TRIAL STATISTICAL ANALYSIS PLAN

c41327713-01

BI Trial No.:	1366-0005
Title:	Randomised, double-blind (within dose groups), placebo controlled and parallel group trial to investigate the effects of different doses of oral BI 685509 given over 20 weeks on UACR reduction in patients with diabetic kidney disease
Investigational Product(s):	BI 685509
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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
BP	Blood Pressure
C-SSRS	Columbia-Suicide Severity Rating Scale
COVID-19	Corona Virus Disease 2019
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DV	Deviation
ECG	Electrocardiogram
EDMS	Electronic Document Management System
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EoS	End of Study
EoT	End of Treatment
ES	Entered Set
FAS	Full Analysis Set
FMV	First Morning Void
F/U	Follow-Up
GLP1R	Glucagon-Like Peptide 1 Receptor
ICE	Intercurrent Events
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iPD	Important Protocol Deviation

Term	Definition/description
LOCF	Last Observation Carried Forward
MAP	Mean Arterial Pressure
MCP-MoD	Multiple Comparisons Procedure - Modelling
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model Repeat Measurement
PD	Pharmacodynamics
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
REP	Residual Effect Period
RPM	Report Planning Meeting
RS	Randomised Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SDL	Subject Data Listings
SGLT2i	Sodium-Glucose co-Transporter-2 Inhibitor
TEAE	Treatment-Emergent Adverse Events
tid	*Ter in* die (3 times a day)
TMF	Trial Master File
TOM	Trial Oversight Meeting
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 working environment CARE, including SASTM (current Version 9.4, by [redacted]), and a number of SASTM-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)

Please refer to the protocol.

The three different approaches for handling intercurrent events (ICEs) are summarised in the table below:

Estimand strategy name	Treatment	ICE handling
Primary approach	Randomised treatment	Study med d/c: include data prior to study med d/c. Death: include data prior to death. SGLT2i initiation/discontinuation: include data prior to SGLT2i start/stop.
Supplementary 1	Randomised treatment	Study med d/c: include all available data. Death: include data prior to death. SGLT2i initiation/discontinuation: include all available data.
Supplementary 2	Actual final treatment	Study med d/c: include data prior to study med d/c. Death: include data prior to death. SGLT2i initiation/discontinuation: include data prior to SGLT2i start/stop.

SGLT2i = Sodium-Glucose co-Transporter-2 Inhibitor

Note that the table above should be used along with Table 6.6.2.1:1 to derive endpoints for primary, supplementary 1, and supplementary 2 analysis.

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)

Please refer to the protocol.

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 comparison of BI 685509 to investigate the effects of 3 different doses of oral BI 685509 given over 20 weeks on urine albumin creatinine ratio (UACR) reduction in patients with diabetic kidney disease.

Eligible patients will be randomised in the trial in a 3:1 ratio (BI 685509 3 times a day [tid]/placebo tid) within dose groups and will be treated for 20 weeks. The randomisation will be stratified by type of diabetic kidney disease and use of SGLT2i at randomisation. Following the 20-week treatment period, or at the time trial treatment is permanently discontinued, patients will have an End of Treatment (EoT) visit, which will be the start of a 4-week follow-up period.

Section 1.2 of the CTP: The Residual Effect Period (REP) of BI 685509 is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic (PD) effects still likely to be present.

Section 7.2.5 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 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 due to AE will be provided.

For the analysis of AEs, the following study phases are defined:

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	Screening	Date of informed consent	Date/time of first administration of study drug
On-treatment	**Placebo,** **BI 685509,** respectively	Date/time of first administration of study drug	12:00 a m on the day after last administration of study drug + REP (7 days), or 12:00 a m on the day after patient’s trial termination date, whichever occurs earlier
Follow-up[1]	**F/U Placebo,** **F/U BI 685509,** respectively	12:00 a m on the day after last administration of study drug + 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.

For treatment interruptions, the occurrence of AEs between the start of interruption and re-start of treatment will be assigned to the randomised treatment. 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 to be discussed 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)" (3).

If any iPDs are identified, they are to be summarised into categories and will be captured in the TOM minutes and additionally via an accompanying Excel spreadsheet. The iPDs may lead to exclusion of patients from analysis sets (e.g. the Per Protocol Set). 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.

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

6.3 SUBJECT SETS ANALYSED

The subject sets for statistical analysis will be used as defined in the CTP, Section 7.2.1. 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	RS	TS	FAS	PKS
Disposition	X				
Exposure			X		
IPDs		X			
Demographic/baseline		X			
Primary endpoint				X	
Secondary endpoint				X	
Other safety/tolerability			X		
Further efficacy endpoints				X*	
Further PK endpoints					X

* Analyses on further endpoints such as serum potassium, vital signs, and body weight, are based on TS since they are not efficacy endpoints.

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) for UACR at baseline is (/are) missing, all available UACR samples in week -2, -1, and 0 will be used to derive UACR at baseline.

- If any UACR value after randomisation is missing, the missing UACR will not be imputed; missing UACR due to ICEs will not be imputed.

The Mixed-effect Model for Repeated Measures (MMRM) approach used for the primary analysis (see Section 7.4.1) allows for missing data, assuming the missing data mechanism is ignorable. Even patients with only one post-baseline assessment can be included in the model and can, therefore, participate in variance estimation. The statistical model assumes that patients who had an ICE would have behaved similarly to those who remained in the study. The table below describes how/when to derive UACR values for MMRM:

Table 6.6.2.1: 1 Principal rule of UACR derivation for MMRM

UACRs for MMRM	UACR at baseline	UACR at visit 6	UACR at visit 7	UACR at EoT
Visits need to be included	First Morning Void (FMV) or 10-hour urine UACR baseline is defined as the mean of all non-missing assessments from Visit 2 until prior to the first intake of trial medication.	All available scheduled visits at visit 6	All available scheduled visits at visit 7	All available scheduled visits between visit 8 and EoT
Derivation	Average of all available UACR measurements defined at each visit			

Note: all available/scheduled UACR measurements will be used: no imputation for missing UACR measurement; this rule will be applied to FMV and 10-hour urine samples, respectively.

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 for MMRM in Table 6.6.2.1:1 will be used for derivation of UACR at baseline and EoT.

For the change from baseline in log transformed UACR measured in 10-hour urine (/FMV urine) after 20 weeks of trial treatment, the same rule as in the primary endpoint will be applied for statistical analysis.

Missing UACR imputation might be considered as well.

Details about implementation into the statistical analysis are described in Section 7.

[redacted]

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 and 10-hour urine UACR. Baseline for the FMV and 10-hour urine UACR, is defined as the mean of all available samples prior to Visit 2 up to and including those 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 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 (which is scheduled for Visit 3).

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 use of SGLT2i (Yes/No), type of diabetes mellitus (type 1/type 2), dose group of study treatment (placebo/BI 685509), 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 (for non-PK parameters) is:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
SE	standard error
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	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} 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]).

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 group of study treatment, and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the CTR, based on the RS.

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 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.

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 on-treatment period (cf. Section 6.1).

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 and starting any time during the on-treatment period (cf. Section 6.1).

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

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned according to percentage of patients meeting the compliance. Descriptive statistics will be provided overall (see Section 5.4.2).

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

The primary endpoint will be analysed in combination with the primary approach of handling ICEs (see Section 5.1). The FAS is the main analysis set for the analysis of efficacy: the patient set includes all patients who had at least one baseline measurement of 10 hour UACR in week -2, -1, or 0 and at least one post-baseline measurement after week 6.

Refer to Section 7.2.2 of the CTP for a description of the statistical analysis for the change from baseline in log transformed UACR measured in 10-hour urine at 20 weeks of trial treatment.

The adjusted mean reduction in log transformed UACR in 10-hour urine from baseline at 20 weeks and its standard deviation will be obtained from MMRM for the placebo and treatment groups. For the MMRM model, derived UACRs at baseline, visit 6, visit 7, 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 = base*visit visit*trt typediabetes  SGLT2ibase / 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.

Multiple Comparisons Procedure - Modelling (MCP-Mod) Analysis

For the primary analysis, the dose-response relationship will be modelled using the total daily doses: 3 mg, 6 mg, and 9 mg. 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 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)

The analysis of the change of UACR in FMV urine after 20 weeks of trial treatment will be performed by using the same MMRM/MCPMod as for the primary analysis.

For the secondary endpoints,

- Proportion of patients achieving UACR decreases in 10-hour urine of at least 20% from baseline after 20 weeks of trial treatment
- Proportion of patients achieving UACR decreases in FMV urine of at least 20% from baseline after 20 weeks of trial treatment

the following analyses will be implemented:

- A logistic regression with Last Observation Carried Forward (LOCF)
- A logistic regression excluding patients with missing UACR at baseline/EoT
- A two sample proportion test with LOCF
- A two sample proportion test excluding patients with missing UACR at baseline/EoT

Treatment, SGLT2i use at baseline, and type of diabetes will be used as covariates in the logistic regression model.

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. All safety analyses will be performed on treatment set.

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 first drug intake until 7 days after last drug intake will be assigned to the randomised treatment. All AEs occurring before first drug intake will be assigned to ‘screening’ and all AEs occurring after last drug intake + 7 days will be assigned to ‘follow-up’ (for listings only). AEs that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’. For details on the treatment definition, see 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 BI 685509 administration will be assigned to the on-treatment phase. AEs will also be summarised by the treatment at the onset of AE for any drug-related AE. In addition, a summary of patients with down-titration due to AE will be provided.

An overall summary of AEs will be presented.

Frequencies [N (%)] of patients with AEs will be summarised by dose group, primary system organ class, preferred term (using MedDRA), and intensity. Separate tables will be provided for patients with serious AEs (SAEs), patients with AEs of Special Interest (AESIs), patients with fatal AEs, and patients with discontinuations due to AEs.

Regarding AESIs, summaries of AESIs of hypotension and syncope will be presented for both patient-based and event-based analyses. An individual episode of hypotension will be considered as significant or non-significant based on baseline BP and the lowest BP during the episode. Criteria for significant hypotensive episode are:

- For patients with baseline SBP <=140: decrease ((lowest SBP during the episode – baseline SBP)/(baseline SBP)) ≥30%
- For patients with baseline SBP >140: decrease ((lowest SBP during the episode – baseline SBP)/(baseline SBP)) ≥40%
- Or, lowest SBP during the episode <90
- For patients with baseline DBP <=70: ((lowest DBP during the episode – baseline DBP)/(baseline DBP)) ≥30%
- For patients with baseline DBP >70: ((lowest DBP during the episode – baseline DBP)/(baseline SBP)) ≥40%
- Or, lowest DBP during the episode <50
- Lowest mean arterial pressure (MAP) during the episode <70

Details of the AESI of Hypotension and Syncope will be also listed.

Category	Safety topic	Definition
AESI	Hypotension	Investigator-reported, as a dedicated AE category on the AE eCRF page
AESI	Syncope	Investigator-reported, as a dedicated AE category on the AE eCRF page

In addition, potential DILI, acute kidney injury, and QT-interval prolongation are defined as follows:

- Potential DILI, defined as: Narrow sub-SMQ ‘Liver related investigations, signs and symptoms’, narrow sub-SMQ ‘Cholestasis and jaundice of hepatic origin’, narrow sub-SMQ ‘Hepatitis, non-infectious’ and narrow sub-SMQ ‘Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions’, or investigator-reported AESIs.
- Acute kidney injury, defined as: SMQ ‘Acute renal failure’, narrow scope
- QT-interval prolongation, defined as: SMQ ‘Torsade de points/QT prolongation’, narrow scope excluding the PT ‘Syncope’.

Summaries of potential DILI, acute kidney injury, and QT-interval prolongation will be presented for patient-based analyses.

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 first randomised treatment prior to the first drug administration at visit 3 is chosen as the baseline value.

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 (SBP,DBP, and pulse rate) will be described by differences of vital signs from baseline (see Section 6.7) to the EoS visit.

Clinically relevant findings in vital signs 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.

7.9 ANALYSIS OF COVID19 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.

7.10 POOLING OF TRIALS

A list of trials that might be covered in the efficacy analysis of BI 685509 is summarized here, including how each trial will contribute to the understanding of the efficacy of the compound, and how studies will be pooled and combined.

Study groupings are defined based mainly on design characteristics of the clinical studies and address general or particular aspects of the efficacy of the investigational therapy.

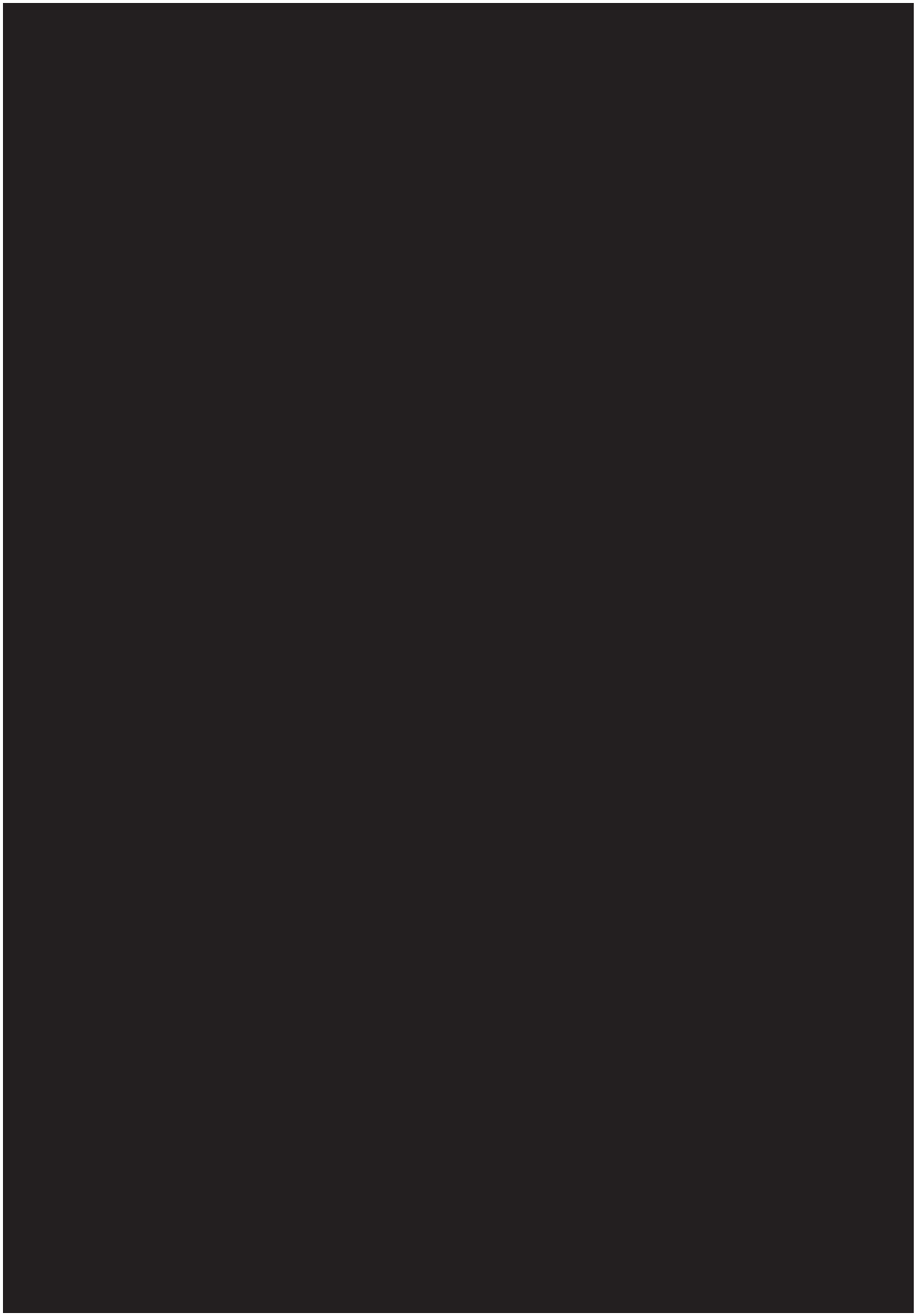
Table 7.10: 1 summarizes plans of a pooled analysis of two trials with BI 685509. The table displays treatment arms included in each of the defined study groupings and describes what summaries/analyses will be presented for the defined study grouping.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released to unblind the trial database after the last patient has completed their EoS/Follow-up visit 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.



11. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**18-OCT -2022**	[redacted]	None	This is the final TSAP without any modification.
2	**23-JAN-2023**		5.1	Guidance about how to use Table 6.6.2.1: 1 was added.
			[redacted]	
			7.4.1	Definition of FAS was added to clarify.
			[redacted]	
			7.10	[redacted]

APPROVAL / SIGNATURE PAGE

Document Number: c41327713 **Technical Version Number:1.0**

Document Name: 8-01-tsap-core-ver2

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

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	24 Jan 2023 13:32 CET
Author-Trial Statistician		24 Jan 2023 13:33 CET
Approval-Clinical Program [redacted]		24 Jan 2023 16:03 CET
Approval-Medical Writer		25 Jan 2023 14:36 CET
Approval-Clinical Pharmacokinetics		25 Jan 2023 14:39 CET
Approval-Project Statistician		25 Jan 2023 22:13 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed