Clinical Trial Protocol

	Document Number: **c34875109-06**
EudraCT No.	2021-001434-19
BI Trial No.	1378-0005
BI Investigational Medicinal Product(s)	BI 690517 and empagliflozin
Title	Randomised, double-blind, placebo-controlled and parallel dose group trial to investigate efficacy and safety of multiple doses of oral BI 690517 over 14 weeks, alone and in combination with empagliflozin, in patients with diabetic and non-diabetic chronic kidney disease
Lay Title	A study to test whether different doses of BI 690517 alone or in combination with empagliflozin improve kidney function in people with chronic kidney disease
Clinical Phase	Phase II
Clinical Trial Leader	[redacted] Tel: [redacted]
Coordinating Investigator	[redacted] ; Tel: [redacted]
Current Version and Date	Final Version 4.0, 19 Aug 2022
Original Protocol Date	Final Version 1.0, 29 Apr 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	29 Apr 2021
Revision date	19 Aug 2022
BI trial number	1378-0005
Title of trial	Randomised, double-blind, placebo-controlled and parallel dose group trial to investigate efficacy and safety of multiple doses of oral BI 690517 over 14 weeks, alone and in combination with empagliflozin, in patients with diabetic and non-diabetic chronic kidney disease
Coordinating Investigator	[redacted] Tel: [redacted]
Trial site(s)	Multi-centre trial conducted in approximately 30 countries
Clinical phase	Phase II
Trial rationale	The aim of this trial is to investigate the efficacy and safety of three oral doses of BI 690517 over 14 weeks, alone and in combination with empagliflozin, in male and female patients with diabetic and non-diabetic CKD. The results of this trial will be crucial for the decision about further development of BI 690517 and will support the dose selection for future trials
Trial objective(s)	The main objectives of the trial are to demonstrate the efficacy of BI 690517, alone and in combination with empagliflozin, and to characterise the BI 690517 dose-response relationship in patients with diabetic and non-diabetic CKD by assessing 3 doses and placebo
Trial endpoints	**The primary endpoint** is the change from baseline in log transformed Urine Albumin Creatinine Ratio (UACR) measured in First Morning Void urine after 14 weeks. **Secondary endpoints:** UACR response I, defined as a decrease of at least 30% absolute change in First Morning Void urine of UACR from baseline to 14 weeks. • UACR response II, defined as a decrease of at least 15% absolute change in First Morning Void urine of UACR from baseline to 14 weeks
Trial design	Randomised, double-blind, parallel dose group, placebo-controlled clinical trial to investigate the effect of three doses of BI 690517 alone and in combination with empagliflozin over 14 weeks in

	patients with diabetic and non-diabetic chronic kidney disease. The trial will include a 1:1 randomised run-in period of 8 weeks for empagliflozin 10 mg/ placebo followed by a randomised treatment period of 14 weeks for BI 690517 / placebo in combination with the background medication assigned in the randomised run-in period.
Total number of patients randomised	At least, 552
Number of patients per treatment group	A minimum of 60 patients completed per arm in the Treatment Period, overall 480 completed patients
Diagnosis	Diabetic or non-diabetic Chronic Kidney Disease
Main inclusion and exclusion criteria	Inclusion: • Male or female patients of legal adult age (according to local legislation) and aged ≥ 18 years at time of consent. • eGFR ≥ 30 and < 90 mL/min/1.73 m². • UACR ≥ 200 and < 5000 mg/g. • Stable treatment with either ACEi or ARB (not both). • Serum potassium ≤ 4.8 mmol/L Exclusion: • Current or planned SGLT2i / SGLT-1/2i treatment • Type 1 Diabetes Mellitus
Test product(s)	BI 690517 and empagliflozin
dose	BI 690517 3 mg daily (QD) or 10 mg daily (QD) or 20 mg daily (QD) Empagliflozin 10 mg daily (QD)
mode of administration	p.o
Comparator product(s)	Placebo matching each dose of BI 690517 and empagliflozin
dose	Not applicable
mode of administration	p.o.
Duration of treatment	22 weeks (8 weeks run-in with empagliflozin/placebo and 14 weeks of treatment with BI 690517/placebo alone or in combination with empagliflozin/ placebo)
Statistical methods	A mixed-effect model for repeated measures (MMRM) will be used to obtain adjusted mean changes from baseline for the treatment effects of continuous endpoints. This MMRM model will include fixed effect of treatment as categorical variable, and fixed effect of baseline at each visit as continuous variable. Visit will be considered as repeated measures with an unstructured covariance structure for the within-patient variability. For dose-finding, predicted average response for each dose group and the estimated covariance matrix from the MMRM will be used in the multiple comparison procedures and modelling (MCPMod) analysis. Several possible dose-response patterns will be evaluated in the MCPMod to identify the best-fitting model and optimal dose for further development.

FLOW CHART

Trial Period	**Screening**	**Randomised Run-in Period**				**Treatment Period**								**Follow Up Period**			
Visit[1]	**1[2]**	**2**	**3**	**3.1 Home sampling without visit**	**4**	**5[3]**		**6**	**7**	**8**	**9**	**9.1 Home sampling without visit**	**9.2 Home sampling without visit**	**EoT[4]**	**FUp1[5]**	**FUp1.1 Home sampling without visit[27]**	**FUp1.2 Home sampling without visit[27]**	**FUp2[27]**
Visit may be conducted at patient's home[6]					X		X			X							X
Telemedicine Contact[7]			X	(X)								(X)	(X)			(X)	(X)	
Weeks (overall)	-11	-8	-4	-2	-1	0		1	2	6	10	12	13	14	15	16	17	18
Day[29]	-77	-56	-28	-14	-7	1		8	15	43	71	85	92	99	106	113	120	127
Time window for visits (days)[29]	Up to 21 days before Visit 2	+/- 2	+/- 2	+/- 2	+ 2	none		+/- 2	+/- 2	+/- 3	+/- 3	+/- 2	+/- 2	+/- 2	+3	+/- 2	+/- 2	+/- 3
						Pre-dose	Post-dose											
Informed consent[8]	X																	
Demographics, medical history including historical creatinine data, baseline conditions	X																	
Check of in-/exclusion criteria	X	X				X												
Concomitant therapies	X	X	X		X	X	X	X	X	X	X			X	X			X
Height	X																	
Weight	X					X				X				X				
Physical examination	X	X				X				X				X	X			
Vital signs	X	X			X	X		X	X	X	X			X	X			X
12-lead electrocardiogram (ECG), local assessment[9]	X					X				X				X	X			
ACTH challenge test[10]	X						(X)	(X)	(X)	(X)	(X)			(X)				
Safety laboratory (blood, urine)[11]	X	X			X	X		X	X	X	X			X	X			X
eGFR[12]	X	X			X	X		X	X	X	X			X	X			X

Trial Period	**Screening**	**Randomised Run-in Period**				**Treatment Period**								**Follow Up Period**			
Visit[1]	**1**[2]	**2**	**3**	**3.1 Home sampling without visit**	**4**	**5**[3]		**6**	**7**	**8**	**9**	**9.1 Home sampling without visit**	**9.2 Home sampling without visit**	**EoT**[4]	**FUp1**[5]	**FUp1.1 Home sampling without visit**[27]	**FUp1.2 Home sampling without visit**[27]	**FUp2**[27]
Visit may be conducted at patient's home[6]					X			X			X							X
Telemedicine Contact[7]			X	(X)								(X)	(X)			(X)	(X)	
Weeks (overall)	-11	-8	-4	-2	-1	0		1	2	6	10	12	13	14	15	16	17	18
Day[29]	-77	-56	-28	-14	-7	1		8	15	43	71	85	92	99	106	113	120	127
Time window for visits (days)[29]	Up to 21 days before Visit 2	+/- 2	+/- 2	+/- 2	+ 2	none		+/- 2	+/- 2	+/- 3	+/- 3	+/- 2	+/- 2	+/- 2	+3	+/- 2	+/- 2	+/- 3
						Pre-dose	Post-dose											
[redacted]					[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]			[redacted]	[redacted]			[redacted]
Serum cortisol[14]	X					X	X[15]	X	X	X	X			X	X			X
[redacted]		[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]				
Biomarker sampling (serum, plasma, urine)		X				X				X				X				X
Pharmacogenomic sampling						X[17]												
Optional biobanking sampling (serum, plasma, urine)[18]		X				X				X				X				X
Pregnancy test[19]	X		X			X				X	X			X				X
Spot urine (UACR)[20]	X																	
Train patient on FMV and 24-hour urine sampling	X																	
Dispense urine container for FMV urine sampling	X	X			X				X	X	X				X			
UACR First Morning Void[21]		X		X	X	X				X	X	X	X	X		X	X	X
Dispense urine container for 24-hour urine sampling					X						X							
24-hour urine sample[21]						X								X				
Paper diary handout[22]		X			X		X	X	X	X	X							
Collect and review paper diary					X	X		X	X	X	X			X				

Trial Period	**Screening**	**Randomised Run-in Period**				**Treatment Period**								**Follow Up Period**			
Visit[1]	**1**[2]	**2**	**3**	**3.1 Home sampling without visit**	**4**	**5**[3]	**6**	**7**	**8**	**9**	**9.1 Home sampling without visit**	**9.2 Home sampling without visit**	**EoT**[4]	**FUp1**[5]	**FUp1.1 Home sampling without visit**[27]	**FUp1.2 Home sampling without visit**[27]	**FUp2**[27]
Visit may be conducted at patient's home[6]					X		X			X							X
Telemedicine Contact[7]			X	(X)							(X)	(X)			(X)	(X)	
Weeks (overall)	-11	-8	-4	-2	-1	0	1	2	6	10	12	13	14	15	16	17	18
Day[29]	-77	-56	-28	-14	-7	1	8	15	43	71	85	92	99	106	113	120	127
Time window for visits (days)[29]	Up to 21 days before Visit 2	+/- 2	+/- 2	+/- 2	+ 2	none: Pre-dose / Post-dose	+/- 2	+/- 2	+/- 3	+/- 3	+/- 2	+/- 2	+/- 2	+3	+/- 2	+/- 2	+/- 3
Randomisation (via IRT)		X				X											
Dispense study drug(s) (via IRT)		X				X		X	X	X							
Administer Empa/ matching placebo during visit[23]		X			X	X	X	X	X	X			X				
Administer BI 690517 / matching placebo during visit						X	X	X	X	X			X				
Treatment compliance[28]					X	X	X	X	X	X			X				
Drug accountability (via IRT)						X		X	X	X			X				
Termination of study drug (via IRT)													X				
AEs/SAEs/AESIs[24]	X	X	X		X	X	X	X	X	X			X	X[25]			X[26]
Completion of patient participation																	X

[1] Additional visits may have to be scheduled - for example, in case of dose reduction due to potassium elevation or when an ACTH Challenge test is required for patients whose cortisol level is ≥ 3 µg/dL (82.8 nmol/L) and < 11 µg/dL (303.5 nmol/L) with suggestive signs or symptoms of adrenal insufficiency.

[2] 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. The Screening Period should be no more than 21 days from first screening procedure to first randomisation. Screening assessments may be conducted over more than one day. The Randomised run-in Period may start as soon as all screening procedures have been performed and laboratory results have been

received and reviewed. Therefore the 21 days prior to Visit 2 that are indicated in the flow chart may be less. Screening procedures may be repeated once during the screening period if the patient is not eligible for 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 taken again from the patient. IRT must be contacted to register the re-screening and obtain a new patient number.
- If screening is not completed within 21 days, 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).

[3]Visit 5 should be no more than 7 days after Visit 4. Where the patient does not meet the additional inclusion criteria 13 and 14 based on lab tests performed at Visit 4, the eGFR and potassium cannot be re-tested and the patient should permanently discontinue the study. In case of unexpected delay of Visit 5, a repeat safety sample must be taken to obtain potassium and eGFR results needed to confirm eligibility for the Treatment Period.

[4] In case a patient needs or wishes to terminate all trial treatment prematurely and if the patient agrees, the patient should undergo the procedures for End of Treatment (EoT). Please see section 6.2.5 for details.

[5] Follow-up Visit 1 (FUp1) must always take place at least 7 days after the EoT visit.

[6] 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 6.2.2 for further details.

[7] 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 sampling at home 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. Visit 3 must be performed as telemedicine contact for all patients, unless they prefer to come to the trial site instead.
3. Phone/ video calls may also take place at any other time if needed to support the patient.

[8] Informed consent must be obtained before the first screening assessment. It can be obtained on the day of the screening visit or within 4 weeks prior to the first screening assessment. The consent discussion should include showing the patient the home sampling kits and explaining this procedure.

[9] All ECGs will be done prior to the daily dose and evaluated by the investigator or a designee. See section 5.2.4.

[10] ACTH Challenge test is required for all patients at screening, and for all patients whose morning serum cortisol level at EoT (or at the time of premature discontinuation of BI 690517 / placebo) is < 18 µg/dL (496.6 nmol/L). After the start of BI 690517 / placebo treatment at Visit 5, if morning serum cortisol level is ≥ 3 µg/dL (82.8 nmol/L) and < 11 µg/dL (303.5 nmol/L) and the patient shows suggestive signs or symptoms of adrenal insufficiency, an ACTH Challenge test should be performed as soon as possible. Serum cortisol basal sample must be performed before ACTH- injection (0.25 mg). Injection time must be recorded and has to be done within 4 hours of the patient's usual waking time. Post-dose samples for serum cortisol must be taken 30 (± 5) minutes after the injection, to ensure patients have normal adrenal function. The time for the post ACTH-injection blood samples must be recorded in the patient's medical record. See section 5.2.5.1.

[11] Patients do not need to be fasted for the blood sampling for the safety laboratory. See section 5.2.3.

[12] eGFR at clinic visits will be determined from serum creatinine analysed by the central laboratory. To confirm eligibility, the eGFR at screening will be used.

[13] [redacted]

[14] Lab samples for serum cortisol must be collected within 4 hours of the patient's usual waking time.

[15] Post-dose serum cortisol should be taken 1 hour (+/- 10 minutes) after drug administration.

[16] [redacted] See [redacted] Flow Chart for samples and timings. For further instructions see section 6.1.

[17] The pharmacogenomics samples may be collected at Visit 5 or anytime afterwards.

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

[19] A pregnancy test is required for all women of child-bearing potential. This will be a serum pregnancy at Screening (Visit 1). Thereafter a urine pregnancy test will be performed. A home pregnancy test may be used at the Visit 3 timepoint. If urine pregnancy test is not acceptable to local authorities, a blood test can be done at a local laboratory. More frequent pregnancy testing should be done if required by local regulation and /or authority or per investigator judgment.

[20] 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 not match inclusion criteria due to UACR variability, this can be repeated once. If the second result does not meet the eligibility criteria the patient should be screen failed.

[21] Please refer to FMV and 24-hour Urine Sampling Flowchart.

[22] Patients will need to complete a paper diary at home in the 2 days prior to [redacted] to record times of trial drug intake. Patients will also need to record start and stop times for 24-hour urine samples in a paper diary before Visit 5 and EOT.

[23] Study medication at Visit 4, Visit 6 and EoT will be taken from the medication kit supplied at the previous visit as there is no dispensing at these visits. At all other visits, study medication should be taken from the kit dispensed at the visit.
[24] All AEs, SAEs and AESI will be collected from informed consent until FUp1 (end of residual effect period). Please see section 5.2.6.2.1.
[25] 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 trial treatment related AESIs. Please see section 5.2.6.2.1.
[26] After the individual patient's end of 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, but not on the CRF.
[27] In the case of premature discontinuation during the Randomised Run-in Period, FUp1.1, FUP1.2 and FUp2 do not need to be conducted.
[28] At Visits 4 and 5, only compliance to Empagliflozin/placebo will be calculated. At Visits 6, 7, 8, 9 and EOT, compliance will be calculated for both Empagliflozin/placebo and BI 690517/placebo.
[29] Days and associated time windows are relative to Visit 5.

FMV AND 24-HOUR URINE SAMPLING FLOW CHART

All samples listed in the following table should be collected by the patient, unless the patient is not able to do it.

Visit	**1**	2		3	**3.1 Home sampling without visit**		4		5		6	7	8	9	**9.1 Home sampling without visit**		**9.2 Home sampling without visit**		EoT		FUp1	**FUp1.1 Home sampling without visit**		**FUp1.2 Home sampling without visit**		FUp 2	
Week of Visit	-11	-8		-4	-2		-1		0		1	2	6	10	12		13		14		15	16		17		18	
Period	**Screening**			**Randomised Run-In Period**								**Treatment Period**											**Follow-up**						
			Start Empa/ plc Tx								**Start BI 690517 / plc Tx**												**End Tx**						
Days before visit	0	1	0	0	8 ■	7 ■	1	0	3[3]	1	0	0	0	1	0	1	0	15 ▲	14 ▲	8 ▲	7 ▲	3[3]	1	0	0	15 ●	14 ●	8 ●	7 ●	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
24-hour urine sample									X													X[4]									
Bring samples to clinic visit[1]			X					X			X				X		X							X						X
Samples collected from home[2]						X													X		X						X		X		

■days before planned Visit 4, ▲ days before regular EoT at week 14, ● days before FUp2

[1] Samples to be brought to clinic if visit is conducted at investigational site. If visit is conducted at patient's home, samples may be picked up from home.

[2] When samples are picked-up from home, this will be the following day at the latest. Where collection from the patient's home is not possible, alternative arrangements will be made, e.g. samples taken to the investigational site

[3] Start of 24-hour urine sample can be from the day after Visit 4 and up to 3 days before Visit 5; any time after Visit 9.2 and up to 3 days before EoT. In the event of Visit 5 or EoT visit being delayed, the 24-hour urine samples must not be older than 10 days at the time of the visit. 24-hour urine sample must be completed before FMV samples for that visit.

[4] 24-hour urine sample not required at EOT if patient discontinues prematurely prior to start of treatment with BI 690517 / matching placebo.

[redacted]

Visit	Day	Time relative to administration (dose at Visit)	Time Point [hh:min]	Event	
				Drug[5] admin.	[redacted]
2	-56	-0:30 (+ 29 /- 15 min)	-1344:30		
		0:00	-1344:00	X	
4[2]	-7	-0:30 (+ 29 /- 15 min)	-168:30		
		0:00	-168:00	X	
		0:30 (+/- 5 min)	-167:30		
		1:00 (+/- 10 min)	-167:00		
		2:00[1] (+ 15 min)	-166:00		
5[2]	1	-0:30 (+ 29 /- 15 min)	-0:30		
		0:00	0:00	X	
		0:30 (+/- 5 min)	0:30		
		1:00 (+/- 10 min)	1:00		
		2:00[1] (+ 15 min)	2:00		
6	8	-0:30 (+ 29 /- 15 min)	167:30		
		0:00	168:00	X	
7	15	-0:30 (+ 29 /- 15 min)	335:30		
		0:00	336:00	X	
8[2]	43	-0:30 (+ 29 /- 15 min)	1007:30		
		0:00	1008:00	X	
		0:30 (+/- 5 min)	1008:30		
		1:00 (+/- 10 min)	1009:00		
		2:00[1] (+ 15 min)	1010:00		
9	71	-0:30 (+ 29 /- 15 min)	1679:30		
		0:00	1680:00	X	
EoT[2,3]	99	-0:30 (+ 29 /- 15 min)	2351:30		
		0:00	2352:00	X	
		0:30 (+/- 5 min)	2352:30		
		1:00 (+/- 10 min)	2353:00		
		2:00[1] (+ 15 min)	2354:00		
FUp 1[3]	106	-0:30[4] (+/- 30 min)	2519:30		
FUp 2[3]	127	-0:30[4] (+/- 30 min)	3023:30		

[1]Please note: on all occasions the 2 hour sample cannot be earlier than 2 hours after administration of the dose at the visit.
[2] From the [redacted] the patient should only drink water and eat no food unless it is medically needed.
[3] In the case of premature discontinuation during the Run-In phase, only [redacted] need to be taken at EoT. No[redacted] should be taken at FUp1 or FUp2
[4] relative to usual time of drug administration during the treatment period of the study
[5] Drug = empagliflozin / BI 690517 / placebo
[6] [redacted] do not need to be taken if the patient has prematurely discontinued or temporarily interrupted empagliflozin/matching placebo and is still continuing on BI 690517 /matching placebo. [redacted] do not need to be taken if the patient has prematurely discontinued or temporarily interrupted BI 690517 /matching placebo and is still continuing on empagliflozin /matching placebo.

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS AND DEFINITIONS

ACEi	Angiotensin-Converting Enzyme Inhibitor
ACTH	Adrenocorticotropic Hormone
ADME	Absorption, Distribution, Metabolism and Excretion
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
AxMP	Auxiliary Medicinal Products
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
ARB	Angiotensin Receptor Blocker
AS	Aldosterone Synthase
ASI	Inhibitor of Human Aldosterone Synthase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUEC	Area Under the Effect Curve
b.i.d.	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
CA	Competent Authority
CK	Creatine Kinase
[redacted]	
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CS	Cortisol Synthase
CTGF	Connective Tissue Growth Factor
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol

CTR	Clinical Trial Report
CV	Cardiovascular
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interactions
DILI	Drug Induced Liver Injury
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
[redacted]	[redacted]
DPP	Dipeptidyl Peptidase-4
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
ES	Entered Set
ESKD	End Stage Kidney Disease
EoT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FMV	First Morning Void
FSGS	Focal Segmental Glomerulosclerosis
FUP	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gammaglutamyl transferase
GLP1	Glucagon-Like Peptide-1
GMP	Good Manufacturing Practice
HbA1c	Glycated Haemoglobin
HDL	High-Density Lipoprotein
hERG	human Ether-à-go-go-Related Gene
HF	Heart Failure
HFrEF	Heart Failure with Reduced Ejection Fraction
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IMP	Investigational Medicinal Product
INR	International Normalised Ratio

IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
K^+	Potassium
KDIGO	Kidney Disease: Improving Global Outcomes
K-EDTA	Potassium Ethylenediaminetetra-Acetic Acid
LADA	Latent Autoimmune Diabetes
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
LDL	Low Density Lipoprotein
LLA	Lower Limb Amputation
LPLT	Last patient last treatment
LPLV	Last patient last visit
LPLVPE	Last patient last visit primary endpoint
LVEF	Left Ventricular Ejection Fraction
MAR	Missing at Random
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCPMod	Multiple Comparisons Procedure - Modelling
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial Infarction
MMRM	Mixed-effect model for repeated measures
MR	Mineralocorticoid Receptor
MRA	MR antagonist
MRD	Multiple Rising Dose
NOAEL	No-Observed-Adverse-Effect Level
NOA	Not Analysed
NOP	No Peak Detectable
NOR	No Valid Result
NOS	No Sample Available
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
[redacted]	[redacted]
8-OHdG	8-Hydroxydesoxyguanosin
OPU	Operative Unit
PD	Pharmacodynamics

P-gp	P-glycoprotein
p.o.	per os (oral)
PoC	Proof of Concept
[redacted]	[redacted]
[redacted]	[redacted]
PPARγ	Peroxisome Proliferator-Activated Receptor gamma
PT	Prothrombin Time
q.d.	quaque die (once a day)
R1	First randomisation
R2	Second randomisation
RAAS	Renin-Angiotensin-Aldosterone System
RBC	Red Blood Cell
RDW	Red Blood Cell Distribution Width
REP	Residual effect period
RRR	Relative Risk Reduction
RS	Randomised Set
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic Blood Pressure
SC	Steering Committee
SGLT-2i	Sodium-glucose cotransporter 2 inhibitor
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
[redacted]	[redacted]
[redacted]	[redacted]
T2DM	Type 2 Diabetes Mellitus
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TMF	Trial Master File
UACR	Urine Albumin Creatinine Ratio
[redacted]	[redacted]
ULN	Upper limit of normal
UTI	Urinary Tract Infection
WBC	White Blood Cell
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Chronic Kidney Disease (CKD) is the leading cause of kidney damage and end-stage kidney disease (ESKD). The 5-year survival rate of dialysis patients is 35%, which decreases to only 25% in diabetic dialysis patients. As a result, CKD puts a large burden on healthcare systems worldwide, e.g. in the U.S. costs per patient exceed $75,000 annually. In addition to direct renal consequences, reduced kidney function is also a major trigger for cardio-vascular events. Overall, around 12% of the general population in Europe have CKD stages 3 to 5 [R19-1388], with considerable variation across countries, ranging from 4.1% to 25.5% [R19-1184].

Diabetes is the main cause of CKD in most countries, accounting for 40% or more of new cases [R19-0901]. 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 with patients with GFR >60 mL/min/1.73m² [R14-4475]. Declining kidney function is associated with an increasing risk for coronary heart disease, stroke, and heart failure [R15-5158; R15-2265]. Diabetic nephropathy is the leading cause of kidney damage and end-stage kidney disease (ESKD), accounting for >40% of patients on dialysis.

At present, only a limited number of therapeutic options are available to delay kidney function decline in patients with CKD. Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) can reduce albuminuria and slow the rate of progression in proteinuric diabetic kidney disease. However, in clinical trials in patients with diabetic nephropathy, the relative risk reduction for the composite primary endpoint of all-cause death, ESKD and doubling of serum creatinine in trials was only moderate (16% in the RENAAL trial and 19% in the IDNT trial) [R02-0327; R02-2101].

Recently, the sodium glucose cotransporter 2 (SGLT-2) inhibitor empagliflozin has been shown to reduce the risk of kidney disease progression in people with type 2 diabetes. An exploratory analysis of the EMPA-REG OUTCOME trial indicated that empagliflozin reduced the incidence of the composite outcome of doubling of creatinine, the need to start kidney replacement therapy, or renal death by 46% (HR 0.54, 95% CI 0.40-0.75). These benefits were similar regardless of baseline ACEi or ARB use and there was no evidence of an increased risk of hyperkalaemia or acute kidney injury [P16-06807)]. In the EMPEROR-Reduced trial, which was conducted in patients with heart failure with reduced ejection fraction, empagliflozin reduced the risk of the exploratory composite renal endpoint (chronic dialysis, kidney transplant, or sustained reduction in eGFR) by 50% in the overall trial population and was consistent on patients with and without CKD at baseline. Cardio-Kidney benefits of empagliflozin are currently being investigated in patients with CKD and a high risk for progression in the ongoing EMPA-KIDNEY study [P18-10838].

Increasing evidence is indicating that SGLT-2 inhibitors are likely to become a new treatment option for patients across a broad range of CKD phenotypes. The SGLT-2 inhibitor canagliflozin has received FDA approval for the treatment of patients with diabetic kidney disease and albuminuria >300 mg/g. In the CREDENCE trial, canagliflozin provided a

relative risk reduction of 30% for the composite endpoint of doubling of serum creatinine, ESKD or renal/CV death on top of standard of care [R19-1356]. A large-scale clinical outcome trial (DAPA-CKD) evaluating the SGLT-2 inhibitor dapagliflozin in patients with CKD (with or without type 2 diabetes and albuminuria >200 mg/g) was stopped early due to overwhelming efficacy. Data reported in August 2020 showed that dapagliflozin resulted in 39% relative risk reduction (RRR) for the composite primary endpoint (≥50% eGFR decline/ESKD/renal or CV death). Dapagliflozin also resulted in 39% RRR for composite secondary endpoint of CV death and HF hospitalisation and 31% RRR for all-cause mortality [R21-1080].

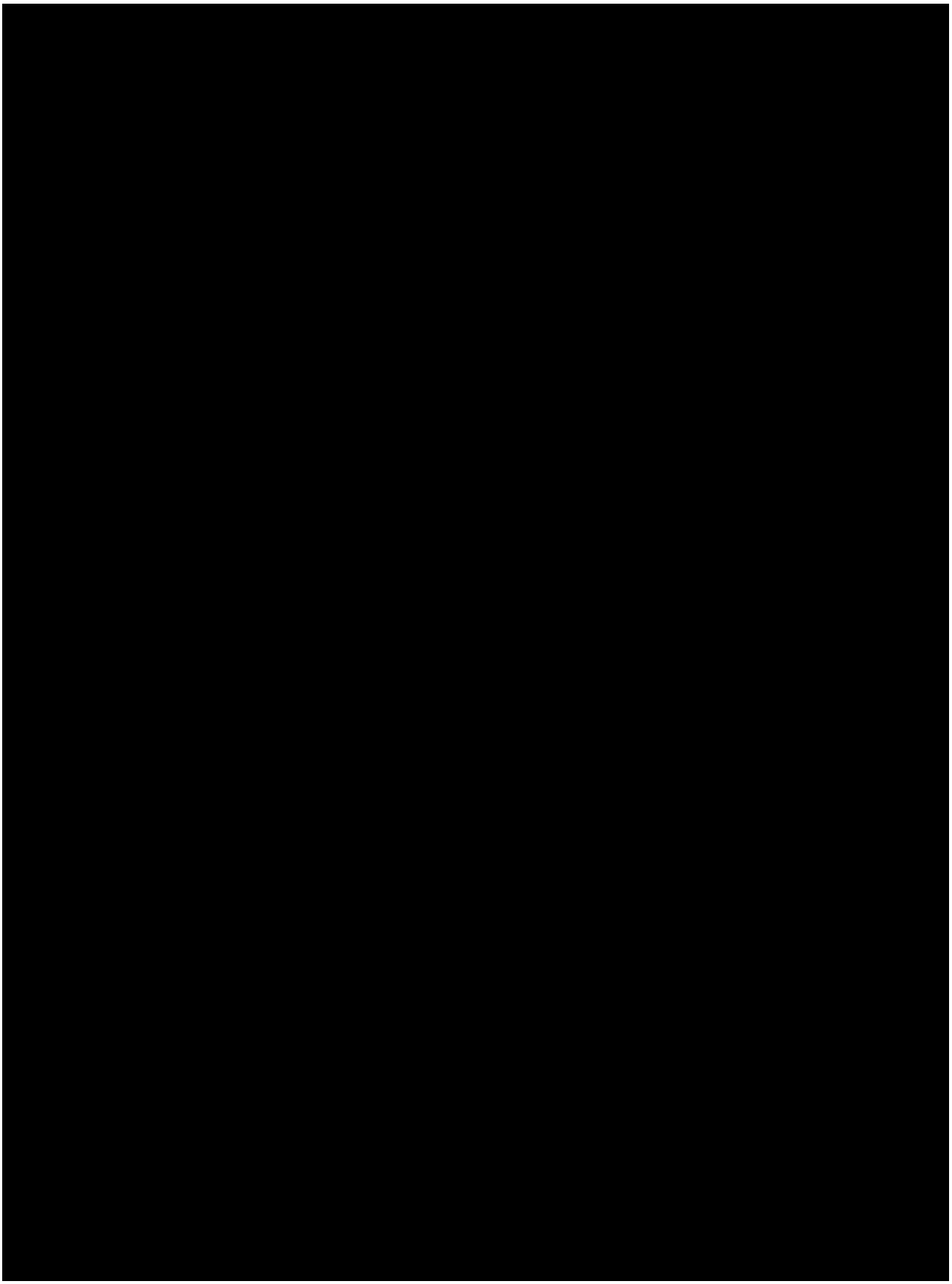
Current guideline recommendations have started to incorporate this new evidence by recommending SGLT2i with proven benefits as an integral part of the treatment regimen for patients with type 2 diabetes and CKD or CV risk [P20-09106]. Recommendations for non-diabetic kidney disease are likely to follow soon in the light of the new and upcoming evidence. Despite this advance, the residual renal and cardiovascular risks for patients remain unacceptably high for patients with CKD, warranting continued efforts to provide new treatments, particularly for fast-progressing patients (with GFR reductions >3 ml/min/1.73m²/year) that are at considerably increased risk.

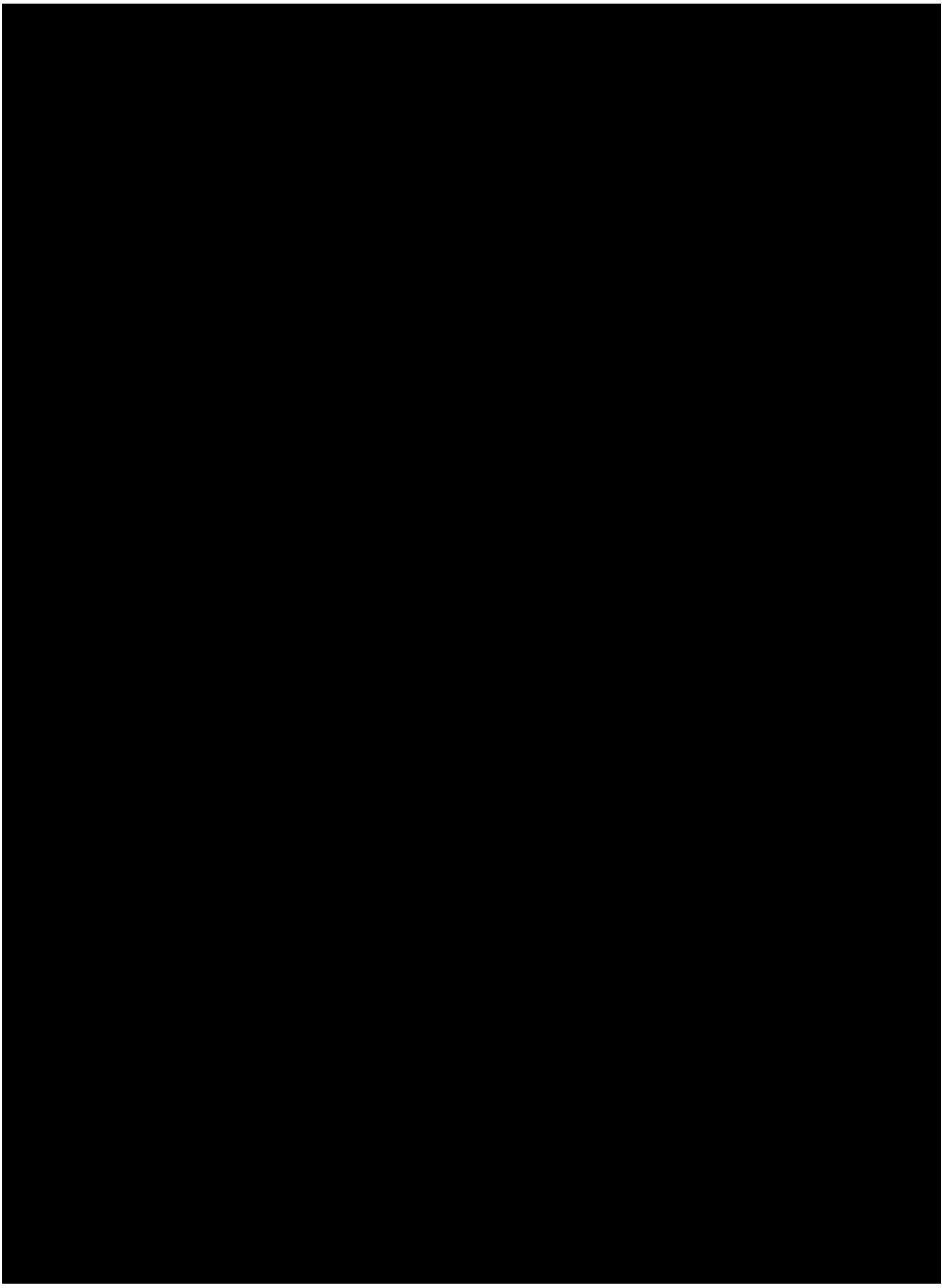
1.2 DRUG PROFILE

1.2.1 BI 690517

BI 690517 is an oral, small-molecule inhibitor of human aldosterone synthase. It is being developed for the treatment of CKD in patients with and without diabetes.

Mode of action
BI 690517 is a potent and specific inhibitor of human aldosterone synthase [redacted]





1.2.2 Empagliflozin

Empagliflozin is indicated for reduction of blood glucose in patients with Type 2 Diabetes Mellitus (T2DM), and for cardiovascular (CV) death risk reduction in patients with T2DM and established CV disease.

Mode of action
Empagliflozin is an orally available SGLT-2 inhibitor, promoting urinary glucose excretion. Empagliflozin also reduces blood pressure, arterial stiffness and measures of myocardial workload, likely through various mechanisms, as well as improving other CV risk factors (e.g. uric acid, visceral fat mass, albuminuria; [P15-00589, P15-09541]).

Key pharmacokinetic characteristics
In humans, empagliflozin predominantly showed linear pharmacokinetics both after single oral doses and at steady-state. Empagliflozin was rapidly absorbed, reaching peak levels at approximately 1.5 h, followed by a biphasic decline with the terminal elimination half-life ranging from 10 to 19 h.

Drug interaction
! o clinically relevant pharmacokinetic interactions are anticipated with BI 690517 (see section 1.2.1).

Residual Effect Period
The Residual Effect Period (REP) of empagliflozin 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 clinical studies
Empagliflozin has been studied as part of a global development program including more than 20,000 patients with type 2 diabetes treated in clinical studies of which more than 13,000 were treated with empagliflozin, either alone or in combination with metformin, a sulfonylurea, a PPARγ agonist, dipeptidyl peptidase-4 (DPP-4) inhibitors, or insulin.

In the EMPA-REG OUTCOME trial, empagliflozin was shown to be superior in reducing the primary endpoint, a composite of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke driven by 38% reduction of CV death compared to placebo on top of standard of care in patient with type 2 diabetes mellitus and established cardiovascular disease. An improved overall survival driven by a reduction in CV death was also observed. Empagliflozin reduced the risk of hospitalisation for heart failure and the composite of cardiovascular death or hospitalisation for heart failure compared with placebo. The risk of new or worsening nephropathy (including onset of macroalbuminuria, doubling of serum creatinine, and initiation of renal replacement therapy (i.e. haemodialysis)) was reduced in the empagliflozin group compared to placebo.

In the EMPEROR-Reduced study in patients with HFrEF with LVEF<40%, with or without T2DM, empagliflozin significantly reduced the risk of cardiovascular death or hospitalisation due to heart failure compared with placebo. Additionally, empagliflozin significantly reduced the risk of recurrent hospitalisation due to heart failure, and significantly reduced the rate of eGFR decline.

In completed clinical studies, empagliflozin was well tolerated in non-diabetic healthy volunteers, patients with type 2 diabetes, and patients with heart failure (NYHA class II-IV) and reduced ejection fraction with or without diabetes mellitus. The frequencies of overall AEs, AEs leading to discontinuation and SAEs were similar to placebo. There was an increase in frequency of genital infections with the use of empagliflozin. Empagliflozin treatment also increased urination and thirst. There was a small increase in total cholesterol, low density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol and no significant changes of LDL/HDL cholesterol ratio and in triglycerides. In addition, increases in haematocrit, haemoglobin and red blood cell were observed with empagliflozin. No clinically relevant changes in electrolytes, including potassium, were observed with empagliflozin. No changes to heart rate and no QTc prolongation have been observed. The safety profile of empagliflozin in patients with kidney impairment and decreased eGFR down to 15 mL/min/1.73m^2 was consistent with that reported in patients with normal kidney function; there is no experience in patients with end-stage kidney disease and in patients on dialysis.

For a more detailed description of the empagliflozin profile, please refer to the current Investigator's Brochure [c01678844].

1.3 RATIONALE FOR PERFORMING THE TRIAL

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the development and progression of kidney disease in patients with diabetic and non-diabetic CKD. Aldosterone is a key element of the RAAS and exerts its effects primarily via the mineralocorticoid receptor (MR). In patients with CKD and type 2 diabetes, treatment with the MR antagonist (MRA) finerenone in the FIDELIO DKD trial resulted in lower risks of CKD progression and cardiovascular events than placebo [R20-3706]. However, use of MRAs, particularly in patients with reduced kidney function, is limited by the risk for hyperkalaemia associated with MRAs.

BI 690517 is a potent and highly selective inhibitor of human aldosterone synthase (ASI). It is under development for the treatment of CKD in patients with and without diabetes. While MRAs block only MR-dependent aldosterone effects, BI 690517 acts to lower the circulating aldosterone level, thereby decreasing both MR-dependent and MR-independent effects of aldosterone. It is expected that this dual mechanism will lead to greater therapeutic benefit with less effect on MR-mediated electrolyte regulation (potassium (K^+) effects). BI 690517 therefore has the potential to slow or even stop the progression of CKD and may also have beneficial extra-renal effects on the cardiovascular system.

The main aim of this trial is to investigate the efficacy and safety of three oral doses of BI 690517 alone and in combination with empagliflozin over 14 weeks versus placebo in male and female patients with CKD as adjunctive to ACEi or ARB treatment. PK and PD will also be investigated as a further endpoint. The results of this trial will be crucial for decisions about further development of BI 690517 and will support the dose selection for future trials.

In keeping with the assumption that SGLT2i will become an integral part of the standard of care for patients with CKD in the upcoming years, the proposed study has been designed to provide data on the effects of BI690517 with and without combination of empagliflozin. There is a strong hypothesis that the kidney-protective mode of action of both drugs is complementary in nature.While empagliflozin mainly impacts the tubular sodium handling leading to a reduced intraglomerular pressure via modulating the tubuloglomerular feedback mechanism, BI 690517 additionally exerts anti-fibrotic and and-inflammatory effects by ameliorating the deleterious effects of aldosterone. All three aspects are playing a pivotal role in kidney disease progression, providing a good reason to believe that the combination of both drugs might result in synergistic effects on slowing kidney disease progression.

The proposed phase II study design will allow to understand the treatment effects of BI 690517 alone and in combination with empagliflozin which is mimicking the expected standard of care for the treatment of CKD and will allow an evaluation of the potential to further develop the combination of both drugs in phase III.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Potential benefits of treating patients with CKD with BI 690517 result from the prediction of slowing progression of the disease and risk reduction of cardiovascular events, which is only partially achieved by current standard of care. Treatment with BI 690517 will potentially result in decreased progression towards dialysis or kidney transplantation due to slowing/preventing the progression of kidney damage, which may directly translate into relevant improvements for patients' morbidity, mortality, and quality of life. Beyond that, it may reduce the risk of cardiovascular events in the target population. The potential advantage of BI 690517 is the reduction in circulating and local aldosterone with its potentially harmful effects on heart and vascular tissue.

Potential benefits of SGLT2i treatment include a reduction in albuminuria and slowing of the annual decline in estimated glomerular filtration rate in people with type 2 diabetes. Additionally, cardio-kidney outcome trials have shown clinically meaningful benefits of SGLT2i treatment in albuminuric CKD patients with and without diabetes. Therefore, empagliflozin may have beneficial effects on kidney disease progression and cardiovascular risk. The EMPA-KIDNEY study is extending the current knowledge as it is assessing clinical benefits in patients with diabetic and non-diabetic CKD irrespective of the presence of albuminuria.

The combination of BI 690517 and empagliflozin, which have complmentary modes of action, have the potential to have synergistic effects on slowing kidney disease progression in patients with CKD.

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 690517		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Potential adverse effects such as serum potassium increase	Primarily related to the mechanism of action	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.[1] Patients at higher risk of adverse effects related to the study drug will be excluded from the trial according to the exclusion criteria in section 3.3.3. Drugs that may increase the potassium level will be restricted. Serum potassium will be monitored closely during the trial and certain mitigations will be applied where required (see section 3.1 and 4.2.1.1)
Risks related to drug-drug interactions (DDI).	Pharmacokinetics and pharmacodynamics based DDIs (see section 1.2.1)	Close monitoring of patients and the prohibited co-administration of impacted drugs such as treatment with a similar mechanism of action. For further guidance, investigators are referred to the Investigator's Brochure [c09064107], 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.

[1] 1378-0002 is a multiple rising dose trial that investigated the safety, tolerability, PK and PD of rising doses of BI 690517 over a treatment period of 14 days in healthy volunteers and 1378-0008 is a multiple rising dose trial that investigated the safety, tolerability, PK and PD of rising doses of BI 690517 over a treatment period of 28 days in patients with diabetic nephropathy.

Table 1.4.2:1 Overview of trial related risks (cont'd)

Investigational Medicinal Product Empagliflozin		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Potential adverse effects such as ketoacidosis, genital infections, complicated UTI (pyelonephritis, urosepsis), Fournier's gangrene, hypoglycaemia (with concomitant use of insulin or sulfonylurea), and volume depletion	Primarily related to the mechanism of action	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 trials, and that are commercially available. Patients at higher risk of adverse effects related to the study drug will be excluded from the trial according to the exclusion criteria in section 3.3.3. Study treatment will be stopped in patients with suspected ketoacidosis or suspected Fournier's gangrene. Study treatment interruption should be considered in patients with complicated UTI or with volume depletion (see section 3.3.4).
Risks related to drug-drug interactions (DDI).	Pharmacokinetics and pharmacodynamics based DDIs	Close monitoring of patients and the prohibited co-administration of impacted drugs such as treatment with a similar mechanism of action. For further guidance, investigators are referred to the Investigator's Brochure [c01678844], Investigator Site File (ISF) or may contact the sponsor.

Other risks		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Patients may develop AKI or ESKD due to underlying disease or other causes	Rare but severe event related to the trial diagnosis, requiring medical treatment and hold of some medications including investigational drugs.	Treatment withdrawal criteria include AKI and ESKD as factors to remove the patient from treatment.

Table 1.4.2:1 Overview of trial related risks (cont'd)

Other risks		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Patients may develop SARS-CoV-2 infection	Based on the mode of action BI 690517 is not expected to have a significant impact on the susceptibility to or the course of an infection. Travelling to the site or being at the site for trial visits may potentially increase the risk of contracting a SARS CoV-2 infection. The underlying disease studied in this trial and the expected higher age of the impacted population increase the risk of hospitalisation and intensive care in case of a SARS-CoV-2 infection. Contracting SARS-CoV-2 infection, as with all acute illnesses, has the potential to increase the risk of ketoacidosis in patients treated with empagliflozin	Even though the risks associated with BI 690517 treatment are considered low, patients with active or recent SARS CoV-2 infection will not be included in the trial (see section 3.3.3). In the case of severe SARS COV-2, the trial medication will be interrupted until recovery. Investigator and sponsor will closely align on the appropriate measures for monitoring, treatment and quarantine. Measures are in place to ensure continued patient treatment, monitoring, and safety even if site visits are not possible (see sections 4.1 and 6.2). Physical visits to the sites may be replaced with home visits or telemedicine and procedures (including local lab testing) followed as far as the situation allows. Direct shipment of the trial medication will be managed by the site or the provider directly as permitted by local regulations. All decisions regarding the appropriate measures will be fully documented by the Sponsor. These measures ensure the safety of the patients throughout the trial.
Patients may develop an analphylactic shock or severe allergic reaction to tetracosactide (Synacthen® or equivalent for the ACTH challenge test)	This tends to be more severe in people who suffer from allergies (especially asthma)	Patients at higher risk of adverse effects related to the Synacthen® will be excluded from the trial according to the exclusion criteria in section 3.3.3. Patients will be monitored closely for at least 30 minutes after the injection.

A Data Monitoring Committee (DMC) will be established to review safety data at regular intervals. For further details see section 8.7.

1.4.3 Discussion

Based on pre-clinical results, BI 690517 has the potential to slow progression of kidney damage, delay end stage kidney disease (ESKD) and reduce the risk of cardiovascular events such as cardiovascular death, myocardial infarction, stroke and hospitalisation for heart failure, in patients with CKD. Based on results of completed clinical trials, empagliflozin also has the potential to slow the progression of CKD and reduce the risk of cardiovascular events.

A placebo arm for each treatment (empagliflozin and BI 690517) is needed to allow for a true assessment of the effects of BI 690517 given with or without empagliflozin on the UACR in patients with CKD. All patients will be on stable background standard of care therapy of at least either ACEi or ARB, and patients will only be enrolled in the trial if treatment with SGLT2i is not required (see section 3.3.1), therefore the inclusion of placebo treatment 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 690517 and empagliflozin. 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 690517 could provide to the treatment of CKD.

Overall, in the context of the unmet medical need and the anticipated effect on progression of CKD in humans and based on the safety profile of BI 690517, the benefit-risk evaluation of this compound, as well as empagliflozin, 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 trial will compare 3 doses of BI 690517 with placebo in patients with diabetic and non-diabetic CKD randomised to empagliflozin or placebo as background therapy (established during the randomised run-in).

The trial will characterise the dose-response curve for BI 690517 in patients with diabetic and non-diabetic CKD by assessing 3 doses and placebo. The response is the change from

treatment period baseline in log-transformed UACR measured in First Morning Void urine after 14 weeks. The primary objectives are (1) to demonstrate a non-flat dose response curve, evaluate the quantitative treatment effect size and evaluate the dose-response relationship, (2) to determine an optimal dose of BI 690517 by comparing the change from treatment period baseline in log-transformed UACR measured in First Morning Void urine after 14 weeks between the 3 doses of BI 690517 and placebo.

One set of secondary objectives will be as above but in subpopulations of (1) placebo background therapy (2) empagliflozin background therapy.

These analyses will include all data prior to BI 690517 discontinuation, down-titration of BI 690517, or death, regardless of change in concurrent SGLT2-inhibitor use.

2.1.2 Primary endpoint(s)

Change from treatment period baseline in log transformed Urine Albumin Creatinine Ratio (UACR) measured in First Morning Void urine after 14 weeks.

2.1.3 Secondary endpoint(s)

UACR response I, defined as decrease of at least 30% absolute change in First Morning Void urine of UACR from treatment period baseline to 14 weeks.

UACR response II, defined as decrease of at least 15% absolute change in First Morning Void urine of UACR from treatment period baseline to 14 weeks.

For further details regarding UACR response I and UACR response II, please see section 7.2.4.

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This trial is a multicentre, randomised, double-blind, parallel dose group, placebo-controlled clinical trial to investigate the effect of three doses of BI 690517 alone, and in combination with empagliflozin, in patients with diabetic and non-diabetic CKD who are on background treatment with either ACEi or ARB. Empagliflozin versus placebo use will be established during a 1:1 randomised run-in period.

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

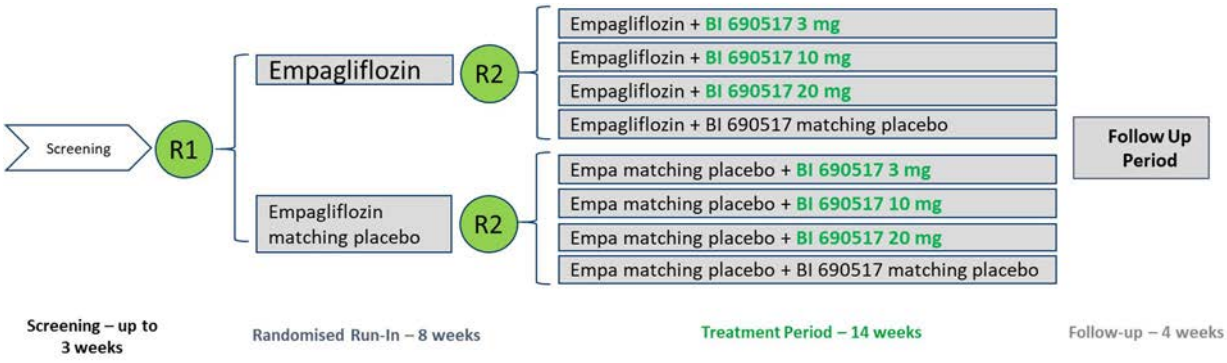


Figure 3.1: 1 Trial design

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

After their eligibility has been confirmed at screening, patients will enter the Randomised Run-in Period. Patients will be randomised equally to receive either empagliflozin 10 mg or placebo matching to empagliflozin 10 mg in a 1:1 ratio and will continue taking the assigned study treatment for 8 weeks. After 8 weeks of treatment in the Run-in Period, patients will enter the Treatment Period. Patients who received empagliflozin in the Run-in Period will be randomised equally into one of four parallel dose groups in a 1:1:1:1 ratio (see Figure 3.1: 1) to receive one of 3 doses of BI 690517 (3 mg QD, 10 mg QD or 20 mg QD) in combination with empagliflozin, or empagliflozin alone (empagliflozin plus placebo matching to BI 690517). Patients who received placebo in the Run-in Period will be randomised equally into one of four parallel dose groups in a 1:1:1:1 ratio to receive one of 3 doses of BI 690517 (3 mg QD, 10 mg QD or 20 mg QD) or placebo. Patients will continue receiving the assigned treatment for 14 weeks.

The study will be blinded to both empagliflozin and BI 690517. As the BI 690517 film coated tablets of the different dose strengths (3 and 10 mg) and empagliflozin have different dimensions, in order to minimise possible observer bias and ensure the study is blinded across dose groups the patients will each take 4 tablets a day during the Treatment Period, as described in section 4.1.4.

Eligible patients will be randomised to treatment using a stratification algorithm that helps ensure balance between the treatment groups with respect to prognostic variables such as eGFR and UACR. A target of approximately 30% of patients will be randomised during the run-in period in each of the disease types: diabetic kidney disease and non-diabetic kidney disease. Patients with diabetes may have diabetic kidney disease, non-diabetic CKD aetiologies, or a combination; for the purpose of categorising diabetic status, they will be classified as having diabetic kidney disease.

From the start of the screening until the end of the trial, at various time points patients will collect their First Morning Void urine for UACR analysis. These timepoints are listed in the FMV and 24-hour Urine Sampling Flow Chart. First morning void urine will be collected before the daily dose of study medication. 24-hour urine samples will also be collected prior to the start of the Treatment Period and at EOT. The patient will be equipped with urine collection containers to collect 24-hour urine and First Morning Void urine.

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 from the patient's home to a central laboratory for analysis. Where this is not possible alternative arrangements will be made, e.g. samples taken to the investigational site. Samples taken directly prior to a physical visit at the site will be taken to the site to be processed by the site staff.

Beyond analysis for safety, urine and blood samples in this trial will serve for biomarker analysis including UACR.

Following the Treatment Period, or at the time trial treatment in the Run-in Period or the Treatment Period is permanently discontinued, patients will have an End of Treatment (EoT) visit. This will be followed by a 4-week follow-up period off-treatment. A first follow-up visit (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. Patients who discontinue prematurely during the Run-In Period must attend FUp1 at least. All other patients should be encouraged to complete the full follow-up period.

During the follow-up period the patient will not be treated with trial medication, but should, if possible, continue with any background treatment they are on, and will collect additional urine at home. After the 4-week follow-up period the patient will have a final visit where again blood and urine samples will be collected. With the conclusion of this visit the trial participation is complete for the individual patient.

A rise in serum potassium and a drop in eGFR under treatment with BI 690517 cannot be excluded. Therefore, patients will be monitored closely (weekly for 2 weeks) after starting treatment with BI 690517 or matching placebo, and regularly thereafter.

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 understanding of drug effects and thereby better match patients with therapies.

[redacted]

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This trial has been designed to assess efficacy and safety of BI 690517 alone, and in combination with empagliflozin, as likely initiated in clinical practice. It also allows the opportunity to find the optimal dose of BI 690517 to be used for future development, on its own and / or as a fixed dose combination with empagliflozin.

Patients will initially start on 8 weeks of empagliflozin or placebo in the Randomised Run-in Period and will then receive 14 weeks of treatment with BI 690517 or placebo in the Treatment Period in addition to the empagliflozin or placebo treatment. It is important that patients run in on empagliflozin first, before starting treatment with BI 690517, for safety reasons since both drugs have potentially similar haemodynamic effects. 8 weeks of empagliflozin treatment is considered sufficient to reach stable haemodynamic levels, before starting with BI 690517.

A parallel group design was chosen to investigate three different dose regimens of BI 690517 alone and in combination with empagliflozin. The first parallel group will investigate three different dose regimens of BI 690517 and placebo. The second parallel group will

investigate three different dose regimens of BI 690517, in combination with empagliflozin, versus empagliflozin+placebo. Placebo is used to control for observer and subject bias, and randomisation to control for assignment bias.

The study design involves two randomisations. The first run-in randomisation to empagliflozin and placebo is required for two purposes. Firstly, the run-in randomisation will ensure an equally distributed patient population to the empagliflozin and placebo groups followed by second randomisation to treatment groups. Secondly, a staggered approach starting empagliflozin during the run-in period, followed by later initiation of BI 690517 was chosen to enhance patient safety. Both, empagliflozin and BI 690517, have a haemodynamic effect which leads to an acute eGFR decrease. Staggered treatment initiation is planned to reduce such effect.

UACR was chosen as primary endpoint (First Morning Void collection) and secondary endpoint (responder rate) 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. Furthermore, the change in UACR correlates with long-term clinical and patient relevant outcomes.

Since UACR is a parameter that varies intra-individually over time, multiple measurements are required at treatment period baseline and during the treatment period especially towards the end of treatment where a stable response to the drug should be achieved. UACR measurements will therefore be collected on 2 consecutive days at 3 timepoints (6 measurements in total) from Week -2 to Week 0 for treatment period baseline, and from Week 12 to Week 14 during the treatment period. Sequential collection of urine during a 4-week follow-up period may deliver exploratory results of response stability and potential rebound effects.

[redacted]

In order to detect and mitigate the potential risk of adrenal insufficiency and Cushing's syndrome, several measures will be implemented. An ACTH Challenge test will be performed at screening to exclude patients with adrenal insufficiency. Serum cortisol will be measured at all visits from Visit 5 until EoT and a further ACTH Challenge test will be performed if adrenal insufficiency is suspected. Furthermore, free cortisol will be measured in 24-hour urine just prior to the start of BI 690517 treatment and at the end of BI 690517 treatment to determine whether BI 690517 increases cortisol levels. Patients with adrenal insufficiency or Cushing's syndrome will be discontinued from treatment with BI 690517.

A data monitoring committee (DMC) will be established to review safety data at regular intervals. For further details see section 8.7.

3.3 SELECTION OF TRIAL POPULATION

It is expected that at least 552 patients will be randomised to the Randomised Run-in Period from approximately 200 sites. Investigators are expected to be nephrologists, endocrinologists or general practitioners. 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. Patients already in screening at this time will be allowed to continue to randomisation if eligible.

A minimum of 552 patients will be randomised to the Run-in Period to ensure that at least 480 will complete the study treatment in order to preserve the trial power by increasing sample size. If, during the study conduct, the drop out rate is higher than projected, recruitment may continue until the required number of patients complete treatment.

A log of all patients enrolled 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.

The investigator will make every effort to avoid the inclusion of a patient who does not meet all the inclusion criteria and/or meets at least one exclusion criterion. Should such an error nevertheless occur, this patient might be immediately excluded from the clinical trial based on individual benefit-risk assessment by the investigator. The sponsor or delegate will be informed as soon as possible.

3.3.1 Main diagnosis for trial entry

Chronic kidney disease.

If the investigator judges that the participant must receive empagliflozin (or any other SGLT-2 or SGLT-1/2 inhibitor) in the context of prevailing local, national or international guidance, the patient should not be included in the trial due to the risk the patient may be assigned to placebo alone in the trial.

No potential participant currently being treated with empagliflozin (or other SGLT-2 or SGLT-1/2 inhibitor) should be taken off this therapy to meet the eligibility criteria.

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 of legal adult age (according to local legislation) and aged ≥ 18 years at time of consent.
3. eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) ≥ 30 and < 90 mL/min/1.73 m^2 at Visit 1 by central laboratory analysis.
4. UACR ≥ 200 and < 5,000 mg/g in spot urine (midstream urine sample) by central laboratory analysis at Visit 1.[1]
5. If the patient is taking any of the following medications they should be on a stable dose for at least 4 weeks prior to visit 1 and until first randomisation prior to run-in with no planned change of the therapy during the trial: anti-hypertensives, NSAIDs, endothelin receptor antagonists, low dose systemic steroids (e.g. prednisolone ≤10 mg or equivalent).
6. Treatment with a clinically appropriate, stable dose of either ACEi or ARB (but not both together), for ≥ 4 weeks prior to visit 1 and until first randomisation with no planned change of the therapy during the trial.
7. In the Investigator's opinion, any kind of diagnosed chronic kidney disease[5]. Patients with diabetic kidney disease must have type 2 diabetes mellitus and their treatment (including GLP1 receptor agonist) should be unchanged or changes deemed minor (according to investigator's judgement) within 4 weeks prior to Visit 1 and until first randomisation.
8. Glycated Haemoglobin (HbA1c) < 10.0% at Visit 1 measured by the central laboratory.
9. Serum potassium ≤ 4.8 mmol/L at Visit 1 measured by the central laboratory. (For further details, see section 4.2.1.1)
10. Seated SBP ≥ 110 and ≤ 160 mmHg and DBP ≥ 65 and ≤ 110 mmHg at Visit 1 (mean values from three BP measurements) and optimised anti-hypertensive treatment according to local standard of care and investigator's judgement.
11. Body Mass Index (BMI) ≥ 18.5 and < 50 kg/m^2 at Visit 1.
12. Women of child-bearing potential[2] (WOCBP) must be ready and able to use highly effective methods of birth control according to section 4.2.2.3. Such methods should be used throughout the trial. Men must be vasectomised or willing and able to use a condom if their partner is a WOCBP.

Additional inclusion criteria to be assessed before second randomisation (start of Treatment Period):

13. Serum potassium ≤ 4.8 mmol/L measured by local or central laboratory within 7 days prior to randomisation to the Treatment Period.
14. eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) ≥ 20 mL/min/1.73 m^2 measured by local or central laboratory within 7 days prior to randomisation to the Treatment Period.

3.3.3 Exclusion criteria

1. Treatment with inhibitors of aldosterone mediated effects (e.g., mineralocorticoid receptor antagonists such as spironolactone), or intake of other potassium sparing diuretics (e.g., amiloride) within 7 days prior to first randomisation or planned during trial treatment phase.
2. Treatment with other Renin Angiotensin Aldosterone System (RAAS) interventions (apart from either ACEi or ARB) within 4 weeks prior to Visit 1 and throughout screening or planned during the trial. 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.

3. Type 1 diabetes mellitus, or history of other autoimmune causes of diabetes mellitus (e.g. LADA)
4. Patients at increased risk of ketoacidosis (see empagliflozin Investigator Brochure [c01678844]) in the opinion of the investigator.
5. Currently receiving SGLT-2 or SGLT-1/2 inhibitor or planned initiation during the trial.
6. Use of biotin (Vitamin B7, Vitamin H, or coenzyme R) at doses ≥ 5 mg/day (including food supplements) within 72 hours of Visit 1 or planned during the trial.
7. Absolute cortisol value of < 18 µg/dL (496.6 nmol/L) 30 minutes (± 5 min) after injection of ACTH, at Visit 1, as measured by local or central laboratory.
8. Known history of severe symptomatic orthostatic dysregulation as judged by the investigator before first randomisation.[3]
9. Intermittent or persistent 2nd or 3rd degree atrioventricular block, sinus node dysfunction with clinically significant bradycardia or sinus pauses, not treated with a pacemaker.
10. Serum cortisol < 5 µg/dL (138.0 nmol/L) or any clinically relevant abnormal laboratory value, at Visit 1 or until first randomisation, which in the investigator's judgement puts the patient at additional risk.
11. Any systemic immunosuppression therapy or immunotherapy in the last 3 months prior to Visit 1 or before first randomisation. This also applies to systemic steroids except oral prednisolone ≤10 mg or equivalent.
12. 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 or until first randomisation.
13. End stage kidney disease, maintenance dialysis, functioning kidney transplant at Visit 1 or before first randomisation; planned kidney transplant or chronic renal replacement therapy during the trial.
14. Heart failure, patients with NYHA III / IV or coronary heart disease not compensated by medical treatment.
15. Active infection with SARS-CoV-2 from Visit 1 until first randomisation, or a positive acute infection confirmatory test within 4 weeks prior to Visit 1.
16. Any documented active or suspected malignancy at the time of screening or history of confirmed malignancy within 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]) or treatment for cancer within 2 years prior to Visit 1.
17. Major surgery (investigator's judgement) planned during the trial.
18. History of clinically relevant allergy/ hypersensitivity that would interfere with trial participation including allergy to investigational product / placebo / tetracosactide (injection for ACTH test) or their excipients (e.g. lactose monohydrate) – see Investigator Brochures [c09064107] and [c01678844].
19. Patients who are unable to comply with trial procedures or have any other medical condition that in the investigator's opinion poses a safety risk for the patient or may interfere with the trial objectives.
20. Previous randomisation in this trial.
21. 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) or receiving other investigational treatment(s).

22. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial participant or unlikely to complete the trial.
23. Women who are pregnant, nursing or who plan to become pregnant while in the trial.
24. Patients with known hepatic cirrhosis (Child Pugh A, B or C), or other liver disease causing impaired liver function according to investigator's judgement.
25. Patients with one of the following aetiologies as the underlying cause:
    - CKD secondary due to malignancy (e.g. Cast-Nephropathy, AL-amyloidosis)
    - CKD secondary to infectious disease (e.g. Hepatitis-/HIV-associated)
    - Autosomal-dominant polycystic kidney disease

Additional exclusion criteria to be assessed before second randomisation (start of Treatment Period):

26. Patients with known hepatic cirrhosis (Child Pugh A, B or C), or other liver disease causing impaired liver function, according to investigator's judgement

[1]In case of out of range borderline results UACR testing may be repeated once before the Randomised Run-in Period starts.
[2]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 24 months without an alternative medical cause.
[3] Severity of symptomatic orthostatic dysregulation is based on the standard Adverse Event severity classification (see section 5.2.6.1.5).
[4]Definition of AKI according to Kidney Disease: Improving Global Outcomes (KDIGO):
- 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 baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume < 0.5 mL/kg/h for 6 hours.

[5]Diagnosis can be reached by standard clinical method, no biopsy required.

3.3.4 Discontinuation of patients from treatment

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) 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 section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

Permanent Discontinuation

An individual patient will permanently discontinue all randomised trial treatment if:

1. The patient develops Acute Kidney Injury as per clinical judgement by the investigator. The Kidney Disease: Improving Global Outcomes (KDIGO) definition [R17-2439] (see section 3.3.3) is going to be used for guidance.
2. The patient experiences a drop in eGFR[1]:
   - ≥ 30% from the last measurement of eGFR before the first dose of empagliflozin / placebo up to Visit 6; and/or
   - ≥ 40% at any time since the last measurement of eGFR before the first dose of empagliflozin/placebo
3. The patient progresses to end stage kidney disease defined by either a kidney function decline below an eGFR[1] of <15 mL/min/1.73 m^2 and/or requires renal replacement therapy by kidney transplant or dialysis.
4. The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer.
5. The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of the investigator, the safety of the patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
6. 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 can be consulted.
7. The patient can no longer receive trial treatment for medical reasons such as surgery, serious or severe Drug Induced Liver Injury attributable to the trial drug (see section 5.2.6.1.4), other adverse events, or other diseases.
8. The patient requires treatment for cancer. Some exclusions apply e.g. for Basal Cell Carcinoma – please discuss with sponsor.
9. 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.
10. The patient does not meet the additional inclusion criteria (see section 3.3.2) or the additional exclusion criteria (see section 3.3.3) assessed before second randomization (start of Treatment Period).

An individual patient will permanently discontinue BI 690517 / placebo if:

1. The patient's serum potassium measures ≥ 6.0 mmol/L by central or any local laboratory, or ≥ 5.6 mmol/L if down-titration is considered inappropriate.

[1] Where the eGFR drop occurs before the start of BI 690517 / placebo in the Treatment Period (i.e., at Visit 5), but the result is not available until after the patient starts BI 690517/placebo treatment, the patient must still permanently discontinue all randomised study treatment, including BI 690517 / placebo.

2. The patient develops Cushing's syndrome, adrenal insufficiency (including cortisol level <18 µg/dL 30 min (±5 min) after ACTH application) or the patient's cortisol level is < 3 µg/dL (82.8 nmol/L) at any point in the trial. The patient must be followed according to local guidelines until resolution of the event and the event is going to be reported to the sponsor (see section 5.2.6.1.4).

An individual patient will permanently discontinue empagliflozin / placebo if:
1. Ketoacidosis is suspected.
2. Fournier's gangrene is suspected.

If empagliflozin / placebo is permanently discontinued during the Randomised Run-In period, the patient should permanently discontinue the trial. If one of the study medications (either empagliflozin/placebo or BI 690517/placebo) is permanently discontinued during the Treatment Period / after the second randomisation at Visit 5, the patient may continue to receive treatment with the other study medication and should continue with scheduled study visits according to the Flowchart.

Treatment interruption

In the following case, all randomised study medication must be interrupted:
- severe SARS-COV-2 infection

In the following cases, the empagliflozin / placebo must be interrupted:
- complicated UTI
- symptomatic volume depletion

In the following cases, the BI 690517 / placebo must be interrupted:
- serum potassium ≥ 5.6 mmol/L (see section 4.2.1.1)
- serum potassium ≥ 5 mmol/L if the patient is unable or unwilling to return to the investigational site (see section 4.2.1.1)

In these cases, trial treatment could be restarted upon recovery if medically justified, please see section 4.1.4.

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 6.2.5 and 6.2.6 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.

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:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further treatment and follow up of patients affected will occur as described in section 3.3.4.1. 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

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 BI 690517 3 mg

Substance:	BI 690517 film-coated tablets 3 mg
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	3 mg
Posology:	QD
Method and route of administration:	Oral (p.o)

Table 4.1.1:2 BI 690517 10 mg

Substance:	BI 690517 film-coated tablets 10 mg
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg
Posology:	QD
Method and route of administration:	Oral (p.o)

Table 4.1.1:3 Placebo matching BI 690517 3 mg

Substance:	Placebo to BI 690517 film-coated tablets 3 mg
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	QD
Method and route of administration:	Oral (p.o)

Table 4.1.1:4 Placebo matching BI 690517 10 mg

Substance:	Placebo to BI 690517 film-coated tablets 10mg
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	QD
Method and route of administration:	Oral (p.o)

Table 4.1.1:5 Empagliflozin 10 mg

Substance:	Empagliflozin film-coated tablets 10mg
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10mg
Posology:	QD
Method and route of administration:	Oral (p.o)

Table 4.1.1:6 Placebo matching empagliflozin 10 mg

Substance:	Placebo to empagliflozin film-coated tablets 10mg
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	QD
Method and route of administration:	Oral (p.o)

Table 4.1.1:7 Synacthen (for ACTH test, may be required to be an IMP in certain countries – see section 5.2.5)

Substance:	Synacthen®
Pharmaceutical formulation:	Solution for injection or infusion.
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	250 µg
Posology:	As defined in the Flow Chart
Method and route of administration:	i.v. or i.m. injection

4.1.2 Selection of doses in the trial and dose modifications

During the Randomised Run-in Period, patients will receive either empagliflozin 10 mg or matching placebo. This dose was selected based on the dose used in the ongoing phase III empagliflozin in CKD trial (BI 1245-0137).

During the Treatment Period, patients will receive either BI 690517 or matching placebo on top of empagliflozin or matching placebo. The target doses of BI 690517 used for this trial will be 3 mg QD, 10 mg QD and 20 mg (2 x 10mg) QD.

In healthy volunteer phase I trials, doses ranging from 0.7 to 80 mg QD were tested. [redacted]. In the Phase 1c MRD study 1378-0008, three doses of BI 690517 (3 mg, 10 mg and 40 mg QD) were tested over 28 days of treatment. There was a numerical increase with dose for the change from baseline in serum potassium level. Since the increase of serum potassium tends to increase with dose, it is expected that 20 mg dose would have less hyperkalaemia cases compared to 40 mg dose. Therefore, to enhance patient safety during this trial, it is proposed to investigate 3, 10 and 20 mg (QD) doses. The other important factor in selection of 20 mg dose was suppression of aldosterone. The 40 mg dose resulted in a substantial suppression of aldosterone, and it is expected that the lower 20 mg dose will result in less aldosterone suppression, reducing the risk of hyperkalaemia.

Down titration (dose reduction) may be considered based on serum potassium levels (see section 4.2.1.1).

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria at visit 2, each eligible patient will be randomised into the Randomised Run-in Period according to a randomisation plan. Patients will be randomised in a 1:1 ratio via Interactive Response Technology (IRT) to either receive empagliflozin 10 mg QD or placebo matching to empagliflozin 10 mg QD in a blinded manner.

At Visit 5, following the Randomised Run-in Period, patients will be randomised into the Treatment Period via IRT according to a randomisation plan. Patients will be randomised in a 1:1:1:1 ratio to receive one of three doses of BI 690517 (3 mg QD, 10 mg QD or 20 mg QD) or placebo, in a blinded manner, in addition to the blinded treatment assigned during the Run-in Period.

Randomisation codes will be generated using 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

At Visit 2, all eligible participants will be randomised into the Run-In period to receive either empagliflozin 10 mg or matching placebo in a blinded manner. The patient will be dispensed enough medication for the duration of the Randomised Run-in Period. The first dose of empagliflozin/placebo will be administered at Visit 2. 1 tablet will be taken daily for the 8-week duration of the run-in period.

At Visit 5 (start of the Treatment Period), participants will be be randomised into the Treatment period to receive one of three doses of BI 690517 (3 mg, 10 mg or 20 mg QD) or placebo and this will be given in addition to the empagliflozin or placebo assigned in the run-in period. During the Treatment period, both empagliflozin/placebo and BI 690517/placebo medication will be dispensed at visits 5, 7, 8 and 9. The medication will be administered during the visit on the days of study visits. At the visits where medication is not dispensed (Visit 4, Visit 6 and EoT), medication will be administered from the kits dispensed at the previous visit. At all other visits medication may be administered from the kits dispensed at the current visit.

Empagliflozin or matching placebo will be dispensed in wallets of 35 tablets to cover 28 days plus 7 days reserve:

- 2 wallets at Visit 2
- 1 wallet at Visit 5, Visit 7, Visit 8 and Visit 9

BI 690517 or matching placebo will be dispensed in kits to cover 28 days plus 7 days reserve. Each kit will contain 5 wallets. Each wallet will contain 7 days' supply (21 tablets in total, comprising 7 x Tablet 2, 7 x Tablet 3 and 7 x Tablet 4 – see Table 4.1.4: 1 below).

- 1 kit at Visit 5, Visit 7, Visit 8 and Visit 9

In order to blind the dose of BI 690517 or matching placebo, 4 tablets will need to be taken daily during the Treatment Period, according to the treatment assignments shown in Table 4.1.4: 1.

Table 4.1.4: 1 Treatment assignments during the Treatment Period

Dose group	Tablet 1	Tablet 2	Tablet 3	Tablet 4
	Empagliflozin or matching placebo	BI 690517 or matching placebo		
Empagliflozin + BI 690517 3mg	10 mg active	3 mg active	10 mg placebo	10 mg placebo
Empagliflozin + BI 690517 10mg	10 mg active	3 mg placebo	10 mg active	10 mg placebo
Empagliflozin + BI 690517 20mg	10 mg active	3 mg placebo	10 mg active	10 mg active
Empagliflozin alone	10 mg active	3 mg placebo	10 mg placebo	10 mg placebo
BI 690517 3mg	10 mg placebo	3 mg active	10 mg placebo	10 mg placebo
BI 690517 10mg	10 mg placebo	3 mg placebo	10 mg active	10 mg placebo
BI 690517 20mg	10 mg placebo	3 mg placebo	10 mg active	10 mg active
Placebo	10 mg placebo	3 mg placebo	10 mg placebo	10 mg placebo

Empagliflozin or matching placebo will be administered orally on a once daily basis (QD) during the Run-in Period and Treatment Period. BI 690517 and/or placebo will be administered orally on a once daily basis (QD) during the Treatment Period, and should be taken at the same time as the empagliflozin or matching placebo dose.

To ensure a dose interval of about 24 hours, the medication should be taken in the morning at approximately the same time every day. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. No double doses should be taken. Both medications should be taken together with a glass of water and can be taken with or without food.

Down-titration (dose reduction) should be considered to manage serum potassium elevations (see section 4.2.1.1). Down-titration to the next lower dose is performed in a blinded manner. If the patient has been initially assigned to the lowest dose of BI 690517 (3 mg QD), the patient will be down-titrated to placebo in a blinded manner. If the patient has been initially assigned to the matching placebo to BI 690517, the patient will be ‘pseudo’-down-titrated to

placebo. Patients will only be allowed to down-titrate once during the study and no re-escalation is allowed. Down-titration may only be performed to manage hyperkalaemia and not for the management of other adverse events.

All trial medication assignments including down-titrations and replacement kits will be managed through the IRT system.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see section 6.2), physical patient visits to the sites may not be feasible or 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 trial treatment. Where permitted by local law and regulations, trial medication may be shipped directly to the patient's home. Shipment of trial medication from the site to the patient's home will also be allowed to support regular visits performed at the patient's home.

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 in this double-blind trial will remain blinded with regard to the randomised treatment assignments until a snapshot after Last Patient Last Visit Primary Endpoint (LPLVPE), with the exception of the Trial Pharmacometrician, PK programmer and Trial Bioanalyst. This snapshot will be taken after the last patient completes the EoT Visit, and will be used to obtain efficacy, safety, and PK/PD results, to guide further development plans for BI 690517. At the timepoint of unblinding of this snapshot, patients and investigators will continue to be blinded and will remain so until after database lock when the database is declared ready for final analysis according to the sponsor's SOPs. Further details regarding the timepoint of unblinding the database for analysis are documented in the TSAP. The access to the randomisation code will be kept restricted until its release for analysis.

The randomisation codes will be provided to bioanalytics before the last patient completed the trial to exclude placebo samples from the PK analysis. Bioanalytics will not disclose the randomisation code or the results of their measurements prior to the LPLVPE snapshot.

In order to expedite the population PK and PK-PD analyses and ensure timely delivery of PK/PD results after database lock and to provide PK data to DMC for consideration when evaluating safety of the trial, 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 the LPLVPE snapshot.

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 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.

Synacthen® (or equivalent) is either provided by the site or where this is necessary through the sponsor. Where Synacthen® is provided by the sponsor, supplies will be managed via the IRT system.

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 or delegate 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 or delegate 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,
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 at each resupply visit and EoT.
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.

If a patient has an adverse event that the Investigator believes may be related to trial medication (either empagliflozin and/or BI 690517) then the Investigator may interrupt the medication. Trial treatment may be restarted at any time after a temporary reason for treatment discontinuation if medically justified (see section 3.3.4.1).

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.

4.2.1.1 Management of serum potassium elevation

Increased potassium levels are not uncommon in patients with CKD and are often multifactorial in nature. A rise in serum potassium under treatment with BI 690517 cannot be excluded and therefore regular measurements of potassium levels are an integral part of the

visit schedule. For any episode of increased potassium level above 5.0 mmol/L, a clinical evaluation should be performed to make individual treatment decisions if a prompt intervention is required. For BI 690517 the dose might be adjusted to keep potassium levels in an acceptable range. The investigator should consider whether a down-titration is appropriate from a clinical perspective considering symptoms, relevant ECG changes, dynamics of potassium changes, intercurrent disorders, and lower ranges of eGFR. For detailed guidance on how to manage serum potassium elevations, please refer to Table 4.2.1.1: 1.

Table 4.2.1.1: 1 Management of serum potassium

Serum Potassium	Actions (BI 690517 / placebo)
< 5.0 mmol/L	Continue on current dose if deemed appropriate (e.g. in absence of clinical symptoms or slow/small increase over time) For *clinically relevant* serum potassium increases to < 5.0 mmol/L, the investigator may consider interruption and/or down-titration of BI 690517 /placebo.
≥ 5.0 to <5.6 mmol/L	**Option 1**: Continue on current dose. Recheck K^+ within 72 hours. If levels continue to be ≥5.0 mmol/L, either continue dose with weekly monitoring, or follow Option 2 or Option 3. **OR** **Option 2**: Down-titration If down titration is deemed appropriate, the BI 690517 / placebo should be temporarily stopped and the next lower dose will be allocated by IRT as soon as possible. After restarting on a lower dose, investigator should recheck K^+ within 72 hours. If levels continue to be >5.0 mmol/L, permanently discontinue. **OR** **Option 3**: If down titration is considered inappropriate, permanently discontinue BI 690517 / placebo
≥ 5.6-< 6.0 mmol/L	**Option 1**: Interruption followed by down titration Study medication should be temporarily interrupted. Investigator should recheck K^+ every 72 hours and can restart study medication at the next lower dose once K^+ falls to < 5.0mmol/L. After restarting on a lower dose, investigator should recheck K^+ within 72 hours. If levels continue to be >5.0, permanently discontinue. **OR** **Option 2**: If down titration is considered inappropriate permanently discontinue BI 690517 / placebo
≥ 6.0 mmol/L	Discontinue BI 690517 / placebo permanently.

In case of symptomatic hyperkalaemia initiation of potassium lowering treatment might be considered as medically indicated, like diuretics, potassium binding resins or other treatments as described in local or global guidelines for treatment of hyperkalaemia.

If BI 690517 or matching placebo must be permanently discontinued due to raised serum potassium, the patient may still continue to receive empagliflozin / matching placebo (see section 3.3.4).

In the event of elevated potassium ≥ 5 mmol/L, if the patient is unable or unwilling to return to the investigational site, for example during pandemic situation, the BI 690517 or matching placebo should be temporarily interrupted until the patient can return to the investigational site.

For patients taking potassium supplements, serum potassium should be monitored closely, and if serum potassium is ≥ 4.5 mmol/L, the investigator should consider reducing or discontinuing the potassium supplements, according to investigator judgement.

4.2.1.2 Management of eGFR decrease

After the start of the double-blinded treatment with BI 690517 / placebo, if the eGFR decreases by >15% since the last visit, the investigator should recheck the eGFR and potassium after 48-72 hours. The decision about continuing or discontinuation of the study drug should be based on the criteria specified in section 3.3.4.1 and the overall assessment of the patient's status. In case of increased potassium, the management of the patient should be done according to the rules in section 4.2.1.1.

4.2.1.3 Management of serum cortisol decrease

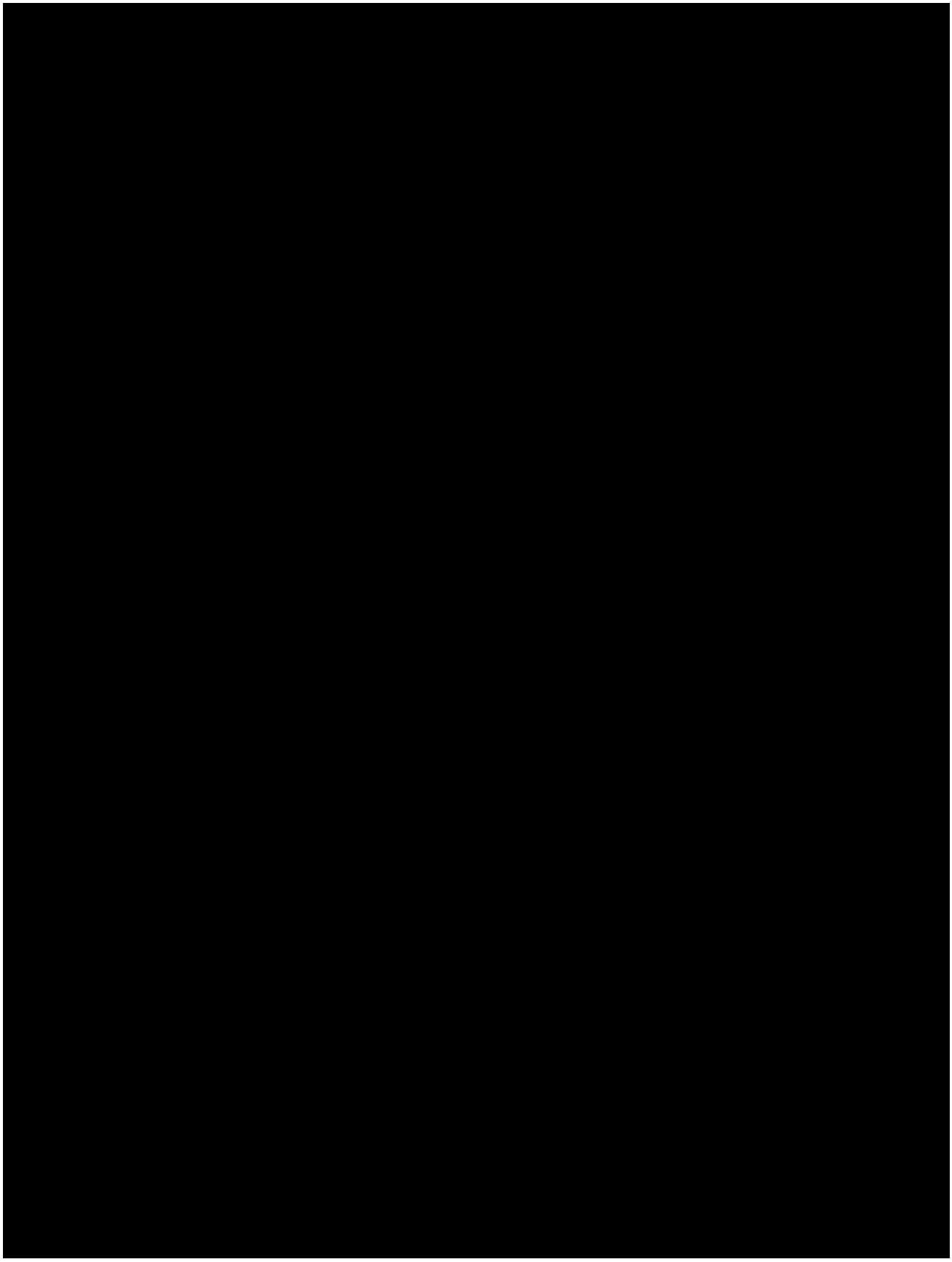
If, during the trial, cortisol level is < 3 µg/dL (82.8 nmol/L) the patient must be withdrawn from BI 690517 / placebo (see section 3.3.4).

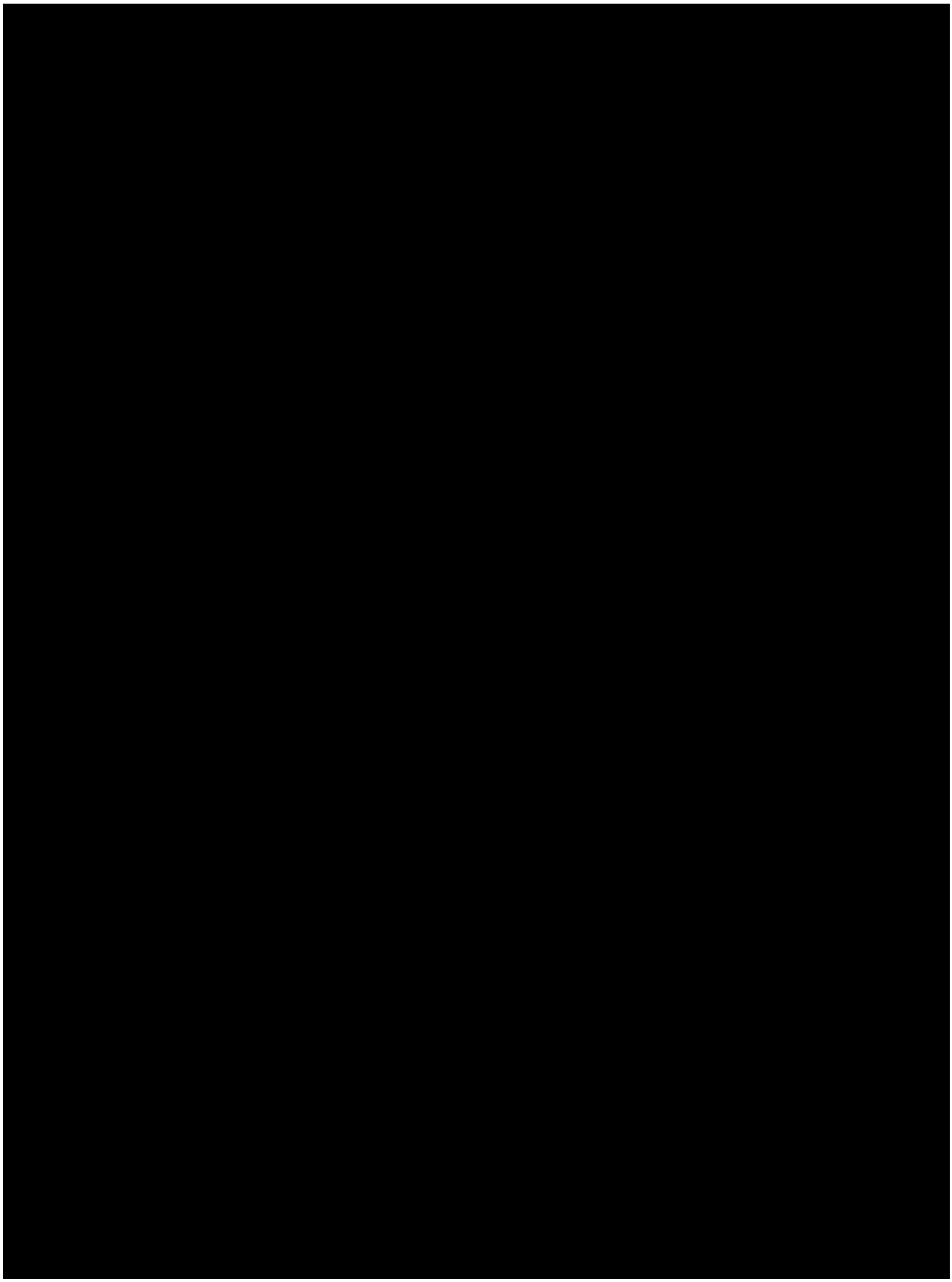
If, during the trial, the cortisol level is ≥ 3 µg/dL (82.8 nmol/L) and < 11 µg/dL (303.5 nmol/L) and the patient shows suggestive signs or symptoms of adrenal insufficiency (including but not limited to: fatigue, weight loss, abdominal pain, hypotension, volume depletion, hyperpigmentation, hypoglycaemia, hyperkalaemia, hyponatraemia), an ACTH test must be performed to investigate for potential adrenal insufficiency (see section 5.2.5.1). If absolute cortisol value is < 18 µg/dL (496.6 nmol/L) 30 minutes (± 5 min) after injection of ACTH, the patient should discontinue BI 690517 / placebo.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

[redacted] Please refer to the list of relevant drugs in ISF.





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.

If a patient develops hyperkalaemia they should be advised to avoid potassium-rich foods.

4.2.2.3 Contraception requirements

WOCBP (for the definition please refer to section 3.3.3) trial participants must use two medically approved methods of birth control throughout the trial, and for a period of at least 7 days after last trial drug intake, one barrier method, and one highly effective non-barrier method.

Highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly include:

- 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

Male trial participants 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.

Based on tablet counts, treatment compliance will be calculated separately for both empagliflozin and BI 690517 (or matching placebo) as shown in the formula below.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken as directed by the investigator}}$$

If the number of doses taken is not between 80-120%, site staff will explain to the patient the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 UACR

At Visit 1 (screening), a midstream urine sample for the analysis of UACR will be taken. UACR at screening will be analysed and calculated by the central laboratory to determine the eligibility of the patient.

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

The first morning void is the urination after the patient wakes up to start their day. Thus, if the patient goes back to sleep after urinating early in the morning e.g. at 4am, this void does not need to be collected and this does not need to be documented. This applies also to any urinations earlier during the night in patients who have nocturia. (However, if the patient is an early riser and gets up 'for good' e.g. at 4am, this would qualify as their FMV.) Of course, there may be cases when a patient might go back to bed after their usual rising time. In those cases, the void after the usual rising time constitutes the first morning void.

After the screening period, UACR will be determined on two consecutive days to average biological variability at the timepoints indicated in the FMV and 24-hour Urine Sampling Flowchart. On each collection day a sample must be obtained from the patient's FMV. 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 may be reminded e.g. by telephone contacts ahead of sampling time points on how to collect and store their urine samples. Further collection and sample storage instructions are given in the laboratory manual in the ISF and instructions to the patient.

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

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Measurement of height and body weight will be performed at the time points specified in the Flow Chart.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The blood pressure at screening will be performed in triplicate, and a mean of the 3 measurements will be used to confirm eligibility. 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 will be used for 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 send 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 transient medical condition, the patient may continue in the screening phase but not be randomised at Visit 2 until the re-test of the lab result has shown eligibility of the patient. Ineligible lab parameters may only be re-tested once during the screening period.

In case the criteria for hepatic injury 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 or delegate.

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

Functional lab group	**Test name**
Haematology	Haematocrit Haemoglobin Red blood cells (RBC) White blood cells (WBC) Platelet count MCV MCH MCHC RDW

Table 5.2.3:1 Safety laboratory tests (cont'd)

Functional lab group	Test name
Automatic WBC differential (relative and absolute)	Neutrophils Eosinophils Basophils Monocytes Lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin Time (PT) International Normalised Ratio (INR)
Enzymes	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Gammaglutamyl transferase (GGT) Creatine kinase (CK) Lipase Amylase
Substrates	Glucose HbA1c (at Visit 1, Visit 5 and EoT) Creatinine Urea Nitrogen Uric Acid Total bilirubin Direct bilirubin Total protein Albumin Globulin Albumin / Globulin ratio C-Reactive Protein (CRP) Total cholesterol
Electrolytes	Calcium Sodium Potassium Chloride Phosphate Bicarbonate (Calculated) anion gap
Hormones	Testosterone (only for female participants at Visits 5 and EoT) Serum cortisol (at Visit 1, Visit 5 pre- and post-dose, Visit 6, Visit 7, Visit 8, Visit 9, EOT)
Serum Pregnancy test (only for female participants of childbearing potential) at Visit 1 and if urine pregnancy test is positive	Human Serum Chorionic Gonadotropin

Table 5.2.3:1 Safety laboratory tests (cont'd)

Functional lab group	Test name
Urinalysis	Urine nitrite Urine protein Urine ketone Urine bilirubin Urine Blood Urine leukocyte esterase Urine pH Specific gravity
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (e.g. presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)
Urine Pregnancy test (only for female participants of childbearing potential) at Visits 5, 8, 9, EoT and FUp2	Human Chorionic Gonadotropin in the urine

Urinalysis should be performed by central laboratory only. Local testing of urine should be avoided where possible, especially testing for urine glucose, as this could potentially unblind the investigator to treatment with empagliflozin.

In case qualitative urinalysis parameters are abnormal, a quantitative analysis will be performed by the central laboratory.

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. Changes in laboratory test results, if they are judged clinically relevant by the investigator, must be entered as adverse event(s). Minimum required safety lab parameters are listed in Table 5.2.3: 2.

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

Functional lab group	**Test name**
Haematology	Haemoglobin Red blood cells (RBC) White blood cells (WBC) Platelet count
Enzymes	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (ALP)
Substrates	Creatinine Urea Nitrogen Total bilirubin
Electrolytes	Sodium Potassium Chloride Bicarbonate
Hormones	Serum cortisol (at Visit 5 pre- and post-dose, Visit 6, Visit 7, Visit 8, Visit 9, EOT)
Urine Pregnancy test (only for female participants of childbearing potential) at Visits 5, 8, 9, EoT and FUp2	Human Chorionic Gonadotropin in the urine

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart. 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.

5.2.5 Other safety parameters

5.2.5.1 ACTH challenge test

An ACTH challenge test will be performed for all patients at screening to ensure patients have normal adrenal function.

An ACTH Challenge test will also be performed during the study:

- between the start of BI 690517 / matching placebo treatment at Visit 5 and end of BI 690517 / placebo treatment, if the morning serum cortisol level is ≥ 3 µg/dL (82.8

nmol/L) and < 11 µg/dL (303.5 nmol/L) and the patient shows suggestive signs or symptoms of adrenal insufficiency (see section 4.2.1.3), and
- after the end of BI 690517 / matching placebo treatment (either at EoT, or when BI 690517 / placebo is prematurely permanently discontinued), if the morning serum cortisol level is < 18 µg/dL (496.6 nmol/L).

In these cases, the ACTH Challenge test should be performed as soon as possible.

A serum cortisol basal sample must be taken before the ACTH injection (iv or im 0.25 mg Synacthen®; an equivalent product may be used if Synacthen® is not authorised locally or provided by the sponsor). The injection time must be recorded. Serum cortisol will be determined 30 (±5) minutes after the injection. The time for the post-ACTH injection blood samples must be recorded. The ACTH Challenge test can be performed by a local or central laboratory.

Patients will be monitored closely for at least 30 minutes after the injection.

Alternative conduct of the ACTH test is allowed only if it is in accordance with the local practice of diagnosis of adrenal insufficiency. If adrenal insufficiency is diagnosed with an alternative conduct of ACTH test, the details of the ACTH test should be documented in the AESI report to the sponsor.

In this trial, the Synacthen® (or equivalent product) for the ACTH challenge test is considered as auxiliary medicinal product (AxMP). In some countries, however, (for example, Germany) it is considered as investigational medicinal product (IMP) for regulatory reasons. For a more detailed description of Synacthen® please refer to the current Summary of Product Characteristics (SmPC).

5.2.5.2 eGFR

eGFR will be analysed and calculated by the central laboratory at the timepoints indicated in the Flow Chart.

eGFR will be calculated by using the CKD-EPI formula (see section 10.2)

5.2.5.3 Urinary free cortisol

24-hour urine will be collected by the patient in containers before visits indicated in the FMV and 24-hour Urine Sampling Flowchart. Details of urine collection, processing and shipment will be provided in the Lab Manual. The patient will be given instructions and containers to collect the urine. The concentration of urinary free cortisol will be measured in the urine by the central laboratory.

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 considered related or not.

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 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:

1) Potential Severe DILI
2) Events leading to lower limb amputation (LLA)
3) Ketoacidosis
4) Cushing's syndrome
5) Adrenal insufficiency

Potential Severe DILI

A potential severe Drug Induced Liver Injury (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 after the start of study treatment 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.

Events leading to lower limb amputation (LLA)

Any event leading to a lower limb procedure of amputation, auto-amputation or disarticulation as defined below is considered as an AESI.

Amputation is a resection of a limb through a bone. Disarticulation is a resection of a limb through a joint. Auto-amputation is a spontaneous separation of non-viable portion of the lower limb.

Not included in this definition are debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation). (International Working Group of Diabetic Foot, 2015).

Each lower limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure and if the patient had some of the known risk factor(s) for lower limb amputation.

Ketoacidosis

If metabolic acidosis, ketoacidosis or DKA is suspected further investigations should be done according to medical judgement and the clinical course until a diagnosis is made and/or the patient is recovered.

Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of ketoacidosis which may occur at lower plasma glucose levels in patients with DM and potentially also in non-diabetic patient population. The diagnosis of ketoacidosis in these patients can be based on arterial pH ≤ 7.30, serum bicarbonate levels < 15mmol/L and measurement of serum beta-hydroxybutrate levels. Other diagnostic criteria which can support the diagnosis of ketoacidosis are urine ketones and anion gap >10mmol/L.

Investigators should note that not all criteria mentioned above need to apply for the diagnosis of ketoacidosis, and clinical judgment should also be taken into consideration.

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 the relationship between the adverse event and the BI investigational compound (BI 690517 / empagliflozin / placebo), 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 trial 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 trial 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.
- There is an 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 drug related SAEs and all trial drug 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 drug related SAEs and trial drug 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 AE and SAE eCRF pages immediately (within 24 hours) of becoming aware of the event. 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 the AE and SAE eCRF pages.

With receipt of any further information to these events, the SAE eCRF page(s) has to be updated. 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.

In exceptional cases when the EDC is unavailable for longer than 24 hours, the following applies:
The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the existing SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF).
Once the EDC is available again, information from the BI SAE form should be entered in the applicable eCRF pages.

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 Clinical Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

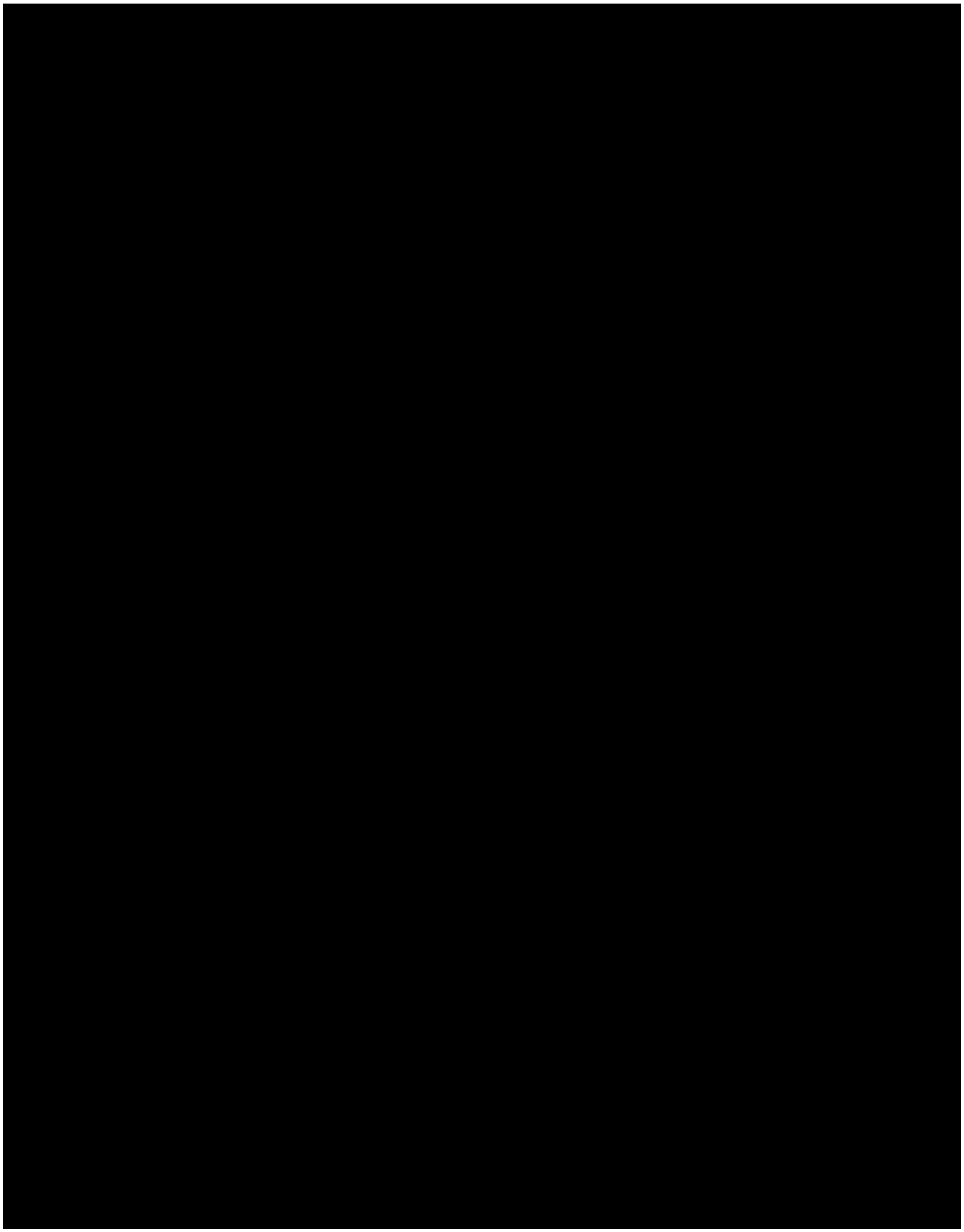
As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and / or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and / or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.6.2.4 Safety monitoring and adverse events with additional information collection

Additional details (on top of standard AE and SAE reporting) will be collected in the eCRF for the adverse events:

- Acute Kidney Injury (see section 3.3.3 for definition of AKI),
- Adrenal insufficiency,
- Hyperkalaemia,
- Hypotensive event,
- Hypoglycaemic event,
- Events leading to lower limb amputation (LLA),
- Ketoacidosis/ metabolic acidosis,
- Bone fractures.

[redacted]



[redacted]

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

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

[redacted]

[redacted]

5.4.1.1 Method and timing of sample collection

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 aldosterone and cortisol and their precursors
Blood will be drawn into a K-EDTA blood collection tube at multiple time points as indicated in the PK and aldosterone profile 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.

All urine, plasma and serum samples remaining at the end of the study will be destroyed no later than the sign-off of the separate biomarker report no more than two years after the last patient has completed the trial.

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

5.4.2 Pharmacogenomic 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 participant. In case of unexplainable variability in aldosterone level or of PK or PD parameters, DNA may be extracted from these samples and used for exploratory analysis of variants of the aldosterone synthase 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 discarded no later than 2 years after the last patient has completed the trial.

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

5.4.2.1 Method of sample collection

One blood sample will be taken from an arm vein in a PAXgene blood DNA drawing tube at the time point indicated in the Flow Chart.

5.4.2.2 Analytical determinations

Genomic DNA will be extracted from blood samples according to standard molecular genetics methods and analysed by Drug Metabolism Enzymes and Transporters (DMET™) analysis or other standard genotyping technologies.

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.

In some countries, for example China, biobanking samples will not be collected due to regulatory reasons.

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 after tubes for exploratory biomarkers (see section 5.4.1) have been filled. The urine will be taken from the urine sample collected for safety.

As no genetic testing is planned, no dedicated sample will be taken for the analysis of DNA and no DNA will be extracted from any of the biobanking sampled described above.

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 empagliflozin and BI 690517 in an appropriate way.

The scheduled measurements are appropriate to assess drug induced changes in kidney function with regards 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 kidney 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.

[redacted]

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All visits should be scheduled according to the Flow Chart. Each visit date in the Randomised Run-in Period (with its window) is to be counted from Day -56 (first randomisation). All visits in the Treatment Period and Follow-up Period are to be counted from Day 1 (second 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 time windows.

All trial visits should be initiated preferentially in the morning. Patients should be instructed to not take their dose of the study medication at home in the morning of 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 [redacted] From the first [redacted] 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.

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual (remote) patient visits and assessments, home healthcare nurse visits, and direct-to-patient shipments of trial treatment. Such alternative measures will be mentioned in the patient information leaflet. The implementation of these measures will depend on patient's consent, operational feasibility,

local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study measurements and assessments should be performed according to the Flow Chart. All assessments should be performed before study drug administration, with the exception of the post-dose PK and aldosterone profile samples.

Where the following assessments occur at a visit they should be performed in the following order:
Vital signs
ECG
Blood draws including trough PK and plasma aldosterone – other PK and plasma aldosterone samples are drawn after drug administration (see PK and aldosterone Flow Chart). Post dose-serum cortisol at Visit 5 is also drawn after drug administration.

There will be home sampling without a visit at Week -4 ('Visit' 3.1 during Randomised Run-in), Weeks 12 and 13 ('Visits' 9.1 and 9.2 respectively, during the Treatment Period), and at Weeks 16 and 17 ('Visits' FUp1.1 and FUp1.2 respectively, during the Follow-up Period). The patient will be required to collect urine samples for UACR over two consecutive days according to the FMV and 24-hour Urine Sampling Flow Chart at these times.

In this study the following visits may be performed as Telemedicine Contacts and Home Visits if all local approvals are in place. These contacts are used to help support patients with protocol procedures and compliance (see section 6.2.1 and 6.2.2):

- Telemedicine Contact: Visit 3
- Home Visits: Visits 4, 6, 9, FUp2

All other visits must be performed at the Investigational Site. The only exception to this is in the event of force majeure or other disrupting circumstances where physical patient visits to the sites may not be feasible or may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the following visits may be performed at the patient's home or remotely, e.g. via telephone and/or internet-based means of communication:

- Visit 2 (first randomisation) – may be performed as a home visit only
- Visit 5 (second randomisation) – may be performed as a home visit only
- Visits 7 and 8 (Treatment Period) – may be performed as a home and/or remote visit
- EoT – may be performed as a home and/or remote visit
- FUp1 – may be performed as a home and/or remote visit

Where Visit 2 and/or Visit 5 are conducted as a home visit, eligibility assessment and randomisation must be performed prior to the visit to allow time for the study medication to be shipped to the patient's home.

All deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

If blood sampling for central lab at the trial site is not possible, 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. Minimum required safety lab parameters are listed in table 5.2.3:2 . Urine pregnancy tests (for women of childbearing potential only, where required according to the Flow Chart) may be done at local lab / local doctor, or at home.

In the event of elevated potassium > 5 mmol/L, if the patient is unable or unwilling to return to the investigational site, the BI 690517 or matching placebo should be temporarily interrupted until the patient can return to the investigational site.

If remote visits and/or lab assessments cannot be performed within the time window for the visit, or if patient safety cannot be guaranteed, all randomised study medication needs to be interrupted until the visit and lab assessments can be conducted.

6.2.1 Telemedicine Contacts

Telemedicine contacts may be via a straightforward phone call between the patient and an appropriately qualified member of the Investigational Site or via a video call. They 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.

In the event of force majeure or other disrupting circumstances, where a patient is not able or willing to come to the site for a trial visit, the following assessments can be done remotely: collect and assess adverse events, concomitant therapies, assess trial medication compliance and review safety laboratory results.

6.2.2 Home Visits

Home visits (i.e. by a nurse or physician) 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. They may be performed at the visits indicated in the Flow Chart, unless the patient prefers to attend the Investigational Site for the visit.

To support visits performed at the patient's home, direct shipment of the trial medication will be managed by the site directly, for example via a courier, as permitted by local regulations. All unused trial medication from the previous visit(s), including empty package material, will be shipped from the patient's home to the site via courier. If needed, the laboratory kits and ancillary materials required by the nurse may also be shipped to the patient prior to the visit. Where country regulations allow, samples taken at home will be shipped from the patient's home to a central laboratory for analysis. Where this is not possible alternative arrangements will be made, e.g. samples taken to the investigational site.

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

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 and should be reviewed by an investigator.

In the event of force majeure or other disrupting circumstances, where a patient is not able or willing to come to the site for a trial visit, the following assessments can be done at the patient's home: collection of blood and urine samples to be sent to the central lab, vital signs, weight, collection and review of paper diaries, collection of adverse events and concomitant therapies, assessment of trial medication compliance.

6.2.3 Screening and run-in period(s)

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. The patient should be recorded on the enrollment log and be registered in the IRT system as a screened patient before any other activities are performed. The screening period begins once the first screening procedure has been performed. Patients who do not start the Randomised 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. 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.

During the screening visit, demographics information will be collected. This includes:

- age on the day of informed consent (in years)
- Sex (male, female in order to describe the participant`s sex at birth),
- For women: confirmation of childbearing potential in order to characterise the patient population and as a basis for contraception requirements
- Ethnicity and race in order to sufficiently characterise the patient population, to support possible subgroup analyses if needed and to support the calculation of the kidney function via the CKD EPI formula, unless not acceptable according to local regulations.

Randomised Run-in Period
The Randomised Run-in Period is 8 weeks. At the start of this period, patients will be randomised to receive empagliflozin or matching placebo. All visit procedures should be completed as indicated in the Flow Chart.

6.2.4 Treatment period(s)

The Treatment Period is 14 weeks. During this period, patients will receive one of three doses of BI 690517 or placebo, in combination with Empagliflozin or matching placebo assigned during the run-in period. All visit procedures should be completed as indicated in the Flow Chart.

6.2.5 Early discontinuation of Treatment

Patients who discontinue empagliflozin/placebo prematurely during the Run-In Period and who do not withdraw their informed consent; and patients who discontinue both empagliflozin/placebo and BI 690517/placebo during the Treatment Period and who do not withdraw their informed consent, should return for an End of Treatment (EoT) visit.

If the patient prematurely discontinues empagliflozin/placebo during the Run-In Period:

- If the patient has stopped taking empagliflozin/placebo the day of a scheduled visit or one day prior, the scheduled visit should be performed as an EoT Visit. Empagliflozin PK and safety samples should be collected. Biomarker, BI 690517 PK, aldosterone and optional biobanking samples do not need to be collected.
- If early discontinuation does not coincide with a scheduled visit, the patient should return for an EOT visit. PK, aldosterone, biomarker and optional biobanking samples do not need to be collected, but all safety assessments must be performed as indicated in the Flow Chart.
- The 24-hour urine sample prior to EOT does not need to be collected.

If the patient prematurely discontinues empagliflozin/placebo and BI 690517/placebo during the Treatment Period:

- If the patient has stopped taking trial drugs the day of a scheduled visit or one day prior, the scheduled visit should be performed as an EoT Visit. All samples including PK, aldosterone profile and all biomarkers 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, aldosterone, biomarker and optional biobanking samples do not need to be collected, but all safety assessments must be performed as indicated in the Flow Chart.

After the EoT visit, all patients will start the off-treatment Follow-up Period (see section 5.2.6).

6.2.6 Follow-up period and trial completion

The Follow-up Period is 4 weeks and consists of two visits, FUp1 and FUp2, with two intermediate home sampling timepoints. Please see the Flow Chart for timelines and visit details. No study medication is taken during the Follow-up Period.

The Residual Effect Period (REP) in this study is 7 days, therefore visit FUp1 should be performed no earlier than 7 days after the End of Treatment Visit.

Other follow up visits and assessments should be scheduled relative to the EoT visit i.e., there will be home sampling without visit at 2 weeks and 3 weeks after EoT, and FUp2 should be 4 weeks after EoT.

Patients who prematurely discontinue during the Run-In Period should have FUp1 as a minimum. Patients randomised to the Treatment Period should be encouraged to complete all visits and procedures in the FUp period. If the patient does not wish to complete all visits or procedures, they should have FUp1 as a minimum.

For patients who prematurely discontinue during the Run-In Period, aldosterone samples do not need to be taken at FUp1 or FUp2.

For patients who have not had [redacted] collected at EOT, these samples do not need to be taken at FUp1 and/or FUp2.

Participation in this trial is concluded once FUp2 has been completed. Additional visits may be scheduled for continued safety monitoring after the FUp2 visit if needed in the opinion of the investigator. Abnormal assessments or lab values judged clinically relevant by the investigator will be monitored until they return to a medically acceptable level.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

In this study, the primary endpoint is the change from baseline in log transformed UACR measured in First Morning Void urine after 14 weeks. The purpose of this trial is to demonstrate clinical activity of BI 690517 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 3 groups of patients with BI 690517 and placebo. In addition, MCPMod will be used to characterise the BI 690517 dose-response relationship separately in (1) patients on a background medication of placebo, and (2) on background medication of empagliflozin.

Dose effects will be assessed separately on each background therapy because both empagliflozin and BI 690517 have a haemodynamic effect which leads to an acute eGFR decrease. It will be important to assess the effects of both drugs alone, and in combination with a staggered treatment initiation.

7.1 NULL AND ALTERNATIVE HYPOTHESES

For the primary endpoint, the null hypothesis is that the dose-response curve is flat across the 3 BI 690517 doses and the placebo, whereas the alternative hypothesis of a non-flat dose-response curve indicates a clinical benefit of BI 690517 in at least one of the doses. The null hypothesis of a flat dose-response curve across the 3 BI 690517 doses and the placebo will be assessed in the following order: (1) in all patients (regardless of background therapy), (2) in patients on a background medication of placebo, and (3) on background medication of empagliflozin.

The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, while protecting the overall probability of Type I error (one-sided α of 5%, which corresponds to two-sided α of 10%). The pre-specified models and their parameters used for this test will be outlined in section 7.2.3.

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 disposition.

Randomised Set (RS): This patient set includes all entered and randomised patients based on the treatment groups they were randomised to at the randomisation prior to the Treatment Period, regardless of being treated by BI 690517 or not. 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 BI 690517 or matching placebo. The TS is based on actual treatment patients have received and will be used for safety analyses.

Full Analysis Set (FAS): This patient set includes all randomised patients who had at least one baseline measurement of UACR at week 6, 7, or 8 and at least one post-baseline measurement. The FAS will be the main analysis set for the analysis of efficacy.

The pharmacokinetic set (PKS): This patient set includes all patients in the TS who provided 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 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are restricted to the Treatment Period and are defined as:

- Premature treatment discontinuation of BI 690517
- Down-titration of BI 690517
- Use of SGLT2i as concomitant medication
- Death

The strategies for handling intercurrent events in this trial are summarised in Table 7.2.2: 1.

Table 7.2.2: 1 Summary of strategies for handling intercurrent events

Estimand strategy	Treatment	Intercurrent event handling
Primary	Randomised treatment	- BI 690517discontinuation: include data prior to study medication discontinuation - Down-titration of BI 690517: include data prior to down-titration - Death: include data prior to death - Use of SGLT2i: include all available data
Supplementary 1	Randomised treatment	- BI 690517discontinuation: include all available data - Down-titration of BI 690517: include all available data - Death: include data prior to death - Use of SGLT2i: include all available data

The primary approach will include all data prior to the intercurrent event, so any data collected after the intercurrent event will be excluded from the primary analysis except for the use of SGLT2i as concomitant medication. Patients will be analysed according to their randomised treatment. The analysis period for the primary approach starts from randomisation to the Treatment Period until either intercurrent event or EoT at week 14, whichever comes first. This approach is analogous to a hypothetical approach with respect to BI 690517.

Supplementary 1 approach will include all data collected even after intercurrent event, except for death. Every attempt will be made to follow up with patients who discontinue treatment prematurely until the end of their planned study participation. Patients will be analysed according to their randomised treatment. The analysis period for the supplementary 1 approach starts from randomisation to the Treatment Period until EoT at week 14. This approach is analogous to the treatment policy approach.

Handling of intercurrent events that are not listed will be decided by blinded review based on the general principle outlined and will be documented in the TSAP.

7.2.3 Primary objective analyses

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

For dose finding, multiple comparison procedures and modelling techniques (MCPMod) will be applied. The primary estimand of interest is the treatment effect using the primary approach (Table 7.2.2: 1).

Treatment effect

The primary analysis will first address a dose-response relationship between doses of BI 690517 and placebo by adopting an MMRM in groups testing the treatment of BI 690517.

Reduction in log transformed UACR from baseline will be used as the response variable in the MMRM.

This model will include fixed effect of treatment at each visit as categorical variable, and fixed effect of log transformed baseline UACR at each visit as continuous variable. Visit will be treated as repeated measure with an unstructured covariance structure for the within-patient variability.

Statistical model (MMRM):

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

where

$$e_{ij} \sim N(0, \Sigma),$$

y_{ijklm} = reduction in log transformed UACR from baseline for participant i at visit j in stratum l receiving dose level k on background therapy m,
U_i = the baseline* measurement of log transformed UACR of participant i,
β_j= coefficient of baseline effect at visit j,
τ_{jkm} = the effect of dose level k at visit j on background therapy m,
η_l = the effect of stratum l for having diabetic kidney disease or not,
e_{ij} = the random error associated with the jth visit of the ith participant. Errors are independent between participants,
Σ = an unstructured covariance matrix.
*: baseline is defined as the mean of all non-missing assessments at weeks -2, -1, and 0 prior to the treatment period.

The estimates will be produced for each background therapy separately, and for all patients combined. For the combined analysis, the individual estimates are weighted by the number of patients randomised at the second randomisation. To perform multiple comparison in the MCPMod across doses, predicted average response for each dose group and the standard errors from the MMRM will be used for the MCPMod analysis. The MCPMod analysis will be run for each background therapy and for all patients combined (three times in total).

A non-flat dose-response relationship is established if for the 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 dose-response models with respect to the one-sided type I error at 5% after multiple comparisons adjustment.

Dose finding

The second primary objective is to determine the therapeutic dose. The trial will characterise the dose-response curve for BI 690517 by assessing 3 doses and placebo. The response is the change from baseline in log transformed UACR measured in First Morning Void urine after 14 weeks of treatment with BI 690517 or matching placebo. Patients will be evaluated by 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 efficacy is established, the statistically significant (best fitting) model(s) from the candidate set will be 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 20 mg, total daily dose) will be considered.

7.2.3.3 Supplementary Analyses

Supplementary analyses will be conducted for the primary endpoint using the Supplementary 1 estimand strategy.

7.2.4 Secondary objective analyses

Descriptive statistics will be provided for the proportion of patients responding to UACR. An adjusted multiple imputation method will be used for missing UACR measurements, after which the response variables will be determined. As a sensitivity analysis, patients missing Week 14 data will be imputed as non-responders.

All secondary endpoints will be displayed for all patients and with each background medication separately.

7.2.6 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 based on their actual treatments. 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 occurring 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 summarised by the treatment at which the subject was randomised, and the treatment at the onset of AE for the drug-related AE.

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 the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Summary of participants with down-titration due to AE will be provided separately. Adverse event of special interest (AESI) and other specific AEs with collection of additional information in the eCRF (which include hyperkalaemia) will be summarised as well. Analysis of serum potassium will further include change from baseline, the incidence of serum potassium levels of 5.6 mmol/L or higher and higher than 6.0 mmol/L.

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.

7.2.7 Other Analyses

Details on the further analyses will be described in TSAP if needed.

7.2.8 Interim Analyses

No interim analysis is planned but a Data Monitoring Committee (DMC) will be in place with tasks as described in section 8.7.

7.3 HANDLING OF MISSING DATA

In the primary analysis of continuous endpoints, missing data will not be imputed. As a sensitivity analysis, missing UACR data will be imputed using an adjusted multiple imputation model (refer to Section 7.2.3.1). Data from this multiple imputation will be used to compute responder endpoints.

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 internal procedures. PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.4 RANDOMISATION

BI will arrange for the creation of the randomisation scheme and the packaging and labelling of trial medication. Patients will be randomised to double-blind treatment. Approximately equal numbers of patients will be randomised to each treatment group. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting randomisation scheme 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 this study, patients will undergo a 2-step randomisation, with the first randomisation performed prior to the Randomised Run-in and the second randomisation performed prior to the Treatment Period. Patients must fulfil the criteria (as described in section 3.3.2) in order to be randomised into the Treatment Period. In order to ensure a balance of patients between treatment groups, the trial will use stratified randomisation according to prognostic variables eGFR (< 45 and ≥ 45 mL/min/1.73 m^2), UACR (≤ 750 and >750 mg/g). At the first step, patients will be randomised to the treatment of empagliflozin or matching placebo in a 1:1 ratio for 8 weeks. At the second step, patients will be randomised to the Treatment Period in a 1:1:1:1 ratio for the treatment of 3 doses of BI 690517 (3 mg QD, 10 mg QD, and 20 mg QD) and matching placebo for 14 weeks, on the top of empagliflozin or matching placebo from the first randomisation.

7.5 DETERMINATION OF SAMPLE SIZE

The sample size calculation is conducted assuming effect size of BI 690517 versus placebo, (0, 0.10, 0.20, 0.35) for (placebo, BI 690517 3 mg, BI 690517 10 mg, BI 690517 20 mg total daily dose) in log transformed UACR measured in morning void urine after 14 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 690517 3 mg, 10 mg, and 20 mg in terms of total daily dose.

Emax: 80% of the maximum effect is achieved at 10 mg.
Exponential: 15% of the maximum effect is achieved at 10 mg.
Linear: No assumption is needed.

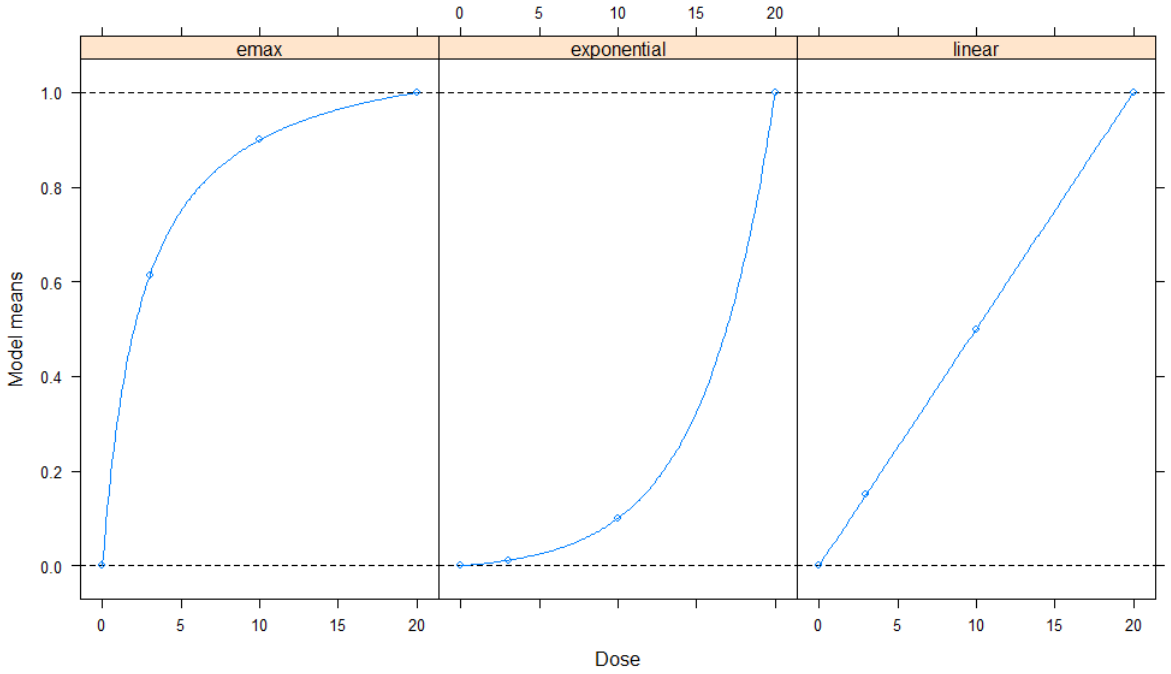


Figure 7.5: 1 Shape of the considered dose response patterns for the MCPMod analysis (dose reflects planned daily dose)

In a scenario with assumed effect of (0, 0.10, 0.20, 0.35) in log (UACR) change from baseline after 14 weeks in the Treatment Period (placebo, BI 690517 3 mg, BI 690517 10 mg, BI 690517 20 mg), the trial will have 89.7% power to detect a non-flat curve using MCPMod considering one-sided 5% alpha with sample size of 60 patients per treatment arm (in patients randomised to placebo during the run-in period).

In a scenario with assumed effect of (0, 0.10, 0.16, 0.22) in log (UACR) change from baseline after 14 weeks in the Treatment Period (placebo, BI 690517 3 mg, BI 690517 10 mg, BI 690517 20 mg), the trial will have 83.1% power to detect a non-flat curve using MCPMod considering one-sided 5% alpha with sample size of 120 patients per treatment arm (all patients combined).

The sample size/power calculation were determined based on 10,000 simulations for the scenario using R4.0.2. To achieve 60 patients per group (480 total patients), 552 patients will be randomised during the Run-in period to account for a dropout rate of at most 15% before the second randomisation. A one-sided alpha of 5% will be used to keep the sample size reasonably low in this Phase 2 trial.

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. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

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 participant protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, 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: sex, 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 imaging or 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 and copies of printouts)
- Source documentation for telemedicine visits
- Source documentation for visits performed at the patient's home
- Historical kidney-related data

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 or delegate will also monitor compliance with the protocol and GCP.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see section 6), site access may be restricted thus limiting the ability to perform standard site monitoring activities on site such as on-site source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralised monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) 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 World Health Organisation (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 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) 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, including scientific input and operational oversight, will be agreed in contracts between the SC members and the sponsor and also summarised in a SC charter.

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.
The DMC will evaluate safety data, in particular adverse events related to serum potassium, PK data (organised according to eGFR stratification) and some efficacy data. The DMC will receive urgent significant safety concerns for immediate evaluation. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs) / Health Authorities (HAs), IRBs / ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a 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 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.

In the participating countries the trial 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 Central Laboratory Manual and IRT Manual, available in the ISF.

9. REFERENCES

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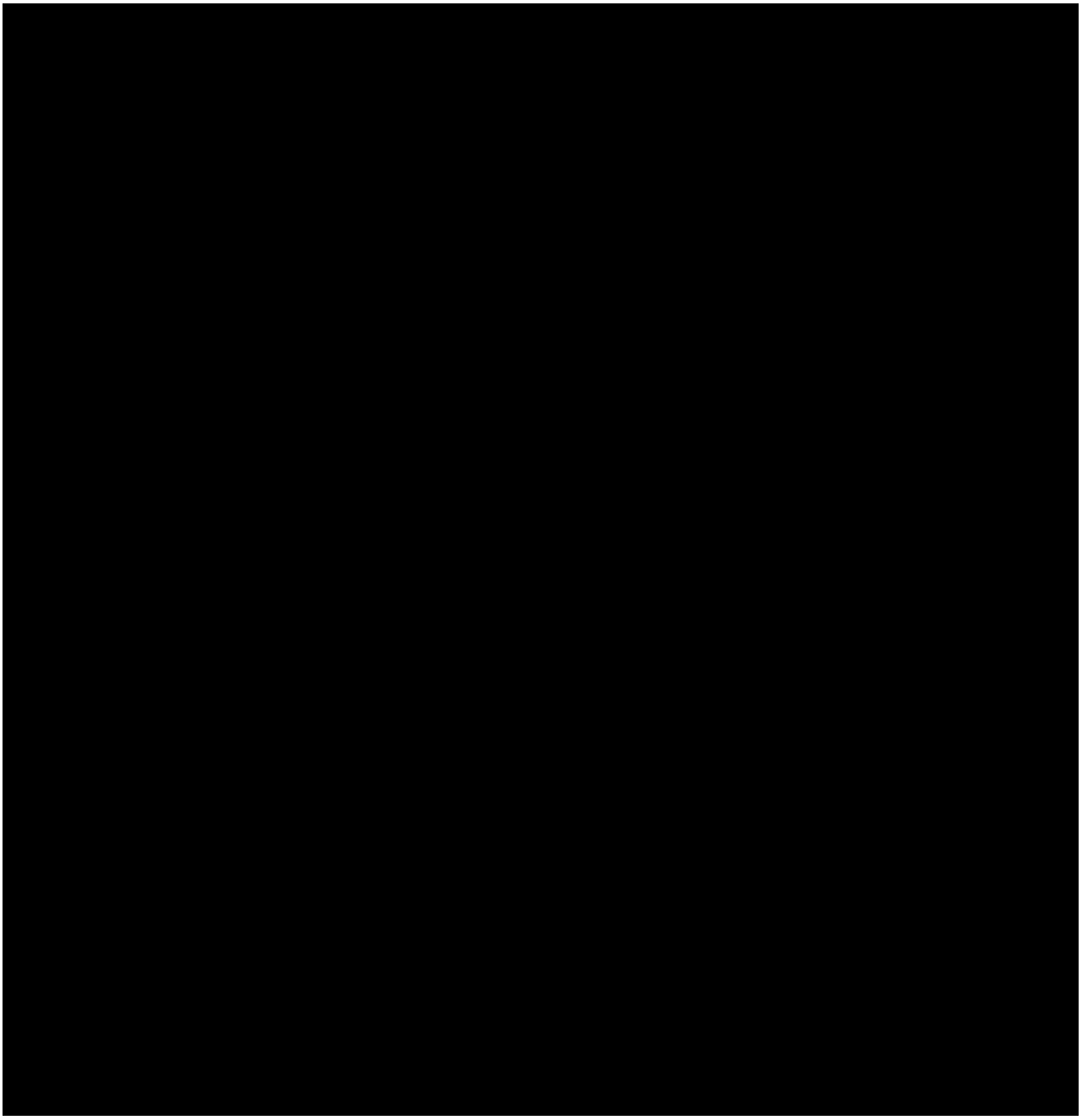
10. APPENDICES

[redacted]



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	mL/min/ 1.73m²	0

Calculation Name	**GFR CKD-EPI**	
Formula	**Units**	**Decimal Places**
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} 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	mL/min/ 1.73m²	0

Calculation Name	**GFR CKD-EPI**	
Formula	**Units**	**Decimal Places**
to 2 decimal places. This creatinine result will be used in the GFR Conventional formulas listed above.		
Limitations/Special Notes:	Age is truncated to a whole number prior to performing the calculation.	

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of Amendment		25 October 2021
EudraCT number		2021-001434-19
BI Trial number		1378-0005
BI Investigational Medicinal Product(s)		BI 690517 and empagliflozin
Title of protocol		Randomised, double-blind, placebo-controlled and parallel dose group trial to investigate efficacy and safety of multiple doses of oral BI 690517 over 14 weeks, alone and in combination with empagliflozin, in patients with diabetic and non-diabetic chronic kidney disease
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title page; Clinical Trial Protocol Synopsis
Description of change		Co-ordinating Investigator address and phone number updated.
Rationale for change		Correction
Section to be changed		Flow Chart, FMV and 24-hour Urine Sampling Flow Chart, 3.1
Description of change		Extended the maximum screening time window to first randomisation from 14 to 21 days throughout the protocol.
Rationale for change		More time is needed to allow screening procedures to be repeated where permitted and will give sufficient buffer for IMP to be delivered to the site.
Section to be changed		Flow Chart

Description of change		Addition of serum cortisol sample at Visit 1, pre and post dose Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, EoT, FUp1 and FUp2. Addition of ACTH Challenge Test (if required) at Visit 5, Visit 6, Visit 7, Visit 8, Visit 9 and EoT. Addition of 24-hour urine samples at Visit 5 and EoT. Added 'and 24-hour urine' to 'Train the patient on FMV sampling'. Addition of 'Dispense urine container for 24-hour sampling' at Visits 4 and 9. Footnote 1: ACTH Challenge Test added as an example of a reason for additional visit. Footnote 10: Clarification of when ACTH Challenge Test is required added. Footnote 14: added that lab samples for serum cortisol must be collected before 10am. Footnote 15: added the timing of the post-dose serum cortisol sample relative to drug administration. Footnote 22 (previously #20): Added requirement to collect start and stop times for 24-hour urine on paper diary.
Rationale for change		Serum cortisol samples added to detect and mitigate the potential risk of adrenal insufficiency. ACTH Challenge Test added (if required based on cortisol levels) to investigate potential adrenal insufficiency during the study. 24-hour urine samples collected to measure urinary free cortisol to determine whether BI 690517 may increase cortisol levels (Cushing's syndrome). 24-hour urine collection times need to be recorded by the patient on a paper diary.
Section to be changed		Flowchart
Description of change		Footnote 19 (previously #17): added "More frequent pregnancy testing should be done if required by local regulation and /or authority or per investigator judgment."

Rationale for change		In some countries pregnancy testing is required more frequently.
Section to be changed		Flowchart
Description of change		The text in footnote 20 (previously #18) about pre-screening for UACR has been moved to footnote 2. 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 patients could potentially fail screening for this. Allowing pre-screening for eGFR means fewer 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		Flowchart
Description of change		Addition of "post-dose" in the split column header of Visit 5. Removal of plasma aldosterone sample at Visit 2, paper diary handout at Visit EoT and FUp1 and collection / review of paper diary at Visit FUp 1 and FUp2. Footnote 4: added 'all trial' to the sentence 'In case a patient needs or wishes to terminate [all trial] treatment prematurely…' Footnote 3: added eGFR to potassium as another safety parameter that must be repeated in case of an unexpected delay of Visit 5. Footnote 10: In the following sentence 'in the patient's medical record' was added: The time for the post ACTH-injection blood samples must be recorded in the patient's medical record.
Rationale for change		Clarifications and corrections to ensure consistency with other sections of the protocol. eGFR and potassium are both critical parameters for start of treatment with BI 690517. There will be no requirement to record the time of post ACTH-injection blood samples taken in the clinical database, as there is no analysis done with it. Instead adherence to the protocol is going to be monitored by reviewing the medical records at the site.

Section to be changed		FMV Sampling Flowchart
Description of change		Title changed to 'FMV and 24-hour Urine Sampling Flowchart' 24-hour urine samples added at Visit 5 and EOT Footnote 3: timepoints for 24-hour urine sample specified
Rationale for change		24-hour urine samples will be collected to measure urinary free cortisol to determine whether BI 690517 may increase cortisol levels.
Section to be changed		[redacted] Flow Chart
Description of change		Corrected footnote 3: No aldosterone samples should be taken at FUp1 or FUp 2.
Rationale for change		Correction.
Section to be changed		1.2.1 BI 690517
Description of change		[redacted]
Rationale for change		Correction
Section to be changed		3.1 Overall Trial Design
Description of change		Removal of diabetes as a prognostic variable for stratification.
Rationale for change		This was erroneously left in the original protocol by mistake. A third stratification factor would result in too small strata and was therefore not further pursued. Instead for the purpose of classifying diabetic status patients with diabetes will be classed as having diabetic kidney disease
Section to be changed		3.1 Overall Trial Design
Description of change		The following sentence: 'To decrease the burden on patients, where country regulations allow, samples taken at home between visits will be shipped from the patient's home to a central laboratory for analysis.' Was replaced by: '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 from the patient's home to a central laboratory for analysis.' The following sentence;

		'Patients with diabetes may have diabetic kidney disease, non-diabetic CKD aetiologies, or a combination; for the purpose of stratification, they will be classed as having diabetic kidney disease'. Was replaced by: 'Patients with diabetes may have diabetic kidney disease, non-diabetic CKD aetiologies, or a combination; for the purpose of categorising diabetic status, they will be classified as having diabetic kidney disease'.
Rationale for change		Clarifications
Section to be changed		3.1 Overall Trial Design
Description of change		24-hour urine samples added at Visit 5 and EOT
Rationale for change		24-hour urine samples will be collected to measure urinary free cortisol to determine whether BI 690517 may increase cortisol levels.
Section to be changed		3.2 Discussion of Trial Design
Description of change		Measures to detect and mitigate the potential risk of adrenal insufficiency and Cushing's syndrome added.
Rationale for change		BI 690517 has the potential to affect cortisol levels so these measures are required to mitigate any risks.
Section to be changed		3.3.2 Inclusion criteria and Clinical Trial Protocol Synopsis
Description of change		Added 'of legal adult age (according to local legislation)' to inclusion criterion 2.
Rationale for change		Clarification that patients must be the legal age of consent as well as 18 or over to enter the trial
Section to be changed		3.3.2 Inclusion criteria
Description of change		Re-numbering of additional Inclusion criteria assessed prior to second randomisation from 1. and 2. to 13. and 14.
Rationale for change		To enable all inclusion criteria to be distinct in trial systems.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Added "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." to exclusion criterion #2
Rationale for change		To ensure patients don't go into the trial if they need to take a restricted medication.
Section to be changed		3.3.3 Exclusion criteria

Description of change		Addition of exclusion criterion number 6: Treatment with biotin (Vitamin B7, Vitamin H, or coenzyme R) at daily doses ≥ 5 mg (including food supplements) within 72 hours of Visit 1 or planned during the trial.
Rationale for change		Intake of higher biotin doses has an influence on certain lab results and may display false results, e.g. for serum pregnancy tests and some hormone tests.
Section to be changed		3.3.3 Exclusion criteria
Description of change		For exclusion criterion 7 (previously #6), instead of an increase in serum cortisol of 200 nmol/L at 30 minutes post-injection, an absolute cortisol value of < 18 µg/dL (496.6 nmol/L) will be used as the diagnostic threshold for adrenal insufficiency.
Rationale for change		ACTH Challenge test to be performed in accordance with the Cosyntropin label and current U.S. guidelines, where the threshold for exclusion of adrenal insufficiency should be an absolute cortisol value of >18 µg/dL 30 minutes post-injection. Both conventional and SI units are specified to align with central laboratory reporting.
Section to be changed		3.3.3 Exclusion criteria
Description of change		For exclusion criterion 10 (previously #9), 'Serum cortisol < 5 µg/dL (138.0 nmol/L)' added to 'Any clinical significant laboratory abnormality'.
Rationale for change		Patients with serum cortisol < 5 µg/dL are at greater risk of adrenal insufficiency and should not be included in the trial.
Section to be changed		3.3.3 Exclusion criteria
Description of change		For exclusion criterion 16 (previously #15), 'at the time of screening' added to 'Any documented active or suspected malignancy' and 'confirmed' added to 'history of confirmed malignancy within two years prior to Visit 1.'
Rationale for change		To clarify that the suspected malignancy is at the time of screening and not within two years prior to Visit 1, and that any history of malignancy is confirmed.
Section to be changed		3.3.3 Exclusion criteria and 4.2.2.1 Restrictions
Description of change		For exclusion criterion 21 (previously #20), removal of 'for an oral agent which is not specified in any other exclusion criteria, or less that 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 tables in section 4.2.2.'

		'Biologics are not permitted within 12 months prior to visit 1' also removed from Concomitant medication Restrictions table 4.2.2.1: 1.
Rationale for change		It is not necessary to exclude patients who were on a trial for a biological agent more than 30 days, up to 12 months, prior to Visit 1.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Footnote 4 Definition of AKI according to KDIGO changed from 'Increase in serum creatinine to ≥ 1.5 times, which is known or presumed to have occurred within the prior 7 days' to 'Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days'
Rationale for change		The word 'baseline' was omitted in error
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		An individual patient will permanently discontinue <u>all randomised trial treatment</u> if: 1. The patient develops Acute Kidney Injury as per clinical judgement by the investigator and/or according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition [R17-2439] (see section 3.3.3). was changed to: The patient develops Acute Kidney Injury as per clinical judgement by the investigator. The Kidney Disease: Improving Global Outcomes (KDIGO) definition [R17-2439] (see section 3.3.3) should be used for guidance.
Rationale for change		The definition of AKI according to KDIGO cannot always be applied in an outpatient setting, therefore AKI should be primarily judged by the investigator based on clinical presentation, and KDIGO can be used for guidance.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Added patients who develop Cushing's syndrome, adrenal insufficiency (including cortisol level <18 µg/dL 30 min (±5 min) after ACTH application), or cortisol levels <3 µg/dL (82.8 nmol/L) at any point in the trial should be withdrawn permanently from BI 690517 / placebo. Added requirement to permanently discontinue patients who permanently discontinue empagliflozin/placebo during the randomised run-in period.

Rationale for change		Cortisol levels added to detect and mitigate the potential risk of adrenal insufficiency or Cushing's syndrome. Patients will only be eligible to receive BI 690517/placebo if they continue to receive empagliflozin/placebo. If one of the study medications (either empagliflozin/placebo or BI 690517/placebo) is permanently discontinued during the Treatment Period / after the second randomisation at Visit 5, the patient may continue to receive treatment with the other study medication.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Added the following statement: 'Shipment of trial medication from the site to the patient's home will also be allowed to support regular visits performed at the patient's home.'
Rationale for change		IMP shipments to the patient's home are required to allow for home health care visits as permitted by the Flow Chart.
Section to be changed		4.2.1.1 Management of serum potassium elevation
Description of change		Added 'episode of' to the following sentence: For any episode of increased potassium level above 5.0 mmol/L, a clinical evaluation should be performed to make individual treatment decisions if a prompt intervention is required.
Rationale for change		Clarified that the rules set forth in this section apply for any episode of hyperkalemia and may apply more than once per patient.
Section to be changed		4.2.1.2 Management of eGFR decrease
Description of change		New section
Rationale for change		Further eGFR monitoring is required after the start of the double-blinded treatment with BI 690517 / placebo, if the eGFR decreases by >15% since the last visit. The decision about continuing or discontinuation of the study drug should be based on the criteria specified in section 3.3.4.1 and the overall assessment of the patient's status.
Section to be changed		4.2.1.3 Management of serum cortisol decrease
Description of change		New section added
Rationale for change		If a patient's serum cortisol level is ≥ 3 µg/dL (82.8 nmol/L) and < 11 µg/dL (303.5 nmol/L), an ACTH test should be performed. If cortisol levels are < 3 µg/dL (82.8 nmol/L) patient should be withdrawn. This is to detect and mitigate the potential risk of adrenal insufficiency.

Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		[redacted]
Rationale for change		
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Footnotes were added to the table to provide further guidance about action to be taken with trial medication if concomitant medications that are not permitted are taken during the study.
Rationale for change		Clarification that temporary concomitant use of medications that are not permitted do not necessarily mean that all study medication must be discontinued permanently.
Section to be changed		4.2.2.3
Description of change		The following sentence has been removed: No contraceptive is required for the WOCBP participant's partner.
Rationale for change		This sentence could be misleading since the female participant must use a barrier method of contraception (as well as a non-barrier method).
Section to be changed		5.1.1 UACR
Description of change		The following sentence has been removed: 'Urinary creatinine may also be used for normalisation of exploratory urinary biomarkers (see section 5.4.1).'
Rationale for change		The additional evaluations originally mentioned will not apply in this trial.
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Removed total from Neutrophils and removed Lymphocyts total.
Rationale for change		Corrections as these were duplications. Relative and absolute WBC differentials already mentioned in the first column.
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Added serum cortisol to the list of hormones to be tested
Rationale for change		Serum cortisol added to detect and mitigate the potential risk of adrenal insufficiency.
Section to be changed		5.2.3 Safety laboratory parameters

Description of change		Added clarification of why a safety laboratory may not be done at the central lab and that table 5.2.3:1 applies for local labs required in such cases.
Rationale for change		Clarifications
Section to be changed		5.2.5.1 ACTH Challenge Test
Description of change		Requirements for ACTH challenge tests during the study and at the end of treatment were added.
Rationale for change		ACTH Challenge Test added to detect and mitigate the potential risk of adrenal insufficiency.
Section to be changed		5.2.5.1 ACTH Challenge Test and Flowchart
Description of change		Plasma ACTH basal sample removed and only serum cortisol basal sample must be taken before ACTH injection.
Rationale for change		Pre-injection plasma ACTH is not required to be tested as part of the test for adrenal insufficiency.
Section to be changed		5.2.5.3 Urinary free cortisol
Description of change		New section added
Rationale for change		Urinary free cortisol added as an assessment to evaluate whether BI 690517 may increase cortisol levels.
Section to be changed		5.2.6.1.4 Adverse Events of Special Interest
Description of change		Addition of Cushing's syndrome and adrenal insufficiency as AESI
Rationale for change		To investigate potential risk of BI 690517 for adrenal insufficiency or increase of cortisol levels (Cushing's syndrome).
Section to be changed		5.3.2 Method of sample collection
Description of change		After completion of the trial the plasma samples may be used for further methodological investigations, e.g. for stability testing. was rephrased to After analysis the plasma samples may be used for further methodological investigations, e.g. for stability testing or to address Health Authority questions regarding the results/methodology.
Rationale for change		Increase the flexibility to start analysis earlier for a potential need to address Health Authority questions
Section to be changed		5.4.2 Pharmacogenomic Biomarkers

Description of change		Pharmacogenomic samples will be discarded no later than 2 years after the last patient has completed the trial, rather than no later than the sign off of the CTR.
Rationale for change		Clarification since the sign off of the CTR could be performed at any time.
Section to be changed		5.5 Biobanking
Description of change		The following sentence was added: For China, samples for biobanking will not be collected, due to regulatory restrictions.
Rationale for change		Clarification for regulatory purposes.
Section to be changed		6.1 Visit schedule
Description of change		Rephrased the following sentence: Patients should be instructed to not take their dose of the study medication at home at scheduled visit days as they will be dosed whilst at the study site. With: Patients should be instructed to not take their dose of the study medication at home in the morning of scheduled visit days as they will be dosed whilst at the study site.
Rationale for change		Clarification.
Section to be changed		6.2 Details of Trial Procedures
Description of change		Post dose- serum cortisol at Visit 5 is also drawn after drug administration.
Rationale for change		Clarification
Section to be changed		6.2.2 Home Visits
Description of change		Rephrased text to clarify direct to patient shipments of IMP and lab kits/ancillary material for home visits. Added instruction that where a CRO is used all source information should be reviewed by an investigator.
Rationale for change		Clarifications and additional information.
Section to be changed		6.2.3 Screening and run-in period(s) and 8.3.1 Source documents
Description of change		Removed the following information to be collected by the site: • Gender identity (male, female, other in order to describe how the participant self-identifies regardless of their genotypic or phenotypic sex)
Rationale for change		There is no requirement for this trial to collect gender information as this has no impact on the results.

Section to be changed		6.2.5 Early discontinuation of treatment
Description of change		Section rephrased to distinguish between the two separate scenarios for early discontinuation: 1. premature discontinuation of empagliflozin/placebo during Run-In Period 2. premature discontinuation of both trial drugs during the Treatment Period
Rationale for change		Further clarification on procedures that apply in case of early discontinuation.
Section to be changed		6.2.6 Follow up period and trial completion
Description of change		Added the following sentences: For patients who prematurely discontinue during the Run-In Period, [redacted] For patients who have not had [redacted]
Rationale for change		Further clarification on the procedures that apply during follow-up in the case of early discontinuation.
Section to be changed		7.2.6 Safety analysis
Description of change		Adverse events will be summarised by the treatment at which the subject was randomised, and the treatment at the onset of AE for the drug-related AE.
Rationale for change		Further information on the intended safety analysis.
Section to be changed		7.4 Randomisation
Description of change		Thresholds added to be used for stratification and prior diabetes removed as another stratum.
Rationale for change		Further information. A third stratification factor would result in too small strata and was therefore not further pursued.

11.2 GLOBAL AMENDMENT 2

Date of Amendment		30 March 2022
EudraCT number		2021-001434-19
BI Trial number		1378-0005
BI Investigational Medicinal Product(s)		BI 690517 and empagliflozin
Title of protocol		Randomised, double-blind, placebo-controlled and parallel dose group trial to investigate efficacy and safety of multiple doses of oral BI 690517 over 14

		weeks, alone and in combination with empagliflozin, in patients with diabetic and non-diabetic chronic kidney disease
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		FMV and 24-hour Urine Sampling Flowchart
Description of change		Addition of a footnote for 24-hour urine sample at EOT: '24-hour urine sample not required at EOT if patient discontinues prematurely prior to start of treatment with BI 690517 / matching placebo'
Rationale for change		24-hour urine sample is required to assess the effect of BI 690517 on urinary free cortisol, therefore this sample is not required at EOT if a patient discontinues prematurely during the Randomised Run-in period.
Section to be changed		1.4.2
Description of change		'Steering committee (SC)' removed from the sentence 'A steering committee (SC) and Data Monitoring Committee (DMC) will be established to review safety data at regular intervals.'
Rationale for change		Only the DMC will review safety data at regular intervals. The SC will provide scientific input and operational oversight.
Section to be changed		3.1 Overall Trial Design
Description of change		Figure 3.1:1 Trial Design updated to include duration of Follow Up Period (4 weeks).
Rationale for change		Correction
Section to be changed		3.1 Overall Trial Design
Description of change		'or genetic' removed from the sentence '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.'
Rationale for change		No genetic testing of banked samples will be performed.
Section to be changed		3.2 Discussion of Trial Design, including the choice of control group(s)
Description of change		Measurement of 24-hour urine changed from 'at screening' to 'just prior to the start of BI 690517 treatment,'
Rationale for change		Correction

Section to be changed		3.3.1 Inclusion criteria
Description of change		Inclusion criteria #7 was changed from: In the Investigator's opinion, one or more of the following underlying kidney disease causes: • Diabetic kidney disease. These patients must have type 2 diabetes mellitus and their treatment (including GLP1 receptor agonist) should be unchanged or changes deemed minor (according to investigator's judgement) within 4 weeks prior to Visit 1 and until first randomisation. • Hypertensive kidney disease • Chronic glomerulonephritis defined as one of the following: o IgA nephropathy, o Membranous nephropathy o Focal Segmental Glomerulosclerosis (FSGS) to: In the Investigator's opinion, any kind of diagnosed chronic kidney disease[5]. Patients with diabetic kidney disease must have type 2 diabetes mellitus and their treatment (including GLP1 receptor agonist) should be unchanged or changes deemed minor (according to investigator's judgement) within 4 weeks prior to Visit 1 and until first randomisation. [5]Diagnosis can be reached by standard clinical method, no biopsy required.
Rationale for change		Broaden criteria to allow enrolment of patients with other non-diabetic kidney diseases
Section to be changed		3.3.3 Exclusion criteria
Description of change		Additional exclusion criterion: 'Patients with known hepatic cirrhosis (Child Pugh A, B or C), or other liver disease causing impaired liver function according to investigator's judgement.' to be reviewed at screening (exclusion #24) and also prior to the second randomisation (exclusion # 26).
Rationale for change		[redacted] No dedicated trial in patients with liver impairment has been done. Experience from other compounds metabolised mainly by UGT2B7 enzymes show that in patients with cirrhosis and liver impairment the exposure may increase up to 4-fold, therefore these patients should be excluded. These patients were to be excluded by exclusion criteria 10 (abnormal laboratory value) but is clarified with this additional criteria.
Section to be changed		3.3.3 Exclusion criteria

Description of change		Additional exclusion criterion #25: 25. Patients with one of the following aetiologies as the underlying cause: • CKD secondary due to malignancy (e.g. Cast-Nephropathy, AL-amyloidosis) • CKD secondary to infectious disease (e.g. Hepatitis-/HIV-associated) • Autosomal-dominant polycystic kidney disease
Rationale for change		To exclude patients with certain causes of CKD where no benefit to treatment is expected.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		For #1, the sentence 'The Kidney Disease: Improving Global Outcomes (KDIGO) definition [R17-2439] (see section 3.3.3) should to be used for guidance.' was changed to 'The Kidney Disease: Improving Global Outcomes (KDIGO) definition [R17-2439] (see section 3.3.3) is going to be used for guidance'
Rationale for change		Administrative change
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		For #2, the % drop in eGFR will be measured from when the patient starts the empagliflozin/placebo treatment. The individual patient will permanently discontinue all randomized trial treatment if: The patient experiences a drop in eGFR: • ≥ 30% from the last measurement of eGFR before the first dose of empagliflozin / placebo up to Visit 6; and/or • ≥ 40% at any time since the last measurement of eGFR before the first dose of empagliflozin/placebo
Rationale for change		Correction to add an omitted time interval specification
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		The sentence 'The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future' has been changed to 'The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of the investigator, the safety of the patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future'
Rationale for change		Clarification that it is just the investigator's opinion that should be considered.

Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		The sentence 'In this case the sponsor should be consulted' was changed to 'In this case the sponsor can be consulted'.
Rationale for change		Clarification.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		The following reason to discontinue all randomised trial treatment was added: The patient does not meet the additional inclusion criteria (see section 3.3.2) or the additional exclusion criteria (see section 3.3.3) assessed before second randomization (start of Treatment Period).
Rationale for change		Clarification that if the additional eligibility criteria for starting BI690517 / matching placebo are not met, the patient should permanently discontinue.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		The sentence 'The patient should be followed according to local guidelines until resolution of the event and the event should be reported to the sponsor' was changed to 'The patient must be followed according to local guidelines until resolution of the event and the event is going to be reported to the sponsor'
Rationale for change		Administrative change
Section to be changed		4.1.2 Selection of doses in the trial and dose modifications
Description of change		The sentence 'The 40 mg dose resulted in total aldosterone suppression, and therefore a lower 20 mg dose is expected to have a partial aldosterone suppression and a reduced risk of hyperkalaemia.' was changed to 'The 40 mg dose resulted in a substantial suppression of aldosterone, and it is expected that the lower 20 mg dose will result in less aldosterone suppression, reducing the risk of hyperkalaemia.'
Rationale for change		Clarification that the 40 mg dose causes substantial suppression of aldosterone instead of total suppression and that 20 mg dose causes less aldosterone suppression.
Section to be changed		4.1.5 Blinding and procedures for unblinding
Description of change		'and to provide PK data to DMC for consideration when evaluating safety of the trial' was added to the sentence: In order to expedite the population PK and PK-PD analyses and ensure timely delivery of PK/PD results after database lock and to provide PK data to DMC for consideration when evaluating safety of the trial, specific data must be unblinded

		and the treatment information must be made available to selected individuals.
Rationale for change		Provision of unblinded PK data to the DMC will support the understanding of the safety data.
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Addition of [redacted]
Rationale for change		To be consistent with the first paragraph in the section and to clarify that only [redacted] should not be used.
Section to be changed		6.2.5 Early discontinuation of Treatment
Description of change		The following bullet point was added under 'If the patient prematurely discontinues empagliflozin/placebo during the Run-In Period' • The 24-hour urine sample prior to EOT does not need to be collected.
Rationale for change		24-hour urine sample is required to assess the effect of BI 690517 on urinary free cortisol, therefore this sample is not required at EOT if a patient discontinues prematurely during the Randomised Run-in period
Section to be changed		8.7 Administrative Structure of the Trial
Description of change		'PK data (organised according to eGFR stratification)' added to the data that will be evaluated by the DMC
Rationale for change		PK data will support the understanding of the safety data.
Section to be changed		Appendix 10.1
Description of change		Addition of plasma aldosterone and its precursors to the list of exploratory biomarkers.
Rationale for change		To ensure consistency with section 5.4.1 Exploratory biomarkers where plasma aldosterone and its precursors are also included.

11.3 GLOBAL AMENDMENT 3

Date of Amendment		19 August 2022
EudraCT number		2021-001434-19
BI Trial number		1378-0005
BI Investigational Medicinal Product(s)		BI 690517 and empagliflozin
Title of protocol		Randomised, double-blind, placebo-controlled and parallel dose group trial to investigate efficacy and

		safety of multiple doses of oral BI 690517 over 14 weeks, alone and in combination with empagliflozin, in patients with diabetic and non-diabetic chronic kidney disease
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Flowchart
Description of change		Time window for Screening 'up to 21 days before Visit 2' added
Rationale for change		Clarification to make it clear that screening period should be no longer than 21 days
Section to be changed		Flowchart
Description of change		Treatment compliance added for Visits 4, 5, 6, 7, 8, 9 and EOT (including footnote #28)
Rationale for change		Clarification to distinguish between treatment compliance, which is required at all visits, and drug accountability which is not required at visits 4 and 6 (see change below).
Section to be changed		Flowchart
Description of change		Requirement for Drug Accountability (via IRT) removed at Visits 4 and 6
Rationale for change		Study drugs do not need to be accounted for in IRT at visits 4 and 6 as study drugs are not returned at these visits.
Section to be changed		Flowchart
Description of change		Footnote 2 additional sentence added: 'The Screening Period should be no more than 21 days from first screening procedure to first randomisation.'
Rationale for change		Clarification to make it clear that screening period should be no longer than 21 days
Section to be changed		Flowchart
Description of change		Footnote 2 – 'once' added to the sentence 'Screening procedures may be repeated once during the screening period if the patient is not eligible for a transient medical condition
Rationale for change		Clarification that screening procedures should not repeatedly be retested until an eligible result is obtained.
Section to be changed		Flowchart
Description of change		Footnote 5 additional sentence added: 'Where the patient does not meet the additional inclusion criteria 13 and 14 based on lab tests performed at Visit 4, the eGFR and

		potassium cannot be re-tested and the patient should permanently discontinue the study.'
Rationale for change		Clarification
Section to be changed		Flowchart
Description of change		Footnotes 10 and 14: Change of timing of collection of the serum cortisol. Changed from ' before 10 am' to 'within 4 hours of the patient's usual waking time'.
Rationale for change		Serum cortisol is affected by diurnal rhythm and this allows patients who are regular late risers to still participate in the trial whilst not affecting the validity of the results.
Section to be changed		Flowchart
Description of change		Additional footnote 27 (associated with FUp1.1, FUp1.2 and FUp2): In the case of premature discontinuation during the Randomised Run-in Period, FUp1.1, FUP1.2 and FUp2 do not need to be conducted.
Rationale for change		Clarification as these visits are only relevant for patients who have started BI690517 / placebo treatment.
Section to be changed		Flowchart
Description of change		Footnote 29 added: Days and associated time windows are relative to Visit 5
Rationale for change		Clarification
Section to be changed		[redacted] Flow Chart
Description of change		Time window for the pre-dose samples changed from -0:30 (+/- 15 min) to -0:30 (+ 29 / - 15 min)
Rationale for change		It is acceptable for the pre-dose samples to be taken immediately before the dose, up to 45 mins before the dose.
Section to be changed		[redacted] Flow Chart
Description of change		Footnote #3 - added that only pre-dose (-0:30) [redacted] samples need to be taken at EoT in case of premature discontinuation during run-in phase.
Rationale for change		Clarification
Section to be changed		[redacted] Flow Chart
Description of change		Additional footnote #6 added: [redacted]

Rationale for change		[redacted]
Section to be changed		Abbreviations
Description of change		LPLVPE (Last Patient Last Visit Primary Endpoint) added
Rationale for change		Abbreviation used in section 4.1.5.1
Section to be changed		3.1 Overall Trial Design
Description of change		'A minimum of 40% of patients will be required to be randomised during the run-in period in each of the disease types: diabetic kidney disease and non-diabetic kidney disease.' Was changed to: 'A target of approximately 30% of patients will be randomised during the run-in period in each of the disease types: diabetic kidney disease and non-diabetic kidney disease.'
Rationale for change		Based on the type of sites (e.g. general practices to sites specialized in nephrology) involved in this study, observed actual distribution of diabetic kidney disease vs. non-diabetic kidney disease is approximately 70% vs. 30%. Therefore, the trial is unlikely to reach 40% of non-diabetic kidney disease patients within the required recruitment time, and reducing the minimum required from 40% to 30% will not affect study primary objectives or main outcomes since the study outcomes are combined for both disease types.
Section to be changed		3.3 Selection of Trial Population
Description of change		If a patient has been randomised in error (did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not. Was changed to: The investigator will make every effort to avoid the inclusion of a patient who does not meet all the inclusion criteria and/or meets at least one exclusion criterion. Should such an error nevertheless occur, this patient might be immediately excluded from the clinical trial based on individual benefit-risk assessment by the investigator. The sponsor or delegate will be informed as soon as possible.
Rationale for change		It should be the investigator who determines the benefit-risk assessment in case a patient is randomised in error, and not the sponsor.

Section to be changed		3.3.3 Exclusion criteria
Description of change		'Systemic' and 'or before first randomisation' was added to exclusion criteria #11: 'Any systemic immunosuppression therapy or immunotherapy in the last 3 months prior to Visit 1 or before first randomisation. This also applies to systemic steroids except oral prednisolone ≤10 mg or equivalent.'
Rationale for change		To allow local immunotherapy (e.g., cyclosporine eye drops) which does not have impact on study endpoints; and clarification that systemic immunosuppression or immunotherapy is not allowed before first randomisation.
Section to be changed		3.3.3 Exclusion criteria
Description of change		The following was added to exclusion criterion # 19: 'Patients who are unable to comply with trial procedures'
Rationale for change		Clarification to exclude patients who are unable to comply with trial procedures
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Footnote #1 (associated with eGFR drop) added: 'Where the eGFR drop occurs before the start of BI 690517 / placebo in the Treatment Period (i.e., at Visit 5), but the result is not available until after the patient starts BI 690517/placebo treatment, the patient must still permanently discontinue all randomised study treatment, including BI 690517 / placebo.'
Rationale for change		Clarification
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		'and should continue with scheduled study visits.' has been added to the sentence 'If one of the study medications (either empagliflozin/placebo or BI 690517/placebo) is permanently discontinued during the Treatment Period / after the second randomisation at Visit 5, the patient may continue to receive treatment with the other study medication'.
Rationale for change		Clarification
Section to be changed		4.1.5.1 Blinding
Description of change		'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 until the database is declared ready for analysis according to the sponsor's SOPs.' Was changed to:

		'Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until a snapshot after Last Patient Last Visit Primary Endpoint (LPLVPE), with the exception of the Trial Pharmacometrician, PK programmer and Trial Bioanalyst. This snapshot will be taken after the last patient completes the EoT Visit, and will be used to obtain efficacy, safety, and PK/PD results, to guide further development plans for BI 690517. At the timepoint of unblinding of this snapshot, patients and investigators will continue to be blinded and will remain so until after database lock when the database is declared ready for final analysis according to the sponsor's SOPs.' 'Bioanalytics will not disclose the randomisation code or the results of their measurements until the database lock.' Was changed to: 'Bioanalytics will not disclose the randomisation code or the results of their measurements prior to the LPLVPE snapshot.' 'It should be noted no PK/PD results will be communicated to the project and trial team prior to database lock.' Was changed to: 'It should be noted no PK/PD results will be communicated to the project and trial team prior to the LPLVPE snapshot.'
Rationale for change		To allow an earlier start of analysis, data will be unblinded after the last EoT visit instead of database lock
Section to be changed		4.1.6 Packaging, labelling, and re-supply
Description of change		'(or equivalent)' added to 'Synacthen® (or equivalent) is either provided by the site or where this is necessary through the sponsor.'
Rationale for change		Clarification
Section to be changed		4.2.1.3 Management of serum cortisol decrease
Description of change		'from BI 690517 / placebo added to the sentence, 'If, during the trial, cortisol level is < 3 µg/dL (82.8 nmol/L) the patient must be withdrawn from BI 690517 / placebo.'
Rationale for change		Clarification
Section to be changed		4.2.2.1 Concomitant medication restrictions
Description of change		[redacted]

Rationale for change		[redacted] This change will not compromise the integrity of the trial or introduce bias.
Section to be changed		4.2.2.1 Concomitant medication restrictions
Description of change		For [redacted] 'or deemed minor in the opinion of the investigator' added to the sentence 'Stable dose permitted if used prior to entry, change should be avoided' in the columns 'During run-in and Treatment Period' and 'In the Follow-up Period' and 'in the opinion of the investigator' added in the columns 'Prior to trial (Visit 1)' and 'During screening (prior to first randomisation)'.
Rationale for change		Clarification
Section to be changed		4.2.2.1 Concomitant medication restrictions
Description of change		[redacted]
Rationale for change		Clarification
Section to be changed		5.2.3 Safety Laboratory Parameters
Description of change		Sentence added: Ineligible lab parameters may only be re-tested once during the screening period.'
Rationale for change		Clarification that screening procedures should not repeatedly be retested until an eligible result is obtained.
Section to be changed		5.2.5.1 ACTH Challenge test
Description of change		Paragraph added: Alternative conduct of the ACTH test is allowed only if it is in accordance with the local practice of diagnosis of adrenal insufficiency. If adrenal insufficiency is diagnosed with an alternative conduct of ACTH test, the details of the ACTH test should be documented in the AESI report to the sponsor.
Rationale for change		Clarification that alternative methods of diagnosing adrenal insufficiency are accepted if it is in accordance with local practice since some countries do not use the Short Synacthen test as standard.
Section to be changed		5.2.5.1 ACTH Challenge Test

Description of change		'A serum cortisol basal sample must be taken before the ACTH injection (iv or im 0.25 mg Synacthen® or equivalent product if Synacthen® is not authorised locally).' Was changed to 'A serum cortisol basal sample must be taken before the ACTH injection (iv or im 0.25 mg Synacthen®; an equivalent product may be used if Synacthen® is not authorised locally or provided by the sponsor).'
Rationale for change		Clarification
Section to be changed		5.2.5.1 ACTH Challenge Test
Description of change		'In this trial, the Synacthen® (or equivalent product if Synacthen® is not authorised locally) for the ACTH challenge test is considered as auxiliary medicinal product (AxMP).' Was changed to 'In this trial, the Synacthen® (or equivalent product) for the ACTH challenge test is considered as auxiliary medicinal product (AxMP).'
Rationale for change		Clarification
Section to be changed		5.2.6.1.4 Adverse events of special interest
Description of change		Clarification that lab findings constituting a hepatic injury only need to be followed up according to the DILI checklist after the start of study treatment.
Rationale for change		Clarification
Section to be changed		5.5 Biobanking
Description of change		Paragraph added: 'In some countries, for example China, biobanking samples will not be collected due to regulatory reasons.'
Rationale for change		Correction. This should have been added in Amendment 1 (see Appendix 11.1) but was missed from the section in error. Since Amendment 1, other countries will not be collecting biobanking samples so the sentence has been updated.
Section to be changed		6.2.3 Screening and run-in period(s)
Description of change		'after discussion with the sponsor' removed from the sentence '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.'
Rationale for change		It is not necessary to discuss with the sponsor before rescreening a patient.

Section to be changed		11.2 Global Amendment 2
Description of change		Reference to exclusion criteria 11 changed to exclusion criteria 10 in relation to abnormal laboratory value.
Rationale for change		Correction

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Biostatistics	[redacted]	19 Aug 2022 17:07 CEST
Approval-Team Member Medicine		19 Aug 2022 17:08 CEST
Author-Clinical Trial Leader		19 Aug 2022 17:30 CEST
Approval-Therapeutic Area [redacted]		19 Aug 2022 18:14 CEST
Author-Trial Clinical Pharmacokineticist		22 Aug 2022 15:32 CEST
Verification-Paper Signature Completion		23 Aug 2022 12:45 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed