protocol (total 4 urine samples). i.e. a day before baseline visit and on baseline visit (Visit 2/Day 1) and on day before EOT visit and on EOT visit.

5. Training on how to use the Mitra® microsampling device and how to do the FMV urine sampling will be provided to the patient at the screening visit. This will include instructions regarding sample shipments / what to bring in for clinic visits.

6. At home (using Mitra® Device) blood samples will be collected on a **biweekly basis for the first 12 weeks** and thereafter on a 4-weekly basis until **Week 48**. If site visit coincides, Mitra® device sample will be collected in combination with venous sample on site. When Mitra® microsampling is performed at home, Mitra® cartridges can be returned by e.g. post or courier (if permitted by country-specific regulations and other local guidance). If shipment is not allowed locally, the patient should return Mitra® cartridges to the investigational site.

7. If the patient chooses to, they will be able to download the app to their phone at visit 1 or 2. The app will also be used for the video calls and can be used for patient reminders. If this is not possible, alternatively a paper diary will be handed out to the patient.

8. eGFR at clinic visits will be determined from serum creatinine analysed by the central laboratory and also from Mitra® micro-sampling. To confirm eligibility the eGFR at screening will be used.

TABLE OF CONTENTS

ABBREVIATIONS

ACEi	Angiotensin Converting Enzyme inhibitor
ADPKD	Autosomal Dominant Polycystic Kidney Disease
AE	Adverse Event
AKI	Acute Kidney Injury
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
cGMP	Cyclic Guanosine Monophosphate
CKD	Chronic Kidney Disease
CKD-EPI	CKD Epidemiology Collaboration (formula)
cGMP	Cyclic Guanosine Monophosphate
COVID-19	Corona Virus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CT Leader	Clinical Trial Leader
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DBP	Diastolic Blood Pressure
DKD	Diabetic Kidney Disease
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
ESRD	End Stage Renal Disease
EU	European Union

EudraCT	European Clinical Trials Database
FC	Flow Chart
FDA	Food and Drug Administration
FMV	First Morning Void
FUp	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
K-EDTA	Potassium ethylenediaminetetraacetic acid
KDIGO	Kidney Disease: Improving Global Outcomes
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Activities
N/AP	Not applicable
NO	Nitric Oxide
Non DKD	Non Diabetic Kidney Disease
NSAID	Non-steroidal anti-inflammatory drug(s)
PCR	Proteine Creatinine Ratio
PD	Pharmacodynamics
PV	Pharmacovigilance
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic Blood Pressure
sGC	Soluble Guanylate Cyclase
SGLT2	Sodium-Glucose Co-Transporter-2
SGLT2i	SGLT2 Inhibitor
SOP	Standard Operating Procedure
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
UACR	Urine Albumin Creatinine Ratio

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Chronic Kidney Disease (CKD) is frequently characterized by poor clinical outcomes and high healthcare utilization costs, and its increasing worldwide prevalence represents a significant public health challenge[R17-2620]. Although the vast majority of patients with CKD have early-stage disease,[R13-4387, R10-1168, R21-0998] patients with late-stage disease and especially those with End-Stage Renal Disease (ESRD), suffer from an especially high burden of comorbid conditions, have extremely poor outcomes, and consume a disproportionate amount of health care resources [P21-03068] It is, thus, important to explore additional interventions to slow kidney disease progression/transition to ESRD and appropriately consider patients who are most prone to experience a progressive disease course.

At present, only a limited number of pharmaceutical therapeutic options are available to delay renal decline in CKD patients. ACE inhibitors (ACEis) and angiotensin receptor blockers (ARBs) have demonstrated efficacy in this regard. However, the relative risk reduction in the respective trials is only moderate (16% in RENAAL and 19% in IDNT for the composite primary endpoint of all-cause death, ESRD and doubling of serum creatinine). The SGLT2 inhibitor canagliflozin, has shown a relative risk reduction of 30% for the composite endpoint of doubling of serum creatinine, ESRD or renal/CV death on top of Standard of Care (SoC).The recently published results from DAPA-CKD confirm and expand the CREDENCE data showing a 39% relative risk reduction for the primary composite endpoint of sustained decline in eGFR of at least 50%, end stage renal disease and CV/renal death. Notably, the results in DAPA-CKD are very similar for the diabetic and non-diabetic sub-populations of the study. In summary, data from the canagliflozin and dapagliflozin programs are largely consistent and render it likely that SGLT2 inhibitors will become an essential pillar for the treatment of renal patients in the future.

Despite the advances summarized in the paragraph above, the residual renal and cardiovascular risk for patients remains unacceptably high, warranting continued efforts to provide further treatment options. Unfortunately, in has been challenging in the past to accurately identify the patients at considerably increased risk of suffering renal function decline and subsequent renal outcome events. One of the traditional ways to determine risk in this population has been through the measurement of single/few eGFR as well as UACR values and use this approach to include patients into the respective clinical outcome trials. Although this approach is relatively easy to implement and does definitely identify a certain percentage of those at highest risk, it is far from optimal. There is a considerable percentage of patients who display increased UACR / decreased eGFR values but will ultimately not decline or only decline very slowly. The reverse does also occur, i.e. patients with UACR / eGFR wirhin an acceptable range that subsequently deline precipitously and thus get exposed to a significantly elevated risk of renal events. Hence, it would benefit patients and clinicians to have an improved method of identifying high-risk patients.

One approach to potentially better identify these patients at increased risk could be the use of eGFR slopes, i.e. considering not only single/few eGFR values but calculating an eGFR slope

that would represent the development of eGFR over time and thus be a more realistic reflection of renal function over a longer time frame.

This study is intended to investigate the usefulness of eGFR slopes derived from retrospective routine clinical practice data, compare those retrospective slopes with those generated in a prospective fashion and successively identify rapidly progressing CKD patients. It has been devised as a supportive study to the currently ongoing /planned phase II programs (BI 685509, BI 690517 etc.) to support inclusion of high-risk renal patients into future phase III trials.

1.2 DRUG PROFILE

Not applicable.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Many studies have confirmed the importance of eGFR and albuminuria as measures of progressive renal function loss. However, baseline eGFR and albuminuria do not correlate with progression for all individuals. A large proportion of individuals do not progress despite their high albuminuria and low eGFR values, and many individuals progress without having high levels of albuminuria and/or low eGFR. Including non-progressive patients in clinical trials results in the need for longer and larger clinical trials. Given that fast progressing CKD disease is associated with worse clinical outcomes, it is critical for clinicians to appropriately determine a progressing patient. While many other factors influence the rate of progression, including age,[R21-1003, R21-1004] comorbid conditions, such as diabetes mellitus or hypertension,[R21-1004, R15-5162, R21-0999] race-ethnicity,[R21-1000] and genetic mutations[R21-1001], these factors do not completely account for the observed variability in kidney disease progression [R21-1002].

Current clinical practice guidelines consider assessing the future risk of kidney disease progression from the past slope of eGFR over time [R13-4387]. Despite the general acceptance of this practice, only a limited number of studies have evaluated past eGFR decline as a predictor of ESRD after taking into account the current level of eGFR [R21-1138]. In clinical practice, both the level of creatinine at the point of assessment and its past eGFR trajectory over time are often available, but the relative contribution of each to the risk of subsequent ESRD is not clear. As an additional aspect, other factors, such as diet, medications, background diseases and different laboratories might also affect past eGFR values and therefore slopes and must not be disregarded in this context.

During a Scientific Advice Meeting in 2019 with the European Medicines Agency (EMA), the use of eGFR slopes was discussed as a potential future endpoint in clinical trials as well as a potential risk marker for renal events, the latter to a lesser degree though.
During this meeting and based on subsequent additional written feedback, EMA generally supported this approach but advised further evaluation of retrospective eGFR slopes and how this may be based on data available from clinical patient records. To further inform the use of retrospective eGFR measures in the establishment of eGFR slopes, and subsequent selection

of high renal risk patients, BI intends to conduct a study to examine retrospective eGFR slopes and generate additional prospective data among the same population.
This study will provide information on the availability, frequency and continuity of retrospective eGFR and UACR/PCR data in patient medical records, as collected via routine clinical practice. The study will also compare eGFR slopes derived via retrospective serum creatinine values collected up to 5.5 years prior to visit 1 in routine clinical practice, with prospectively generated eGFR values and resulting slopes. In addition, methodological aspects of slope establishment, such as varying baseline eGFR and UACR/PCR levels, length of baseline period, [redacted] will be explored.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking section 5.5. If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

This study will provide additional information on how high-risk renal disease patients might be more accurately identified for future trials. It will contribute to providing the participating patients with a better assessment of their own risk for progression and potentially respective treatment considerations. Patients may also benefit from more frequent clinical monitoring as a result of being part of the study. In conclusion, the benefit/risk assessment is considered acceptable.

1.4.2 Risks

During this study, 1 venous blood sample for serum creatinine (5 mL) will be collected at screening, and 3 venous blood samples for serum creatinine (5 mL), chemistry (5 mL), and hematology (2 mL) will be collected during site visits at baseline, and Week 12, Week 24, Week 36 and Week 48 (end of study). 2 tubes (5 mL and 2 mL) are used for assessing the safety parameters (chemistry and hematology) and 1 tube (5 mL) for serum creatinine. No office/hospital visits beyond those will be required. Additional blood collection by finger prick (2 x 10 microL per time point) will be conducted on a biweekly basis for the first 12 weeks and every 4 weeks thereafter at home (until Week 48) using the Mitra® micro sampling device*. There is minimal risk posed to patients with the use of the Mitra® device sampling. Most CKD patients are expected to provide venous blood samples for eGFR assessment at least every 3 – 6 months as a part of clinical practice. Hence, the blood collection planned in this study will be associated with a minimal risk for patients beyond what they would be exposed to in routine clinical practice.

* The Mitra® Microsampling Device is CE-certified under the European Directive on In Vitro Diagnostic Medical Devices (Council Directive 98/79/EC) and was registered at the

U.S. Food and Drug Administration (FDA) as a Class 1 Medical Device. A method for the measurement of creatinine in human capillary blood using LC-MS/MS (including extraction of the sample from the inert porous plastic tip of the Mitra® device and stability for up to three months) has been established following the 2018 FDA Guidance on Bioanalytical Method Validation.

Sampling with the Mitra® Microsampling Device is straightforward: after performing a finger prick with the supplied lancet the device is placed adjacent to the forming blood drop and approximately 10 microL of blood is absorbed by the porous tip of the device. This is done for both tips in the cartridge, which is then closed and sent away for analysis. The procedure can be easily performed by the patient or a caregiver.

1.4.3 Discussion

No study drug administration is involved in the prospective phase of this study. However, all patients will be on stable background standard of care therapy according to locally applicable guidelines. Moreover, the site visit schedule approximates routine practice for progressive CKD patients, and Mitra® sampling risks are very low. Patients may also benefit from more frequent clinical monitoring as a result of being part of the study. It will provide the participating patients with a better assessment of their own risk for progression and potentially respective treatment considerations.

Overall, in the context of the unmet medical need in fast progressing CKD patients, careful monitoring throughout the trial and the limited risk associated with venus/capillary blood collection the benefit-risk evaluation of the study is considered favourable for the intended trial population.

2. TRIAL OBJECTIVES AND OUTCOMES

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY OUTCOMES

2.1.1 Main objective

The aim of this trial is to examine homogeneity between eGFR slopes derived via retrospective and prospective eGFR values.

2.1.2 Primary outcome

Homogeneity (eGFR slope shift table) between eGFR slopes derived from retrospective and prospective eGFR values.

2.1.3 Secondary outcome

Not applicable.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This trial is a multicentre, non-randomized, low-intervention trial that does not involve administration of study drug and includes both a retrospective and prospective phase in patients with chronic kidney disease who are on stable background treatment according to respective local guidelines.

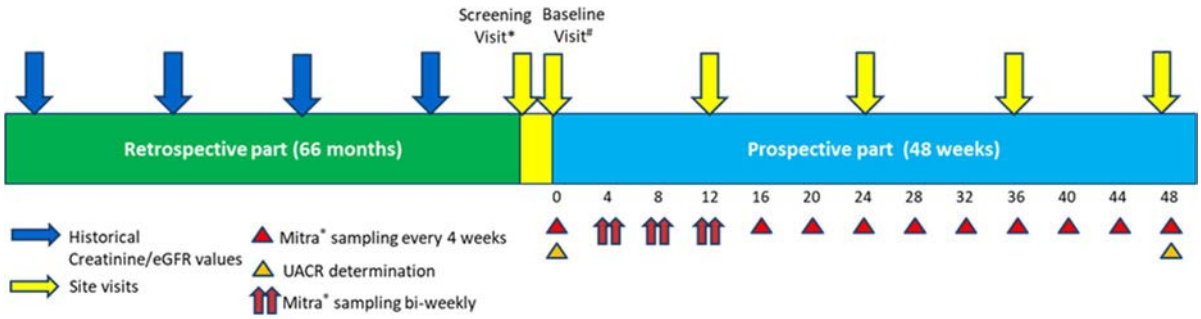
The trial targets to enrol at least 33% (up to 60%) of non DKD patients; the remaining patients will consist of DKD patients.

In this study, eGFR slopes will be calculated from historically available creatinine values (retrospective phase of study) that were collected during routine clinical care of the patients prior to enrolment in this study. In the prospective phase of the study, creatinine values will be systematically collected at predefined time points. The eGFR slopes will then be calculated from the retrospective and prospective phases.

A schematic illustration of the trial design is presented in Figure 3.1: 1.

 # Retrospective phase: At least 4 Serum Creatinine measurements at minimum. However, it is desirable to have as many as available.

Prospective phase: 48 weeks duration.
Site visits – Blood sample collection at baseline and every 12 weeks (i.e. Week 12, Week 24, Week 36, Week 48). Urine sample collection (for UACR determination) at baseline and Week 48. At home (using Mitra® Device) blood samples will be collected on a biweekly basis for the first 12 weeks and thereafter on a 4-weekly basis until Week 48. If site visit coincides, Mitra® device sample will be collected in combination with venous sample on site.



* Screening period of up to 2 weeks between retrospective and prospective phases.
# Baseline visit is considered as Visit 2/Day1 of prospective phase

Figure 3.1: 1 Trial design

Patients will be screened in the trial once they have signed the informed consent. They will undergo a screening period of up to 2 weeks from the time of informed consent. All available historical eGFR values, UACR/PCR within the 5.5 years prior to screening Visit 1 will be

collected for each patient. Patients who successfully complete the screening and meet the inclusion / exclusion criteria, including the availability of requisite historical eGFR data, will qualify for enrollment into the 48 weeks prospective phase of the study (see Figure 3.1: 1).

Retrospective phase:

To be documented in the CRF:

- All available serum creatinine values (at least 4 serum creatinine values should be available for a patient with the most recent creatinine value not more than 6 months prior to Visit 1 (Screening Visit). The most recent and oldest serum creatinine values should be no less than 1 year apart and no greater than 5 years apart and there should be no gap of creatinine values of 2 years or longer.
- All available UACR values or respective values to determine UACR.
- All available PCR values or respective values to determine PCR.
- Medications that could potentially have an impact on calculation of slopes during the retrospective phase e.g. ACEi/ARB.
- Medical history as outlined in the CRF.

Prospective Phase:

The serum eGFR and UACR value obtained at the Baseline Visit will be used as the first eGFR and UACR value. The prospective eGFR slope (i.e. the individual rate of eGFR decline) will be established over 48 weeks, during which time the patient will be on background optimal standard of care. Patients need to attend the investigational site in person six times during the study (at Screening Visit, baseline visit, 12 weeks, 24 weeks, 36 weeks and 48 weeks visit) for venous blood samples, and collection of data with regards to the patients' current treatments and other medications. In order to minimize the number of visits required, all other eGFR values will be calculated from the finger prick blood samples taken at home using the Mitra® micro sampling device during the prospective phase of the study. Mitra® samples taken at home between visits will be shipped by the patient to the central laboratory or the site, if allowed by local regulations. Where this is not possible alternative arrangements will be made, e.g. samples taken to the investigational site. Samples taken directly prior to a physical visit will be taken to the site to be processed by the site staff. To allow a comparison of the patient kits with conventional collection methods, sites will use the Mitra® kits to process samples in parallel to the collection of a certain volume of blood. Both serum and Mitra® measurements will form the basis for the eGFR slope calculation.

Patients will be advised to collect 2 UACR samples for each visit planned in the protocol (total 2 visits and 4 urine samples). i.e a day before baseline visit and on baseline visit (Visit 2/Day 1) and also on day before EOT visit and on EOT visit. The patient will be equipped with urine collection containers to sample urine from their First Morning Voids in collection container (latter only for visit at which urine collection is scheduled, i.e. baseline and Week 48).
Throughout the study duration, AEs as defined in section 5.2.6.2 and changes to background medication will be collected, documented and reported. Patients who receive ARBs, ACEis and SGLT2 inhibitors will be required to maintain stable treatment during the trial duration.

At the end of the 48 weeks prospective phase period, or at the time that a patient is permanently discontinued, patients will have an EOT visit. Database lock will occur after the last patients have completed their final visit.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

Not applicable.

3.3 SELECTION OF TRIAL POPULATION

The study population will consist of both diabetic chronic kidney disease (DKD) as well as non-diabetic chronic kidney disease (ndCKD). The proportion of ndCKD population required to be enrolled in the study is in the range of 33%-60%. The selected Chronic Kidney Disease population will only include approximately 33% of patients with eGFR decline at least 1 ml/min/1.73m²/year and approximately 66% of rapid progressors with eGFR decline of at least 3ml/min/1.73m²/year or 8% eGFR decline/year determined via retrospective eGFR assessments.

3.3.1 Main diagnosis for trial entry

Both diabetic chronic kidney disease as well as non-diabetic chronic kidney disease patients will be screened.

3.3.2 Inclusion criteria

1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
2. Patients with available medical records for data abstraction to meet the objectives of the study.
3. Male or female patients aged ≥ 18 years at time of consent.
4. Body Mass Index (BMI) ≥ 18.5 and < 50 kg/m^2 at Visit 1.
5. Clinical diagnosis of CKD.
6. eGFR decline of at least 1ml/min/1.73m²/year based on historical data from (electronic) medical records.
7. eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) 20 – 90 ml/min/1.73m² at Visit 1 calculated from serum creatinine measured by a central laboratory.
8. Patients are expected to be on optimal and stable background treatment (according to local therapy guidelines).
9. At least 4 serum creatinine values in the retrospective phase:
   - The most recent creatinine value not more than 6 months prior to Visit 1 (Screening Visit).
   - The most recent and oldest serum creatinine values should be no less than 1 year apart and no greater than 5 years apart.
   - There should be no gap of creatinine values of 2 years or longer.

3.3.3 Exclusion criteria

1. Changes in CKD or other key background treatments (including dose changes) known to impact eGFR values, over the past 4 weeks for ACEis and ARBs and 8 weeks for SGLT2 inhibitors prior to Screening.
2. Autosomal Dominant Polycystic Kidney Disease (ADPKD), uncontrolled lupus nephritis, in the opinion of investigators.
3. Any iv immune suppression therapy within the last 3 months prior to Visit 1 or anyone currently on >45 mg prednisolone (or equivalent).
4. Acute kidney injury (AKI) according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition in the 30 days prior to Visit 1 until the start of trial assessments.
5. Planned start of chronic renal replacement therapy during the trial or end stage renal disease (i.e < 15 ml/min at 2 measurements 30 days apart) before start of trial assessments.
6. Medical history of cancer or treatment for cancer in the last two years prior to Visit 1 (except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix, and prostatic cancer of low grade [T1 or T2]).
7. Major surgery (investigator's judgement) planned during the trial.
8. Currently enrolled in an investigational device or drug trial, i.e., less than 30 days before Visit 1 since ending an investigational device or drug trial(s) or receiving investigational treatment(s).
9. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial subject or unlikely to complete the trial.
10. Any medical condition or clinically relevant laboratory value, that will put the patient at increased risk.

3.3.4 Withdrawal of patients from assessments

Patients may discontinue assessments or withdraw consent to trial participation as a whole ("withdrawal of consent"); please see sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the patients in the trial, if possible. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial assessments and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue the trial or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see sections 5.2.6.1 and 5.2.6.2).

3.3.4.1 Discontinuation of trial

An individual patient will discontinue trial if:

- The patient wants to discontinue trial assessement, without the need to justify the decision.

- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that is not permitted, see section 4.2.2. However, if the patient needs to modify a dose, where a stable dose is permitted only, this will not automatically require a discontinuation. In this case the sponsor should be consulted.
- The patient progresses to end stage renal disease and needs to obtain renal replacement therapy.
- The patient experiences a severe infection, e.g. with SARS-CoV-2, as determined by the investigator.
- The patient can no longer provide trial assessments for any other medical reasons such as surgery, serious adverse events with other concomitant medications, adverse events, or other diseases.
- The patient has missed trial assessments for at least 2 consecutive site visits or has not given the trial assessments at a total of 60 days during the trial. In case of a temporary reason, trial assessment should be restarted if medically justified.

Please see section 6.2.5 for details of the procedures to be performed if trial assessments are discontinued.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial discontinuation and withdrawal of consent to trial participation.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

- Failure to meet expected enrolment goals overall or at a particular trial site.
- New trial data or information invalidating the earlier positive benefit-risk-assessment, please see section 1.4.
- Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

No trial medication will be provided or administered by Boehringer Ingelheim.

4.1.1 Identity of the Investigational Medicinal Products

Not applicable.

4.1.2 Selection of doses in the trial and dose modifications

Not applicable.

4.1.3 Method of assigning patients to treatment groups

Not applicable.

4.1.4 Drug assignment and administration of doses for each patient

Not applicable

4.1.5 Blinding and procedures for unblinding

Not applicable

4.1.6 Packaging, labelling, and re-supply

Not applicable

4.1.7 Storage conditions

Not applicable

4.1.8 Drug accountability

Not applicable

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

No other treatments and standard of care medications are provided as part of this clinical trial Also, there are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Patients should keep their existing therapies as stable as possible, particularly their therapy with ACEi/ARB or SGLT2 inhibitors from screening at Visit 1 until the End of trial visit. It is recommended to avoid medication exposures that might impact eGFR slopes in a clinically relevant manner. New therapies should only be initiated if necessary. Should an investigator anticipate starting a patient on ACEi/ARB or SGLT2 inhibitor over the subsequent 48 weeks after enrolment, the investigator is to judge with caution if the respective patient should be included in the trial since initiating the patient on ACEi/ARB or SGLT2i could distort the results of this study. Any specific usage of such relevant drugs must be reported in relevant source documentation and filed in the investigator site file. Medications that could potentially have an impact on calculation of slopes during the retrospective phase e.g. ACEi/ARB, should be documented in the CRF.

4.2.2.1.1 Restrictions on diet and lifestyle

There are no restrictions on lifestyle. However, any drastic changes of diet and lifestyle during the trial should be avoided.

4.2.2.2 Contraception requirements

Not applicable as there is no trial drug involved.

4.3 TREATMENT COMPLIANCE

N/AP

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

No efficacy assessments are planned in this trial.

5.1.1 Creatinine

Serum creatinine:
Samples for the determination of serum creatinine will be collected at the time points indicated in the flow chart and analysed at a central laboratory using the enzymatic method.

Creatinine from capillary blood:
Using the Mitra® microsampling device (with two tips per cartridge, each capable of absorbing 10 uL of blood) two blood samples will be collected after a finger prick with the supplied lancet at the time points indicated in the flow chart. The closed cartridge will be shipped to the central laboratory. Details of shipment procedures will be provided in the laboratory manual in the ISF and the instructions to the patient. Samples will be analysed using a validated mass spectroscopy method.

All capillary blood samples remaining at the end of the study will be destroyed no later than the sign-off of the clinical trial report.

5.1.2 UACR

Urine samples for the determination of urine albumin creatinine ratio (UACR) will be collected by the patient at home from first morning void (FMV) urine at the baseline visit and the end of trial visit. At each visit, the patient will collect an FMV urine sample on the day before the visit and the day of the visit itself. An appropriate number of urine cups will be provided to the patient for collection at home. Patients will be reminded e.g. by telephone contacts ahead of sampling time points on how to collect and store their urine samples. Further collection and sample storage instructions are given in the laboratory manual in the ISF and instructions to the patient.

Urinary albumin and creatinine will be analysed at a central laboratory using routine validated methods.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the flow chart. Assessments include at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Measurement of height and body weight will be performed at the time points specified in the flow chart.
The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flow chart, prior to blood sampling.
This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. BP measurements should be recorded to the nearest 1 mmHg. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling time points please see the flow chart.

A central laboratory result will be used to confirm eGFR for eligibility; the respective reference ranges will be provided in the ISF.

To ensure sufficient hydration, patients should be strongly encouraged to come not fasted to their study visits.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF. Where samples are collected by the patient directly, appropriate instructions in lay language will be provided.

The central laboratory will provide reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to section 5.2.6).

Lab tests may need to be repeated in case of required medical follow-up due to an adverse event or if a test was not successful due to incorrect specimen handling or storage.

To test the eGFR throughout the trial, the site will collect a small capillary blood volume from the patient with the Mitra® tool at visits indicated in the flow chart. The Mitra® tool will also allow the patient to collect blood at home. Therefore, at home patients will need to collect one blood sample on their own (one Mitra® cardridge with two sampling tips) and ship them to the central lab or the site, if permitted by local legislation. Alternatively, the patient will need to take the specimens to the site directly.

The central laboratory will transfer the results of the analysis to the CRO.

The CKD-EPI Equation is used for reporting eGFR based on serum creatinine (see appendix section 10.2).

5.2.3.1 Safety laboratory tests

Safety lab samples will be collected at the time points shown in the flow chart. Sample analyses will be performed at a central lab. The results of the lab tests must be transferred to the investigator who ensures medical review and proper documentation in the eCRF. Clinically relevant procedure related safety issues have to be entered as adverse event (if applicable, see 5.2.6.2). The required safety lab parameters are:

Table 5.2.3.1: 1 Safety laboratory tests

Short name	Name assay	Substrate	Other information
Blood serum			
HGB	Haemoglobin	Haemoglobin	N/
RBC	Red blood cell count	Erythrocytes	N/
WBC	White blood cell count	Leukocytes	N/
PLTCT	Platelets	Platelets	N/
SGPT	ALT/SGPT, SGPT	Alanine Aminotransferase	N/
SGOT	AST/SGOT, SGOT	Aspartate Aminotransferase	N/
ALKP	Alkaline phosphatase	Alkaline Phosphatase	N/
TBILI	Bilirubin, total	Bilirubin	N/
UREA	Urea	Urea	N/AP
NA	Sodium	Sodium	N/
K	Potassium	Potassium	N/

5.2.4 Electrocardiogram

N/AP.

5.2.5 Other safety parameters

N/AP

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following are also considered AEs:
- Worsening of the underlying disease or of other pre-existing conditions.
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only, if applicable.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:
- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency (EMA) initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above.
The latest list of “Always Serious AEs” can be found in the ISF. These events should always be reported as SAEs as described in section 5.2.6.2.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in section 5.2.6.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

5.2.6.1.4 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate: Sufficient discomfort to cause interference with usual activity.
Severe: Incapacitating or causing inability to work or to perform usual activities.

5.2.6.1.5 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the concomitant mediations being used in this trial, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
- Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).

5.2.6.2 Adverse Event Collection and Reporting

This interventional clinical trial does not involve administration of any study medication. Therefore, the following applies:

The following must be collected and documented on the appropriate CRF(s) by the investigator: from signing the informed consent onwards until the End of trial visit - all AEs associated with trial procedure (non-serious and serious). AEs have to be followed up until they are resolved.

In addition, the investigator should report to BI all adverse events related to any BI products as determined by the investigator via established channels of reporting in the country e.g. local forms or call center number. This includes any drug exposure during pregnancy with and without adverse events.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

No Pharmacokinetic assessments planned in this trial.

5.3.2 Methods of sample collection

N/AP

[redacted]

5.3.4 Pharmacokinetic-pharmacodynamic relationship

N/AP

5.4 ASSESSMENT OF BIOMARKERS

5.4.1 Exploratory biomarkers

No exploratory biomarker assessments planned in this trial.

5.4.2 Pharmacogenomics biomarkers

No pharmacogenomic investigations are planned.

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

5.5.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see flow chart.
Approximately 20 mL blood will be drawn for plasma and serum banking purposes. In addition, 10 mL of urine will be collected.

5.6 OTHER ASSESSMENTS

N/A

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to estimate eGFR slopes and UACR to monitor the risk of dieseae progression in an appropriate way.

Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All visits should be scheduled according to the flow chart. Each visit date (with its window) is to be counted from Day 1 (Baseline visit). If any visit has to be rescheduled, subsequent visits should follow the original visit schedule.

All trial visits should be initiated preferentially in the morning. Patients should be instructed to take their FMV urine samples at home before attending the scheduled visit at the study site.

To ensure sufficient hydration, patients should be strongly encouraged to come not fasted to their study visits.

Unscheduled visits will be possible at the discretion of the investigator at any time in order to check the safety of the patient e.g following an interruption of 2 consecutive site visits.
If the reason for removal of a patient from treatment is an adverse event or a clinically significant laboratory test result, the patient must be followed-up until complete resolution or stabilisation of the event or until follow-up is agreed adequate by the Investigator and sponsor.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study measurements and assessments should be performed according to the flow chart. All assessments should be performed preferentially in the morning.

Where the following assesments occur at a visit they should be performed in the following order:
- Vital signs – see flow chart for when additional measurements are required
- Venous Blood draws and Mitra® sampling – (see flow chart)

Please refer to the following sections for specific details about alternatives to visits at the site (the type of visit needs to be recorded on the CRF):
- Flow chart – overview of what procedures should be performed and at what timepoints.
- Section 5.2.1 – Physical exam
- Section 5.2.2 – Vital signs
- Section 5.2.3 – Safety laboratory parameters
- Section 6.2.1 –Remote patient visits by telephone

6.2.1 Remote patient visits by telephone

Remote patient visits conducted by telephone can replace scheduled patient visits at the site, if COVID-19 or similar pandemic restrictions are in place and due to this pandemic a patient is not able or willing to travel to the site and if local regulatory and legal regulations allow telephone visits. Implementation of remote patient visits by telephone need to be approved by the sponsor. Local regulatory and legal requirements of the participating country still apply.

6.2.2 Screening period

Screening Period

No trial procedures should be done unless the patient has consented to taking part in the trial. Once informed consent is obtained, the patient is enrolled in the trial and has started screening. The patient should be recorded on the enrolment log or relevant source document as a screened patient before any other activites are performed. Patients who do not fulfil all eligibility criteria for a reason stated in the protocol should be registered as a screen failure in relevant source document. Patients who do not fulfil all eligibility criteria for a reason that later resolves and allows eligibility criteria to be met, may be re-screened after discussion with the sponsor. Re-screening will only be allowed once.

The footnotes to the flow chart provide details about when screening procedures may be repeated and when re-screening is allowed.

6.2.3 Treatment period

N/AP

6.2.4 Early discontinuation of Treatment

N/AP

6.2.5 Trial completion

Patients should be encouraged to complete all visits and procedures up to the Week 48 visit which is at the same time the End of Trial Visit.

Patients who discontinue the trial prematurely and who do not withdraw their informed consent should return for a trial completion visit or End of Trial visit and undergo the assessments as indicated in the flow chart. All samples including venous blood, Mitra® (for creatinine values) and UACR should be collected in addition to safety samples.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

No formal statistical hypothesis is planned for this trial.

7.2 PLANNED ANALYSES

7.2.1 General considerations

All available patient data will be included for the estimation of the retrospective slope. The Patient data will be stratified according to SGLT2 inhibitors use. Data up to the time at which patients dropped, either in or out of SGLT2 or an unexpected case where a change in ACEi/ARB dose occurs, will be included in the estimation of the prospective slope.

[redacted]

Further Analysis Sets will also be defined in the TSAP, if needed.

7.2.2 Primary outcome analyses

Retrospective and prospective slopes will be derived using a linear random slope model. The prospective eGFR slope for each patient will be derived using eGFR values in the prospective phase as the dependent variable and time in the prospective phase as the continuous independent variable with random intercept and random slope. The trial targets to be included in the linear random slope model and the most appropriate data to be used for this analysis will be determined based on residual variance. Details will be found in the TSAP.

The retrospective eGFR slope for each patient will be derived similarly using the data in the retrospective phase. Summary statistics (mean, SD, min, median, max) will be provided for the overall population and by patient population (DKD vs. ndCKD).

The residual variance (i.e. mean squared error) of the slope estimates will be estimated using the linear random slope model, for both the retro- and prospective slopes, to assess the reliability of slope estimation.

Homogeneity will be primarily evaluated via a shift analysis:

- A shift table of patients with categories of eGFR slopes of 1 to < 3 (slow progression) and ≥ 3 mL/min/1.73m^2/year (fast progression), in each of the retrospective and prospective phases, will be provided. The shift analysis will be considered as the primary analysis to evaluate homogeneity.

Further analyses include:

- A categorical analysis of the number and proportion of patients with eGFR slopes >1, > 3 and >5 mL/min/1.73m^2/year will be provided for both retro- and prospective phases via tabular and graphical presentations.

- Histograms will be plotted for retro- and prospective slopes to evaluate their distributions graphically.

- The Pearson's linear correlation coefficient between retro- and prospective slopes will be derived for overall population and by patient population.

- A descriptive summary of the proportion of "shifters" and non-"shifters".

- A "shifter" is defined as a patient whose:
    1) Retrospective relative to prospective slope category shifts from slow to fast or fast to slow, respectively and
    2) Percent change from retrospective to prospective phase in slope exceeds 20%.

- McNemar's test will also be conducted to further assess the homogeneity between retro- and prospective slopes for categories of < 3 and ≥ 3 mL/min/1.73m2.

In addition to the above analyses,

- - A descriptive summary of the percent change in retrospective to prospective slopes will be provided.

Furthermore, the association between retrospective and prospective slopes will be assessed as a continuous endpoint, the details of which will be provided in the Trial Statistical Analysis Plan (TSAP).

7.2.3 Secondary outcome analyses

Not applicable.

[redacted]

7.2.5 Safety analyses

The safety analyses are limited to the "AE' related to study procedures. Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of (MedDRA) at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Further details will be provided in the TSAP.

7.2.6 Other Analyses

Other analysis details will be documented in the TSAP.

7.2.7 Interim Analyses

An interim analysis can be considered at any time but might be triggered by the following combinations of number of patients and follow-up in case of substantial recruitment or feasibility issues:

300 patients with 40 weeks follow-up
400 patients with 32 weeks follow-up
500 patients with 24 weeks follow-up.

The purpose of a potential interim analysis is based on recruitment/feasibility. Its purpose is to best utilize all available data collected up to these timepoints, if it is identified that enrolment is not sufficient to reach our recruitment goal by the currently targeted study end.

If performed, the appropriate type of analyses will be based on the percentage of the total number of expected patients in the cohort and what types of data are present, at the timepoint at which the interim analysis occurs. At a minimum, summary statistics for study endpoints will be provided for the overall population and by-patient population (DKD vs. ndCKD) for both the retrospective and prospective phases. Additionally, shift tables of patients to categories of retro- and prospective phases will also be provided.

Please note, however, if it is observed that enrolment meets or exceeds the expected recruitment goals, then the right is reserved not to perform the above proposed interim analyses.

7.3 HANDLING OF MISSING DATA

In the primary analysis of all continuous endpoints, missing data will not be imputed. Missing or incomplete AE dates will be imputed according to BI standards. [redacted]

7.4 RANDOMISATION

Not applicable.

7.5 DETERMINATION OF SAMPLE SIZE

The trial will be conducted in a cohort of 600 patients, pending feasibility and enrolment period. To obtain a good representation of subjects across eGFR slopes spectrum, 600 patients will be enrolled. The goal is to achieve 400 fast progressors with an eGFR slope ≥3ml/min/1.73m²/year and 200 slow progressor patients with an eGFR slope between 1 and 3ml/min/1.73m²/year).

The sample size determination is not based on statistical considerations, but on feasibility, and there is no formal statistical hypothesis defined in the study. However, the sample size of 600 patients is considered adequate to evaluate the homogeneity of the retro- and prospective slopes. If the true (unobserved) proportion of patients have an eGFR slope ≥ 3 mL/min/1.73m^2 based on retrospective data and in the prospective observed period is 70%, 600 patients will provide an estimate of the proportion of at least 67% with a probability of 95%.

On the other hand, if the true (unobserved) proportion of patients have an eGFR slope ≥ 3 mL/min/1.73m2 based on retrospective data and in the prospective the observed period is 50%, 600 patients will provide an estimate of the proportion of at least 47% with a probability of 95%. Results based on these parameters would be considered less than success, i.e. that we are less likely to be able to suggest or “conclude” that the retrospective and prospective slopes are homogeneous.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI and CRO Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014, and other relevant regulations.

Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation". Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. The certificate of insurance cover is made available to the investigator and the patients and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA)) as applicable according to national and international regulations. The same applies for the implementation of changes introduced by amendments. Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form.

If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor or sponsor's designee.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations).
- Patient participation in the trial (trial number, patient number, date patient was informed).
- Medical history (including trial indication and concomitant diseases, if applicable).
- Medication history.
- Adverse events and outcome events (onset date (mandatory), and end date (if available)).
- Serious adverse events (onset date (mandatory), and end date (if available)).
- Concomitant therapy (start date, changes).
- Originals or copies of laboratory results and other testing results, with proper documented medical evaluation (in validated electronic format, if available).
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. This includes the values for eGFR and their method of analysis at or before screening to confirm eligibility. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.
- In case electronic data are available that can be uploaded to the CRF via an electronic interface, the data stored and secured on the system to collect the data will be considered the source data and the data transferred must be a validated copy of it.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial sites:
The trial sites must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular:

- Sample and data usage have to be in accordance with the separate biobanking informed consent.
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place.
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage.
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data.
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF.

8.5.2 Future use of the trial data

The trial data are planned to be included in a database which also includes retrospective data from other phase II clinical trials primarily. Inclusion of a patient's data in this database is voluntary and not a prerequisite for participation in the trial and will only occur after informed consent has been given in accordance with local ethical and regulatory requirements.

The mixed effect model with repeated measures will be performed using the database to estimate the subject-level slope to identify the fast progressing patients for the Phase III clinical development.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI). Coordinating and a Co-coordinating Investigator are responsible to coordinate investigators at the different sites participating in this trial.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The trial will be performed in accordance with applicable regulations. The majority of the organisation of the trial will be delegated to a Clinical Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. The SOPs to be followed will be documented. Data Management and Statistical Evaluation will be done by the CRO according to CRO SOPs.

Central laboratory services will be used in this trial. Details will be provided in the Central Laboratory Manual, available in the ISF.

9. APPENDICES

9.1 TRIAL BIOMARKER PLAN

Urine:

- Albumin
- Creatinine

Capillary blood (collected with Mitra® microsampling device):

- Creatinine

10. REFERENCES

10.1 PUBLISHED REFERENCES

R17-2620 Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Köttgen A, Levey AS, Levin A: Evolving importance of kidney disease: From subspecialty to global health burden. Lancet 382: 158–169, 2013

R13-4387 Kidney Disease: ImprovingGlobalOutcomes (KDIGO) CKDWorkGroup: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3: 1–150, 2013

R10-1168 Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS: Prevalence of chronic kidney disease in the United States. JAMA 298: 2038–2047, 2007

R21-0998 Grams ME, Chow EK, Segev DL, Coresh J: Lifetime incidence of CKD stages 3-5 in the United States. Am J Kidney Dis 62: 245–252, 2013

P21-03068 US Renal Data System: USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2010

R21-1003 Levin A, Djurdjev O, Beaulieu M, Er L: Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. AmJ Kidney Dis 52: 661–671, 2008

R21-1004 Johnson ES, Thorp ML, Platt RW, Smith DH: Predicting the risk of dialysis and transplant among patients with CKD: A retrospective cohort study. Am J Kidney Dis 52: 653–660, 2008

R15-5162 Fox CS, Matsushita K, Woodward M, Bilo HJG, Chalmers J, Heerspink HJL, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M, Vassalotti JA, Yamagishi K, Coresh J, de Jong PE, Wen C-P, Nelson RG; Chronic Kidney Disease Prognosis Consortium: Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: A meta-analysis. Lancet 380: 1662–1673, 2012

R21-0999 Mahmoodi BK, Matsushita K, Woodward M, Blankestijn PJ, Cirillo M, Ohkubo T, Rossing P, Sarnak MJ, Stengel B, Yamagishi K, Yamashita K, Zhang L, Coresh J, de Jong PE, Astor BC; Chronic Kidney Disease Prognosis Consortium: Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: A meta-analysis. Lancet 380: 1649–1661, 2012

R21-1000 Derose SF, Rutkowski MP, Crooks PW, Shi JM, Wang JQ, Kalantar-Zadeh K, Kovesdy CP, Levin NW, Jacobsen SJ: Racial differences in estimated GFR decline, ESRD, and mortality in an integrated health system. Am J Kidney Dis 62: 236–244, 2013

R21-1001 Freedman BI, Parekh RS, Kao WH: Genetic basis of nondiabetic end-stage renal disease. Semin Nephrol 30: 101–110, 2010

R21-1002 Tangri N, Kitsios GD, Inker LA, Griffith J, Naimark DM, Walker S, Rigatto C, Uhlig K, Kent DM, Levey AS: Risk prediction models for patients with chronic kidney disease: A systematic review. Ann Intern Med 158: 596–603, 2013

R21-1138 Turin TC, Coresh J, Tonelli M, Stevens PE, de Jong PE, Farmer CK, Matsushita K, Hemmelgarn BR: Short-term change in kidney function and risk of end-stage renal disease. Nephrol Dial Transplant 27: 3835– 3843, 2012

10.2 GFR CKD-EPI FORMULA

Calculation Name	**GFR CKD-EPI**	
Formula	**Units**	**Decimal Places**
<u>Conventional</u>: **Black or African American formulas:** Female with a serum creatinine value of ≤0.7 mg/dL 166 x (Serum Creatinine (mg/dL) / 0.7) $^{-0.329}$ x (0.993)^{age} Female with a serum creatinine value of >0.7 mg/dL 166 x (Serum Creatinine (mg/dL) / 0.7) $^{-1.209}$ x (0.993)^{age} Male with a serum creatinine value of ≤0.9 mg/dL 163 x (Serum Creatinine (mg/dL) / 0.9) $^{-0.411}$ x (0.993)^{age} Male with a serum creatinine value of >0.9 mg/dL 163 x (Serum Creatinine (mg/dL) / 0.9) $^{-1.209}$ x (0.993)^{age} **White, American Indian, Alaska Native, Asian, Native Hawaiian, Other Pacific Islander, Other formulas:** Female with a serum creatinine value of ≤0.7 mg/dL 144 x (Serum Creatinine (mg/dL) / 0.7) $^{-0.329}$ x (0.993)^{age} Female with a serum creatinine value of >0.7 mg/dL 144 x (Serum Creatinine (mg/dL) / 0.7) $^{-1.209}$ x (0.993)^{age} Male with a serum creatinine value of ≤0.9 mg/dL 141 x (Serum Creatinine (mg/dL) / 0.9) $^{-0.411}$ x (0.993)^{age} Male with a serum creatinine value of >0.9 mg/dL 141 x (Serum Creatinine (mg/dL) / 0.9) $^{-1.209}$ x (0.993)^{age} Creatinine in mg/dL is rounded to 2 decimal places prior to applying the formula.	mL/min/ 1.73m²	0
<u>SI</u>: Serum creatinine in µmol/L will be rounded to zero decimal place and converted to mg/dL by multiplying by 0.01131. This creatinine value in mg/dL will be rounded to 2 decimal places. This creatinine result will be used in the GFR Conventional formulas listed above.	mL/min/ 1.73m²	0
Limitations/Special Notes:	Age is truncated to a whole number prior to performing the calculation.	

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		19 May 2021
EudraCT number **EU number**		Not applicable
BI Trial number		1366-0026
BI Investigational Medicinal Product(s)		Not applicable
Title of protocol		Evaluation of homogeneity between eGFR slopes derived from retrospective clinical practice data and eGFR slopes derived from prospectively collected, protocol-driven data
Global Amendment due to urgent safety reasons		No
Global Amendment		Yes
Section to be changed		Flow chart
Description of change		Training of patient on Mitra sampling and urine collection will be at Screening instead of Baseline.
Rationale for change		Correction of an error
Section to be changed		Section 1.4.2
Description of change		During this study, 2 venous blood samples (each 2 mL) will be collected during site visits at baseline, and Week 12, Week 24, Week 36 and Week 48 (end of study) in separate tubes. 1 tube (2mL) is used for assessing the safety parameters and the other tube (2mL) for serum creatinine. **Was changed to:** During this study, ~~2 venous blood samples (each 2 mL)~~ **1 venous blood sample for serum creatinine (5 mL) will be collected at screening, and 3 venous blood samples for serum creatinine (5 mL), chemistry (5 mL), and hematology (2 mL)** will be collected during site visits at baseline, and Week 12, Week 24, Week 36 and Week 48 (end of study) ~~in separate tubes. 1 tube (2mL) is~~ **2 tubes (5 mL and 2 mL) are** used for assessing the safety parameters **(chemistry and hematology)** and ~~the other tube (2mL)~~ **1 tube (5 mL)** for serum creatinine.
Rationale for change		Blood sample volumes and number of blood samples per visit that are needed for the respective analyses required correction.

11.2. GLOBAL AMENDMENT 2

Date of amendment		25 Apr 2022
EudraCT number **EU number**		Not applicable
BI Trial number		1366-0026
BI Investigational Medicinal Product(s)		Not applicable
Title of protocol		Evaluation of homogeneity between eGFR slopes derived from retrospective clinical practice data and eGFR slopes derived from prospectively collected, protocol-driven data
Global Amendment due to urgent safety reasons		No
Global Amendment		Yes
Section to be changed		Study Protocol Synopsis - Trial design
Description of change		Non-randomized, low-intervention design with no trial drug administration except background therapy. The trial will consist of a retrospective phase of up to 3.5 years prior to Screening visit (i.e. visit 1), and a prospective phase of 48 weeks duration. **Was changed to:** Non-randomized, low-intervention design with no trial drug administration except background therapy. The trial will consist of a retrospective phase of up to **5.5** ~~3.5~~ years prior to Screening visit (i.e. visit 1), and a prospective phase of 48 weeks duration.
Rationale for change		To allow patients to participate in the clinical trial that have the required minimum of 4 creatinine values only within a broader time span.
Section to be changed		Study Protocol Synopsis – Inclusion criteria
Description of change		Inclusion criterion • eGFR 20 – 75 ml/min/1.73m² at Visit 1 calculated from serum creatinine measured by a central laboratory. **Was changed to:** • eGFR 20 – **90** ~~75~~ ml/min/1.73m² at Visit 1 calculated from serum creatinine measured by a central laboratory.
Rationale for change		To broaden the study population.
Section to be changed		Study Protocol Synopsis – Inclusion criteria
Description of change		Inclusion criterion

		• At least 4 serum creatinine values in the retrospective phase. The most recent and oldest serum creatinine values should be no less than 2 years apart and no greater than 3 years apart. **Was changed to:** • At least 4 serum creatinine values in the retrospective phase**:** - **The most recent creatinine value not more than 6 months prior to Visit 1 (Screening Visit)**. - The most recent and oldest serum creatinine values should be no less than **1** ~~2~~ year~~s~~ apart and no greater than **5** ~~3~~ years apart - **There should be no gap of creatinine values of 2 years or longer.**
Rationale for change		To allow patients to participate in the clinical trial that have the required minimum of 4 creatinine values only within a broader time span and at the same time ensure robust eGFR slope assessments.
Section to be changed		Section 1.3 Rationale for performing the trial
Description of change		The study will also compare eGFR slopes derived via retrospective serum creatinine values collected up to 3.5 years prior to visit 1 in routine clinical practice, with prospectively generated eGFR values and resulting slopes. **Was changed to:** The study will also compare eGFR slopes derived via retrospective serum creatinine values collected up to **5.5** ~~3.5~~ years prior to visit 1 in routine clinical practice, with prospectively generated eGFR values and resulting slopes.
Rationale for change		To allow patients to participate in the clinical trial that have the required minimum of 4 creatinine values only within a broader time span.
Section to be changed		Section 3.1 Overall Trial Design
Description of change		In figure 3.1: 1 Retrospective part (42 months) **Was changed to:** Retrospective part (**66** ~~42~~ months)
Rationale for change		To allow patients to participate in the clinical trial that have the required minimum of 4 creatinine values only within a broader time span.

Section to be changed		Section 3.1 Overall Trial Design
Description of change		All available historical eGFR values, UACR/PCR within the 3.5 years prior to screening Visit 1 will be collected for each patient. **Was changed to:** All available historical eGFR values, UACR/PCR within the **5.5** ~~3.5~~ years prior to screening Visit 1 will be collected for each patient.
Rationale for change		To allow patients to participate in the clinical trial that have the required minimum of 4 creatinine values only within a broader time span.
Section to be changed		Section 3.1 Overall Trial Design
Description of change		To be documented in the CRF: All available serum creatinine values (at least 4 serum creatinine values should be available for a patient). The most recent and oldest serum creatinine values should be no less than 2 years apart and no greater than 3 years apart. **Was changed to:** To be documented in the CRF: All available serum creatinine values (at least 4 serum creatinine values should be available for a patient **with the most recent creatinine value not more than 6 months prior to Visit 1 (Screening Visit)**). The most recent and oldest serum creatinine values should be no less than **1** ~~2~~ year~~s~~ apart and no greater than **5** ~~3~~ years apart **and there should be no gap of creatinine values of 2 years or longer.**
Rationale for change		To allow patients to participate in the clinical trial that have the required minimum of 4 creatinine values only within a broader time span and at the same time ensure robust eGFR slope assessments.
Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		Inclusion criterion 7. eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) 20 – 75 ml/min/1.73m² at Visit 1 calculated from serum creatinine measured by a central laboratory. **Was changed to:** 7. eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) 20 – **90** ~~75~~ ml/min/1.73m² at Visit 1 calculated from serum creatinine measured by a central laboratory.
Rationale for change		To broaden the study population.

Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		Inclusion criterion 9. At least 4 serum creatinine values in the retrospective phase. The most recent and oldest serum creatinine values should be no less than 2 years apart and no greater than 3 years apart. **Was changed to:** 9. At least 4 serum creatinine values in the retrospective phase**:** - **The most recent creatinine value not more than 6 months prior to Visit 1 (Screening Visit)**. - The most recent and oldest serum creatinine values should be no less than **1** ~~2~~ year~~s~~ apart and no greater than **5** ~~3~~ years apart - **There should be no gap of creatinine values of 2 years or longer.**
Rationale for change		To allow patients to participate in the clinical trial that have the required minimum of 4 creatinine values only within a broader time span and at the same time ensure robust eGFR slope assessments.

APPROVAL / SIGNATURE PAGE

Document Number: c35391746 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: Evaluation of homogeneity between eGFR slopes derived from retrospective clinical practice data and eGFR slopes derived from prospectively collected, protocol-driven data

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	25 Apr 2022 14:19 CEST
Approval-Biostatistics		25 Apr 2022 15:35 CEST
Approval-Therapeutic Area [redacted]		25 Apr 2022 16:21 CEST
Approval		27 Apr 2022 12:22 CEST
Verification-Paper Signature Completion		27 Apr 2022 13:27 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**