TRIAL STATISTICAL ANALYSIS PLAN

c02190563-04

BI Trial No.:	1293.10
Title:	A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year of treatment, in patients with active lupus nephritis Including Protocol Amendment 6 1293.10-revised-protocol-06 [c03085195-07]
Investigational Product(s):	BI 655064
Responsible trial statistician(s):	 Phone: Fax:
Date of statistical analysis plan:	17 AUG 2020 REVISED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AESI	Adverse events of special interest
ARB	Angiotensin receptor blocker
Anti-dsDNA	Anti-double stranded DexoxyriboNucleic Acid
AUC	Area under the curve
BI	Boehringer Ingelheim
C3	Complement Component C3
C4	Complement Component C4
CD	Cluster of Differenciation
CMH	Cochran-Mantel-Haenszel
CRR	Complete Renal Response
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End of study
EoT	End of text
EOT	End of trial
FU	Follow Up
GFR	Glomerular Filtration Rate
h	hour
HRQoL	Health Related Quality of Life
IA	Interim analysis
ICH	International Conference on Harmonisation

Term	Definition / description
iPD	important Protocol Deviation
IRT	Interactive Response Technology
ITT	Intent To Treat
IV	Intravenous
KOL	Key Opinion Leader
LLN	Lower limit of normal
LN	Lupus Nephritis
MCPMod	Multiple Comparison Procedure with modelling
MedDRA	Medical Dictionary for Regulatory Activities
min	minute
MQRM	Medical Quality Review Meeting
MRR	Major Renal Response
ms	millisecond
PCSA	Possible clinically significant abnormality
PK	Pharmacokinetics
PPS	Per protocol set
PR	Time interval of ECG
PRR	Partial Renal Response
PT	Preferred term
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual effect period
RPM	Report Planning Meeting
QRS	Time interval of ECG
QT	Time interval of ECG
QTcB	Heart rate corrected QT interval (using Bazett adjustment)
QTcF	Heart rate corrected QT interval (using Fredericia adjustment)
SAS	Statistical Analysis System (SAS® System, SAS Institute Inc., Cary, North Carolina)
SD	Standard deviation
SELENA	Safety of Estrogens in Lupus National Assessment
SLE	Systemic Lupus Erythematosus

Term	Definition / description
SOC	System organ class
TOC	Table of contents
TSAP	Trial statistical analysis plan
UP	Urine protein
UC	Urine creatinine
WBC	White blood cell
WHO-DD	World Health Organization-Drug dictionary

3. INTRODUCTION

The purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis than was described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

This TSAP 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, randomization.

R version 3.6.1 with "DoseFinding" package (1) will be used for analysis based on MCPMod.

SAS® Version 9.4 (or later version) will be used for all other analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The primary endpoint, Complete Renal Response (CRR), as defined in the CTP, is derived from urine protein (UP) determined from the 24-hour (24h) urine collections and eGFR calculated from serum creatinine. To account for incomplete 24h collections, an alternate derivation of CRR is added with this version of the TSAP. The alternate derivation is based on the ratio of urine protein/urine creatinine (UP/UC) determined from the 24h collections and eGFR calculated from serum creatinine. This alternate derivation will be analysed and presented using the same methods/format used for CRR derived from UP, as adjustment for UC is considered an important correction for incomplete collections. See Section 6.6.1 for further details.

The definition for the secondary endpoint, major renal response (MRR), specified in the CTP was incomplete. See Section 5.2 for a revision affecting only patients who entered the trial with baseline proteinuria >= 3 g/day. There is no change for patients who entered the trial with baseline proteinuria<3 g/day.

Alternate derivations of PRR & MRR based on UP/UC determined from the 24h urine collections and eGFR calculated from serum creatinine are also added with this version of the TSAP. As with CRR, the alternate PRR & MRR derivations will be analyzed and presented using the same format as used for derivations using UP.

A second alternate derivation of CRR is based on UP/UC as determined from the spot urines and eGFR calculated from serum creatinine. This allows defining CRR based on the samples collected at Weeks 1, 2, 4, 6, 8, 12, 16, 21, 26, 30, 35, 40, 46 and 52. For comparison to the derivations based on the 24h samples, observed proportions at Weeks 26 and 52 were tabulated and pairwise comparisons of each dose to placebo were performed.

Important Protocol Deviations (iPDs) and populations for analysis were updated to reflect learnings and input from Key Opinion Leaders (KOLs).

The logistic regression model specified in the CTP included one of the two stratification variables used at randomization as a covariate, namely race (Asian/non-Asian). The other stratification variable used for the randomization was proteinuria at screening. Proteinuria at screening <3g/day or ≥ 3g/day (respectively UP/UC<3 or UP/UC≥3) was added to the model as a covariate via the TSAP.

5. ENDPOINT

5.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of patients with CRR at week 52, where CRR is defined as:

UP<0.5 g/d at week 52

and either

eGFR within normal range at week 52

or

decrease in eGFR<20% from baseline at week 52 if eGFR is below normal range (i.e., below Lower Limit of Normal, where LLN =90 ml/min)

For the assessment of proteinuria for the primary and secondary endpoints, 24h urine collection was performed at baseline, 26 and 52 weeks. Collection was performed in duplicate (2 times 24h collection). The value of proteinuria is the average of the two values. Blinded review of the volumes of the 24h collections and durations of collection raised concern that some collections may have been incomplete. It was decided that the 24h samples should be ≥500mL/day and at least 19.5 hours (approximately 80% of 24 hours) to be evaluable. With respect to UP, any collections <500mL/day or < 19.5 hours were not evaluated.

Rules for deriving UP from 24h urine collections to determine CRR

Protein excretion rates were transferred to BI in units of mg/dL. The following steps were performed to convert to g/day for deriving CRR.

Protein excretion rate (mg/dL) x 1/100 = Protein excretion rate (mg/ml)

Protein excretion rate (mg/ml) x 24-hour total volume (ml) = UP (mg)

UP (mg) * 1/1000= UP (g/day)

After the interim analysis the team had concerns around how well the thresholds (≥500mL/day and at least 19.5 hours) set for evaluability compensated for incomplete 24h collections. Another method to account for incomplete 24h collections was introduced and CRR was also derived based on the ratio of urine protein/urine creatinine (UP/UC) determined from the 24h collections. As the total amount of creatinine excreted daily in the urine is quite stable, UC is used to stabilize the estimate of proteinuria and is generally accepted as a correction for incomplete collections. With this version of the TSAP, this alternate derivation is incorporated. CRR derived using the UP/UC determination will be analysed and presented using the same methods/format used for CRR derived from UP. There is no change to the eGFR component of the definition; it will be calculated from serum creatinine as defined in the CTP.

Another alternate derivation of CRR is to base it on UP/UC as determined from the spot urines (and eGFR calculated from serum creatinine.) This allows defining CRR based on the samples collected at Weeks 1, 2, 4, 6, 8, 12, 16, 21, 26, 30, 35, 40, 46 and 52. For comparison to the derivations based on the 24h samples, observed proportions at Weeks 26 and 52 were tabulated and pairwise comparisons of each dose to placebo were performed.

One of the KOLs consulted, suggested an assessment of how the eGFR threshold for patients below the lower limit of normal (LLN) affected determination of CRR. The suggestion was to allow less of a decrease (10%) in eGFR for those patients below the lower limit of normal (LLN) to acheive CRR compared to the protocol-allowed decrease of 20%.

Rules for imputing missing data or data that was not evaluable are provided in Section 6.6.1. Also specified in Section 6.6.1 are rules for defining CRR for patients who discontinued study medication and/or participation in the trial.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

This section is not applicable as there is no key secondary endpoint.

5.2.2 Secondary endpoints

- Proportion of patients with CRR at week 26
- Proportion of patients with partial renal response (PRR) at week 26 and week 52.

  PRR is defined as at least 50% reduction of proteinuria from baseline if eGFR within normal range at time of assessment or decrease of eGFR < 20% from baseline if eGFR below normal range at time of assessment.
- Proportion of patients with major renal response (MRR) at week 26 and 52

  MRR is defined as follows depending on proteinuria at baseline:

  - If baseline proteinuria<3 g/day **and** patient has CRR
  - If baseline proteinuria >= 3 g/day **and** proteinuria <1g/day

    and either

    eGFR within normal range

    or

    decrease in eGFR<20% from baseline at week 26 if eGFR is below normal range (below Lower Limit of Normal, where LLN =90 ml/min)

The secondary endpoints, CRR at week 26, PRR at week 52 and MRR at week 52 will be derived using UP and using UP/UC from the 24h collections, each along with eGFR determined from serum creatinine

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For reporting purposes, all randomised patients will be classified into one of the following treatment groups:

Sort order	Treatment	Long label	Short label
01	B	BI 655064 120mg	BI 120mg
02	C	BI 655064 180mg	BI 180mg
03	D	BI 655064 240mg	BI 240mg
04	A	Placebo	Placebo

These will be the default labels and sort order for reporting the treatment groups.

The following study periods based on actual start and stop dates of study treatment administration are defined:

Screening: day of informed consent to day prior to the start of randomised medication

Treatment: start date of randomised double-blind medication to date of last dose

Follow-up: day after the last dose of randomised double-blind medication through trial completion and after trial completion

Rules for assigning AEs/laboratory data to the study periods are as follows.

AEs/laboratory data will be assigned to the treatment period if they occur/samples were taken after the first injection of study medication to the date of last administration of study medication plus 50 days.

Since AE onset time was not recorded, investigators were asked to provide more information for AEs with date of onset equal to date of first injection. Additional information was to be provided in the AE comment field. The trial team will review the comments & will impute a time to capture onset as prior to or following first injection of study medication. An analysis data set will be created to incorporate this information. If the site indicates that the AE onset time is prior to trial medication administration then the AE will be assigned to the screening period. If the site indicates that the AE onset time is after trial medication administration or there is no information regarding onset then the AE will be assigned to the treatment period.

Adverse events with onset on or after the 51st day after the last administration of trial medication will be considered ‘Follow-up’ events. However, if the patient rolls over to the extension trial (1293.13) & receives the first dose of trial medication in 1293.13, any new events or worsening of existing events will be assigned to the treatment period of 1293.13.

Laboratory data on or after the 51st day after the last administration of trial medication will be considered ‘Follow-up’ data.

6.2 IMPORTANT PROTOCOL DEVIATIONS

The following table defines the different categories of important protocol deviations (iPDs). The final column indicates which iPDs will be used to exclude patients from the different patient analysis sets.

Patients with iPDs will be documented. The following list of iPDs will be used; note that this is a working list and may not be finalised until the final Report Planning Meeting (RPM) prior to database lock.

Excluded from 'None' denotes a safety iPD.

Table 6.2: 1 Handling of iPDs

Category/ Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A1.1	Inclusion criteria 3, 4 or 5 not met	Inclusion criteria, 3, 4 (including biopsy class, active or active/chronic disease and time between biopsy & screening) or 5 not met as specified in the protocol **(automatic PD)**	PPS
	A1.2	Inclusion criteria 1 not met	Inclusion criteria 1 not met as specified in the protocol **(automatic PD)**	None
	A2	Exclusion criteria 2, 3, 4, 7, 10-12 met*	Exclusion criteria 2, 3 [4], 4 [5], 7 [8B], 10 [11], 11 [12A or 12B] ,12 [13] met as specified in the protocol **(automatic PD)**	PPS/ (TBD at MQRM/ BRPM)
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing **(automatic PD)**	All
	B2	Informed consent too late	Informed consent date <*actual consent date*> was after Visit 1date <*Visit 1 date*> **(automatic PD)**	None
C		**Trial medication and randomization**		
	C1	Randomization not followed	Patient not treated according to randomization.	PPS/ (TBD at MQRM/ BRPM)
	C2	Wrong dosage schedule	Wrong dose of BI 665064 taken or syringes used in the wrong order	PPS/ (TBD at MQRM/ BRPM)
	C3	Non-compliance with study medication	Any evidence of gross non-compliance **(manual or automatic PD)** as defined in Section 5.4. iPDs were not assigned if a patient had documented reasons for non-compliance such as AE (which was allowed per protocol) or drug not at site.	PPS/ (TBD at MQRM/ BRPM)

Table 6.2: 1 (continued) Handling of iPDs

Category/ Code		Description	Example/Comment	Excluded from
	C4	Medication code broken inappropriately	Medication code broken inappropriately - reason for medication code break <reason> (manual PD)	PPS
D		**Concomitant medication**		
	D1	Prohibited medication use	• Azathioprine during weeks 0-26 • Cyclophosphamide 6 months prior to randomization through Week 52 • Cyclosporine-Tacrolimus during 4 weeks prior to randomization through Week 52 • Any biologic B-cell depleting therapy (e.g. anti-CD20, anti-CD22) or Abatacept during 12 months prior to randomization through Week 52 • anti-Blyss 3 months prior to randomization for non renal SLE or 12 months for renal SLE through Week 52 • Investigational medication for 6 months or 5 half lives prior to randomization through week 52 • IV glucocortoids during Week 40-52. **(Manual iPDs)**	PPS/ (TBD at MQRM/ BRPM)
	D2	Non-permitted oral steroid use	Patient used more than 10 mg per day of oral steroid at any time during the interval from week 40 to week 52.	PPS/ (TBD at MQRM/ BRPM)
	D3	Non-permitted MMF dose	MMF >3g per day up to week 26 or average MMF >2.5 g per day after week 26	PPS/ (TBD at MQRM/ BRPM)
G		**Trial specific**		
	G1	Failure to remove patient from therapy	As described in CTP section 3.3.4.	PPS/ (TBD at MQRM/ BRPM
Z		**Other**		
	Z1	Other iPDs affecting efficacy and possibly safety		PPS/ (TBD at MQRM/ BRPM
	Z2	Other iPDs affecting safety only		None

*The numbering of exclusion criteria changed with one or more of the protocol amendments. The numbering, reflected in the data sets and in later eCRFs, is shown in brackets.

6.3 SUBJECT SETS ANALYSED

- Randomised set:
  This patient set includes all randomised patients, whether treated or not.

- Treated set:
  This patient set includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

- Intent to treat (ITT) set:
  This patient set includes all patients from the treated set who have a baseline (or screening) proteinuria (spot urine can be a used if patient does not have 24-hour collections) and baseline or screening eGFR

- Per protocol set (PPS):
  This patient set includes all patients in the ITT who completed at least 46 weeks of the treatment regimen and do not have iPDs leading to exclusion from the PPS as defined in Table 6.2: 1

Table 6.3: 1 Subject sets analysed

	Patient set		
Class of endpoint	Treated set	ITT	PPS
Primary endpoint: CRR at week 52		X (primary analysis)	X
Secondary endpoints		X	X
Safety endpoints	X		
Demographic/baseline endpoints	X		

Note that the number of patients with available data may differ across endpoints. For details, see Section 6.6 “Handling of missing data”.

6.5 POOLING OF CENTRES

Centre is not a term in the model. Therefore, no pooling of centres needs to be performed.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Primary and secondary endpoints

As CRR is defined based on UP (and UP/UC) from the two 24h urine collections and eGFR calculated from serum creatinine, rules for derivation of CRR when one or both of the urine samples and/or the serum sample is missing are specified below.

If one 24h urine collection is missing at any time point, then calculations should be based on the available 24h collection at that time point. If one 24h urine collection at any time point is suspected to be incomplete (<500mL/day or time of collection is <19.5 hours) or otherwise not evaluable, then calculations should be based on the unaffected collection at that time point.

Note that the restrictions on volume and duration of collection do not apply to the UP/UC derivation as the adjustment using UC is thought to compensate for incomplete collections.

If both 24h urine collections at baseline are missing, suspected to be incomplete or not evaluable, then UP/UC from the spot urine at baseline should be used to impute baseline UP (or UP/UC) from a 24h collection.

Handling missing data for patients who do not prematurely stop trial medication
If a patient does not have 24h urine collections at week 26 or at week 52, then UP from a 24h collection will be imputed as follows:

- For the week 26 UP, use the mean of UP/UC from the spot urines at weeks 21 and 26
- For the week 52 UP, use the mean of UP/UC from the spot urines at weeks 46 and 52

UP/UC from two weeks are used to get a more stable estimate of UP as it is generally accepted that estimates from the spot urines are not as reliable as estimates from the 24h collections.

For the derivation of CRR using UP/UC from the 24h collection, averages of the two weeks as described above will also be used to impute missing UP/UC from the 24h collection.

For the derivation of CRR using UP/UC from the spot urine, the imputation would be as follows: If UP/UC from the spot urine is missing at week 26, then use week 21. If UP/UC from the spot is missing at 52; use 46.

If no serum creatinine value (to determine eGFR) is available at baseline, then it will be imputed using the value at the screening visit. If no serum creatinine value is available at week 26 or week 52 then it will be imputed using the value at week 21 or week 46, respectively.

For secondary endpoints based on proteinuria and eGFR, the same imputation rules will be applied to derive response at weeks 26 and 52.

Definition/derivation of CRR for patients who prematurely stop trial medication
The rules below will be applied to derive CRR/PRR/MRR for the ITT:

- (1) If the reason for discontinuation of treatment is 'Lack of efficacy' or AE type is 'Worsening of disease under study', then CRR will be defined as 'Non-responder'.

- (2) If the patient used prohibited meds known to impact CRR following discontinuation of study med, then CRR will be defined as 'Non-responder'.

- (3) If neither #1 or #2 apply and treatment duration ≥ 46 weeks, then use the lab data collected at Visit 16-EOT/Week 52 to derive the endpoints. If there is no lab data at Visit 16-EOT /Week 52, then use the lab data closest to 52 weeks that is within 6 weeks prior to week 52.

- (4) If neither #1 or #2 apply and treatment duration < 46 weeks, then CRR will be defined as 'Non-responder'.

Note that patients handled with the above rules are included in the ITT population. They would only be included in the PPS if they complete 46 weeks of the treatment regimen.

For patients who took study drug for < 46 weeks, continued to participate in the trial and have urine collections and serum creatinine determinations, their data will be displayed in a listing.

6.6.2 Other endpoints and safety endpoints

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates"). (*2*)

All other endpoints will be analysed without imputing for any missing data.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study day will be calculated relative to the date and time of the first dose of double-blind randomised treatment. The day prior to the start of double-blind randomised treatment will be 'Day -1' and the day of the start of double-blind randomised treatment will be 'Day 1'; therefore 'Day 0' will not exist.

Unless otherwise specified, baseline is defined as the latest time-point on or before the date of the first randomised treatment administration (the date of the first dose is acceptable because the first dose of medication is to be taken in clinic on the day of randomisation AFTER all

baseline assessments have been made.) If there is no measurement for a particular variable on or before the date of first randomised treatment administration then no baseline will be derived for that variable.

The following visit labels will be used in all tables & graphics. As specified in the CTP, EOT refers to the End of Treatment visit. EOS is the End of Study visit. FU is Follow Up.

For discontinued patients (only):

EOT = 'EOT'

For completed patients who do not roll over to trial 1293.13:

Week 52='Week 52/ EOT'

Week 56='FU'

Week 60='EOS'

For completed patients who roll over to trial 1293.13:

Week 52='Week 52/ EOT'

For patients who discontinue trial drug but continue participation in trial:

EOT='EOT'

Visit 5='Visit 5/FU'

Visit 8='Visit 8/FU'

Visit 11='Visit 11/FU'

Visit 14='Visit 14/FU'

EOS ='EOS/FU'

Visit labels containing 'Visit' or 'FU' occurred after the EOT visit; patient was not on drug for these visits.

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

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 (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

All calculated statistics will be presented to one more decimal place than the original measurement accuracy of the variable being summarised.

All p-values will be displayed to four decimal places (or "<0.0001" if appropriate).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. The display will include the following variables: gender, ethnicity, race, age, time since diagnosis (months), height, weight, smoking status, alcohol status, LN class, activity score and anti-dsDNA, C3 and C4 at baseline, eGFR at baseline, UP/UC from the spot urine at baseline, UP from the 24h collection at baseline and UP/UC from the 24h collection at baseline.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant disease and medications will be summarized. Frequency counts are planned.

Concomitant diseases will be coded using the current version of MedDRA coding system.

Medications will be coded using the WHO Drug dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

In addition to the standard display showing all concomitant medications, separate displays will be provided to characterize usage of ACEi (Angiotensin-converting enzyme inhibitors) and ARB (Angiotensin receptor blockers) by treatment group. As usage of these meds may impact renal response, it is of interest to capture the number of patients who use these meds at:

- Baseline
- On-treatment
- At week 52 (when patient is evaluated for the primary endpoint)
- And to capture patients who had any change during the trial (i.e., patients who start use of these meds and who increase or reduce doses). This last group, may be determined programmatically or from manual review using a spreadsheet to identify patients.

Concomitant diagnoses and medications will be listed by patient. Subjects without any concomitant diagnosis or therapy should be marked with a "No" in the respective column.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report.

7.4 PRIMARY ENDPOINT

7.4.1 Primary analysis of the primary endpoint

Primary analyses of the primary endpoint will be performed using the ITT patient set.

The Multiple Comparison Procedures and Modeling (MCP-Mod) approach (4, 5) is implemented in two main steps: (1) trial design stage; (2) trial analysis stage. The procedures for the trial design stage, including the selection of candidate models covering a suitable range of dose-response shapes and sample size and power calculations, are provided in the CTP Section 7.3.1 and 7.7. The procedures for the trial analysis stage are outlined below with more specification (including SAS code & R code) in Section 9.1.

CRR at week 52 (derived using UP and derived using UP/UC from the 24h urine collections) will be analysed using a logistic regression model. Factors in the model will include treatment and the covariates: race (Asian/non-Asian) and proteinuria at screening <3g/day or ≥ 3g/day (respectively Uprot/Ucreat<3 or Uprot/Ucreat≥3). Use of proteinuria at screening as a covariate was not specified in the CTP. It was added via the TSAP as both race and proteinuria were stratification variables at randomization.

From this model, placebo-adjusted treatment estimates for each active dose group, as well as their corresponding variance-covariance matrix will be estimated. These results will be used in the MCPmod analysis.

Pairwise comparisons of the *modelled proportion* of patients at each dose level who are CRRs will be compared to placebo. In keeping with the exploratory nature of the trial, p-values will be interpreted in a nominal fashion (no adjustment for multiplicity will be performed). While the interim TSAP specified that an alpha level of 0.10 (two-sided) would be the cut-off for declaring statistical significance, this was changed via the Decision log prior to conducting the interim analysis. For consistency with a team-reviewed relevant external publication it was decided that an alpha level of < 0.20 (two-sided) would be the cut-off for declaring statistical significance.

Pairwise comparisons of the *observed* proportions of patients at each dose level to placebo who are CRRs will be performed. Confidence intervals will be calculated using the Newcombe method. P-values from Barnard tests of association will be displayed.

Pairwise comparisons of *stratified observed* proportions of patients at each dose level to placebo who are CRRs will be performed. Confidence intervals will be calculated using the Cochran-Mantel-Haenszel (CMH) method. A single p-value from a CMH test of general association will be displayed.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

There are no key secondary endpoints defined for this trial.

7.5.1.1 Primary analysis of the key secondary endpoint

7.5.1.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the key secondary endpoint

7.5.2 (Other) Secondary endpoints

Analysis of all secondary endpoints will be performed using the ITT and PPS populations.

Pairwise comparisons of the *observed* proportions of patients at each dose level to placebo will be performed for the secondary endpoints. Confidence intervals will be calculated using the Newcombe method. P-values from Barnard tests of association will be displayed.

Pairwise comparisons of the *observed* proportions of patients at each dose level to placebo who are CRRs *at week 26* will be stratified *by race* (Asian vs. non-Asian) as a sensitivity analysis. Confidence intervals will be calculated using the Newcombe method. P-values from Barnard tests of association will be displayed. This same analysis will be performed for *observed* placebo-adjusted proportions of patients at each dose stratified *by proteinuria at screening* (UP/UC < 3 vs. UP/UC ≥ 3) as per the lab results.

7.7 EXTENT OF EXPOSURE

Duration of time on treatment will be derived for each patient & summarized by treatment group.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set and performed in accordance with BI standards. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

The format of the listings and tables will follow the BI guideline 'Reporting of clinical trials and project summaries' (*6*).

The individual values of all subjects will be listed, sorted by treatment, subject number and visit. The listings will be contained in Appendix 16.2.

7.8.1 Adverse events

AEs will be analysed using BI standards, as described in the guideline, 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (*7*).

Unless otherwise specified, the analyses of adverse events 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.

The analysis of AEs will be based on the concept of treatment emergent AEs. This means that all AEs occurring between first drug intake and end of the residual effect period (REP) will be assigned to the randomised treatment. The residual effect period is defined as 50 days. All AEs occurring before first drug intake will be assigned to 'Screening' and all AEs occurring after last drug intake + 50 days will be assigned to 'Follow-up' (and presented in listings only). For details on the treatment definition, see Section 6.1

According to ICH E3 (*8*), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for patients with adverse events leading to treatment discontinuation, other significant adverse events according to ICH E3 (*8*), related adverse events and serious adverse events. AEs will also be summarised by maximum RCTC grade.

Adverse events of special interest (AESI) will be presented in tables and listings for the following:

- Injection site reactions and hypersensitivity, including anaphylaxis reaction
- Malignancies, lymphoproliferative disorders
- Severe infections and opportunistic infections
- Thromboembolism (Thrombosis and adjunct immunosuppression)
- Cytokine release syndrome
- Drug induced liver injury (DILI) (if applicable)

The system organ classes will be sorted by frequency, PTs will be sorted by frequency (within SOC).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (*9*).

The residual effect period of 50 days will be applied to the laboratory data. Laboratory data will be assigned to the treatment period if samples were taken after the first injection of study medication to the date of last administration of study medication plus 50 days. Laboratory data from samples taken on or after the 51st day after the last administration of trial medication will be considered 'Follow-up' data.

Tables and figures in Section 15 of the CTR will include laboratory data from the treatment period; data from the follow-up period will not be included. Listings of laboratory data will display on-treatment and follow-up data, with follow-up data flagged to identify they are from samples taken during the follow-up period.

Possible clinically significant abnormalities (PCSA) were identified using BI standard rules plus RCTC.

Figures displaying mean and median WBC and neutrophils over time will be provided.

Descriptive statistics for anti-double stranded DexoxyriboNucleic Acid (anti-dsDNA), Complement Component C3 (C3) and Complement Component C4 (C4) counts over time will be displayed for all patients in the treated set. For anti-dsDNA, descriptive statistics for patients who are positive at baseline [i.e., >ULN (=75 IU/mL)] will tabulated and displayed in a figure. For C3 and C4, patients who are below lower limit of normal (LLN) at baseline will tabulated and displayed in figures. LLN for C3 is 0.9 g/L. LLN for C4 is 0.1 g/L.

Descriptive statistics over time for erythrosedimentation rate will be provided.

IgG & IgM values will be listed by treatment, patient and visit. Values outside the normal range will be flagged. Possibly clinically significant abnormalities will be flagged.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

7.8.4 ECG

Descriptive statistics for mean heart rate, PR interval, QRS interval, QT interval, QTcB and QTcF absolute values and changes from baseline over time will be provided. Frequencies of subjects with notable findings in mean heart rate, PR interval, QRS interval, QT interval, QTcB at any time on treatment will be tabulated.

Notable findings for each parameter are defined as:

- HR: Increase from baseline in HR >= 25%, when the corresponding on treatment HR is > 100 bpm or decrease from baseline in HR >= 25%, when the corresponding on treatment HR is < 50 bpm.
- PR: Increase from baseline in PR >= 25%, when the corresponding on treatment PR is > 200 ms.
- QRS: Increase from baseline in QRS >= 10%, when the corresponding on treatment QRS is > 110 ms.
- New onset of QTcF > 500 ms, or increase from baseline in QTcF > 60 ms.
- New onset of QT > 500 ms.

(New onset means 'not present at baseline'.)

Patients with notable findings for any of these parameters will have all ECG parameters displayed in one listing with flags indicating the notable findings.

7.8.5 Others

Not applicable.

8. REFERENCES

1	Bornkamp B, Pinheiro J, Bretz F. Package 'DoseFinding' (February 19, 2015). http://cran.r-project.org/web/packages/DoseFinding/DoseFinding.pdf (access date: 28 April 2015) ; Comprehensive R Archive Network (2015) [R15-2001]
2	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED platform.
3	*001-MCS-36-472:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
4	Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat 16 (5), 639 - 656 (2006) [R10-1424]
5	Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. Stat Med 33 (10), 1646 - 1661 (2014) [R15-4293]
6	*BI-KMED-BDS-HTG-0045:* "Reporting of clinical trials and project summaries", current version, KMED platform.
7	*BI-KMED-BDS-HTG-0041:* "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; KMED platform.
8	*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.
9	*BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version, KMED platform.

10. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	15-AUG-16		None	This is the initial TSAP with necessary information for trial conduct
Draft	17-MAY-17		Primary endpoint rewritten to clarify calculation Figure 7.4.1 renumbered to 7.3.1 Section 3: R version added for analysis Section 7.2: verbiage added for table for cumulative exposure to corticosteroids Section 8: references added for statistical position papers	
Draft	06-JUL-17		Clarification provided for section 5.2, definition of PRR Section 6.6 updated to handle missing 24h urine collection Figure 7.4 updated	
Final	25-MAY-18		Updated verbiage for section 5.1 Primary Endpoint. Added verbiage related to ADA in section 7.8.5. Updated formats and hyperlinks.	This is the final TSAP
Revised	17-AUG-20		All	This is a revised TSAP updated to reflect issues identified during data review, learnings from project team & KOLs and specifications to execute the statistical analysis.