Clinical Trial Protocol

	Document Number:	**c32274622-05**
EudraCT No.	2020-002929-28	
BI Trial No.	1366-0005	
BI Investigational Medicinal Product	BI 685509	
Title	Randomised, double-blind (within dose groups), placebo-controlled and parallel group trial to investigate the effects of different doses of oral BI 685509 given over 20 weeks on UACR reduction in patients with diabetic kidney disease	
Lay Title	A study to test the effect of different doses of BI 685509 on kidney function in people with diabetic kidney disease	
Clinical Phase	Phase II	
Clinical Trial Leader	[redacted] Phone: +[redacted], Fax: +[redacted]	
Coordinating Investigator	[redacted] Tel: +[redacted], Fax +[redacted]	
Status:	**Final Protocol (Revised Protocol (based on global amendment 4))**	
Version and Date	**Version: 5.0**	**Date: 14 Mar 2022**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	19 October 2020
Revision date	14 March 2022
BI trial number	1366-0005
Title of trial	Randomised, double-blind (within dose groups), placebo-controlled and parallel group trial to investigate the effects of different doses of oral BI 685509 given over 20 weeks on UACR reduction in patients with diabetic kidney disease
Coordinating Investigator	[redacted] Tel: +[redacted] Fax +[redacted]
Trial sites	Multi-centre trial
Clinical phase	II
Trial rationale	The aim of this trial is to investigate the efficacy, safety, tolerability, PK and PD of three oral doses of BI 685509 over 20 weeks in male and female patients with DKD as adjunctive to ACEi or ARB treatment plus local standard of care according to respective guidelines. The results of this trial will be crucial for the decision about further development of BI 685509 and will support the dose selection for future trials.
Trial objectives	The main objectives of the trial are to demonstrate the effectiveness of BI 685509 and to characterize the dose-response relationship for BI 685509 in patients with DKD by assessing 3 doses and placebo.
Trial endpoints	Primary endpoint: Change from baseline in log transformed UACR measured in 10-hour urine after 20 weeks of trial treatment. Secondary endpoints: Change from baseline in log transformed UACR measured in First Morning Void urine after 20 weeks of trial treatment. Proportion of patients achieving UACR decreases in 10-hour urine of at least 20% from baseline after 20 weeks of trial treatment. Proportion of patients achieving UACR decreases in First Morning Void urine of at least 20% from baseline after 20 weeks of trial treatment.
Trial design	Randomised, parallel design comparison of 3 dose groups over 20 weeks of treatment, double-blind within dose group, placebo controlled
Total number of patients randomised	240

Number of patients on each treatment	60
Diagnosis	Diabetic Kidney Disease (DKD)
Main in- and exclusion criteria	Inclusion: • Male or female patients aged ≥ 18 years at time of consent. • eGFR ≥ 20 and < 90 mL/min/1.73 m². • UACR ≥ 200 and < 3,500 mg/g. • Stable treatment with either ACEi or ARB (not both). • Patients with stable type 1 or type 2 diabetes mellitus. Exclusion: • Non-diabetic chronic kidney disease. • planned start of chronic renal replacement therapy during the trial or end stage renal disease before start of trial treatment.
Test product	BI 685509
Dose	3 mg / 6 mg / 9 mg total daily dose
mode of administration	Per os / oral (p.o.)
Comparator product	Placebo
dose	Matching
mode of administration	Per os / oral (p.o.)
Duration of treatment	20 weeks
Statistical methods	The purpose of this trial is to demonstrate proof of concept of clinical activity of BI 685509 on the primary endpoint. For the proof of concept an evaluation of the benefit of BI 685509 compared to placebo will be conducted. To account for the repeated nature of the primary endpoint data and the covariates in the model, MMRM analysis will be carried out for change from baseline of log transformed UACR measured in 10-hour urine after 20 weeks of trial treatment in each patient group. The analysis will include the fixed, categorical effect of treatment at each visit, and the fixed continuous effects of baseline log transformed UACR at each visit. Visit will be treated as the repeated measure with an unstructured covariance matrix used to model the within-patient measurements. The adjusted mean change from baseline (and the related standard error) will be calculated for each group and will be used for the MCPMod to determine therapeutic dose. The analyses for dose-finding will be performed using MCPMod whereby several possible dose response models (patterns) will be evaluated to identify the best-fitting model or subset of models. Regarding analyses of the secondary endpoints, 1. MMRM will be used for the analysis for the change of UACR in First Morning Void.

	2. Descriptive statistics will be provided for the change of UACR in First Morning Void urine/10-hour urine and the UACR response rate along with figures.

FLOW CHART

Please refer to the UACR AND EGFR SAMPLING FLOW CHART as well as FLOW CHART FOR PROCEDURES that follow the main visit flow chart for specific sampling timepoints.
Procedures should be performed in the order they appear in this flow chart.

Trial Period	**Screening**	**Baseline Run-in[x]**		**Randomised Treatment**								**Follow Up Period[i]**			
Visit[ii]	**1[iii]**	**2**	**Home sampling without visit**	**End of Baseline/ Start of Treatment 3[iv]**		**4[v]**	**5[v]**	**6**	**7**	**8**	**Home sampling without visit**	**EoT[xi] Start of FUp**	**FUp1**	**FUp2**	**Home sampling without visit**	**FUp3**
Visit may be at patient's home[vii]		X						X	X	X				X		X
Telemedicine Contact[viii]		X	(X)					O			(X)		X	O	(X)	
Weeks before or after Visit 3	-5	-2	-1	0		2	4	6	12	18	19	20	21	22	23	24
Days	-35	-14	-7	1		15	29	43	85	127	134	141	148	155	162	169
Time window for visits (days)		+/- 2	+/- 2	none		+ 2	+ 2	+/- 2	+/- 4	+/- 2	+/- 2	+/- 2	+3	+/- 2	+/- 2	+/- 3
				Pre-dose	Post-dose											
Informed consent[ix]	X															
Demographics, medical history including historical creatinine data, baseline conditions	X			X												
Check of in-/exclusion criteria	X[x]			X												
Concomitant therapies	X	X		X		X	X	X	X	X		X	X	X		X
Height	X															
Weight	X			X				X				X		X		X
Physical examination	X			X				X				X		X		
Vital signs	X	X		X[xi]	2X[xi]	3X[xi]	3X[xi]	3X[xi]	3X[xi]	3X[xi]		X		X		X

Trial Period	**Screening**	**Baseline Run-in**[x]		**Randomised Treatment**								**Follow Up Period**[i]			
Visit[ii]	**1**[iii]	**2**	**Home sampling without visit**	**End of Baseline/ Start of Treatment 3**[iv]		**4**[v]	**5**[v]	**6**	**7**	**8**	**Home sampling without visit**	**EoT**[vi] **Start of FUp**	**FUp1**	**FUp2**	**Home sampling without visit**	**FUp3**
Visit may be at patient's home[vii]		X						X	X	X				X		X
Telemedicine Contact[viii]		X	(X)					O			(X)		X	O	(X)	
Weeks before or after Visit 3	-5	-2	-1	0		2	4	6	12	18	19	20	21	22	23	24
Days	-35	-14	-7	1		15	29	43	85	127	134	141	148	155	162	169
Time window for visits (days)		+/- 2	+/- 2	none		+ 2	+ 2	+/- 2	+/- 4	+/- 2	+/- 2	+/- 2	+3	+/- 2	+/- 2	+/- 3
				Pre-dose	Post-dose											
12-lead electrocardiogram (ECG), local assessment[xii]	X			X	2X	3X	3X	3X	X	X		X		X		
Safety laboratory (blood, urine)	X	X		X		X	X	X	X	X		X		X		X
eGFR[xiii]	X	X		X		X	X	X	X	X		X		X		X
PK sampling[xiv]				X	3X	4X	4X	4X	4X	4X		X				
Biomarker sampling (urine, serum and plasma)				X				X	X			X				X
Pharmacogenomic sampling				X[xv]												
Optional biobanking sampling (serum, plasma, urine)[xvi]				X				X	X			X				X
Pregnancy test[xvii]	X			X				X	X	X		X				
Spot urine (UACR)	X[xviii]															
Train patient on UACR and [redacted]	X															
Provide home sampling kit[xix]	X	X			X	X	X	X	X	X		X		X		
UACR First Morning Void		X	X	X		X		X	X	X	X	X		X	X	X
UACR 10-hour urine sample		X	X	X		X		X	X	X	X	X		X	X	X

Trial Period	**Screening**	**Baseline Run-in**[x]		**Randomised Treatment**								**Follow Up Period**[i]			
Visit[ii]	**1**[iii]	**2**	**Home sampling without visit**	**End of Baseline/ Start of Treatment 3**[iv]		**4**[v]	**5**[v]	**6**	**7**	**8**	**Home sampling without visit**	**EoT**[vi] **Start of FUp**	**FUp1**	**FUp2**	**Home sampling without visit**	**FUp3**
Visit may be at patient's home[vii]		X						X	X	X				X		X
Telemedicine Contact[viii]		X	(X)					O			(X)		X	O	(X)	
Weeks before or after Visit 3	-5	-2	-1	0		2	4	6	12	18	19	20	21	22	23	24
Days	-35	-14	-7	1		15	29	43	85	127	134	141	148	155	162	169
Time window for visits (days)		+/- 2	+/- 2	none		+ 2	+ 2	+/- 2	+/- 4	+/- 2	+/- 2	+/- 2	+3	+/- 2	+/- 2	+/- 3
				Pre-dose	Post-dose											
[redacted] at visits		X		X		X	X	X	X	X		X		X		X
[redacted] at home[xx]			X								X				X	
Provide training on smartphone/ tablet application including provision of app / device[xxi]	X	X														
Paper diary handout	X	X			X	X	X	X	X	X		X		X		
Review of diaries via application or paper diary (to be collected)		X		X		X	X	X	X	X		X		X		X
Randomisation (via IRT)				X												
Dispense study drug (via IRT)				X		X	X	X	X	X						
Administer study drug during visit					X	X	X	X	X	X						
Drug accountability (via IRT)						X	X	X	X	X		X				
Termination of study drug (via IRT)[xxii]												X				

Trial Period	Screening	Baseline Run-in[x]		Randomised Treatment								Follow Up Period[i]			
Visit[ii]	1[iii]	2	Home sampling without visit	End of Baseline/ Start of Treatment 3[iv]		4[v]	5[v]	6	7	8	Home sampling without visit	EoT[vi] Start of FUp	FUp1	FUp2	Home sampling without visit	FUp3
Visit may be at patient's home[vii]		X						X	X	X				X		X
Telemedicine Contact[viii]		X	(X)					O			(X)		X	O	(X)	
Weeks before or after Visit 3	-5	-2	-1	0		2	4	6	12	18	19	20	21	22	23	24
Days	-35	-14	-7	1		15	29	43	85	127	134	141	148	155	162	169
Time window for visits (days)		+/- 2	+/- 2	none		+ 2	+ 2	+/- 2	+/- 4	+/- 2	+/- 2	+/- 2	+3	+/- 2	+/- 2	+/- 3
				Pre-dose	Post-dose											
All AEs/SAEs/AESIs[xxiii]	X	X		X	X	X	X	X	X	X		X	X[xxiii]	X[xxiv]		X[xxv]
Completion of patient participation																X

i Follow-up (FUp) Visit 1 must always take place at least 7 days after the EoT visit. In case of an early discontinuation please follow the guidance in section 6.2.4.

ii In case of dose reduction due to adverse events, additional visits may have to be scheduled.

iii As UACR and eGFR may not be regularly tested, where allowed sites may pre-screen patients by sending a spot urine sample to measure UACR and/or a blood sample to measure eGFR to their local lab. This is optional and requires a specific approved pre-screening informed consent. Pre-screening results will not be collected in the CRF or used to determine final eligibility in this trial. Pre-screening can be performed at any point prior to screening. The full consent form must be signed before screening (Visit 1) procedures are performed. Screening assessments may be conducted over more than one day. The run-in period may start as soon as all screening procedures have been performed and laboratory results have been received and reviewed. Therefore the 35 days prior to randomisation that are indicated in the flow chart may be less.

- Screening procedures may be repeated during run-in 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 on, the patient is allowed to be rescreened once as long as 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. IRT must be contacted to register the re-screening and obtain a new patient number
- As an exception patients with a SBP of >180 mmHg at screening must not be considered for re-screening.

- If screening (including the 2 week baseline period) are not completed within 35 days prior to randomisation, the patient will be a screen failure. IRT should be contacted to record the screen failure. If appropriate the patient may be re-screened (see above).

[iv] The timepoint of first treatment (Visit 3) defines Day 1.

[v] Visits 4 and 5 must be performed at least 14 days after the previous visit.

[vi] In case a patient needs or wishes to terminate the treatment prematurely the patient should have an End of Treatment (EoT) visit, if they agree. Please see section 6.2.4 for details.

[vii] These visits can either be performed at the Investigational site or at the patient's home. All local approvals for this must be in place and confirmed by the sponsor. Consent for home visits must also be obtained from the patient. See section 6.2.1 for further details.

[viii] There are various ways that Telemedicine contacts (phone call or video call) can be used during this trial:

1. Telemedicine contact to provide support for patient's urine sampling. Before the patient does their first UACR and eGFR sampling at home (before Visit 2) the investigational site staff should contact the patient to ensure the patient is comfortable with the sampling process. The other timepoints marked as '(X)' are suggested times to contact the patient if they are shipping samples directly from home to ensure they understand the instructions given to them. The site may, at their discretion, offer support with further home sampling according to the individual needs of a patient.
2. Telemedicine calls at visit 6 (marked as "O") and/or FUp2. If this visit is being performed at the patient's home by a nurse, a telemedicine contact must be established between the nurse, patient and an Investigator who will guide the nurse through the physical exam (see section 6.2.1).
3. FUp1 must be performed as telemedicine contact for all patients, unless they prefer to come to the trial site.
4. Phone/ video calls may also take place at any other time if needed to support the patient.

[ix] Informed consent does not need to be obtained on the day of the screening visit but must be obtained before the first screening assessment and within 35 days of randomisation (Visit 3). The consent discussion should include showing the patient the home sampling kits and explaining this procedure.

[x] Once screening assessments have been completed, a member of the trial team will contact the patient by phone to provide confirmation about eligibility.

[xi] At Visits 3 to 8 vital signs will be measured before the morning dose and approximately 30 min and 120 min after dosing. If applicable this must occur prior to the ECG and PK samples. See FLOW CHART FOR PROCEDURES for further details.

[xii] All ECGs should be performed after the patient has been in the supine position for 5 minutes. They should be evaluated by the investigator or a designee. See FLOW CHART FOR PROCEDURES for details on the timing of ECGs.

[xiii] eGFR at clinic visits will be determined from serum creatinine analysed by the central laboratory and also from [redacted]. To confirm eligibility the eGFR at screening will be used.

[xiv] Patients do not need to be fasted on the days of PK sampling, see FLOW CHART FOR PROCEDURES for further details. For further instructions see section 6.1.

[xv] The pharmacogenomic samples may be collected at Visit 3 or anytime afterwards.

[xvi] Optional biobanking samples will only be collected if the patient has signed the biobanking informed consent separate form the main consent for the trial. See section 5.5.

[xvii] A pregnancy test is required for all women of child-bearing potential. This will be a serum pregnancy test at Screening (Visit 1), thereafter a urine pregnancy test will be performed.

[xviii] To confirm eligibility at Visit 1, UACR measured in spot urine (midstream urine sample) by the central laboratory will be used. Should the first test for UACR at screening be borderline out of range and not match inclusion criteria due to UACR variability, this test can be repeated once. The result must be available and eligibility confirmed before the baseline UACR sampling starts. If the second result does not meet the eligibility criteria the patient should be screen failed.

[xix] Training on how to use the [redacted] device and how to do the FMV and 10-hour 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.

[xx] [redacted] performed at home can be returned by e.g. post or courier (if permitted by Country-specific regulations and other local guidance). If not allowed locally, the patient should return the samples to the investigational site. Countries may be exempted from microsampling if use of the [redacted] is not permitted in that country.

[xxi] Patients will need to complete 2 different diaries. The 'Diary for Urine and Blood Collection and Trial Drug Times' will enable the site to record information entered during urine and [redacted] blood collection at home and 2 days prior to PK sampling including times of trial drug intake, start and stop times of collection and volumes. The 'Daily Diary for Trial Drug Intake' will help to check the compliance of the patient and a possible need for down-titration. If the patient chooses they will be able to download an app containing the diaries to their phone at visit 1 or 2, or will be provided at visit 2 with an electronic device with the app installed. The app will also be used for the videocalls and can be used for patient reminders. If the use of the e-diary is not possible, alternatively a paper diary will be available to the patient.

[xxii] The planned last dose taken by the patient will be the evening dose the day before their EoT visit. If a patient withdraws from treatment early the EoT visit should be performed as close as possible to their last dose.

[xxiii] All AEs, SAEs and AESIs will be collected from informed consent until FUp1 (end of residual effect period). Please see section 5.2.6.2.1.

[xxiv] After FUp1 until the individual patient's end of trial, the investigator should report any cancers of new histology and exacerbations of existing cancer, all trial treatment related SAEs and all trial treatment related AESIs. Please see section 5.2.6.2.1.

[xxv] As detailed in section 5.2.6.2.1 after the individual patient's end of the trial the investigator does not need to actively monitor the patient for new AEs but should report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.6.2.2), but not on the CRF.

UACR AND EGFR SAMPLING FLOW CHART

See FLOW CHART for visit windows. All samples listed in the following table should be collected by the patient, unless the patient is not able to do it.

Visit	Screening	2			Home sampling without visit		3		4			5	6			7			8			Home sampling without visit		EoT		FUp2			Home sampling without visit		FUp3		
Week of VISIT	≤-5	-2			-1		0		2			4	6			12			18			19		20		22			23		24		
Period		Pre-treatment							Treatment Period																	Follow-up							
									Start Tx	Up-titration 1		Up-titration 2														End Tx								
Days before visit	0	2	1	0	8 ■	7 ■	2	1	0	2	1	0	0	2	1	0	2	1	0	2	1	0	8 ▲	7 ▲	2	1	0	2	1	0	8 ●	7 ●	2	1	0
First Morning Void (FMV)		X	X		X	X	X	X		X	X			X	X		X	X		X	X		X	X	X	X		X	X		X	X	X	X	
10-hour urine Sample after FMV		X	X		X	X	X	X		X	X			X	X		X	X		X	X		X	X	X	X		X	X		X	X	X	X	
Bring samples to clinic visit or pick-up at home*				X		X			X			X				X			X			X		X			X			X		X			X
[redacted]				■					■			■	■			■			■			■						■			■					■
[redacted]						■																		■								■				

■ days before planned Visit 3, ▲ days before regular EoT at week 20, ● days before FUp3, * When samples are picked-up from home, this will be after the 10 hour sampling is complete, which at the latest will be the following day.

FLOW CHART FOR PROCEDURES

In all instances when an ECG and blood samples are required at the same timepoint the ECG must be performed prior to the blood sampling and after the patient has been in the supine position for 5 minutes. Vital signs and ECGs must always be performed with sufficient time to allow the PK samples to remain within the time windows specified below.

Visit	**Day** ***See main flow chart for visit windows***	**PK Sampling Time Relative to Administration (morning dose) at Visit hh:mm**	**Time Point [hh:min]**	**Event**	**PK Sample No.**
3	1	Prior to first PK blood draw and drug administration		Urine samples[1], weight and Physical Exam, Vital signs then ECG and then blood samples (other than PK)	---
		Within 30 minutes prior to drug administration	Just before drug administration	PK Blood	1
		0:00	0:00	Drug administration	---
		0:30 (+/- 5 min)	0:30	Vital signs then PK Blood	2
		1:00 (+10 min)	1:00	ECG then PK Blood	3
		2:00[2] (+ 15 min)	2:00	Vital signs then ECG then PK Blood	4
4	15	Prior to first PK blood draw and drug administration		Urine samples[1], Vital signs then ECG and then blood samples (other than PK)	---
		Within 30 minutes prior to drug administration	335:30	PK Blood	5
		0:00	336:00	Drug administration	---
		0:30 (+/- 5 min)	336:30	Vital signs then PK Blood	6
		1:00 (+ 10 min)	337:00	ECG then PK Blood	7
		2:00[2] (+ 15 min)	338:00	Vital signs then ECG then PK Blood	8
5	29	Prior to first PK blood draw and drug administration		Urine samples[1], Vital signs then ECG and then blood samples (other than PK)	---
		Within 30 minutes prior to drug administration	671:30	PK Blood	9

[1] Urine samples, weight and the physical examination (where applicable) can be collected at any time before drug administration
[2] Please note on all occasions the 2 hour PK sample cannot be earlier than 2 hours after the administration of the morning dose at the Visit

Visit	Day *See main flow chart for visit windows*	PK Sampling Time Relative to Administration (morning dose) at Visit hh:mm	Time Point [hh:min]	Event	PK Sample No.
		0:00	672:00	Drug administration	---
		0:30 (+/- 5 min)	672:30	Vital signs then PK Blood	10
		1:00 (+ 10 min)	673:00	ECG then PK Blood	11
		2:00[2] (+ 15 min)	674:00	Vital signs then ECG then PK Blood	12
6	43	Prior to first PK blood draw and drug administration		Urine samples[1], weight and Physical Exam, Vital signs then ECG and then blood samples (other than PK)	---
		Within 30 minutes prior to drug administration	1007:30	PK Blood	13
		0:00	1008:00	Drug administration	---
		0:30 (+/- 5 min)	1008:30	Vital signs then PK Blood	14
		1:00 (+ 10 min)	1009:00	ECG then PK Blood	15
		2:00[2] (+ 15 min)	1010:00	Vital signs then ECG then PK Blood	16
7	85	Prior to first PK blood draw and drug administration		Urine samples[1], Vital signs then ECG and then blood samples (other than PK)	---
		Within 30 minutes prior to drug administration	2015:30	PK Blood	17
		0:00	2016:00	Drug administration	---
		0:30 (+/- 5 min)	2016:30	Vital signs then PK Blood	18
		1:00 (+ 10 min)	2017:00	PK Blood	19
		2:00[2] (+ 15 min)	2018:00	Vital signs then PK Blood	20
8	127	Prior to first PK blood draw and drug administration		Urine samples[1], Vital signs then ECG and then blood samples (other than PK)	---
		Within 30 minutes prior to drug administration	3023:30	PK Blood	21
		0:00	3024:00	Drug administration	---
		0:30 (+/- 5 min)	3024:30	Vital signs then PK Blood	22
		1:00 (+ 10 min)	3025:00	PK Blood	23
		2:00[2] (+ 15 min)	3026:00	Vital signs then PK Blood	24
EoT	141	Prior to PK blood draw		Urine samples, weight and Physical Exam, at any time. Vital signs then ECG and then blood samples (other than PK)	---
		N/A	3360:00 (trough)	PK Blood	25

Visit	**Day** ***See main flow chart for visit windows***	**PK Sampling Time Relative to Administration (morning dose) at Visit hh:mm**	**Time Point [hh:min]**	**Event**	**PK Sample No.**
FUp2	148	N/A	N/A	Urine samples, weight and Physical Exam at any time. Vital signs then ECG and then blood samples.	---
FUp3	169	N/A	N/A	Urine samples and weight at any time. Vital signs then blood samples.	---

TABLE OF CONTENTS

ABBREVIATIONS

ACEi	Angiotensin Converting Enzyme inhibitor
ADME	Absorption, Distribution, Metabolism and Excretion
ADPKD	Autosomal Dominant Polycystic Kidney Disease
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criterion
AKI	Acute Kidney Injury
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
AUC	Area under the Curve
AUC_{SS}	Area under the concentration-time curve of the analyte in plasma at steadystate
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats per minute
CA	Competent Authority
cGMP	Cyclic Guanosine Monophosphate
CKD	Chronic Kidney Disease
CKD-EPI	CKD Epidemiology Collaboration (formula)
C_{max}	Maximum measured concentration of the analyte in plasma
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
CT Manager	Clinical Trial Manager

CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP2C8	Cytochrome P450 2C8
CYP3A4	Cytochrome P450 3A4
DBL	Database Lock
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interaction
DG	Dose Group
DILI	Drug Induced Liver Injury
DKD	Diabetic Kidney Disease
DMETTM	Drug Metabolism Enzymes and Transporters
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
(e)COA	(electronic) Clinical Outcome Assessment
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EoT	End of Treatment
ES	Entered Set
ESRD	End Stage Renal Disease
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FDA	Food and Drug Administration
FMV	First Morning Void
FUp	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP1	Glucagon-Like Peptide 1
GMP	Good Manufacturing Practice
HbA_{1c}	Glycated haemoglobin
hERG	Human Ether-a-go-go Related Gene

HR	Heart Rate
IB	Investigator's Brochure
ICE	Intercurrent Event
ICH	International Council on Harmonisation
IDNT	Irbesartan Diabetic Nephropathy Trial
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
K-EDTA	Potassium ethylenediaminetetraacetic acid
KDIGO	Kidney Disease: Improving Global Outcomes
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
MAR	Missing at Random
MCPMod	Multiple Comparison Procedure with Modelling
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed-effect Model for Repeated Measures
MRD	Multiple Rising Dose
NIDDM	non-insulin-dependent diabetes mellitus
NO	Nitric Oxide
NSAID	Non-steroidal anti-inflammatory drug(s)
NYHA	New York Heart Association
OATP1B1/3	Organic Anion-Transporting Polypeptide 1B1 and 1B3
OPU	Operative Unit
PD	Pharmacodynamics
PDE5	Phosphodiesterase type 5
P-gp	P-glycoprotein
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
p.o.	per os (oral)

PoC	Proof of Concept
PV	Pharmacovigilance
QD	quaque die (once daily)
RAAS	Renin Angiotensin Aldosterone System
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (trial)
REP	Residual Effect Period
RS	Randomised Set
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic Blood Pressure
SC	Steering Committee
sGC	Soluble Guanylate Cyclase
SGLT2	Sodium-Glucose co-Transporter-2
SGLT2i	SGLT2 Inhibitor
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TID	ter in die (3 times a day)
t_{max}	Timepoint of Maximum Plasma Concentration
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
Tx	Treatment
UACR	Urine Albumin Creatinine Ratio
UGT	Uridine 5'-diphosphate -glucuronosyltransferase
ULN	Upper Limit of Normal
UPE	Urinary Protein Excretion
V*x*	Visit *x*
WHO	World Health Organisation
WOCBP	Woman of Child-Bearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Diabetes is a globally prevalent disease that is expected to grow exponentially over the coming decades. Amongst the complications of diabetes, the development of diabetic kidney disease (DKD), also known as diabetic nephropathy, may be the most devastating with respect to patients' quality of life and survival. For example, as glomerular filtration rate (GFR) declines, there is a linear increase in mortality, with 2- to 5-fold increases in patients with GFR < 45 mL/min/1.73 m² compared to patients with a GFR > 60 mL/min/1.73 m² [R14-4475]. Declining renal function is associated with an increasing risk for the occurrence of coronary heart disease, stroke and heart failure [R15-5158], [R15-2265]. DKD is the leading cause of kidney damage and end-stage renal disease (ESRD), accounting for > 40% of dialysis patients. The 5 year survival rate of a dialysis patient is 35% and only 25% in diabetic dialysis patients.

[redacted]

In addition to BI 685509, [redacted].

1.2 DRUG PROFILE

BI 685509 is under development for the treatment of chronic kidney disease (CKD) including the subgroup of diabetic kidney disease. In a parallel phase II trial BI 685509 is investigated in patients with non-diabetic CKD.

Mode of action
BI 685509 is an [redacted]

Key pharmacokinetic (PK) characteristics
The pharmacokinetics of BI 685509 is characterized by rapid absoption, reaching peak plasma concentrations between 0.5-1.0 hour post-dose in healthy volunteers and patients with diabetic nephropathy. Thereafter, BI 685509 plasma concentrations decline in a biphasic manner. Minimal amounts of BI 685509 were excreted unchanged in urine (<1% of dose). The apparent terminal elimination half-life was approximately 9 to 15 hours. After multiple oral administration, limited accumulation was ovserved and steady state appears to be attained by approximately 3 to 5 days after the start of multiple dosing.

Following single and multiple oral administrations of BI 685509, the exposures of BI 685509 (C_{max} and AUC) were comparable between Chinese and Japanese subjects but may be up to 2-fold higher compared to Caucasian subjects. This may be related to the smaller body weight in Asian subjects. Although exposures were higher in Asian subjects, there were no notable differences with respect to BP, HR and AEs between Asian and Caucasian subjects. This leads to the current assumption that no considerable dose adjustments are needed for Asian patients for the phase II program that will recruit patients from Japan and potentially other Asian countries.

Drug interactions

The combination of BI 685509 with other compounds [redacted]. A Drug-Drug Interaction (DDI) potential with CYP3A4 substrates cannot be excluded as BI 685509 is predicted to be a weak CYP3A4 inactivator. Inhibitors or inducers of UGT enzymes (especially UGT1A1) may potentially impact BI 685509 exposures in a clinically relevant manner. BI 685509 is a substrate of P-gp and OATP1B1/3 transporters. Co-administration of single doses of BI 685509 and the P-gp inhibitor itraconazole increased BI 685509 C_{max} approximately 1.35-fold and AUC_{0-tz} approximately 1.55-fold, which is considered not clinically relevant. OATP1B1/3 inhibition by rifampicin increased the exposure of BI 685509 after co-administration of single doses approximately 2.15-fold for C_{max} and 2.74-fold for $AUC_{0-tz,}$ which is considered clinically relevant. Thus, OATP1B1/3 inhibitors will be restricted.

Residual Effect Period

The Residual Effect Period (REP) of BI 685509 is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

Data from non-clinical studies

BI 685509 was evaluated in the rat ZSF1 model of diabetic nephropathy with once daily oral gavage dosing for 10 weeks on top of enalapril as a standard of care. This resulted in a dose-dependent reduction in urinary protein excretion (UPE) which was significant at ≥ 3 mg/kg and resulted in an additional ≥ 51% inhibition of UPE beyond that achieved with enalapril monotherapy. At ≥ 10 mg/kg, BI 685509 significantly inhibited the incidence of glomerulosclerosis when compared to enalapril alone (≥ 40% vs. 8%). A 20% reduction in proteinuria beyond that produced by a clinically relevant dose of enalapril was achieved at 53 nM for BI 685509 based on PK/PD modelling analysis. Taking into account the differences in plasma protein binding between both ZSF1 rat and human, a projected $C_{max,ss}$ of 95 nM or an AUC_{SS} of 540 nM*h is required for efficacy.

The disposition of BI 685509 in preclinical species (rats, dogs, and monkeys) is characterized by low to moderate clearance, moderate volume of distribution, short to moderate half-life, and low to moderate oral bioavailability. In rats, fecal and biliary were the major routes of excretion and urinary excretion was a minor route. In human and in preclinical species, BI 685509 had high plasma protein binding and low partitioning into blood cells. In rats, [14C]-BI 685509-derived radioactivity was absorbed and widely distributed to tissues. In plasma from the human single rising dose and multiple rising dose trials, the only identified metabolite of BI 685509 [redacted]. From in vitro studies

conducted in human liver microsomes, the primary enzyme responsible for glucuronidation of BI 685509 was UGT1A1, with minor contributions from UGT1A9 and UGT1A3.

As a perpetrator, BI 685509 is a weak inactivator of CYP3A4 and CYP2C8, and is a reversible inhibitor of CYP2C8. As such, concomitant administration of medications that are CYP3A4 substrates should be considered with caution. It was estimated that DDIs between BI 685509 and concomitantly administered medications that are metabolized by CYP2C8 are possible at doses >7.3 mg. Thus, DDIs due to CYP2C8 inactivation are unlikely at doses currently planned with the immediate release formulation (3 mg TID) in the phase II study.

So far the toxicity profile of BI 685509 has been assessed in safety pharmacology, genetic toxicity and repeat dose toxicity studies (rat and monkey) with additional investigative renal pathogenesis studies in the rat, embryo-fetal development studies and a phototoxicity assay. In general, BI 685509 appears to be well tolerated at clinically relevant plasma exposures. Delayed gastric emptying and decreased intestinal transit might result in gastrointestinal side effects. Only in rats, mild to moderate renal pelvis inflammation was observed sporadically. This finding is deemed to be rat specific and related to the mechanism of action. It seems to be unlikely that related adverse events (AEs) like urinary tract infections will occur in human subjects. Blood pressure (BP) decreased dose dependently with compensatory increases in HR in respective studies in rats and monkeys. No effects on the central nervous system or the respiratory system were found in respective safety pharmacology studies. BI 685509 revealed no evidence of teratogenicity in embryo-fetal development studies in rats and rabbits.
BI 685509 is considered non-genotoxic and with low risk for photo-toxicity.

Data from clinical studies
In phase I trials to date BI 685509 was investigated in healthy volunteers at single dose levels of 0.5 mg, 1.0 mg, 2.5 mg, and 5.0 mg and multiple rising doses (MRD) of up to 12.0 mg total daily dose. In general, the administration of single and multiple doses of the compound in the given dose range was safe and well tolerated. [redacted] Up-titration and 3 times daily dosing markedly improved the cardiovascular tolerability of the drug.

BI 685509 was also investigated in an MRD trial in patients with diabetic nephropathy up to 9.0 mg total daily dose on top of concomitant ACEi/ARB treatment. Multiple oral doses of BI 685509 up to 3 mg TID were generally safe and well tolerated. The most frequently reported drug-related AEs in this trial were hypotension and diarrhoea. The following adverse events have been reported under treatment with BI 685509 in completed clinical trials and can be reasonably linked to it: orthostatic hypotension and orthostatic intolerance.

No signal for a pharmacodynamic interaction leading to low blood pressure was detected. BI 685509 itself did not lead to an overall relevant blood pressure reduction or heart rate increases in comparison to placebo treatment over a period of four weeks.

In terms of safety, results from the completed multiple rising dose trial in healthy volunteers 1366-0003 and results from the multiple rising dose trial in patients with diabetic nephropathy 1366-0004 support the decision to not dose BI 685509 higher than 3 mg single dose or 9 mg total daily dose in patients.

In the patient MRD trial a responder was defined as a patient whose decrease from baseline in Urine albumin creatinine ratio (UACR) was at least 20%. For UACR measured in morning void urine, 15.8 to 27.8% of analysed patients receiving BI 685509 in DG1 to DG3 (3 to 5 patients) were responders, compared with 1 patient (7.1%) receiving placebo. For UACR measured in 10-hour urine, ≥50% of analysed patients receiving BI 685509 in DG2 and DG3 (8 to 10 patients) were responders, compared with no patients receiving placebo [c30365927-01].

Based on recent data from a clinical trial (1366-0020) in patients with cirrhosis Child-Pugh stage A (24 patients) and B (25 patients), an effect of BI 685509 on the predicted placebo-corrected change from baseline QTcF (ΔΔQTcF) was seen. Dosing regimens up to 3 mg bid, similar to the highest dose group in this trial, were used. In both patient groups, there was a dose dependent increase of ΔΔQTcF up to 13.7 ms, with the upper 90% CI >20 ms. In one patient group (Child-Pugh B) this was concomitant with a change of the predicted placebo-corrected change from baseline heart rate (ΔΔHR) of > 10 beats per minute (bpm), but not in the other patient group. No such effect was seen in a healthy Caucasian volunteers trial (1366-0010) for dosing regimens used in this trial. In a healthy Asian volunteers trial (1366-0013), at a dose regimen relevant for this study (i.e. starting with 1 mg tid up to a final dose of 3 mg tid), an increase of ΔΔQTcF was seen up to 11.7 ms with 90% CI <20 ms, concomitant with an increase of ΔΔHR of nearly 10 bpm.

BI 685509 has no effect on human ether-a-go-go related gene (hERG) channel at doses used in this clinical trial, and no effect on QT-interval was seen in conscious animal studies.

For a more detailed description of the BI 685509 profile, please refer to the current Investigator's Brochure (IB) [c02778238].

1.3 RATIONALE FOR PERFORMING THE TRIAL

Although ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) have demonstrated efficacy in slowing the progression of diabetic kidney disease, the relative risk reduction was moderate (16% in the RENAAL [Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan] trial and 19% in the IDNT [Irbesartan Diabetic Nephropathy Trial]) for the triple composite primary endpoint of all-cause death, ESRD and doubling of serum creatinine [R02-0327], [R02-2101]. The residual risk remains high. Even with the advent of SGLT2 inhibitors that will provide an additional treatment option for renally compromised patients, there is still a large unmet medical need for effective and safe treatments that can further slow, halt or reverse the progression of diabetic kidney disease, and positively impact the patient's quality of life.

The aim of this trial is to investigate the efficacy, safety, tolerability, PK and PD of three oral doses of BI 685509 over 20 weeks in male and female patients with DKD as adjunctive to ACEi or ARB treatment, plus other local standard of care according to respective guidelines. The results of this trial will be crucial for the decision about further development of BI 685509 and will support the dose selection for future trials.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see 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

Potential benefits of treating DKD patients with BI 685509 result from the prediction of slowing progression of the disease and prevention of cardiovascular events, which is only partially achieved by current standard of care. Treatment with BI 685509 will potentially result in decreased progression towards dialysis or kidney transplantation due to preventing the progression of renal damage, which may directly translate into relevant improvements for patients' morbidity, mortality, and quality of life. Beyond that, it may reduce the number of cardiovascular events in the target population.

Patients may also benefit from more frequent clinical monitoring as a result of being part of a clinical trial.

1.4.2 Risks

Table 1.4.2: 1 Overview of trial related risks

Investigational Medicinal Product BI 685509		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Potential adverse events such as hypotension/ orthostatic dysregulation, tachycardia, peripheral oedema and gastrointestinal events such as diarrhoea, abdominal pain and nausea	Primarily related to the [redacted].	To minimise the risk of severe or serious side effects, participants of this trial will only be exposed to doses that have been safely administered to healthy volunteers and patients in the preceding trials[3]. Patients with oedema or gastrointestinal side effects will be managed by standard of care. Patients with a known history of orthostatic dysregulation are excluded. Patients will be monitored carefully. In addition, up-titration to the maximum dose within each dose group will occur in 2-weekly intervals in order to increase tolerability of the drug with regards to cardiovascular effects.

[3] 1366-0003 is a multiple rising dose trial that investigated the safety, tolerability, PK and PD of rising doses of BI 685509 over a treatment period of 14 days in healthy volunteers and 1366-0004 is a multiple rising dose trial that investigated the safety, tolerability, PK and PD of rising doses of BI 685509 over a treatment period of 28 days in patients with diabetic nephropathy.

Table 1.4.2: 1 Overview of trial related risks cont.

Investigational Medicinal Product BI 685509		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Potential QT-interval prolongation	See section 1.2	Patients with long QT / QTcF-interval, patients with a family history of long QT syndrome, or those using concomitant therapies known to increase the risk of Torsade de Points will be excluded from the trial (refer to Sections 3.3.3 and 4.2.2.1). ECGs will be performed at each visit in the randomised treatment period of the trial, and trial medication will be discontinued in the event of a prolonged QT / QTcF-interval (refer to Section 3.3.4.1)

Table 1.4.2: 1 Overview of trial related risks cont.

Investigational Medicinal Product BI 685509		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Risks related to drug-drug interactions (DDI).	See section 1.2	Close monitoring of patients and the prohibited co-administration of impacted drugs such as treatment with a similar mechanism of action [redacted]. The use of drugs inhibiting the activity of OATP1B1/3 is restricted. UGT inhibitors/inducers will be restricted. Patients taking drugs that are sensitive CYP3A4 substrates and/or narrow therapeutic index CYP3A4 substrates will be monitored closely. For further guidance, investigators are referred to the Investigator's Brochure, Investigator Site File (ISF) or may contact the sponsor.
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety.
Patient not treated sufficiently due to placebo.	Placebo comparison needed to enable evaluation of effect of BI 685509 on UACR in patients with DKD.	25% of the patients will receive placebo on top of optimal standard of care treatment according to respective local guidelines, which includes either ACEi or ARB treatment

Table 1.4.2: 1 Overview of trial related risks cont.

Investigational Medicinal Product BI 685509		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Patient may be injured by self-collection of blood.	Patients need to take blood from the tip of their finger to allow frequent creatinine measurements for eGFR calculation as a safety marker and exploratory biomarker for kidney function.	A minimally invasive medical device called [redacted] kit, to take blood from the tip of their finger. This [redacted] tool has been established for easy-to use capillary blood collection at home. Patients will be trained on how to use this. Patients with diabetes are used to glucose determination in blood at home.
Patients may develop AKI or ESRD.	Rare but severe event related to the trial diagnosis. Patients with such an event will need to receive different treatment and are unlikely to benefit from treatment with BI 685509.	Treatment withdrawal criteria include AKI and ESRD as factors to remove the patient from treatment.
Patients may develop SARS-CoV-2 or other severe infection	Based on the mode of action BI 685509 is not expected to have a relevant impact on the susceptibility to or the course of an infection. The underlying disease studied in this trial and the expected higher age of the impacted population increase the risk of hospitalization and intensive care in case of a SARS-CoV-2 or other severe infection.	In case of a confirmed severe infection, trial treatment will be discontinued immediately and appropriate measures for monitoring, treatment and quarantine will be implemented. During a period of an increased risk of a severe infection, physical visits to the sites should be replaced with home visits or telemedicine and procedures (including lab testing) followed as far as the situation allows (see section 6.2.1). Direct shipment of the trial medication will be managed by the site or the provider directly as permitted by local regulations. These measures ensure the safety of the patients throughout the trial.

A steering committee (SC) consisting of the coordinating investigators in trial 1366-0022 (a matching trial to investigate BI 685509 in non-diabetic CKD) and other selected investigators as well as members of the BI trial team will meet in regular intervals and look at blinded safety data to identify potential risks that need further safety measures. A charter will be available before trial initiation to define the specific data reviews and meeting intervals.

1.4.3 Discussion

Based on pre-clinical results, BI 685509 has the potential to slow progression of renal damage, delay end stage renal disease (ESRD) and reduce cardiovascular events such as cardiovascular death, myocardial infarction, stroke and hospitalisation for heart failure, in patients with DKD. In addition, clinical studies in healthy volunteers and DKD patients have shown that it is well tolerated when up-titrated to the doses to be administered in this trial.

A placebo arm is needed to allow for a true assessment of the effects of BI 685509 on the UACR in patients with DKD. All patients will be on stable background standard of care therapy of at least either ACEi or ARB, therefore the inclusion of a placebo arm is considered to be ethically justifiable.

Patients will be carefully monitored for side effects during the trial. The sponsor will continuously assess the risks and benefits of the trial based on accumulating clinical data from all clinical trials with BI 685509. Any significant change in risk-benefit ratio will be communicated to Investigators and patients.

It cannot be excluded that hitherto unknown AEs will be detected in this trial, but given the well characterised mode of action and the careful monitoring throughout the trial, the sponsor feels that the risks to participating patients are minimized and justified when compared with the potential benefit that a successful clinical development of BI 685509 could provide to the treatment of diabetic kidney disease.

Overall, in the context of the unmet medical need and the anticipated effect on progression of DKD in humans and based on the safety profile of BI 685509, the benefit-risk evaluation of the compound is considered favourable for the intended trial population.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of the trial are to demonstrate the effectiveness of BI 685509 and to characterize the dose-response relationship for BI 685509 in patients with DKD by assessing 3 doses and placebo.

2.1.2 Primary endpoint

Change from baseline in log transformed Urine Albumin Creatinine Ratio (UACR) measured in 10-hour urine after 20 weeks of trial treatment.

2.1.3 Secondary endpoints

Change from baseline in log transformed UACR measured in First Morning Void urine after 20 weeks of trial treatment.
Proportion of patients achieving UACR decreases in 10-hour urine of at least 20% from baseline after 20 weeks of trial treatment.
Proportion of patients achieving UACR decreases in First Morning Void urine of at least 20% from baseline after 20 weeks of trial treatment.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This trial is a multicentre, randomised, double-blind (within dose groups), parallel, placebo-controlled clinical trial to compare three doses of BI 685509 with placebo in patients with diabetic kidney disease who are on background treatment with either ACEi or ARB plus any other standard of care according to respective local guidelines.

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

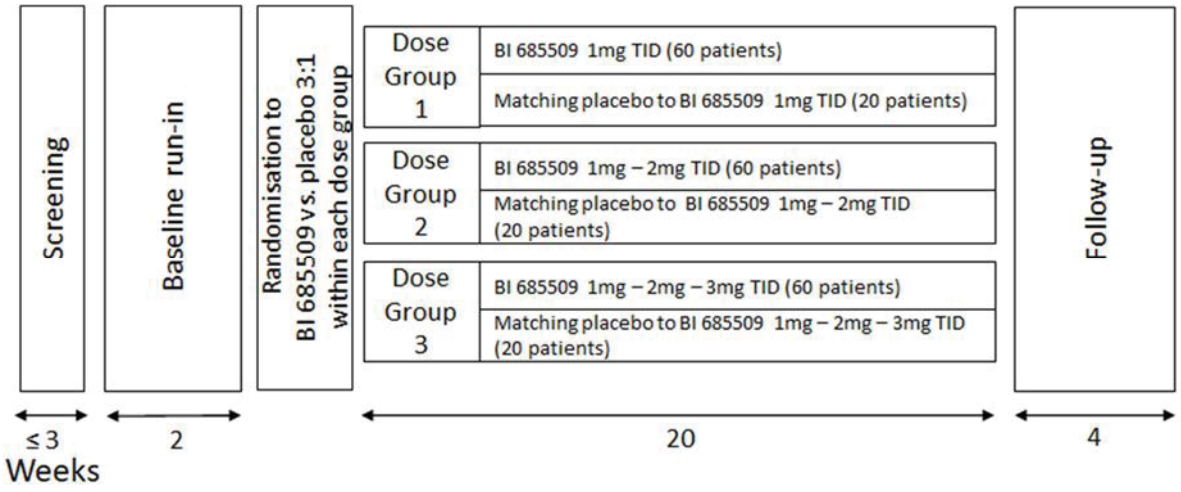

Figure 3.1: 1 Trial design

Patients will be enrolled (screened) in the trial once they have signed the informed consent. They will undergo a screening period of up to 3 weeks from the time of informed consent.

After their eligibility has been confirmed at screening, patients will continue in a 2-week baseline run in period. Patients who successfully complete the screening and baseline run-in period and meet the inclusion / exclusion criteria will be randomised equally into one of three parallel dose groups, and in each dose group to treatment either with BI 685509 or matching placebo in a 3:1 ratio (see Figure 3.1: 1).

From the start of the run-in until the end of the trial, at various time points patients will collect their urine for UACR sampling. These timepoints are listed in the UACR and eGFR flow chart. For each day that UACR is collected patients will start by collecting a First Morning Void urine in the container provided. As soon as the First Morning Void sample is collected the clock starts for the 10-hour urine collection. During this 10-hour period every time the patient urinates, they collect their urine into the provided container. An aliquot of this urine will be taken and used as the 10-hour UACR sample.

Once at each time point of urine collection patients will also give blood samples for eGFR analysis. For each time point where a physical visit to the site is not foreseen, the patient will

be equipped with a [redacted] kit to take blood at home, and urine collection containers to sample urine from their First Morning Voids and 10-hour collection container.

To decrease the burden on patients, where local regulations allow, samples taken at home between visits or when a home visit occurs will be shipped by the patient or a nurse or equivalent function visiting the patient for analysis at a central laboratory. Where this is not possible alternative arrangements will be made, e.g. samples taken to the investigational site.

After end of treatment patients will continue with a 4-week follow-up with further urine and blood sampling. Beyond analysis for safety, urine and blood samples in this trial will serve for biomarker analysis including UACR and eGFR.

The trial will be stratified according to SGLT2 inhibitor use and type of diabetes at the time of randomisation. SGLT2 inhibitors are a promising class of drugs for DKD patients and it is anticipated that their use might increasingly become standard of care. [P20-09106].To avoid a confounding effect, treatment with SGLT2 inhibitors will have to be kept stable prior to trial participation and throughout trial treatment (see section 4.2.2.1). An approximate of 10% patients on Type 1 Diabetes Mellitus patients will be expected.

All patients will start on 1 mg TID BI 685509 or matching placebo. If the medication is tolerated, up-titration to 2 mg TID BI 685509 or matching placebo will occur after 2 weeks for patients in dose groups 2 and 3, and up-titration to 3 mg TID BI 685509 or matching placebo will occur after another 2 weeks for patients in dose group 3. Patients will receive 20 weeks of treatment in total, which is expected to be the duration required to obtain stable effects.

Following the 20-week treatment period, or at the time trial treatment is permanently discontinued, patients will have an End of Treatment (EoT) visit, which will be the start of a 4-week follow-up period. A first follow-up telephone call (FUp1) at least 7 days later is considered as the end of the Residual Effect Period (REP). Until the end of REP all AEs and changes to concomitant medication need to be collected, documented and reported.

During the entire follow-up period the patient will not be treated with trial medication, but should if possible continue with any background treatment they were on, and will collect additional urine and/or blood samples at home. At the end of the 4-week follow-up a last physical visit will occur where again blood and urine samples will be collected. Depending on local regulations and approvals this visit may occur at the site or the patient's home. With the conclusion of this visit the trial participation is complete for the individual patient. Historical serum creatinine data will be collected in the trial over a period of 3 years before start of treatment. This may be used in future to explore the benefit of BI 685509 in patients with rapid CKD progression.

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

A parallel group design was chosen to compare three different dose regimens, including a placebo control within each dose group, to find the optimal dose for phase III. Placebo control is used to control for observer and subject bias, and randomisation to control for assignment bias.

UACR was chosen as primary endpoint (10-hour collection) and secondary endpoint (responder rate and First Morning Void (FMV)) because it was shown in previous phase II trials by others in CKD that it is sensitive, differentiating different doses, broad in its dynamic range and reaching a stable plateau within a reasonable time after start of treatment. It has been accepted by authorities as dose finding biomarker in CKD. In the MRD phase I trial in patients (1366-0004) UACR in 10-hour urine collected over the day (approximately starting with the morning dose) showed a greater difference to placebo compared to FMV urine. It is considered that 10-hour urine is able to capture the drug effect during the dosing schedule, while FMV urine contains the urine produced over night. While a 10-hour urine at daytime may be easier for patient to collect, a 24-h collection would be more burdensome and prone to error during night time collection. Also 10-hour UACR may be superior to FMV urine as the latter is depending on many factors such as nocturia and time of the first urination in the morning.

Furthermore, the change in UACR upon treatment within approximately 16 weeks of full dose correlates with long-term patient relevant outcomes. Based on this and including a 4-week up-titration, until the target dose is achieved, the full duration of treatment has been selected to be 20 weeks. Since UACR is a parameter that varies intra-individually over time, multiple measurements are required at baseline and during the treatment period especially towards the end of treatment where a stable response to the drug should be achieved. Sequential collection of urine during a 4-week follow-up period may deliver exploratory results of response stability and potential rebound effects.

To further characterise haemodynamic effects and potential early benefit on renal function serum creatinine will be measured at regular intervals for exploratory analysis.

In this parallel design, double-blind conditions regarding the patient's treatment (active or placebo) are maintained within each dose group. It is not feasible to apply double-blind conditions between dose groups because the individual tablet strengths and matching placebo look different. Therefore investigators will know which dose group their patient is in but will be blinded to whether they are on active drug or placebo. Patients will be blinded to both the dose group they are on and whether they are taking active drug or placebo. Keeping investigators blinded to the dose group would require patients to take multiple tablets three times a day on top of the extensive background medication they already receive, which is considered too burdensome for this clinical trial. However, in order to minimise possible observer bias with regard to dose dependent effects, the dose group will be blinded to the patient as much as possible by applying the following measures:

The trial medication label will not include dose strengths so the dose will not be identifiable to the patient from the label.

Every effort should be made by the trial team and sites staff that the patient is not informed about the dose group assignment.
Up-titration or "pseudo-titration" will occur for all patients two weeks after start of trial medication and again after another two weeks, regardless of dose group (see Table 4.1.4: 1).
Pseudo-titration is a term used to describe when patients are told that they are potentially assigned to a higher dose, but actually remain on the same dose:

- Patients in Dose Group 1 (1 mg TID) will be "pseudo-titrated" to 1 mg TID after two weeks and to 1 mg TID two weeks after that.
- Patients in Dose Group 2 (2 mg TID) will be up-titrated from 1 mg TID to 2 mg TID after two weeks and then "pseudo-titrated" to 2 mg TID two weeks after that.
- Patients in Dose Group 3 (3 mg TID) will be up-titrated from 1 mg TID to 2 mg TID after two weeks and to 3 mg TID two weeks after that.

However, in case the patient experiences a related adverse event or for any other reason the patient pauses trial treatment, the investigator will need to decide whether a down-titration is needed based on the rules reflected in section 4.1.4 and the dose group the patient is assigned to. The patient will not know the specific rules. This will eliminate an additional burden of the patient to visit the site for a sham-downtitration if the patient is staying on the lowest dose already.

3.3 SELECTION OF TRIAL POPULATION

It is expected that 240 patients will be randomised from approximately 100 sites. Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial unless screening needs to be re-opened due to a higher rate of screen failures.

A log of all patients screened into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If a patient is randomised in error (does not meet all inclusion criteria or meets one or more exclusion criteria), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Diabetic kidney disease.

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

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. Male or female patients aged ≥ 18 years at time of consent.
3. eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) ≥ 20 and < 90 mL/min/1.73 m^2 at Visit 1 by central laboratory analysis. eGFR must remain ≥

20 mL/min/1.73 m^2 after Visit 1 up to the start of Visit 3, measured by central or any local laboratory analysis.

4. UACR ≥ 200 and < 3,500 mg/g in spot urine (midstream urine sample) by central laboratory analysis at Visit 1.[1]
5. Treatment with the highest tolerated dose of either ACEi or ARB (but not both together), and stable dose for ≥ 4 weeks before Visit 1 with no planned change of the therapy during the trial.
6. If the patient is taking any of the following medications they should be on a stable dose at least 4 weeks prior to visit 1 until start of treatment, with no planned change of the therapy during the trial: anti-hypertensives, NSAIDs, endothelin receptor antagonists, systemic steroids or SGLT2 inhibitors.
7. Patients with stable type 1 or type 2 diabetes mellitus, diagnosed before informed consent. Treatment (including SGLT2 inhibitor and/or GLP1 receptor agonist) should have been unchanged or changes deemed minor (according to investigator's judgement) within 4 weeks before Visit 1 and until start of trial treatment.
8. Glycated Haemoglobin (HbA1c) < 10.0% at Visit 1 measured by the central laboratory.
9. Seated SBP ≥ 110 and ≤ 160 mmHg and DBP ≥ 65 and ≤ 110 mmHg at Visit 1 and optimized anti-hypertensive treatment according to local standard of care and investigator's judgement.[2]
10. Body Mass Index (BMI) ≥ 18.5 and < 50 kg/m^2 at Visit 1.
11. Male patients able to father a child must be willing to use condoms if their sexual partner is a Women of child-bearing potential[3] (WOCBP). WOCBP must be ready and able to use highly effective methods of birth control per ICH M3 (R2). Such methods should be used throughout the trial. A list of contraceptive methods meeting these criteria is provided in the patient information and in section 4.2.2.3 of the protocol.

3.3.3 Exclusion criteria

1. Treatment with Renin Angiotensin Aldosterone System (RAAS) interventions (apart from either ACEi or ARB), phosphodiesterase-5 inhibitors, non-specific phosphodiesterase inhibitors (such as dipyridamole and theophylline), NO donors including nitrates, sGC-stimulators/activators (other than trial treatment) or any other restricted medication (including OATP1B1/3 inhibitors, UGT inhibitors/inducers) as provided in the Investigator Site File (ISF) within 4 weeks prior to visit 1 and throughout screening and baseline run-in. Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial are also excluded.
2. Any clinically relevant laboratory value from screening until start of trial treatment, which in the investigator's judgement puts the patient at additional risk.
3. Biopsy or otherwise confirmed non-diabetic chronic kidney disease, or non-diabetic chronic kidney disease in the opinion of investigator, e.g., Autosomal Dominant Polycystic Kidney Disease (ADPKD), uncontrolled lupus nephritis. The presence of a hypertensive etiology does not need to be excluded unless it is evident this is the only cause for the CKD.
4. Any immunosuppression therapy or immunotherapy in the last 3 months prior to visit 1 and throughout screening and baseline run-in (except prednisolone ≤10 mg or equivalent).

5. Acute kidney injury (AKI) according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition[4] [R17-2439] in the 30 days prior to Visit 1 until the start of trial treatment.
6. Planned start of chronic renal replacement therapy during the trial or end stage renal disease before start of trial treatment.
7. Known history of moderate or severe symptomatic orthostatic dysregulation as judged by the investigator before start of trial treatment[5].
8. The patient has an active infection with SARS-CoV-2 (or is known to have a positive test) from screening until randomisation.
9. 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]).
10. Major surgery (investigator's judgement) planned during the trial.
11. History of clinically relevant allergy/ hypersensitivity that would interfere with trial participation including allergy to investigational product/ placebo or its excipients (see Investigator Brochure [c02778238])
12. Any other medical condition[6] that in the investigator's opinion poses a safety risk for the patient or may interfere with the trial objectives.
13. Previous randomisation in this trial.
14. Currently enrolled in another investigational device or drug trial,
    - or less than 30 days or 5 half-lives (whichever is longer) prior to Visit 1 since ending another investigational device or drug trial(s) for an oral agent which is not specified in any other exclusion criteria,
    - or less than 12 months prior to Visit 1 since ending another investigational device or drug trial(s) for a biological agent which is not specified in exclusion criteria or restrictions table in section 4.2.2,
    - or receiving other investigational treatment(s).
15. 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.
16. Women who are pregnant, nursing or who plan to become pregnant while in the trial.
17. QTcF-interval > 450 ms in men or > 470 ms in women at any time from screening (Visit 1) until start of treatment.
18. A family history of long QT syndrome.
19. Concomitant use of therapies with a known risk of Torsade de Pointes at screening (Visit 1) and throughout screening and baseline run-in or planned initiation of such therapies during the trial (refer to Section 4.2.2.1).

[1]In case of borderline out of range results UACR testing may be repeated once before the baseline sampling starts.
[2]A patient with a seated SBP between >160≤180 mmHG at Visit 1 may be re-screened according to the guidance in the flow chart and section 6.2.2. Anyone with a SBP over 180mmHg should be excluded. This re-screening should only occur after appropriate adjustment to their medication and sufficient time to ensure their medication is stable in accordance with the protocol.
[3]A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
[4]Definition of AKI can be found in section 3.3.4.1
[5]Severity of symptomatic orthostatic dysregulation is based on the standard Adverse Event severity classification.
[6]Examples of medical conditions may include, but is not limited to:
- symptomatic heart failure (NYHA III/IV)
- known history of tachycardia and/or atrial fibrillation

- clinically relevant arrhythmias
- coronary heart disease not compensated by medical treatment (supine pulse rate > 70 beats per minute, existing angina pectoris).

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; 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 on treatment, or at least to collect important trial data (UACR and eGFR sampling) according to the flow chart. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
The decision to discontinue trial treatment 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 5.2.6.2.1 and 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, 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 interferes with the safety of the investigational medicinal product, refer to sections 4.2.1 and 4.2.2. If there is no safety concern then the Sponsor will review on a case-by-case basis as to whether it is appropriate for the patients to continue. This decision will be based on factors such as duration of treatment, dose etc. 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 develops Acute Kidney Injury as per clinical judgment by the Investigator. The Kidney Disease: Improving Global Outcomes (KDIGO) definition[R17-2439] should be used for guidance:
    - Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours; or
    - Increase in serum creatinine to ≥ 1.5 times, which is known or presumed to have occurred within the prior 7 days; or
    - Urine volume < 0.5 mL/kg/h for 6 hours.
- The patient progresses to end stage renal disease and needs to obtain renal replacement therapy.
- Patients with a QT or QTcF interval > 500 ms, or an increase of QT or QTcF of > 60 ms from the pre-dose value at Visit 3 (baseline). Such cases must be reported as AEs.
- The patient experiences a severe infection, e.g. with SARS-CoV-2 that precludes their safe participation in the trial, as determined by the investigator.

- The patient can no longer receive trial treatment for any other medical reasons such as surgery, serious or severe Drug Induced Liver Injury (DILI) attributable to the trial drug (see section 5.2.6.1.4), other adverse events, or other diseases.
- The patient has discontinued trial treatment for at least 10 consecutive days* or has not taken medication at a total of 14 days* during the trial. In case of a temporary reason, trial treatment should be restarted if medically justified, please see section 4.1.4 for dose adjustments. * *a missed day is classed as all 3 doses being missed*
- A female patient becomes pregnant. The patient will be followed up until birth or otherwise termination of the pregnancy. The data of the patient will be collected and reported in the clinical trial report until last patient last visit and any events thereafter will be reported in the BI Pharmacovigilance database. See section 5.2.6.2.3.

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Please see section 6.2.4 for details of the procedures to be performed if trial treatment is discontinued.

The sponsor may decide to replace patients if patients terminate early due to a pandemic outbreak.

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 treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see section 6.2.4.

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 efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see section 3.3.4.1.
Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of patients affected will occur as described in section 6.2.4.
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

The trial medication (BI 685509 and matching placebo) will be provided by Boehringer Ingelheim.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the Investigational Medicinal Products are described in Table 4.1.1: 1 to 6.

Table 4.1.1: 1 BI 685509 1 mg

Substance:	BI 685509
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	1 mg
Posology:	TID
Method and route of administration:	Oral (p.o)

Table 4.1.1: 2 BI 685509 2 mg

Substance:	BI 685509
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	2 mg
Posology:	TID
Method and route of administration:	Oral (p.o)

Table 4.1.1: 3 BI 685509 3 mg

Substance:	BI 685509
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	3 mg
Posology:	TID
Method and route of administration:	Oral (p.o)

Table 4.1.1: 4 Placebo matching BI 685509 1 mg

Substance:	Placebo to BI 685509 film-coated tablets 1 mg
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	TID
Method and route of administration:	Oral (p.o)

Table 4.1.1: 5 Placebo matching BI 685509 2 mg

Substance:	Placebo to BI 685509 film-coated tablets 2 mg
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	TID
Method and route of administration:	Oral (p.o)

Table 4.1.1: 6 Placebo matching BI 685509 3 mg

Substance:	Placebo to BI 685509 film-coated tablets 3 mg
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	TID
Method and route of administration:	Oral (p.o)

4.1.2 Selection of doses in the trial and dose modifications

The target doses of BI 685509 used for this trial will be 1 mg TID, 2 mg TID and 3 mg TID. These doses were selected based on the safety and PK results of the 1366-0004 phase I MRD trial.

In healthy volunteer phase I trials doses starting with 0.5 mg QD were tested. At 1 mg TID the first signal of slight pharmacodynamic (PD) effects on blood pressure and heart rate was seen. Doses higher than 3 mg TID were not well tolerated.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria at Visit 3, each eligible patient will be randomised according to a randomisation plan.

Table 4.1.3: 1 Dose Groups and Treatments

	Target dose starting Visit 5	Randomisation ratio	Patients to be enrolled
Dose Group 1	1 mg BI 685509 TID	3	60
	Placebo matching 1 mg BI 685509 TID	1	20
Dose Group 2	2 mg BI 685509 TID	3	60
	Placebo matching 2 mg BI 685509 TID	1	20
Dose Group 3	3 mg BI 685509 TID	3	60
	Placebo matching 3 mg BI 685509 TID	1	20

Randomisation codes will be generated through a validated software and kept blinded to the trial team, sites and patients. An Interactive Response Technology (IRT) system will be used to screen patients, perform drug assignment, manage initial/ re-supply ordering of drug supplies and handle emergency un-blinding.

The investigator will receive all necessary instructions from the sponsor to access the IRT. Detailed IRT functions and procedures will be documented in the User Requirement Specifications mutually agreed by the sponsor and the IRT vendor. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System).

4.1.4 Drug assignment and administration of doses for each patient

All patients, regardless of dose group assigned, will start on a dose of 1 mg TID of BI 685509 or matching placebo. Up-titration or pseudo up-titration will occur after 14 days and after 28 days in each dose group, until the maximum planned dose for that dose group is reached. Patients who do not tolerate an up-titration, e.g., due to orthostatic dysregulation, should follow the guidance in section 4.1.4.2.

The treatment assignments and dose regimen are detailed in Table 4.1.4: 1.

Table 4.1.4: 1 Treatment assignments and dose regimen

Randomisation Allocation	Weeks 1 & 2	Weeks 3 & 4	Weeks 5 to 20
	Dispensed at Visit 3	Dispensed at Visit 4	Dispensed at Visits 5, 6,7 & 8
Dose Group 1	1 mg BI 685509 or matching placebo TID	1 mg BI 685509 or matching placebo TID	1 mg BI 685509 or matching placebo TID
Dose Group 2	1 mg BI 685509 or matching placebo TID	2 mg BI 685509 or matching placebo TID	2 mg BI 685509 or matching placebo TID
Dose Group 3	1 mg BI 685509 or matching placebo TID	2 mg BI 685509 or matching placebo TID	3 mg BI 685509 or matching placebo TID

It is recommended that the first daily dose is taken in the morning, the middle dose around lunchtime, and the third dose in the evening (one tablet at each time point). There must be at least 4 hours in between trial medication intake. If a dose is missed this should not be rectified by taking two doses at the next time point. The medication should be taken with a glass of water and can be taken with or without food. The last dose of trial medication will be administered in the evening of the day before the EoT visit.

All trial medication assignments including up/down-titrations and replacement kits will be managed through the IRT system. Standard up-titrations in the first 4 weeks have to be done in the same manner for all patients to blind the patient to the dose group they're assigned to. If no true up-titration is required for a patient at regular timepoints (i.e. Visit 4 and again at Visit 5), then the patient will still get new medication on the same dose as before. All patients will be told that the medication could either be the same or a higher dose depending on the treatment and dose group to which the patient is allocated.

During a COVID-19 or similar pandemic, physical visits to the sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations (for more details see section 6.2.1). Shipment of trial medication to the patient's home will also be allowed to support regular visits performed at the patient's home.

Potential down-titrations (dose reductions) can be done based on the dose group known by the investigational site. This will be managed via the IRT system. Dose reductions must not be performed by instructing the patient to take less than the three daily doses. While the patient will not get to know the precise rules as listed in sections 4.1.4.1 and 4.1.4.2, the patient will be informed that down-titrations may be needed as decided by the investigator.

4.1.4.1 Rules for titration in case of interruption of trial treatment

Since an interruption of trial medication may have an influence on the tolerance, the following rules will apply for the safety of the patient:

An interruption of trial treatment is defined as any occurrence where 4 consecutive doses* or more were not administered (i.e. missed or dosing temporarily discontinued).**One dose refers to an individual timepoint e.g. morning dose, or middle dose or evening dose.*

- If less than 4 consecutive doses of trial medication are missed then the next dose of trial medication should be taken as scheduled.

After an interruption of trial treatment the patient should be restarted at 1 mg BI 685509/ placebo TID independent from the dose the patient was on before unless the patient was down-titrated due to an adverse event (see section 4.1.4.2) in which case:

- If they had been on 2 mg/3 mg BI 685509/ placebo they would re-start on 1 mg BI 685509/ placebo.
- If they had been on 1 mg BI 685509/ placebo then they should restart on placebo (matching 1 mg BI 685509).

Before any up-titration occurs the patient must have taken the preceding dose for at least 7 consecutive days. This applies throughout the treatment period.

- This may mean that a patient due to be up-titrated at Visit 4 or 5 (as per Table 4.1.4: 1) is held at their current dose until their next scheduled visit. They could also be up-titrated at an unscheduled visit once this requirement is met.

If interruption for any reason occurs after Visit 5, subsequent up-titration will be allowed either at a scheduled or unscheduled visits.
Patients with an interruption on 2 mg or 3 mg or matching placebo will need to return to the clinic either for the next scheduled or an unscheduled visit to receive 1 mg tablets before continuation of trial treatment.

4.1.4.2 Rules for down-titration in case of intolerance to trial treatment

If a patient has an adverse event that the Investigator believes may be related to trial medication then the Investigator may either interrupt a patient's trial medication (re-start to follow the rules above (see section 4.1.4.1) or dose reduce the patient as described below. See Appendix 10.3 for a schematic guidance on down-titration:
If the patient is on 1 mg TID or matching placebo the patient will be down-titrated to placebo matching 1 mg.
If the patient is on 2 mg TID or 3 mg TID (or corresponding matching placebo) and interrupts trial treatment

- less than 4 consecutive doses, then the patient will be down-titrated one level i.e.
  - 2 mg /placebo goes to 1 mg TID/ placebo.
  - 3 mg/ placebo goes to 2 mg TID/ placebo.
- 4 consecutive doses or more, then the patient will be down-titrated to 1 mg TID or placebo.

Dose-reduction must NOT be performed by taking less than the three daily doses or by splitting tablets so that a whole tablet isn't taken.
If the patient experiences a second adverse event that the Investigator believes is related and they have already had an interruption/ down-titration, then the patient should permanently discontinue trial treatment.
In case of persistent adverse events despite dose reduction, or severe effects at any dose, permanent treatment discontinuation should be considered.
Uptitration for patients who were down-titrated or interrupted for a related AE is not permitted.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest except the Trial Pharmacometrician, PK programmer and Trial Bioanalyst in this double-blind trial will remain blinded with regard to the randomised treatment assignments within each dose group until after database lock. The access to the randomisation code will be kept restricted until its release for analysis.

The randomisation codes will be provided to bioanalytics prior to last patient completed to allow for the exclusion from the analyses of PK samples taken from placebo patients. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded.

In order to expedite the population PK and PK-PD analyses and ensure timely delivery of PK/PD results after DBL, specific data must be unblinded and the treatment information must be made available to selected individuals. The unblinding procedure and logistics specific to this purpose will be provided in a separate document. It should be noted no PK/PD results will be communicated to the project and trial team prior to database lock.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the Pharmacovigilance (PV) database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:
Approval of the clinical trial protocol by the IRB / ethics committee,
Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
Approval/notification of the regulatory authority, e.g. competent authority,
Availability of the curriculum vitae of the Principal Investigator,
Availability of a signed and dated clinical trial protocol,
Availability of the proof of a medical license for the Principal Investigator (if applicable),
Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor's appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Patients should keep their existing therapies as stable as possible, particularly their therapy with either ACEi or ARB from screening at Visit 1 until the end of follow-up at Visit Follow-up 2 (FUp2).

New therapies should only be initiated if necessary for medical reasons. Please see the inclusion / exclusion criteria (sections 3.3.2 and 3.3.3 respectively) and Table 4.2.2.1: 1 for full details of restrictions.

Background therapies (ACEi/ARB) or any other standard of care medications are not considered part of the clinical trial supplies, and therefore will not be provided.

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Mitigation of the potential risks can be achieved by close monitoring of patients and the prohibited co-administration of drugs with [redacted]. Special caution is warranted when administering BI 685509 in combination with drugs metabolized *via* CYP3A4, because the exposure of such drugs may potentially increase. In addition, BI 685509 must not be co-administered with OATP1B1/3 inhibitors and drugs known to inhibit or induce UGT enzymes, as this may impact BI 685509 exposures in a clinically relevant manner. List of relevant drugs can be found in the investigator site file.

In addition, intake of concomitant therapies with a known risk of Torsade de Pointes must not be co-administered with BI 685509 (also refer to Table 1.4.2: 1). These restrictions apply from screening (Visit 1), until Visit FUp3. In the event of temporary concomitant use of such a therapy, trial medication must be temporarily stopped and can then be re-started after a period of at least 5 half-lives after the concomitant therapy with the known risk of Torsade de Pointes has been stopped, as long as the interruption rules are followed. Refer to Section 4.1.4.1 for rules for re-starting up-titration in case of interruption of trial medication.

Table 4.2.2.1: 1 Concomitant medication restrictions

Medication	**Prior to trial (Visit 1)**	**During screening/ run-in**	**During Treatment Period**	**In the Follow-up Period**
Either ACEi or ARB	Stable dose for ≥ 4 weeks before Visit 1 required combination of ACEi and ARB not allowed	Stable dose required; combination of ACEi and ARB not allowed	Stable dose required; combination of ACEi and ARB not allowed	Stable dose required; combination of ACEi and ARB not allowed

Table 4.2.2.1: 1 Concomitant medication restrictions cont.

Medication	**Prior to trial (Visit 1)**	**During screening/ run-in**	**During Treatment Period**	**In the Follow-up Period**
Other RAAS intervention	Not permitted within ≥ 4 weeks prior to visit 1	Not permitted	Not permitted	Not permitted
Anti-hypertensive treatment	During the 4 weeks prior to visit 1 permitted if the dose is stable throughout	Stable dose permitted	Stable dose permitted	Stable dose permitted
NSAIDs	During the 4 weeks prior to visit 1 permitted if the dose is stable throughout	Stable dose permitted	Stable dose permitted if used prior to entry, otherwise should be avoided. Use alternative where possible	Stable dose permitted if used prior to entry, otherwise should be avoided. Use alternative where possible
Endothelin receptor antagonists	During the 4 weeks prior to visit 1 permitted if the dose is stable throughout	Stable dose permitted	Stable dose permitted	Stable dose permitted
Systemic steroids (im, iv, po)	Permitted during the 4 weeks prior to visit 1 if the dose is stable throughout and is planned to remain stable throughout the trial and at a dose of prednisolone ≤10 mg or equivalent.	Not permitted except prednisolone (≤10 mg or equivalent)	Should be avoided if alternatives are available, Prednisolone (≤10 mg or equivalent) is permitted	Should be avoided if alternatives are available. Prednisolone (≤10 mg or equivalent) is permitted

Table 4.2.2.1: 1 Concomitant medication restrictions cont.

Medication	**Prior to trial (Visit 1)**	**During screening/ run-in**	**During Treatment Period**	**In the Follow-up Period**
Immunosuppression therapy or immunotherapy (for systemic steroids see above)	Not permitted 3 months prior to visit 1	Not permitted	Not permitted	Not permitted
SGLT2 inhibitors	During the 4 weeks prior to visit 1 permitted if the dose is stable throughout	Stable dose permitted, initiation not permitted	Stable dose permitted, initiation not permitted	Stable dose permitted, initiation not permitted
Other anti-diabetic treatment (e.g. GLP1R agonists)	During the 4 weeks prior to visit 1 permitted if the dose is stable throughout	Stable dose permitted	Stable dose permitted	Stable dose permitted
Phosphodiesterase-5 inhibitors, non-specific phosphodiesterase inhibitors (such as dipyridamole and theophylline)	Not permitted within 4 weeks prior to visit 1	Not permitted	Not permitted	Not permitted
NO donors including nitrates*	Not permitted within 4 weeks prior to visit 1	Not permitted	Not permitted	Not permitted
sGC-stimulators / activators (other than BI 685509)	Not permitted within 4 weeks prior to visit 1	Not permitted	Not permitted	Not permitted
Chronic renal replacement therapy	Not permitted	Not permitted	Not permitted	Not permitted
Treatment for cancer	Not permitted two years prior to visit 1. Some exclusions apply e.g. for Basal Cell Carcinoma – please discuss with sponsor	Not permitted	Not permitted	Not permitted

* In case a sublingual nitrate is needed for suspected acute coronary syndrome, when the patient is on trial treatment, close monitoring of the blood pressure is required.

Table 4.2.2.1: 1 Concomitant medication restrictions cont.

Medication	**Prior to trial (Visit 1)**	**During screening/ run-in**	**During Treatment Period**	**In the Follow-up Period**
Other Investigational Medicinal Product or Investigational Device	Not permitted within 30 days or 5 half-lives (whichever is longer) prior to visit 1. Biologics are not permitted within 12 months prior to visit 1.	Not permitted	Not permitted	Not permitted
Treatment with clinically relevant OATP1B1/3 inhibitors and clinically relevant UGT inhibitors/ inducers as provided in the Investigator. Site File (ISF)	Not permitted within ≥ 4 weeks prior to visit 1	Not permitted	Not permitted	Permitted
Drugs with known risk of Torsade de Pointes	Not permitted at least 5 half-lives of such drug prior to visit 1	Not permitted	Not permitted	Not permitted
Herbal or natural products (Including Traditional Chinese Medicine)	Recommended to be stopped. Should not be initated at or after screening	Initiation not permitted. If used at a stable dose prior to screening may be continued	Initiation not permitted. If used at a stable dose prior to screening may be continued	Initiation not permitted. If used at a stable dose prior to screening may be continued

4.2.2.2 Restrictions on diet and life style

There are no restrictions on diet and life style. Drastic changes of diet and lifestyle in the course of the trial should be avoided. This includes unusual and strenuous exercise for the patient.

4.2.2.3 Contraception requirements

WOCBP (for the definition please refer to section 3.3.3) trial participants, must use a highly effective method of birth control throughout the trial, and for a period of at least 7 days after last trial drug intake, if their sexual partner is a male able to father a child. No contraceptive is required for the WOCBP participant's partner.
Highly effective methods of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly include (examples depending on approval status in each country):
Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
Bilateral tubal occlusion.

A male trial participant must be vasectomised with documented absence of sperm or use a condom until at least 7 days after last trial drug intake , if their sexual partner is a WOCBP. No contraceptive is required for the male participant's partner.

Alternatively, WOCBP participants and male participants able to father a child must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.
A patient will be considered as non-compliant in taking their trial medication if they have missed 4 consecutive doses or more. There are permitted exceptions to this, please see sections 3.3.4.1 (discontinuation of trial treatment) and 4.1.4 (withdrawal and assignment and administration) for further details.

A patient would also be considered as non-compliant if the patient, in the investigator's opinion, has not followed the drug administration guidance on a consistant basis, e.g. repeatedly not taking 3 tablets a day, or repeatedly not following the dosing interval.

Compliance will be verified by the CRA authorised by the sponsor.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 UACR

Urinary albumin and creatinine measurements are the basis for the calculation of urine albumin creatinine ratio (UACR). FMV and 10-hour urine samples will be collected by the patient at home.

The first morning void is the first urination after the patient wakes up at their usual time to start their day. Thus, if the patient goes back to sleep after urinating early in the morning this void does not need to be collected or documented. This applies also to any urinations earlier during the night in patients who have nocturia. There may be cases when a patient might go back to bed after their usual rising time. In those cases, the void at their usual rising time constitutes the first morning void.

Starting with the baseline run-in period, UACR will be determined on two consecutive days to average biological variability at the timepoints indicated in the flow chart. On each collection day a sample must be obtained from the patient's FMV and from the total of urine collected over 10 hours after the FMV on the same day. Intake of trial medication in the morning should always occur after the FMV has been collected. Containers for collection of urine will be provided by the same central lab that will perform specimen management. An appropriate number of containers 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. Urinary creatinine may also be used for normalisation of exploratory urinary biomarkers (see section 5.4.1).

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 the 12-lead ECG and prior to blood sampling as applicable.

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. At Visits 3 to 8 vital signs will be measured before dosing and approximately 30 min and 120 min after dosing. 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 and UACR for eligibility and safety analyses, the respective reference ranges will be provided in the ISF.

Patients do not have to be fasted for the blood sampling for the safety laboratory.

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. Should a patient not fulfil all lab requirements to take part in the trial due to a transitional medical condition, the patient may continue in the run-in phase but not be randomised until the re-test of the lab result has shown eligibility of the patient.

To test the eGFR throughout the trial, a small capillary blood volume will be collected by the patient (if needed with assistance by the site staff or caregiver) with the [redacted] at the time points indicated in the flow chart. Therefore during each period of home based urine collection for UACR analysis patients will need to draw one blood sample on their own and ship 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 samples collected at visits will be compared to the eGFR calculations based on the common safety blood sample to show comparability for future trials.

In case the criteria for a potential severe DILI are fulfilled, a number of additional measures will be performed (please see section 5.2.6.1 and the DILI Checklist provided in the eDC system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

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

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

Table 5.2.3: 1 Safety laboratory tests

Short name	Name of assay	Substrate	Other information
Blood serum			
HCT	Haematocrit	Haematocrit	
HGB	Haemoglobin	Haemoglobin	
RBC	Red blood cell counts	Erythrocytes	
WBC	White blood cell counts	Leukocytes	
PLTCT	Platelets	Platelets	
RETABS	Reticulocytes absolute	Reticulocytes	
NEUABS	Neutrophils absolute	Neutrophils	
EOSABS	Eosinophils absolute	Eosinophils	
BASABS	Basophils absolute	Basophils	
MONABS	Monocytes absolute	Monocytes	
LYMABS	Lymphocytes absolute	Lymphocytes	
SGPT	ALT/SGPT, SGPT	Alanine Aminotransferase	
SGOT	AST/SGOT, SGOT	Aspartate Aminotransferase	
ALKP	Alkaline phosphatase	Alkaline Phosphatase	
GGT	GGT	Gamma Glutamyl Transferase	
LDH	LDH	Lactate Dehydrogenase	
CK	Creatine kinase	Creatine Kinase	
CREE	Creatinine, Enzymatic	Creatinine	Enzymatic
GFRE	GFR/Creatinine cl.-calc (CKD-EPI)	GFR from Creatinine Adjusted for BSA	CKD-EPI ALGORITHM
TBILI	Bilirubin, total	Bilirubin	
BILID	Bilirubin, direct	Direct Bilirubin	If total bilirubin is elevated
TPRO	Protein, total	Protein	

Table 5.2.3: 1 Safety laboratory tests cont.

Short name	Name of assay	Substrate	Other information
Blood serum			
ALB	Albumin	Albumin	
UREA	Urea	Urea	UREA
URIC	Uric acid	Urate	
HBA1C	Hgb A 1c,glycated	Hemoglobin A1C	Visit 1 and EoT
NA	Sodium	Sodium	
K	Potassium	Potassium	
MG	Magnesium	Magnesium	
CA	Calcium	Calcium	
P	Phosphate	Phosphate	
TRIGL	Triglyceride	Triglycerides	
CHOL	Cholesterol, total	Cholesterol	
HDLCHOLD	HDL cholesterol (direct)	HDL Cholesterol	
LDLCHOLD	LDL cholesterol (direct)	LDL Cholesterol	
Urinalysis			
UNIT	Urine nitrite (qual)	Nitrite	QUALITATIVE MEASUREMENT
UPROZ	Urine protein (qual)	Protein	QUALITATIVE MEASUREMENT
UGLU	Urine glucose (qual)	Glucose	QUALITATIVE MEASUREMENT
UKET	Urine ketone (qual)	Ketones	QUALITATIVE MEASUREMENT
UROBZ	Urobilinogen (qual)	Urobilinogen	QUALITATIVE MEASUREMENT
UBILI	Urine bilirubin (qual)	Bilirubin	QUALITATIVE MEASUREMENT
URBCZ	Urine RBC (qual)	Erythrocytes	QUALITATIVE MEASUREMENT
UWBCZ	Urine WBC (qual)	Leukocytes	QUALITATIVE MEASUREMENT
UPH	Urine pH	pH	

In case qualitative parameters are abnormal, a quantitative analysis will be performed by the central laboratory.Pregnancy testing in WOCBP will be performed at Visit 1 (serum), thereafter pregnancy tests will be on urine.

If blood sampling for safety at the trial site or patient's home through a member of site staff or CRO is not possible (due to a force majeure), safety lab analyses can be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and proper documentation in the eCRF. In case only central lab is implemented in the eCRF, a clinically relevant safety issue has to be entered as adverse event. Minimum required safety lab parameters are:

Table 5.2.3: 2 Minimum required safety laboratory tests for local labs

Short name	Name assay	Substrate	Other information
Blood serum			
HGB	Haemoglobin	Haemoglobin	
RBC	Red blood cell count	Erythrocytes	
WBC	White blood cell count	Leukocytes	
PLTCT	Platelets	Platelets	
SGPT	ALT/SGPT, SGPT	Alanine Aminotransferase	
SGOT	AST/SGOT, SGOT	Aspartate Aminotransferase	
ALKP	Alkaline phosphatase	Alkaline Phosphatase	
CREE	Creatinine, Enzymatic	Creatinine	Preferably enzymatic, but any other method is acceptable
TBILI	Bilirubin, total	Bilirubin	
UREA	Urea	Urea	UREA
NA	Sodium	Sodium	
K	Potassium	Potassium	

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified physician, nurse or technologist and results will be recorded as scheduled in the flow chart. Vitals signs will be measured before the ECG is taken. The ECG should be performed after the patient has rested for at least 5 minutes in a supine position and prior to blood sampling. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate. ECG abnormalities will be carefully assessed by the investigator, and if trial discontinuation criteria are met (refer to Section 3.3.4.1), the patient will be discontinued from the trial.

Copies of ECGs will be sent to a central ECG vendor for storage and if required to enable a subsequent centralised and independent re-evaluation.

5.2.5 Other safety parameters

N/A

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 should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- 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.

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.

For Japan only: An event that possibly leads to disability will be handled as 'deemed serious for any other reason' and, therefore, reported as an SAE.

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 eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. 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 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.

The following are considered as AESIs:

- Severe orthostatic dysregulation as judged by the investigator
- Severe hypotension as judged by the investigator
- Syncope
- Potential Severe DILI:

  A potential severe DILI that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - An elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of

total bilirubin ≥2 fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
- ALT and/or AST elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the eDC system.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the "DILI checklist" should be followed.

5.2.6.1.5 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.

5.2.6.1.6 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 given study treatment, 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).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:
From signing the informed consent onwards until the follow-up visit 1 all AEs (non-serious and serious) and all AESIs.
After follow-up-visit 1 until the individual patient's end of trial:
cancers of new histology and exacerbations of existing cancer, all trial treatment related SAEs and all trial treatment related AESIs.
After the individual patient's end of the trial:
the investigator does not need to actively monitor the patient for new AEs but should report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

PK sampling times and periods are indicated in the Flow Chart for Procedures. Date and clock time of drug administration(s) and PK sampling will be recorded in the eCRF. Patients do not need to come fasted to visits, but the fasting status needs to be recorded for PK sampling.

Noncompartmental PK parameters will be calculated based on actual sampling times using a validated PK software (Phoenix® WinNonlin® 8.1). Further PK parameters will be calculated as feasible and may include, but are not limited to:
C_{max} (maximum measured concentration of the analyte in plasma)
t_{max} (time from dosing to maximum measured concentration of the analyte in plasma)
$AUC_{t1\text{-}t2}$ (area under the concentration-time curve of the analyte in plasma over the time interval t1 to t2 after single dose administration)
$C_{max,N}$ (maximum measured concentration of the analyte in plasma following N doses)
$t_{max,N}$ (time from last dosing to maximum measured concentration of the analyte in plasma after administration of N doses)
$AUC_{t1\text{-}t2,N}$ (area under the concentration-time curve of the analyte in plasma over the time interval t1 to t2 after administration of Nth dose)
$C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)
$t_{max,ss}$ (time from last dosing to maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)

$AUC_{t1\text{-}t2,ss}$ (area under the concentration-time curve of the analyte in plasma over the time interval t1 to t2 at steady state)
$C_{pre,N}$ (Predose concentration of the analyte in plasma immediately before administration of the Nth dose after N-1 doses were administered)
$C_{pre,ss}$ (Predose concentration of the analyte in plasma at steady state immediately before administration of the next dose)
$R_{A,Cmax}$ (accumulation ratio of the analayte in plasma at steady state after multiple dose administration over a uniform dosing interval τ, expressed as ratio of C_{max} at steady state and after single dose)
$R_{A,Cmax,N}$ (accumulation ratio of the analayte in plasma after administration of Nth dose over a uniform dosing interval τ, expressed as ratio of C_{max} after the Nth dose and after single dose)

Additional PK parameters may be calculated as appropriate.
Individual plasma concentration data and the PK parameters calculated thereof will be tabulated and graphically displayed. A subject's PK data will be flagged and excluded from the PK analyses in case of protocol deviations relevant to the evaluation of PK or in case of PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Reasons for exclusion of a subject's data will be documented in the CTR.

Protocol deviations relevant to the evaluation of PK may be
Incorrect trial medication taken
Incorrect dose of trial medication taken

PK non-evaluability applies, if for example
The subject experienced emesis that occurred in the time window of two times median t_{max} (median t_{max} is to be determined excluding the subject(s) experiencing emesis)
The subject has missing samples/concentration data at important phases of the PK disposition curve

5.3.2 Methods of sample collection

For quantification of analyte plasma concentrations of BI 685509 blood will be taken from an antecubital or forearm vein at the times indicated in the flow chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. Further details of sample processing for plasma generation will be described in the study-specific lab manual (see ISF).

After analysis the samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations, but no later than 5 years after the final study report has been archived.

[redacted]

5.3.4 Pharmacokinetic-pharmacodynamic relationship

The PK and PD data from this study may be used for an exploratory investigation of the PK-PD relationship of BI 685509. A population PK-PD analysis may be performed at the project level using a non-linear mixed effects modelling approach. This analysis will not be part of the CTR, but will be reported separately.

5.4 ASSESSMENT OF BIOMARKERS

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in sections 5.1 and 5.2.

[redacted]

5.4.2 Method and timing of sample collection

Urine - UACR
See section 5.1.1.

Urine – exploratory biomarkers
Urine samples for exploratory biomarkers will be taken from the urine sample collected for safety at the timepoints shown in the flow chart.

Plasma
Blood will be drawn into a K-EDTA blood collection tube at the time points indicated in the flow chart.

Serum
Blood will be drawn into a serum separation tube at the time points indicated in the flow chart.

5.4.3 Pharmacogenomics biomarkers

Pharmacogenomics investigates genetic variations to explain and to predict an individual's response to drugs. Therefore, a blood sample for pharmacogenomic testing will be taken from each subject. In case of unexplainable variability of PK or PD parameters, DNA may be extracted from these samples and used for exploratory analysis of variants of the sGC gene and genes involved in Absorption, Distribution, Metabolism and Excretion (ADME) of drugs. It is not intended to include these data in the final report. However, the data may be part of the report if necessary. All remaining samples will be destroyed no later than the sign-off of the CTR.

Detailed instructions for pharmacogenomics sampling, including handling and shipment of samples will be provided in the laboratory manual in the ISF.

5.4.4 Method of sample collection

One blood sample will be taken from an arm vein in a PAXgene blood DNA drawing tube preferably at Visit 3.

[redacted]

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

Sampling will be performed at the time points specified in the flow chart.

Plasma banking: Blood will be drawn into a K-EDTA blood collection tube.

Serum banking: Blood will be drawn into a serum separation tube.

Urine banking: Urine will be taken at the timepoints shown in the flow chart, after tubes for exploratory biomarkers (see section 5.4.2) have been filled. The urine will be taken from the urine sample collected for safety.

For all biospecimens collected, detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. Samples will be stored at an external biobanking facility contracted by the sponsor.

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 monitor safety aspects and to determine efficacy, PK and PD markers of BI 685509 in an appropriate way.

The scheduled measurements are appropriate to assess drug induced changes in kidney function with regard to albuminuria (UACR), and safetywise in vital signs, standard laboratory values, and ECG. While UACR is widely accepted as a PD marker for efficacy in renal trials, safety lab, vital signs and ECG are standard to examine the safety of the investigational product and to descriptively identify differences between different doses and placebo.

Instead of the widely used FMV, serial 10-hour urine sampling over day were selected as an appropriate measure for the primary endpoint, as this is supposed to correlate with the immediate effect of BI 685509 after administration and has shown a relevant change in

UACR in the respective phase I MRD trial, while FMV as a standard measure will serve as a secondary endpoint.

[redacted]

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All visits should should be scheduled according to the flow chart. Each visit date (with its window) is to be counted from Day 1 (randomisation). If any visit has to be rescheduled, subsequent visits should follow the original visit schedule. The trial medication packs contain sufficient medication to allow for these time windows.

All trial visits should be initiated preferentially in the morning. Patients should be instructed to not take their morning dose of the study medication at home at scheduled visit days as they will be dosed whilst at the study site.

Patients do not need to come fasted to study visits, but their fasting status will have to be recorded in the CRF for PK sampling timepoints. From the first PK sample before administration of BI 685509 until the PK sample 2 hours after administration the patient should only drink water and eat no food unless it is medically needed.

Unscheduled visits will be possible at the discretion of the investigator at any time in order to check the safety of the patient or to provide trial medication e.g following an interruption. 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 and Flow Chart for Procedures. All assessments should be performed before study drug administration.

Where the following assesments occur at a visit they should be performed in the following order:
Vital signs – see flow chart and Flow Chart for Procedures
ECG – see flow chart and Flow Chart for Procedures
Blood draws including trough PK and [redacted] – other PK samples are drawn after drug administration (see Flow Chart for Procedures)
Spot urine (mid-stream) samples can be collected at any time prior to trial medication. Aliquots should be taken from the urine sample in the following order: first safety and pregnancy sample (if applicable), then if applicable biomarkers, followed by biobanking (if consent obtained).

Please see 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 and Flow Chart for Procedures – 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 – Laboratory Tests
Section 5.2.4 – Electrocardiograms
Section 6.2.1 – Telemedicine Contacts and Home Visits

6.2.1 Telemedicine Contacts and Home Visits

In this study Telemedicine Contacts and Home Visits may be performed if all local approvals are in place and confirmed by the sponsor.

These contacts are used to help support patients with protocol procedures and compliance. The Home visits can be used to reduce the burden of participation on patients, and also to encourage participation following the COVID-19 or similar pandemic in case a patient is otherwise not able to travel to the site.

Telemedicine contacts should be performed as indicated in the flow chart but may also be performed at any time during the course of the trial to support patients with the home sampling and/ or following up on AEs or trial medication compliance. This may be via a straightforward phone call between the patient and an appropriately qualified member of the Investigational Site or via a video call using a smartphone/ tablet application. If the telemedicine contact is being done during a home visit to support a physician guided physical exam this must be done as a video call.

The following visits may be performed at the patient's home, i.e. a home visit by a nurse or physician:
Visit 2 (Run-in)
Visits 7 and 8 (Treatment Phase)
FUp3
Unscheduled visits where a physical exam is not required

If the patient reports an AE during these visits then it's at the discretion of the Investigator as to whether a telemedicine contact is need to support this assessment or even if the patient should attend the site.

The following visits may be performed at the Patient's home by a physician. If allowed by local regulations these visits may also be performed by a nurse if they are qualified to perform a physical exam or if they are guided by a physician via a video call i.e. a home visit with telemedicine. The guided physical exam cannot be done via a phone call as the physician must observe the nurse who is doing the physical examination:

Visits 6 and FUp2

Home visits may be performed either by an appropriately qualified member of the Investigational Site team or by a CRO working on behalf of the sponsor. Where a CRO is used all source information will be made available/ transferred to the Investigational Site.

To support visits performed at the patient's home direct shipment of the trial medication will be managed by the site or the provider directly as permitted by local regulations. Unused medication provided at a previous visit may be returned to the site via a courier. If needed

also the laboratory kits and ancillary materials required by the nurse may be shipped to the patient prior to the visit.

All other visits must be performed at the Investigational Site. The only exception to this is if COVID-19 or similar pandemic restrictions are in place. In these exceptional cases, if the scheduled visits at the trial site are impossible, they may be performed at the patient's home or as a telemedicine contact or as a combination, based on a thorough benefit-risk assessment (see section 1.4.2). Critical safety measures will remain in place. All home visits/telemedicine contact need to be discussed with and approved by the sponsor`s trial team. Local regulatory and legal requirements of the participating country still apply.

6.2.2 Screening and run-in 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 considered to be enrolled in the trial and have started screening. The patient should be recorded on the enrolment log and be registered in the IRT system as a screened patient before any other activites are performed. Patients who do not start the run-in period should be registered as a screen failure in the IRT system. 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.

Run-in Period
The run-in period for this trial lasts for two weeks prior to randomisation. During this period the patient will start to collect their UACR samples as described in the flow chart and in section 5.1.1.

6.2.3 Treatment period

The treatment period in this trial is 20 weeks. All visit procedures should be completed as indicated in the flow chart.

6.2.4 Early discontinuation of Treatment

Patients who discontinue treatment prematurely and who do not withdraw their informed consent should return for an End of Treatment visit.

If the patient has stopped taking trial drug the day of a scheduled visit or one day prior, the scheduled visit should be performed as an EoT Visit. All samples including PK and all biomarkers ([redacted], UACR and others) should be collected in addition to safety samples. If the early discontinuation does not coincide with a scheduled visit, the patient should return for an EoT Visit. PK or biomarker samples should not be collected, but all safety assessments must be performed as indicated in the flow chart.

The patient should be encouraged to complete all visits and procedures in the FUp period (see section 6.2.5). If the patient does not wish to complete all visits or procedures, they should have FUp1 as a mimimum.

6.2.5 Follow-up period and trial completion

The Follow-up Period consists of three visits, FUp1, FUp2 and FUp3 with a timepoint for UACR and [redacted] in between these visits, please see the flow chart for timelines and visit details.

The Residual Effect Period (REP) in this study is 7 days, visit FUp1 should therefore be performed no earlier than 7 days after the End of Treatment Visit.
FUp visits FUp2 and FUp3 should also be scheduled relative to the EoT Visit, i.e. FUp2 will be 2 weeks after EoT, 3 weeks after EoT there will be home sampling without visit, and FUp 3 should be 4 weeks after EoT.

Visit FUp3 may be conducted as a Home visit where permitted (see section 6.2.1), however should a patient have any adverse event(s) that require assessment then the Investigator may request they attend the site for a full assessment.

Participation in this trial is concluded once FUp3 has been completed.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This is a Phase II, randomised, double-blind (within dose groups), placebo-controlled and parallel group trial to investigate the effect of different doses of BI 685509 on UACR reduction over 20 weeks in patients with diabetic kidney disease.

The primary endpoint for patients is Change from baseline in log transformed UACR measured in 10-hour urine after 20 weeks of trial treatment. The purpose of this trial is to demonstrate PoC (proof of concept) of clinical activity of BI 685509 on the primary endpoint and to determine the optimal dose for phase III. The methodology for dose finding employing both multiple comparison procedures and modelling techniques (MCPMod) will be applied to the 4 groups of patients, i.e. the patients on BI 685509 in each of the three dose groups and the combined patients from all dose groups who are not on BI 685509.

7.1 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis is that there is a flat dose response curve for Change from baseline in log transformed UACR measured in 10-hour urine after 20 weeks of trial treatment comparing the placebo and the BI 685509 dose groups whereas the alternative hypothesis is that, there is a non-flat dose response curve indicating a benefit of BI 685509 in at least one of the patient groups.

The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error (one-sided α of 5 %). The pre-specified models and their parameters used for this test are outlined in section 7.2.1.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The following analysis sets will be defined for statistical analyses:

Entered Set (ES): This patient set includes all patients who signed informed consent. The ES will be used for the analysis of patient desposition.

Randomised Set (RS): This patient set includes all entered and randomised patients. The RS will be used for the analyses of protocol deviations as well as demographics and baseline characteristics.

Treated Set (TS): This patient set includes all patients who received at least one dose of study medication. The TS is used for safety analyses and exposure.

Full Analysis Set (FAS): The patient set includes all patients who had at least one baseline measurement of UACR in week -2, -1, or 0 and at least one post-baseline measurement after week 6. The FAS is the main analysis set for the analysis of efficacy.

The pharmacokinetic set (PKS): This patient set includes all patients in the TS who provide at least one PK parameter that was not excluded because of protocol deviations relevant to the statistical evaluation of PK endpoints as defined in section 5.3.

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

7.2.2 Primary endpoint analyses

The primary objectives are to demonstrate a non-flat dose response curve, evaluate the quantitative treatment effect size, and evaluate the dose-response relationship. The primary analysis will be performed on the FAS.

For the proof of concept (PoC) and dose finding, both multiple comparison procedures and modelling techniques (MCPMod) will be applied. The primary estimand of interest is the treatment effect using a primary approach. In the primary approach, trial medication is assumed to be taken as randomised and an intercurrent event is defined as an event of treatment discontinuation, death, or dropin/dropout of SGLT2i. The primary approach for primary analysis will include all data prior to intercurrent event. Any data collected after the intercurrent event will not be included in the primary analysis. The resulting missing data will be assumed to be missing at random (MAR).

[redacted]

The three different approaches for handling ICEs are summarized in the Table 7.2.2: 1 below.

Table 7.2.2: 1 Summary of strategies for handling ICEs

Estimand strategy name	*Treatment*	*ICE handling*
Primary approach	Randomised treatment	Study med d/c: include data prior to study med d/c. Death: include data prior to death. SGLT2i initiation/discontinuation: include data prior to SGLT2i start/stop.

Table 7.2.2: 1 Summary of strategies for handling ICEs cont.

Estimand strategy name	*Treatment*	*ICE handling*
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Treatment effect
The primary analysis will first address a dose relationship between doses of BI 685509 and placebo. The analysis will include the fixed, categorical effect of treatment at each visit, and the fixed continuous effects of baseline log transformed UACR at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

To conduct multiple comparison in MCPMod across doses, covariate adjusted fixed effect estimates of average response for each dose group and the covariance matrix will be extracted from the fit by the following MMRM and used for MCPMod analysis.

Statistical model (MMRM):

$$y_{ijklm} = \beta_j U_i + \tau_{jk} + \eta_l + \psi_m + e_{ij},$$

where
$e_{ij} \sim N(0, \Sigma)$,
y_{ijkm} = reduction in log transformed UACR at visit j from baseline for subject i in stratum m (m=1,2) receiving treatment k (k=1,…,4),
U_i = the baseline* measurement of log-transformed UACR of subject i,
β_j= coefficient of baseline effect at visit j,
τ_{jk} = the effect of treatment k at visit j,
η_l = the effect of stratum l for type of diabetes mellitus,
ψ_m = the effect of stratum m for SGLT2i use at randomisation,
e_{ij} = the random error associated with the jth visit of the ith subject. Errors are independent between subjects,
Σ = an unstructured covariance matrix.
* baseline is defined as the mean of all non-missing assessments from Visit 2 until prior to the first intake of trial medication.

A non-flat dose-response relationship is established if for primary endpoint, the null hypothesis of no dose effect (i.e., a flat dose response curve) is rejected for at least one of the pre-specified models with respect to the one-sided type I error at 5%. PoC is established if for the primary endpoint, at least ≥ 20% mean reduction in UACR at least in one BI 685509 dose

group (0.22 difference in mean log transformed UACR) compared to placebo. For PoC, patients will be analyzed as randomised, according to the primary approach in Table 7.2.2: 1.

The same process will be repeated for the supplemental 1 and 2 approaches in Table 7.2.2: 1.

Dose finding
The second primary objective is to determine therapeutic dose. The trial will characterize the dose-response curve for BI 685509 in patients with diabetic kidney disease (DKD) by assessing 3 doses and placebo. The response is the change from baseline in log transformed UACR measured in 10-hour urine after 20 weeks of trial treatment. Patients will be evaluated in the dose group they were assigned to at randomisation for primary analysis in the MCPMod analysis.

The analyses for dose-finding will be performed using MCPMod whereby several possible dose response models (patterns) will be evaluated to identify the best-fitting model or subset of models (refer to Figure 7.5: 1). If PoC is established, the statistically significant (best fitting) model(s) from the candidate set are refitted to the data to generate new estimates for all model parameters from the data. The final model will be obtained via model averaging across the significant models based on Akaike Information Criterion (AIC). The target dose(s) can be estimated from that model by incorporating information on the minimum clinically relevant effect and accounting for safety. Doses within the dose range investigated (0 to 9 mg, total daily dose) will be considered.

7.2.3 Secondary endpoint analyses

The analysis for the change of UACR in FMV urine will be performed by using MMRM.

Descriptive statistics will be provided for the change of UACR in FMV urine/10-hour urine and the UACR response rate along with figures.

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 7 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

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.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events that occur between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Adverse events will be summarized by the treatment to which the subject was randomised , and the treatment at the onset of AE for any drug-related AE. In addition, summary of subjects with down-titration due to AE will be provided.

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.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Further details will be provided in the TSAP.

7.2.6 Other Analyses

7.2.7 Interim Analyses

No interim analysis is planned in this trial.

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. Handling of missing data for secondary endpoints as well as for sensitivity analysis will be described in the TSAP.
Handling of missing PK data will be performed according to the relevant BI internal procedures.

7.4 RANDOMISATION

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

In order to ensure a balance of patients who are on SGLT2 inhibitors and who are type 1 or 2 diabetes mellitus compared with those who are not, the trial will be stratified according to SGLT2 inhibitor use and type of diabetes mellitusat randomisation. Patients will be randomised to 1 mg tid, matching placebo, 2 mg tid, matching placebo, 3 mg tid, and matching placebo in a 3:1:3:1:3:1 ratio. There will be 60 patients on BI 685509 and 20 on placebo in each dose group (240 in total).

7.5 DETERMINATION OF SAMPLE SIZE

The sample size calculation is conducted assuming effect size of BI 685509 versus placebo, (0, 0.10, 0.20, 0.35) for (placebo, BI 685509 3 mg, BI 685509 6 mg, BI 685509 9 mg total daily dose) in log transformed UACR measured in 10-hour urine after 20 weeks of trial treatment from baseline. The pre-specified models in Figure 7.5: 1 are used for testing null hypothesis. The following models have been selected as the candidate set of possible dose response patterns based on current expectation. Assuming the following dose groups will be tested: placebo, active BI 685509 3 mg, 6 mg, and 9 mg in terms of total daily dose.

Emax: 80% of the maximum effect is achieved at 6 mg.
Exponential: 20% of the maximum effect is achieved at 3 mg.
Linear: No assumption is needed.
Quadratic: 50 % of the maximum effect is achieved at a dose of 3 mg.
90 % of the maximum effect is achieved at a dose of 6 mg.
Sigmoid emax: 30 % of the maximum effect is achieved at a dose of 3 mg.
90 % of the maximum effect is achieved at a dose of 6 mg.

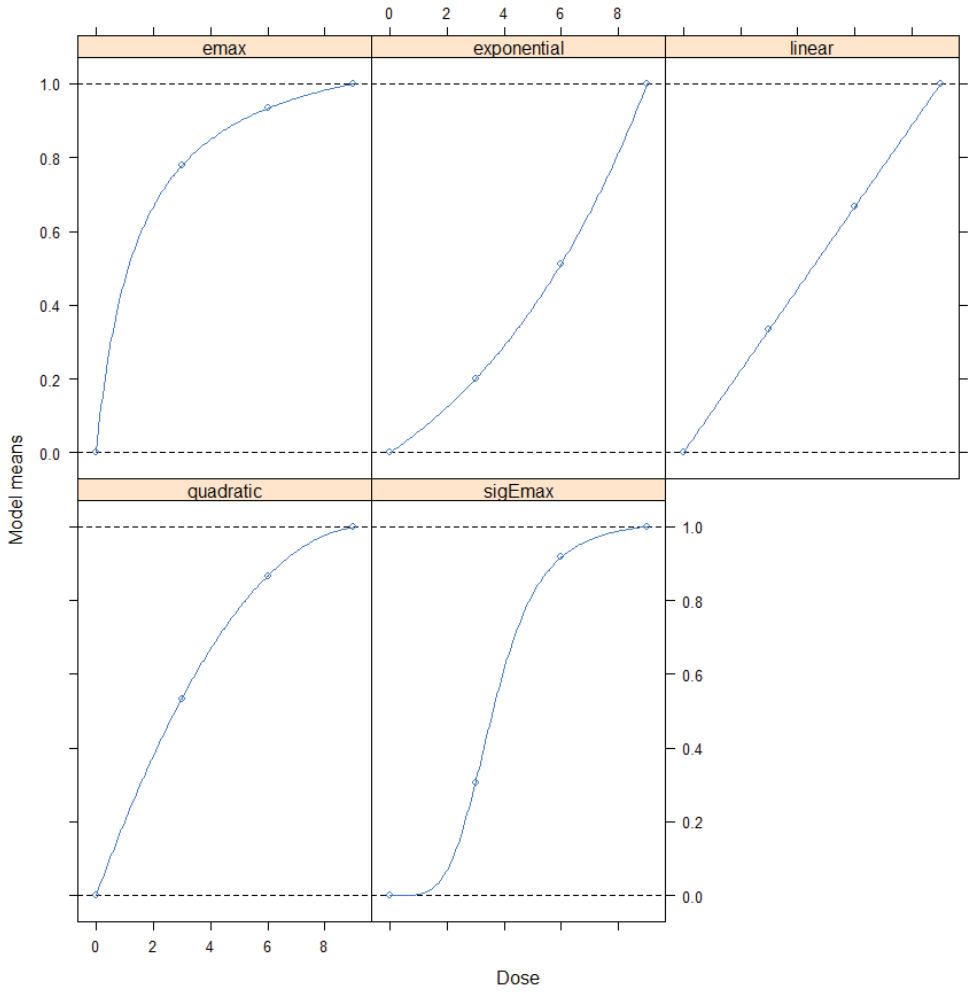

Figure 7.5: 1 Shape of the considered dose response patterns for the MCPMod analysis (dose reflects planned daily dose)

In a scenario with assumed effect of (0, 0.10, 0.20, 0.35) in log (UACR) change from baseline to week 16 for (placebo, BI 685509 3 mg, BI 685509 6 mg, BI 685509 9 mg total daily dose), 88.5% of statistical power considering one-sided 5% alpha was achieved with sample size per treatment from 60. The sample size/power calculation were determined based on 10,000 simulations for the scenario using R3.6.1.

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 Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) 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) 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. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

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 (substance, trial number, patient number, date patient was informed).
Dates of patient's visits, including dispensing of trial medication.
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 to a treatment 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. 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.
ECG results (original or copies of printouts).
For electronic patient reported outcomes the electronic record is the source document.
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.
Source documentation for telemedicine visits.
Source documentation for visits performed at the patient's home.

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 has 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.

8.6 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").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.

Last Patient Last Visit for Primary Endpoint (LPLV PE) is defined as the date when the last patient in the entire trial has had the EoT visit or withdrawn from the trial whatever is later.
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.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A Steering Committee (SC, alternatively: sGC operations committee) consisting of external experts involved in the trial and sponsor representatives will be established. The SC may cover multiple phase II trials taking place at the same time. The composition of the SC will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the SC members and the sponsor and also summarised in a SC charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.
The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to:
- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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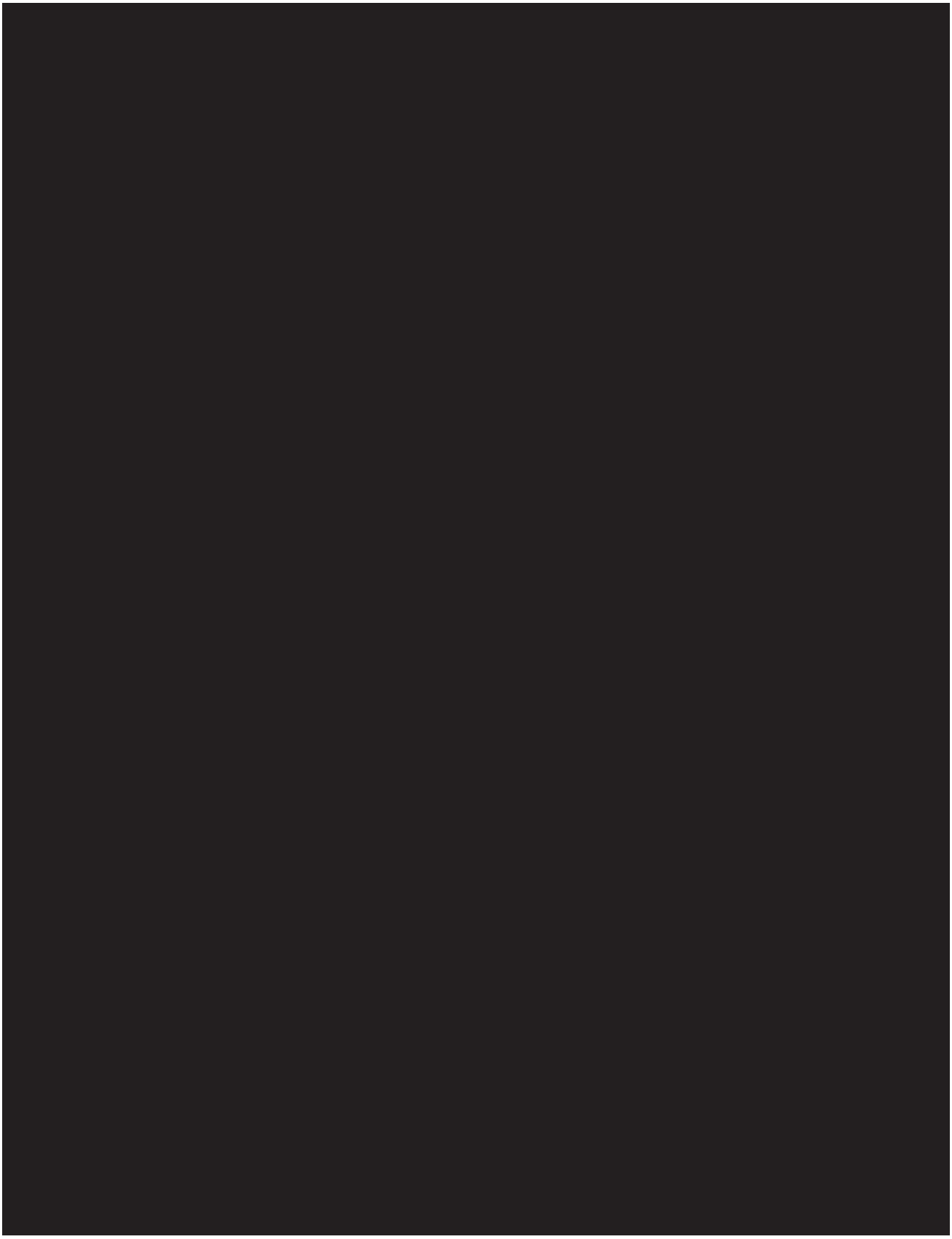
10. APPENDICES



10.2 GFR CKD-EPI FORMULA

Calculation Name	**GFR CKD-EPI**	
Formula	**Units**	**Decimal Places**
Conventional: **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 (except Japanese), 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} **Japanese Formula:** Female with a serum creatinine value of ≤0.7 mg/dL 0.813 x 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 0.813 x 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 0.813 x 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 0.813 x 141 x (Serum Creatinine (mg/dL) / 0.9) $^{-1\,209}$ x (0.993)^{age}	mL/min/ 1.73m^2	0

Creatinine in mg/dL is rounded to 2 decimal places prior to applying the formula.		
SI: 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.	

10.3 DOWN-TITRATION GUIDE

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		15 Dec 2020
EudraCT number **EU number**		2020-002929-28
BI Trial number		1366-0005
BI Investigational Medicinal Product(s)		BI 685509
Title of protocol		Randomised, double-blind (within dose groups), placebo-controlled and parallel group trial to investigate the effects of different doses of oral BI 685509 given over 20 weeks on UACR reduction in patients with diabetic kidney disease
Global Amendment due to urgent safety reasons		
Global Amendment		X
Version 2.0 is considered to be the initial version of the CTP and includes some modifications after version 1.0 has been archived. The original version 1.0 of this protocol was not submitted to any authorities, ethics committees or institutional review board for approval of the clinical trial.		

11.2 GLOBAL AMENDMENT 2

Date of amendment		29 July 2021
EudraCT number **EU number**		2020-002929-28
BI Trial number		1366-0005
BI Investigational Medicinal Product(s)		BI 685509
Title of protocol		Randomised, double-blind (within dose groups), placebo-controlled and parallel group trial to investigate the effects of different doses of oral BI 685509 given over 20 weeks on UACR reduction in patients with diabetic kidney disease
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Flow Chart
Description of change		Added the column header “Post dose” and a cross to indicate post dose ECG at Visit 3. The post dose ECG was already mentioned in footnote xxii.

		Added new footnote xxii to explain timing of the planned last dose.
Rationale for change		Correction and clarification.
Section to be changed		Flow Chart, UACR and GFR Sampling Flow Chart and Section 3.1
Description of change		Extended the maximum time before randomisation from 28 to 35 days throughout the protocol.
Rationale for change		More time is needed to allow screening procedures to be repeated where permitted. Safety assessment such as vital signs, safety labs and physical examination will be performed again at Visit 2 and/or Visit 3 therefore there will be recent safety assessments prior to receiving the first dose of IMP.
Section to be changed		Flow Chart
Description of change		Rephrased footnote xviii from: "Should the first test for UACR at screening not match inclusion criteria due to UACR variability, this can be repeated once." To: "Should the first test for UACR at screening be borderline out of range and not match inclusion criteria due to UACR variability, this test can be repeated once. The result must be available and eligibility confirmed before the baseline UACR sampling starts."
Rationale for change		Clarification that the spot urine retest needs to be done and results received prior to start of baseline UACR sampling.
Section to be changed		1.4.2 Risks
Description of change		Removed "at home".
Rationale for change		Clarification. This relates to [redacted] blood sampling. It's intended that patients will use the [redacted] [redacted] to take capillary blood themselves both at home and also at the (applicable) site visit.
Section to be changed		3.1 Overall trial design
Description of change		Clarified that shipment of samples from patient's home can also be done by a nurse or equivalent function visiting the patient. Also clarified that this is applicable for both samples collected between visits and when home visits are performed.

		Rephrased text to clarify that the FUp3 Visit may occur at the site or the patient's home. Added local regulations and approvals as a requirement for Home Health Care services. Removed analysis of [redacted] as this is exploratory analysis.
Rationale for change		Clarifications
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Added further requirement to inclusion criterion #3: eGFR must remain ≥ 20 mL/min/1.73 m^2 after Visit 1 up to the start of Visit 3, measured by central or any local laboratory analysis.
Rationale for change		To ensure patient safety the eGFR value must not drop below 20 ml/min/1.73 m2 prior to visit 3. For the samples drawn at visit 3 and onwards withdrawal criteria have to be considered.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Rephrased inclusion criterion #6: From: "Stable on anti-hypertensives, NSAIDs, endothelin receptor antagonists, systemic steroids, within at least 4 weeks prior to Visit 1 until start of trial treatment, with no planned change of the therapy during the trial." To: "If the patient is taking any of the following medications they should be on a stable dose at least 4 weeks prior to visit 1 until start of treatment, with no planned change of the therapy during the trial: anti-hypertensives, NSAIDs, endothelin receptor antagonists, systemic steroids or SGLT2 inhibitors."
Rationale for change		Clarification
Section to be changed		4.1.4 and 4.1.4.2 Drug assignment and administration of doses for each patient
Description of change		Moved the descriptions of shipments to patients in a pandemic situation from section 4.1.4.2 to section 4.1.4 and added a statement that shipments will also be allowed for regular visits at the patient's home.
Rationale for change		Clarification
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment

Description of change		Footnote added: "* In case a sublingual nitrate is needed for suspected acute coronary syndrome, when the patient is on trial treatment, close monitoring of the blood pressure is required."
Rationale for change		Clarification on use of restricted nitrates in an emergency.
Section to be changed		4.3 Treatment Compliance
Description of change		Removal of tablet count recorded in the CRF.
Rationale for change		Implementation of the administrative letter. Tablet counts are not required for compliance calculation, but will be provided through accountability procedures at the site.
Section to be changed		5.1.1 UACR
Description of change		Definition of FMV added.
Rationale for change		Clarification.
Section to be changed		5.2.3 Safety laboratory parameters and Flow Chart
Description of change		Replaced requirement to test non-sterilized women <65 years of age with the requirement to test women of child bearing potential for pregnancy. Added clarification of why a safety laboratory may not be done at the central lab and added requirement to check S-creatinine to the minimum tests at the local lab. Added further explanation that capillary blood draws using the [redacted] should always be performed by the patient unless assistance is required.
Rationale for change		Pregnancy testing requirements have been updated as it is unnecessary for a women who is not, for whatever reason, of child bearing potential to undergo pregnancy testing. S-creatinine has been added as an important lab parameter to monitor kidney function. Further clarifications.
Section to be changed		5.3.2 Methods of Sample Collection
Description of change		Rephrased the following: "After completion of the trial the plasma samples may be used for further methodological investigations, e.g., for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations, but no later than 5 years after the final study report has been signed."

		To: "After analysis the samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations, but no later than 5 years after the final study report has been archived."
Rationale for change		Samples may be used for the described purposes directly after their originally intended analysis.
Section to be changed		5.4.1 Exploratory biomarkers
Description of change		Added further explanation on capillary blood draws, which can be assisted by site staff/nurse or a caregiver.
Rationale for change		Further clarification.
Section to be changed		6.2.1 Telemedicine Contacts and Home Visits
Description of change		Added further clarification on shipments to and from patient's home and physical examinations by a qualified nurse.
Rationale for change		Clarifications.
Section to be changed		7.2.5 Safety analyses
Description of change		Adverse events will be summarized by the treatment to which the subject was randomised, and the treatment at the onset of AE for the drug-related AE rather than the treatment at end of the up-titration period as was before.
Rationale for change		The original wording was reliant on a patient completing the up-titration period which may not be the case for all patients. The new wording is aligned with the Sponsor's Company standards.
Section to be changed		8.3.1 Source documents
Description of change		Deleted the following sentence: "This includes the values for eGFR and UACR and their method of analysis at or before screening to confirm eligibility."
Rationale for change		Since this is performed by the central lab and the sentence before already mentions all inclusion criteria, this sentence has been removed for clarification.

11.3 GLOBAL AMENDMENT 3

Date of amendment		13 October 2021

EudraCT number **EU number**		2020-002929-28
BI Trial number		1366-0005
BI Investigational Medicinal Product(s)		BI 685509
Title of protocol		Randomised, double-blind (within dose groups), placebo-controlled and parallel group trial to investigate the effects of different doses of oral BI 685509 given over 20 weeks on UACR reduction in patients with diabetic kidney disease

Global Amendment due to urgent safety reasons	
Global Amendment	X

Section to be changed		3.1
Description of change		Removed duplicate Figure 3.1: 1 from previous protocol version with 2 weeks screening instead of now 3 weeks.
Rationale for change		Correction. The removal of the figure was missed in global amendment 2.
Section to be changed		Flow Chart and Flow Chart for Procedures (Formerly PK Flow Chart)
Description of change		Addition of ECGs at visits where there were previously no ECGs: three ECGs at visits 4, 5 and one ECG at Visits 7 and 8. At Visits 3 and 6 an additional ECG will be done to the two already performed. The main Flow Chart also reflects the number of times these ECGs occur. Footnote xii has been updated to reflect this.
Rationale for change		More frequent ECG monitoring introduced as a response to the recent additional data mentioned in – see section 1.2.
Section to be changed		Flow Chart
Description of change		Where multiple assessments/ procedures are done e.g. ECGs, PK sampling the numbers have been added to the flow chart
Rationale for change		For clarity
Section to be changed		Flow Chart
Description of change		All AEs footnote reference for FUp1 and FUp2 changed
Rationale for change		Typographical error, the references had been written the wrong way round.
Section to be changed		Flow Chart

Description of change		The text in footnote xviii about pre-screening for UACR has been moved to footnote iii. In addition eGFR has been added as a test that patients can be pre-screened for if consent is given.
Rationale for change		The text about eGFR has been added as this is not always done regularly and several patients have failed screening for this. Allowing pre-screening for eGFR means less unnecessary screening procedures for patients who would not be eligible due to eGFR. The UACR pre-screening text has been moved as it is more appropriate to have all screening text together.
Section to be changed		Flow chart footnote ix
Description of change		The text "……. And within 35 days of randomisation (visit 3)" has been added.
Rationale for change		For clarity and consistency.
Section to be changed		Flow chart footnote xi
Description of change		The following text has been added: "…..If applicable this must occur prior to the ECG and PK samples. See FLOW CHART FOR PROCEDURES for details on the timing of ECGs."
Rationale for change		For clarity and consistency.
Section to be changed		Flow Chart for Procedures (Formerly PK Flow Chart)
Description of change		The PK flow chart has been expanded to include all the assessments/ procedures to be performed and the order in which they should be done. The PK Flow Chart has been renamed to "Flow Chart for Procedures". These changes apply throughout the protocol.
Rationale for change		It is important that procedures are done within the order mentioned in section 6.2. The table has been added to make this easier to follow and to include the timings.
Section to be changed		UACR and GFR sampling flow chart
Description of change		Reference added to flow chart for visit windows.
Rationale for change		For clarity.
Section to be changed		Section 1.2 Drug Profile
Description of change		The following text was added: Based on recent data from a clinical trial (1366-0020) in patients with cirrhosis Child-Pugh stage A (24 patients) and B (25 patients), an effect of BI 685509 on the predicted

		placebo-corrected change from baseline QTcF (ΔΔQTcF) was seen. Dosing regimens up to 3 mg bid, similar to the highest dose group in this trial, were used. In both patient groups, there was a dose dependent increase of ΔΔQTcF up to 13.7 ms, with the upper 90% CI >20 ms. In one patient group (Child-Pugh B) this was concomitant with a change of the predicted placebo-corrected change from baseline heart rate (ΔΔHR) of > 10 beats per minute (bpm), but not in the other patient group. No such effect was seen in a healthy Caucasian volunteers trial (1366-0010) for dosing regimens used in this trial. In a healthy Asian volunteers trial (1366-0013), at a dose regimen relevant for this study (i.e. starting with 1 mg tid up to a final dose of 3 mg tid), an increase of ΔΔQTcF was seen up to 11.7 ms with 90% CI <20 ms, concomitant with an increase of ΔΔHR of nearly 10 bpm. BI 685509 has no effect on human ether-a-go-go related gene (hERG) channel at doses used in this clinical trial, and no effect on QT-interval was seen in conscious animal studies.
Rationale for change		To provide new information this also serves as the detailed rationale behind the additional measures being included in this amendment.
Section to be changed		Section 1.4.2, Table 1.4.2:1 Overview of Trial Related Risks
Description of change		Potential QT-interval prolongation was added as a risk along with the summary of data, rationale for the risk and the mitigation strategy.
Rationale for change		Updated due to the new data available.
Section to be changed		Section 3.2 discussion of the trial design
Description of change		From: “In order for patients and investigators to be blinded to dose group, patients would be subjected to taking multiple tablets three times a day on top of the extensive background medication they already receive, which is considered too burdensome for this clinical trial.” To: “Therefore Investigators will know which dose group their patient is in but will be blinded to whether they are on active or placebo medication. Patients will be blinded to both the dose group they are on and whether they are taking active drug or placebo. Keeping Investigators blinded to the dose group would require patients to take multiple tablets three times a day on top of the extensive background medication

		they already receive, which is considered too burdensome for this clinical trial."
Rationale for change		To clarify blinding within this trial.
Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		Exclusion criteria 11) Removal of lactose monohydrate as an example of an excipient.
Rationale for change		Lactose monohydrate is not used in the Phase II formulation.
Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		Addition of the following exclusion criteria: 17. QTcF -interval > 450 ms in men or > 470 ms in women at any time from screening (Visit 1) until start of treatment. 18. A family history of long QT syndrome. 19. Concomitant use of therapies with a known risk of Torsade de Pointes at screening (Visit 1) and throughout screening and baseline run-in or planned initiation of such therapies during the trial (refer to Section 4.2.2.1).
Rationale for change		Added to ensure patients with QTc prolongation or with the potential for QTc prolongation do not participate.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		"• 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. Was rephrased to: "•The patient needs to take concomitant medication that interferes with the safety of the investigational medicinal product, refer to sections 4.2.1 and 4.2.2. If there is no safety concern then the Sponsor will review on a case-by-case basis as to whether it's appropriate for the patients to continue. This decision will be based on factors such as duration of treatment, dose etc. 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."
Rationale for change		The patient may remain on trial treatment in an exceptional case once the patient uses restricted medication, if there are no safety concerns. The patient will be analysed according to the TSAP.
Section to be changed		3.3.4.1 Discontinuation of Trial Treatment
Description of change		The following was added:

		Patients with a QT or QTcF interval > 500 ms, or an increase of QT or QTcF of > 60 ms from the pre-dose value at Visit 3 (baseline). Such cases must be reported as AEs.
Rationale for change		An additional patient safety measure.
Section to be changed		3.3.4.1 Discontinuation of Trial Treatment
Description of change		"The patient develops Acute Kidney Injury according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition[R17-2439]" Was changed to: "The patient develops Acute Kidney Injury as per clinical judgment by the Investigator. The Kidney Disease: Improving Global Outcomes (KDIGO) definition[R17-2439] should be used for guidance"
Rationale for change		The KDIGO guidelines are for use within a clinical setting. Patients with low urine output for reasons other than AKI, for example poor fluid intake, potentially could have been incorrectly discontinued.
Section to be changed		4.1.4
Description of change		The following text was added: "The last dose of trial medication will be administered in the evening of the day before the EoT visit."
Rationale for change		Clarification.
Section to be changed		4.2.2.1 Restrictions Regarding Concomitant Medication and Table 4.2.2.1:1 Concomitant Medication Restrictions
Description of change		The following text was added: "In addition, intake of concomitant therapies with a known risk of Torsade de Pointes must not be co-administered with BI 685509 (also refer to Table 1.4.2: 1). These restrictions apply from screening (Visit 1), until Visit FUp3. In the event of temporary concomitant use of such a therapy, trial medication must be temporarily stopped and can then be re-started after a period of at least 5 half-lives after the concomitant therapy with the known risk of Torsade de Pointes has been stopped, as long as the interruption rules are followed. Refer to Section 4.1.4.1 for rules for re-starting up-titration in case of interruption of trial medication." The restricted medication table was updated to include drugs with known risk of Torsade de Pointes.
Rationale for change		Update to exclude medications that could impact QTc

Section to be changed		Table 4.2.2.1:1 Concomitant Medication Restrictions
Description of change		The following was added for systemic steroids prior to trial (Visit 1): "…….. and planned to remain stable throughout the trial, i.e. must be at a dose of prednisolone ≤10 mg or equivalent."
Rationale for change		Clarification.
Section to be changed		5.2.2 Vital signs
Description of change		"Vital signs will be evaluated at the time points specified in the flow chart." Was changed to: "Vital signs will be evaluated at the time points specified in the flow chart, prior to the 12-lead ECG and prior to blood sampling as applicable."
Rationale for change		For consistency with other changes in this amendment to ensure vitals are done prior to ECG.
Section to be changed		5.2.4 Electrocardiogram
Description of change		Text was added to state that ECGs should be performed prior to blood draws and after the patient has been in the supine position for 5 minutes. Text was also added about the review of ECGs and also about the collection and storage of ECGs
Rationale for change		To ensure ECGs are accurate, any anomalies are correctly reported and to include a new storage procedure.
Section to be changed		6.2 Details of Trial Procedures at Selected Visits
Description of change		Text relating to number of vital signs and ECG assessments was removed to just leave the reference to the Flow Chart. The Flow Chart for Procedures was added.
Rationale for change		For clarity.
Section to be changed		10.3 Down-titration Guide
Description of change		In the first step on the flow chart added in "or more" to the following: Has the Patient missed 4 or more consecutive doses?
Rationale for change		For consistency with other sections of the protocol

11.4 GLOBAL AMENDMENT 4

Date of amendment		14 March 2022
EudraCT number **EU number**		2020-002929-28
BI Trial number		1366-0005
BI Investigational Medicinal Product(s)		BI 685509
Title of protocol		Randomised, double-blind (within dose groups), placebo-controlled and parallel group trial to investigate the effects of different doses of oral BI 685509 given over 20 weeks on UACR reduction in patients with diabetic kidney disease

Global Amendment due to urgent safety reasons	
Global Amendment	X

Section to be changed		1.2 Drug Profile
Description of change		The combination of BI 685509 with other compounds involved in the NO-sGC-cGMP pathway, such as nitrates and PDE5 inhibitors, non-specific PDE inhibitors, sGC-simulators might further increase the risk for hypotensive episodes and potentially reactive heart rate increases and the severity of these effects. Was expanded to: The combination of BI 685509 with other compounds involved in the NO-sGC-cGMP pathway, such as NO-donors including nitrates and PDE5 inhibitors, non-specific PDE inhibitors, sGC-simulators might further increase the risk for hypotensive episodes and potentially reactive heart rate increases and the severity of these effects.
Rationale for change		All NO donors as belonging to NO-sGC-cGMP pathway activating drugs must not be administered due to possible synergistic effects with BI 685509.
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Exclusion criterion #1 was changed from: Treatment with Renin Angiotensin Aldosterone System (RAAS) interventions (apart from either ACEi or ARB), phosphodiesterase inhibitors, nitrates, sGC-stimulators/activators (other than trial treatment) or any other restricted medication (including OATP1B1/3 inhibitors, UGT inhibitors/inducers) as provided in the Investigator Site File (ISF) within 4 weeks prior to visit 1 and throughout screening and baseline run-in. Patients who must or wish to continue the intake of restricted medications

		(see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial. To: Treatment with Renin Angiotensin Aldosterone System (RAAS) interventions (apart from either ACEi or ARB), phosphodiesterase-5 inhibitors, non-specific phosphodiesterase inhibitors (such as dipyridamole and theophylline), NO donors including nitrates, sGC-stimulators/activators (other than trial treatment) or any other restricted medication (including OATP1B1/3 inhibitors, UGT inhibitors/inducers) as provided in the Investigator Site File (ISF) within 4 weeks prior to visit 1 and throughout screening and baseline run-in. Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial are also excluded.
Rationale for change		Exclusion of PDE inhibitors and NO donors specified to match the IB. NO-sGC-cGMP pathway activating drugs must not be administered due to possible synergistic effects with BI 685509.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		The patient experiences a severe infection e.g. with SARS-CoV-2, as determined by the Investigator. Was changed to: The patient experiences a severe infection, e.g. with SARS-CoV-2 that precludes their safe participation in the trial, as determined by the Investigator.
Rationale for change		To avoid discontinuing trial treatment if it is deemed safe for patients to continue on treatment.
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		[redacted]

		NO donors including nitrates
Rationale for change		Exclusion of PDE inhibitors and NO donors specified to match the IB. NO-sGC-cGMP pathway activating drugs must not be administered due to possible synergistic effects with BI 685509.
Section to be changed		7.2.1
Description of change		The TS is used for safety analyses as well as demographics and baseline characteristics. was replaced with: The TS is used for safety analyses and exposure.
Rationale for change		The wording ‘as well as demographics and baseline characteristics’ in definition of Treated Set (TS) in 7.2.1 was deleted since Randomised Set (RS) needs to be used for demographics and baseline characteristics; TS will be used for safety and exposure.

APPROVAL / SIGNATURE PAGE

Document Number: c32274622 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-05

Title: Randomised, double-blind (within dose groups), placebo-controlled and parallel group trial to investigate the effects of different doses of oral BI 685509 given over 20 weeks on UACR reduction in patients with diabetic kidney disease

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area [redacted]	[redacted]	14 Mar 2022 12:16 CET
Author-Trial Clinical Pharmacokineticist		14 Mar 2022 12:45 CET
Author-Trial Statistician		14 Mar 2022 15:59 CET
Author-Clinical Trial Leader		14 Mar 2022 20:26 CET
Approval-Team Member Medicine		15 Mar 2022 11:05 CET
Verification-Paper Signature Completion		18 Mar 2022 08:22 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed