TRIAL STATISTICAL ANALYSIS PLAN

c41181505-02

BI Trial No.:	1378-0005
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
Investigational Product(s):	BI 690517 and empagliflozin
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	26 June 2023
Version:	2.0

1. TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
BMI	Body Mass Index
COVID-19	Corona Virus Disease 2019
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Data Base Lock
DILI	Drug Induced Liver Injury
DV	Deviation
ECG	Electrocardiogram
EDMS	Electronic Document Management System
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EoT	End of Treatment
ES	Entered Set
FAS	Full Analysis Set
FMV	First Morning Void
F/U	Follow-Up
ICE	Intercurrent Events
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iPD	Important Protocol Deviation
LOCF	Last Observation Carried Forward
MCP-MoD	Multiple Comparisons Procedure - Modelling
MedDRA	Medical Dictionary for Drug Regulatory
MMRM	Mixed-effect Model for Repeated Measures

Term	Definition / description
PD	Pharmacodynamics
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
QD	Quaque die (once a day)
REP	Residual Effect Period
RMP	Risk Management Program
RPM	Report Planning Meeting
RRTS	Randomised Run-in Treated Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDL	Subject Data Listings
SGLT2i	Sodium-Glucose co-Transporter-2 inhibitor
TEAE	Treatment Emergent Adverse Events
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UACR	Urine Albumin Creatinine Ratio
ULN	Upper Level of Normal

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP (Trial Statistical Analysis Plan) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g. on study objectives, study design, and population, treatments, definition of measurements and variables, planning of sample size, and randomisation.

The statistical analyses will be performed within the validated Clinical data Analysis and Reporting Environment (CARE), including SAS™ (current Version 9.4, by [redacted]), and a number of SAS™-based tools (e.g. macros for the analyses of Adverse Event [AE] data or laboratory data; Report Appendix Generator system [RAGe] for compilation/formatting of the Clinical Trial Report [CTR] appendices). Pharmacokinetic (PK) parameters will be calculated using WinNonlin™ software (version 8.1, [redacted]).

Analyses of the biomarker and gene expression data are described in a separate biomarker analysis report, unless otherwise specified in this document.

The trial data is stored in the Boehringer Ingelheim (BI) Rave (BRAVE) database system.

SAS® Version 9.4 and R version 4.0.2 will be used for statistical analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

This section is not applicable as no change has been made.

5. ENDPOINTS

5.1 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.

The expected intercurrent events of interest in this trial are restricted to the Treatment Period. The two different approaches for handling intercurrent events (ICEs) are summarised in the table below:

Estimand strategy	Treatment	ICE handling rules
Primary	Randomised treatment	- BI 690517 discontinuation: 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	Randomised treatment	- BI 690517 discontinuation: 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

SGLT2i = Sodium glucose co-transporter-2 inhibitor

5.2 SECONDARY ENDPOINT

5.2.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

5.2.2 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.

[redacted]

[redacted]

5.4.1 Safety endpoint(s)

This section is not applicable as no safety endpoint has been specified in the protocol.

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatment to be administered, assignment of treatment groups, and selection of doses, refer to CTP Sections 3 and 4. This phase II trial will be performed as a 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.

During the Run-in Period, eligible patients will be randomised in a 1:1 ratio to either receive empagliflozin 10 mg once a day (QD) or placebo matching to empagliflozin 10 mg QD in a blinded manner for 8 weeks. During the Treatment Period, patients who received empagliflozin or placebo matching to empagliflozin in the Run-in Period, respectively, 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. The randomisation will be stratified according to prognostic variables eGFR (< 45 and ≥ 45 mL/min/1.73 m^2), UACR (≤ 750 and >750 mg/g). Following the 14-week Treatment Period, or at the time trial treatment is permanently discontinued, patients will have an End of Treatment (EoT) visit, which will be the start of a 4-week follow-up period.

Section 1.2 of the CTP: The Residual Effect Period (REP) of BI 690517 is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic (PD) effects still likely to be present.

Section 7.2.6 of the CTP: Statistical analysis and reporting of AEs will concentrate on treatment-emergent adverse events (TEAEs), i.e. all AEs that occur between start of treatment and end of the REP. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. AEs will be summarised by the treatment groups to which the patient was randomised, and the treatment at the onset of AE for any drug-related AE. In addition, summary of patients with down titration (dose reduction) due to AE will be provided.

For the analysis of AEs, the following study phases are defined in Table 6.1: 1.

Table 6.1:1 Study phases for analysis of AEs

Study Analysis Phase	**Label**	**Start (inclusive)**	• **End (exclusive)**
Screening	Screening	Date of informed consent	Date/time of first administration of empagliflozin / placebo
Run-in	**Placebo, Empagliflozin,** respectively	Date / time of first administration of empagliflozin / placebo	For patients discontinue in Run-in Period, 12:00 a.m on the day after last administration of empagliflozin / placebo + REP (7 days),

			For patients continue in Treatment Period, 12:00 a.m on the day after last administration of empagliflozin / placebo + REP (7 days) or first administration of BI 690517 / placebo, whichever occurs first
On-treatment	**Placebo, BI 690517, Plus Empagliflozin or matching placebo,** respectively	Date / time of first administration of BI 690517 / placebo	12:00 a.m on the day after last administration of BI 690517 / placebo + REP (7 days) Or 12:00 a.m on the day after patient's trial termination date,
Follow-up[1]	**F/U Placebo, F/U BI 690517, plus Empagliflozin or matching placebo,** respectively	12:00 a.m on the day after last administration of BI 690517 / placebo + REP (7 days)	12:00 a.m on the day after patient's trial termination date

[1] Follow-up phase might not exist, e.g. if the patient's trial termination date is within 7 days after last administration of study drug

In the case that the patient is permanently discontinued BI 690517, but is continuing on Empagliflozin during Treatment Period, the occurrence of AEs between REP of BI 690517 and REP of Empagliflozin will be provided in the listing. For treatment interruptions, the occurrence of AEs between the start of interruption and re- start of treatment will be assigned to actual treatment received. These cases will be flagged in the safety listings as occurring during the off-treatment period. AEs will be displayed by dose group and will be provided in the CTR.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Handling of important protocol deviations (iPDs) in the analysis is included in the deviation (DV) domain specifications and stored within the Trial Master File (TMF) in the Electronic Document Management System (EDMS).

Consistency check listings (for identification of violations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided for discussion at the Trial Oversight Meeting (TOM) prior to Data Base Lock (DBL) or at the Report Planning Meetings (RPMs). At these meetings, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an iPD. For definition of iPDs, and for the process of identification of these, refer to "Identify and Manage Important Protocol Deviations (iPD) ".

If any iPDs are identified, they are to be summarised into categories and will be captured in the meeting minutes and additionally via an accompanying Excel spreadsheet. The iPDs may lead to exclusion of patients from analysis sets. The documentation of the iPD categories and

how to handle iPDs in the analysis is included in the DV domain specifications and stored within the TMF in EDMS. If the data show other iPDs, this domain will be supplemented accordingly. iPDs will be summarised during both Run-in and Treatment Period for randomised set, and iPDs of patients discontinued during Run-in Period will be provided by listings.

Non-important Corona Virus Disease 2019 (COVID-19) related PDs will only be listed.

6.3 SUBJECT SETS ANALYSED

In addition to the subject sets for statistical analysis defined in the CTP, Section 7.2.1, the following subject sets will be used:

Run-in Randomised Set (RIRS):

This patient set includes all randomised patients of the Run-in Period, regardless of being treated or not.

Run-in Treated Set (RITS):

This patient set includes all randomised patients of the Run-in Period who were documented to have taken at least one dose of empagliflozin or placebo.

Full Analysis Set (FAS):

This patient set includes all randomised patients who had at least one baseline measurement of UACR at week -2, -1, or 0 and at least one post-baseline measurement when patients are still on treatment of BI 690517. The FAS will be the main analysis set for the analysis of efficacy.

Table 6.3: 1 illustrates the data sets which are to be used for each category class of endpoints.

Table 6.3: 1 Subject sets analysed

Class of endpoint	ES	RIRS	RITS	RS	TS	FAS	PKS
Disposition	X			X			
Exposure / Compliance			X		X		
IPDs				X			
Demographic/baseline		X		X			
Primary endpoint						X	
Secondary endpoint						X	
Other safety/tolerability			X		X		
Further endpoints						X *	
Further PK endpoints							X

* Analyses on further endpoints such as serum potassium, vital signs, and body weight, are based on TS.

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Withdrawals

The reasons for withdrawal from treatment will be reported as indicated on the electronic case report form (eCRF).

6.6.2 Efficacy data

6.6.2.1 Primary endpoint

Missing data for primary analysis will not be imputed:

- If some UACR value(s) at baseline is (/are) missing, all other available UACR samples in week -2, -1, and 0 will be used to derive UACR at baseline.
- If any UACR value after randomisation to the Treatment Period is missing, the missing UACR will not be imputed.
- UACR values excluded from the primary analysis according to the ICEs handling rules will not be imputed.

The Mixed-effect Model for Repeated Measures (MMRM) approach used for the primary endpoint (see Section 7.4.1) allows for missing data, assuming missing data following the "missing at random" assumption. Even patients with only one post-baseline assessment can be included in the model and can, therefore, contribute to the variance estimation. This primary analysis assumes that patients who had ICE(s) should have behaved similarly to those who remained in the study, and therefore is analogues to the hypothetical estimand strategy.

The table below describes how/when to derive UACR values for the statistical analysis:

Table 6.6.2.1: 1 Principal rule of First Morning Void (FMV) UACR derivation for analysis

	FMV UACR at baseline	FMV UACR at visit 8	FMV UACR at visit 9	FMV UACR at EoT
Derivation	Baseline FMV UACR is defined as the mean of all non-missing assessments from week -2 until prior to the first intake of trial medication BI 690517 or placebo in the Treatment Period.	Average of all available FMV UACR measured at visit 8 (week 6)	Average of all available FMV UACR measured at visit 9 (week 10)	EoT FMV UACR is defined as the mean of all non-missing assessments from week 12 to week 14 (EoT visit)

Sensitivity analyses will be conducted to investigate the potential effect of ICE handling approaches on the results of the primary analysis. Details about implementation of the sensitivity statistical analyses are described in Section 7.4.

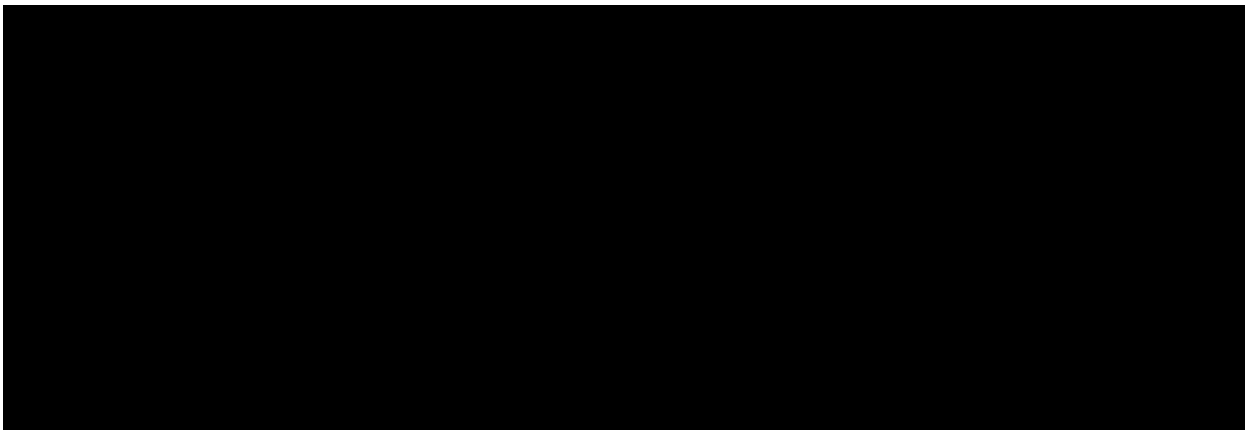
6.6.2.2 Secondary endpoint(s)

The principal rule of UACR derivation specified in Table 6.6.2.1:1 will be used for derivation of UACR at baseline and EoT, and the UACR percent change from baseline to EoT will be calculated accordingly:

$$UACR\ change\ (\%) = \frac{UACR\ at\ EoT - UACR\ at\ baseline}{UACR\ at\ baseline}$$

Missing UACR will be imputed in the sensitivity analysis.

Details about implementation into the statistical analysis are described in Section 7.4.



6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Section 2.2.2 of the CTP:
Throughout this protocol, the term "baseline" refers to the last observation prior to the first intake of trial medication, with the exception of FMV urine UACR. Baseline for the FMV urine UACR, is defined as the mean of all available samples from week -2 until prior to the first intake of trial medication. This does not include the UACR measured in spot urine at Screening.

Measurements taken after start of administration of trial treatment of BI 690517 will be considered on-treatment values based on the definition in Section 6.1, and will be assigned to visits for statistical analysis, if applicable, as defined below.

Analysis of AE data, potentially clinically significant abnormal laboratory values, concomitant medication or non-drug therapies, as well as use of rescue therapy will not be based on visits. Therefore, no assignment to time windows will be necessary for such data.

The derivation of the last value, minimum value and maximum value of laboratory and vital signs data will consider all on-treatment values (whether or not selected in any time window; see Section 6.1 for definition of the on-treatment period) within the period of interest; these will be derived for analysis of laboratory and vital signs data.

All other safety and efficacy measurements will be assigned to visits based on extended time windows around the planned visit dates, defined relative to the day of first trial treatment of BI 690517 (which is scheduled for Visit 5).

Repeated and unscheduled efficacy and safety measurements (except for laboratory data) will be handled similarly to scheduled measurements and will also be assigned to a time window depending upon the date of measurement. For handling of laboratory measurements see also Section 7.8.2.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI standards "Standards for reporting of clinical trials and project summaries" (6), with the exception of those generated for PK calculations following BI standards for PK/PD analysis (7,8).

The individual values of all patients will be listed, sorted by dose groups of study treatment (empagliflozin/ matching placebo + BI 690517/ matching placebo), patient number and visit (if visit is applicable in the respective listing). AE listings will be sorted by study treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics of continuous variables is:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
SE	standard error (except for PK)
Min	minimum
Median	median
Max	maximum

For plasma concentrations, as well as for PK parameters, the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

The data format for descriptive statistics of plasma concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%). Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there actually are missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

Exclusion of PK parameters

The ADS ADPP (PK parameters) contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters if they are not flagged for exclusion, that is APEXC is equal to "Included".

Exclusion of PK concentrations
The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to 'ALL CALC', the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to 'DESC STATS', the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition 'TIME VIOLATION' or 'TIME DEVIATION', the value can be used for further analyses based on actual times. If ACEXCO is set to 'HALF LIFE', the value will be excluded from half-life calculation (and, as a consequence, any calculation that relies on λz) only; the value is included for all other analyses.

Further details are given in BI-KMED-TMCP-MAN-0014 "Noncompartmental PK/PD analyses of Clinical Studies".

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. The data will be summarised by dose groups of study treatment, and in total. Disease characteristics during Run-in Period will be based on available data at Screening for randomised run-in set. Baseline characteristics for randomised set will be based on available data prior to the first intake of BI 690517. Additionally, demographic and baseline characteristics will be displayed for DKD and non-DKD populations of the RS, respectively.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the CTR, based on the RS. Additionally, concomitant medication will also be displayed for DKD and non-DKD populations of the RS, respectively.

Concomitant diseases and concomitant non-drug therapies will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary. The coding version number will be displayed as a footnote in the respective output.

The frequency [N (%)] of patients with different concomitant diseases (baseline conditions) will be presented.

A medication/non-drug therapy will be considered concomitant to treatment if it:

- Is ongoing at the start of randomised trial treatment of BI 690517 or
- Starts within the on-treatment period (see Section 6.1 for a definition of study analysis phases).

A medication/non-drug therapy will be considered as prior medication/non-drug therapy, if the end date of the medication/therapy is at any time prior to the start of the randomised trial treatment of BI 690517.

Concomitant medication use will be summarised with frequency and percentage of patients by ATC3 class and preferred name. Summaries will be presented for concomitant medication starting any time prior to start of trial treatment and starting any time during the BI 690517 on-treatment period (see Section 6.1 for definition of the on-treatment period).

Concomitant use of non-drug therapies will be summarised with frequency and percentage. Summaries will be presented for concomitant non-drug therapies starting any time prior to start of trial treatment of BI 690517 and starting any time during the BI690517 on-treatment period (see Section 6.1 for definition of the on-treatment period).

Restrictions regarding concomitant treatment during the study periods are defined in Section 4.2.2.1 of the CTP.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned according to percentage of patients meeting the compliance.

Compliance of BI 690517 will be displayed by weighted average of percent compliance, where the weight is defined as the time interval (number of weeks) between two consecutive study visits at which compliance data will be collected, i.e., the weight will be 1 (week) for visit 6 and visit 7, and will be 4 (weeks) for visit 8, visit 9, and visit EoT, respectively. Number and percentage of patients with compliance categories <80%, 80%-120%, and >120% will also be presented.

Compliance of empagliflozin will be displayed by percent of calculated compliance based on study medication taken according to protocol for each visit.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

The primary analysis of the primary endpoint will be analysed according to the primary strategy of handling ICEs (see Section 5.1).

Refer to Section 7.2.2 of the CTP for a description of the statistical analysis for the change from baseline in log transformed FMV UACR measured at 14 weeks of trial treatment.

The adjusted mean change in log transformed FMV UACR from baseline at 14 weeks and its standard error will be obtained from MMRM for the placebo and treatment groups. For the MMRM model, derived UACRs at baseline, visit 8, visit 9, and EoT, which were described in Section 6.6.2.1, will be used.

SAS code for **the MMRM model** will be based on the following structure:

```
PROC MIXED DATA=alldat cl method=reml;

CLASS visit trt subject;

MODEL chg = baseline*visit visit*trt stratum / ddfm=kr s CL;

REPEATED visit / subject= subject type=un r rcorr;

LSMEANS visit*trt /pdiff=all om cl alpha=0.05 slice=visit;

RUN;
```

In the event of model non-convergence, the methods described in Section 10.1 will be attempted (in order) to overcome it.

MCPMod Analysis

For the primary analysis the dose-response relationship will be modelled using following doses: placebo, 3mg, 10mg, and 20mg, in combination with empagliflozin or empagliflozin matching placebo, respectively. The multiple comparison procedure will then be implemented using optimal contrast tests which control the family-wise type I error rate at a one-sided $\alpha = 0.05$. For the MCPMod test, the optimal contrasts of each candidate model are calculated using the R-function optCont.

For the final evaluation, the contrast will be provided using the expected model means from the candidate set and the estimated variance-covariance matrix extracted from the MMRM model.

Once the significance of a dose-response signal is established, the dose-response profile and the target dose can be estimated using a model averaging approach for significant models.

To select a dose estimation model out of the set of significant models, estimates for each dose group will be calculated and will be based on the final dose-response model. The choice of the target dose will be based upon efficacy as well as considering safety and other relevant information.

The following displays are planned:

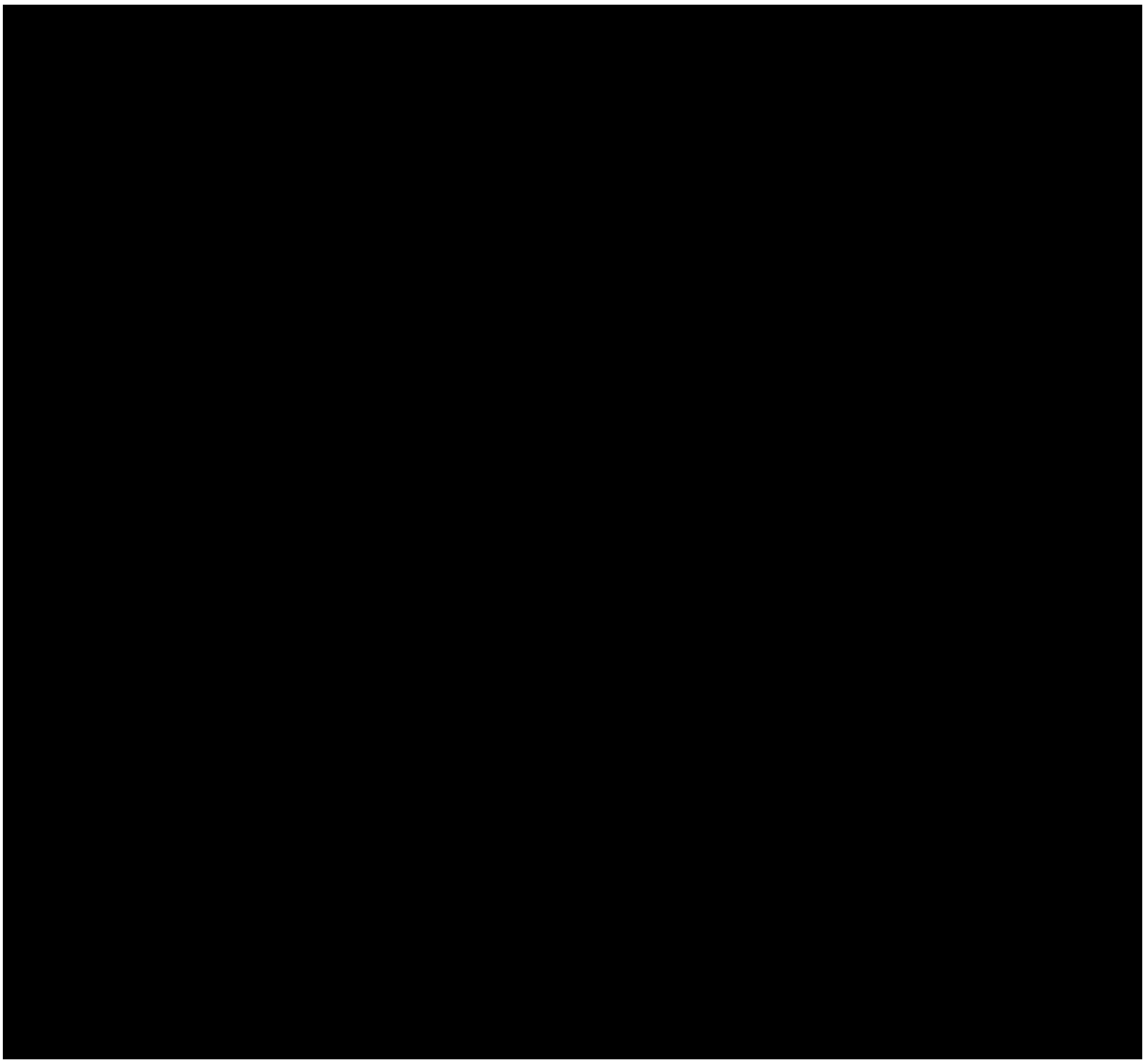
- Table of the updated contrast coefficients per dose group and candidate model, together with the MCPMod test statistics and p-values for each model and the critical value

- For averaging model, figure of the dose-response curve

- For all significant model shapes, figures of the dose-response curve plus 90% and 95% confidence bands (of the predicated shape) and 90% and 95% CIs per dose (estimated from MMRM)

- For all significant model shapes, figure with the placebo corrected dose-response curve plus 90% and 95% confidence band (of the predicated shape).

Estimates for each dose group will be calculated and will be based on the final dose-response model. R code to perform the evaluations is available in Section 10.2.



7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 (Other) Secondary endpoint(s)

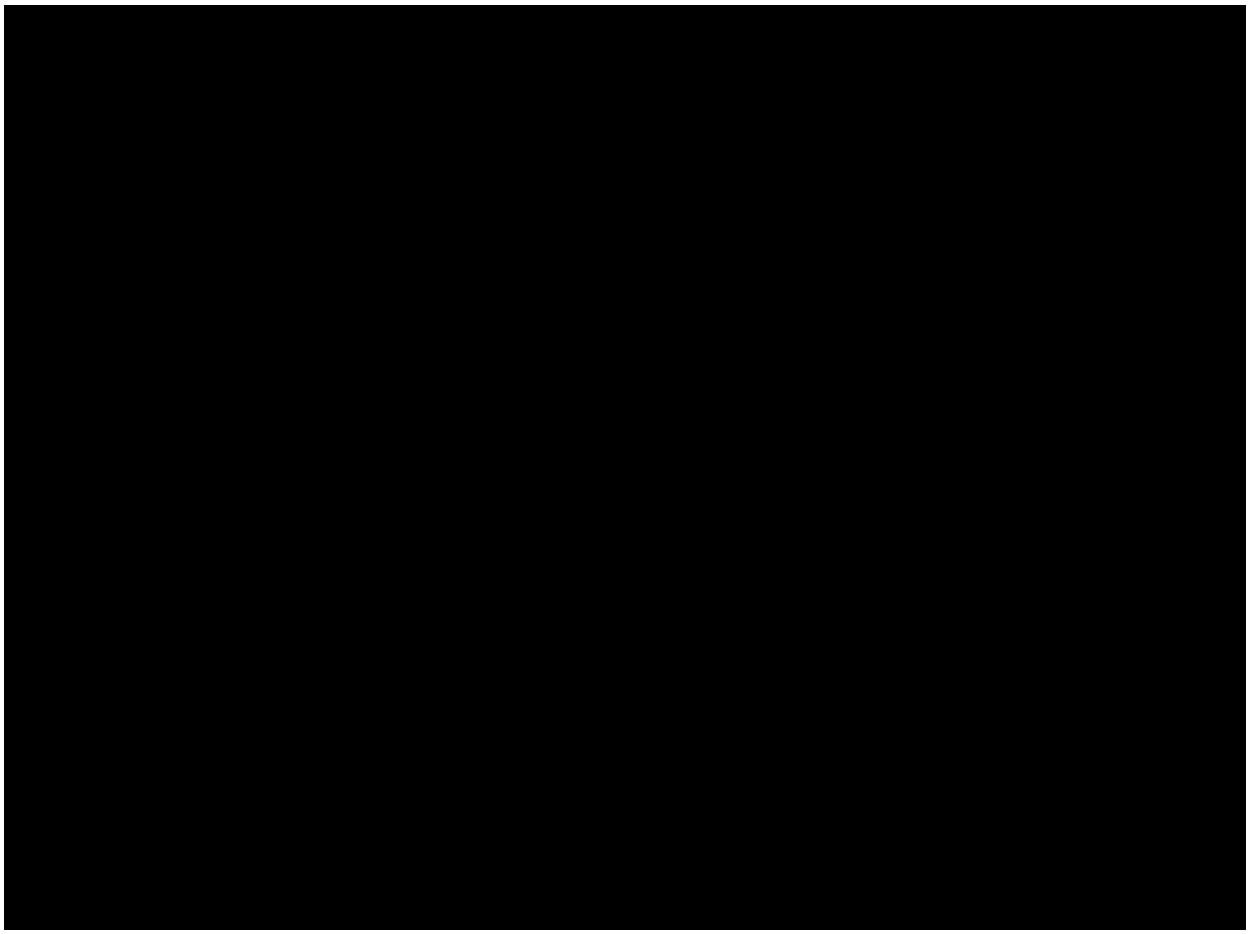
For the secondary endpoints,

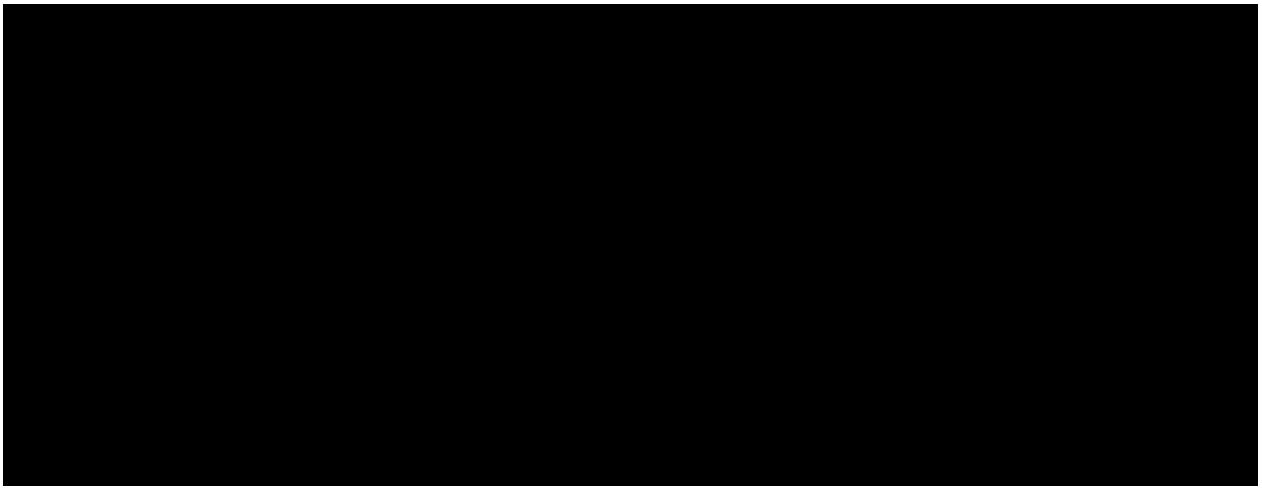
- Patients achieving a decrease of at least 30% absolute change in First Morning Void urine of UACR from baseline after 14 weeks of trial treatment,
- Patients achieving a decrease of at least 15% absolute change in First Morning Void urine of UACR from baseline after 14 weeks of trial treatment.

Descriptive statistics will be provided for the number and percentage of responders in terms of UACR reduction from baseline using complete case analysis, multiple imputation, missing as non-responder, and last observation carried forward (LOCF).

- Complete case analysis uses patients with both baseline and Week 14 data available.
- Multiple imputation fills in missing values at Week 14 based on other data observed in the same patient using regression.
- Missing as non-responder imputes patients with missing Week 14 data as non-responders.
- LOCF uses the last value observed on treatment to substitute all missing values until Week 14.

The odds ratio, 95% confidence interval, and p-value will be calculated based on logistic regression of binary outcome adjusting for treatment, and stratification factors as covariates.





7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the CTR based on the TS. The date and time of each drug administration will be listed for each patient.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS following BI standards. No hypothesis testing is planned. Safety data will be summarised for Run-in Period and Treatment Period, respectively.

7.8.1 Adverse Events

Analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

For further details on summarisation of AE data, please refer to "Analysis and presentation of adverse event data from Clinical Trials" (9) and "Handling of missing and incomplete AE da (4).

The analysis of AEs will be based on the concept of TEAEs. That means that all AEs occurring between the first drug intake until 7 days after last drug intake will be assigned to

actual treatment groups. All AEs occurring before first drug intake of empagliflozin/ placebo will be assigned to 'screening' and all AEs occurring after EoT + 7 days will be assigned to 'follow-up' (for listings only). AEs that start before first drug intake and during Run-in Period and deteriorate under treatment will also be considered as 'treatment-emergent'. For details on the treatment definition, see Table 6.1:1 in Section 6.1.

If only the start date of an AE is collected (without start time), any AE occurrence on the same day as the first empagliflozin or BI 690517 administration will be assigned to the run-in or on-treatment phase, respectively. In addition, a summary of patients with down-titration due to AE will be provided.

An overall summary of AE will be presented for treated set during Run-in and on-treatment periods, respectively. This will show the number and percentage of patients with any AE, severe AEs, any investigator defined drug-related AEs, AEs of Special Interest (AESIs), AEs leading to the discontinuation of empagliflozin or BI 690517, and down-titration (dose reduction) of BI 690517, and serious AEs (SAEs).

Frequencies [N (%)] of patients with AEs during run-in period will be summarised by treatment, primary system organ class, and preferred term (using MedDRA). Separate tables will be provided for patients with SAEs, patients with AESIs, patients with any investigator defined drug-related AEs to empagliflozin, and patients with discontinuations of empagliflozin due to AEs.

Frequencies [N (%)] of patients with AEs during on-treatment period will be summarised by treatment, primary system organ class, preferred term (using MedDRA), and intensity. Separate tables will be provided for patients with SAEs, patients with AESIs, patients with fatal AEs, patients with any investigator defined drug-related AEs (with regards to empagliflozin or BI 690517), patients with down-titration (dose reduction) of BI 690517, patients with ACTH related AEs, and patients with discontinuations (of empagliflozin or BI 690517 or ACTH) due to AEs.

In addition, summary of AEs collected on special AE eCRF pages (AE - hypotension, AE - hyperkalaemia, AE - Ketoacidosis, AE - Adrenal insufficiency, and AE - Acute Kidney Injury) will be presented for both patient-based and event-based analyses.

Subgroup analysis on hypotension based on baseline BP and the lowest BP during the episode will be carried out. Criteria for significant (vs. non-significant) hypotensive episode are as follows:

- Baseline SBP <=140: decrease $\left(\frac{\text{lowest SBP during the episode} - \text{baseline SBP}}{\text{baseline SBP}}\right) \geq 30\%$;
- Baseline SBP >140: decrease $\left(\frac{\text{lowest SBP during the episode} - \text{baseline SBP}}{\text{baseline SBP}}\right) \geq 40\%$;
- Or, lowest SBP during the episode <90.
- Baseline DBP <=70: $\left(\frac{\text{lowest DBP during the episode} - \text{baseline DBP}}{\text{baseline DBP}}\right) \geq 30\%$;
- Baseline DBP > 70: $\left(\frac{\text{lowest DBP during the episode} - \text{baseline DBP}}{\text{baseline SBP}}\right) \geq 40\%$;
- Or, lowest DBP during the episode <50.

- Lowest mean arterial pressure (MAP) during the episode<70, where MAP is calculated as $MAP = \frac{\text{SBP}+2(\text{DBP})}{2}$

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Handling, Display and Analysis of Laboratory Data" (11). Note that data from the central laboratory will be used for all displays described below, unless otherwise specified.

The analysis of continuous laboratory parameters will be based on normalised values, which means transforming to a standard unit and to a standard reference range. The last assessment before the second randomisation at visit 5 is chosen as the baseline value. The laboratory data at EoT visit are defined as EoT values. In the case that the patient is permanently discontinued BI 690517, but is continuing on empagliflozin during Treatment Period, EoT for analysis of laboratory data will be defined as the nearest scheduled lab visit on treatment of BI 690517.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be based upon normalised values and provided by visit, including summaries of the last value on treatment, the minimum and maximum value on treatment.

Laboratory values will be compared to their reference ranges; a shift table will be provided for the number of patients within and outside the reference range at baseline and at the last measurement on treatment. This analysis will be based on standardized laboratory values.

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on converted values and converted reference ranges using SI lab units. These rules will be listed in the SDL appendix of the CTR. Frequency tables will summarise the number of patients with potentially clinically significant abnormalities.

Patients having an abnormal lab value at baseline will be presented separately. A separate listing will present potentially clinically significant abnormal lab values.

All individual laboratory data will be listed. Values outside the reference range will be flagged. In addition, potentially clinically significant values will be flagged in the listing.

To support analyses of liver related adverse drug effects, the frequency of patients with Aspartate Aminotransferase (AST) and/or Alanine Aminotransferase (ALT) ≥ 3x upper level of normal (ULN) combined with a total bilirubin ≥ 2xULN, and the frequency of patients with AST and/or ALT ≥ 10xULN, will be displayed. This analysis will be based on standardized laboratory values. A graphical analysis of the ALT and total bilirubin values during the on-treatment period will also be performed; the so called eDISH plot. In the graph, for each patient, the peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. Two reference lines, 2xULN for total bilirubin and 3xULN for ALT, are drawn onto the graph in order to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range (ALT ≥ 3xULN and total bilirubin < 2xULN).

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

Results from the pregnancy test will only be listed.

7.8.3 Vital signs

The analyses of vital signs (blood pressure and pulse rate) will be described by descriptive statistics and figures of difference in vital signs from baseline (see Section 6.7) to the end of study. Vital signs at EoT visit are defined as EoT values. In the case that the patient is permanently discontinued for BI 690517, but is continuing on empagliflozin during Treatment Period, EoT for analysis of vital signs will be defined as the nearest scheduled visit on treatment of BI 690517.

Marked changes of seated systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR) will be summarised by the number and the percentage of patients at each visit by treatment according to the definition below:

1) Marked Increase: SBP > 150 mmHg and an increase of >= 25 mmHg above baseline
   Marked Decrease: SBP < 100 mmHg and a decrease of > 10 mmHg below baseline
2) Marked Increase: DBP > 90 mmHg and an increase of > 10 mmHg above baseline
   Marked Decrease: DBP < 60 mmHg and a decrease of > 10 mmHg below baseline
3) Marked Increase: PR > 100 bpm and an increase of > 10 bpm above baseline
   Marked Decrease: PR < 60 bpm and a decrease of > 10 bpm below baseline.

Clinically relevant findings in vital signs will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.9 ANALYSIS OF COVID-19 IMPACT

There is currently an outbreak of the respiratory disease COVID-19 worldwide which has impacted the conduct of this trial. This public health emergency has raised more difficulties for patients to meet protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. Site personnel or trial patients are also under the risk to get infection with COVID-19.

Consequently, there are unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public and individual health control measures. To assess the impact on patients' safety and drug efficacy in this trial, the following analyses are planned:

Disposition, PD, and iPD:

Frequency of the patient with missing visits or early discontinuation due to COVID-19 will be listed. PDs and iPDs related to COVID-19 will be also listed if any.

In addition, if there is any case, COVID-19 infection will be reported.
This study started after the COVID-19 disruption. Therefore, evaluations of efficacy or AE assessments by prior versus post disruption are not applicable in this trial.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released to unblind the trial database after Last Patient Last visit Primary Endpoint (LPLVPE)(in Section 4.1.5.1 of the CTP). and all data has been entered and cleaned as defined in the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form.

9. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain- specification)", template, current version, KMED.
3.	*BI-VQD-12045_40-413:* Identify and Manage Important Protocol Deviations (iPD)", version 3.0, Group "Med Clinical Development & Operations". https://bi-docs-vault-quality.veevavault.com/ui/#permalink=V0Z00000002G042
4.	*BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version; KMED.
5.	*BI-KMED-TMCP-MAN-0012*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
6.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
7.	*BI-KMED-TMCP-OTH-0003*: "Graphs and Tables for Clinical Pharmacokinetic and Pharmacodynamic Noncompartmental Analyses", current version; KMED.
8.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.
9.	*KM Asset BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED.
10.	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version, EMA webpage.
11.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.

[redacted]

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**19-Apr-2023**	[redacted]	None	
2	**19-June-2023**		[redacted]	
			7.5.2 (Other) Secondary endpoint(s)	Added analysis plan of secondary endpoint for clarification
			[redacted]	