TRIAL STATISTICAL ANALYSIS PLAN

c21284764-02

BI Trial No.:	1293-0013
Title:	An exploratory maintenance trial evaluating the effect of BI 655064 in Lupus Nephritis patients who have achieved a meaningful response either at the end of 1293.10 or after an induction treatment outside of 1293.10 Including Protocol Amendment 2 1293-0013-revised-protocol-03 [c13795013-04]
Investigational Product(s):	BI 655064
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Date of statistical analysis plan:	17 JUN 2021 REVISED
Version:	2

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LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ACEi	Angiotensin-converting enzyme inhibitor
[redacted]	
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
FACIT-F	Functional Assessment Chronic Illness Therapy-Fatigue
FU	Follow Up
GFR	Glomerular Filtration Rate
h	hour
HRQoL	Health Related Quality of Life
IA	Interim analysis

Term	Definition / description
ICH	International Conference on Harmonisation
iPD	important Protocol Deviation
IRT	Interactive Response Technology
ITT	Intent To Treat
IV	Intravenous
KOL	Key Opinion Leader
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LN	Lupus Nephritis
MedDRA	Medical Dictionary for Regulatory Activities
min	minute
MQRM	Medical Quality Review Meeting
MRR	Major Renal Response
ms	millisecond
PCSA	Possible clinically significant abnormality
[redacted]	
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
SAS	Statistical Analysis System (SAS® System, [redacted], [redacted]
SD	Standard deviation
SELENA	Safety of Estrogens in Lupus National Assessment
SF-36	36-Item Short-Form Health Survey
SLE	Systemic Lupus Erythematosus

Term	Definition / description
SLEDAI	SLE Disease Activity Index
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.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

With Amendment #2 to the CTP (21-Dec-2020), Group 2 was cancelled. Group 2 was to be a cohort of patients who achieved a meaningful response to induction treatment outside of 1293.10. With all patients in 1293.13 now coming from trial 1293.10 (Group 1), the sole focus in 1293.13 can be long-term (now 2-year) assessment of their induction and continued maintenance therapy in 1293.13. Efficacy and safety tables and figures will include data from 1293.10 for assessment of BI655064 doses versus placebo over this 2-year treatment period.

Amendment #2 describes the unblinding of treatment codes for 29 patients (20 on treatment and 9 in follow-up) in the trial on 20-Oct-2020. At that time, the investigator was asked to discuss with the patient their treatment options and continued participation in 1293.13. It is not expected that this partial unblinding introduced meaningful reporting bias. The primary endpoint and most of the secondary endpoints are derived from laboratory measurements. With respect to the SLEDAI, most domains are lab-based and other domains are examination findings. No analyses to address potential bias are planned.

The CTP list of secondary and further endpoints was reviewed (prior to release of treatment codes) resulting in some additions and a few deletions essentially driven by learnings from the 1293.10 trial. Section 5.2 lists the secondary endpoints noting the addition of one endpoint (proportion of patients with partial renal response (PRR) without renal flare) inadvertently left off the CTP list of secondary endpoints (but specified in another section) and one deletion with explanation for the deletion (proportion of patients with CRR at Week 52). [redacted]

Important Protocol Deviations (iPDs) were updated during trial conduct to reflect learnings and input from Key Opinion Leaders (KOLs). The Per protocol set (PPS) was dropped with the second CTP amendment.

Sensitivity, subgroup and exploratory analyses added to the TSAP for the primary endpoint are listed in Sections 7.4.2. Sensitivity, subgroup and exploratory analyses were also added to the TSAP for an important secondary endpoint; these are listed in Sections 7.5.2.

The biomarker analysis will be outlined outside of this TSAP.

[redacted]

5. ENDPOINT

5.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of patients with complete renal response (CRR) and without any renal flares at week 52. 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, 24h urine collection was performed at baseline (which is Week 52 in trial 1293.10) and Week 52 in trial 1293.13. 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 in trial 1293.10 raised concern that some collections may have been incomplete. The rules implemented in 1293.10 that the 24h samples should be ≥500mL/day and at least 19.5 hours (approximately 80% of 24 hours) to be evaluable were applied in 1293.13 also. 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)

An alternative way to derive CRR is 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 can be used to stabilize the estimate of proteinuria and is generally accepted as a correction for incomplete collections. When this derivation was applied, collections <500mL/day or < 19.5 hours were evaluated.

Both derivations of CRR are included in the CTP section on assessments of renal response. The CTP specifies that the decision which derivation to select as primary endpoint will be based on review of blinded data. However, it was decided to use UP from the 24h collection as the primary derivation for CRR to be consistent with 1293.10. The alternate derivation will be analysed and presented using the same methods/format used for CRR derived from UP.

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

The secondary endpoints were re-ordered in order of perceived importance as follows:

- Proportion of patients with confirmed CRR (defined as CRR at both week 42 and week 52 using UP/UC from spot urine) without renal flare
  The endpoint, confirmed CRR, was introduced as a post hoc endpoint for 1293.10 where it proved to be a more sensitive endpoint as it was able to detect treatment effect in the presence of an unexpected large placebo response. With the requirement to demonstrate CRR at both time points, the placebo effect at Week 52 was reduced resulting in meaningful response rates for 180 mg and 240 mg BI655064.

- Proportion of patients with proteinuria <0.8g/d and without any renal flares at week 52.

- Proportion of patients with CRR at week 52 and sustained steroid reduction to ≤5 mg/d from week 26 to week 52.

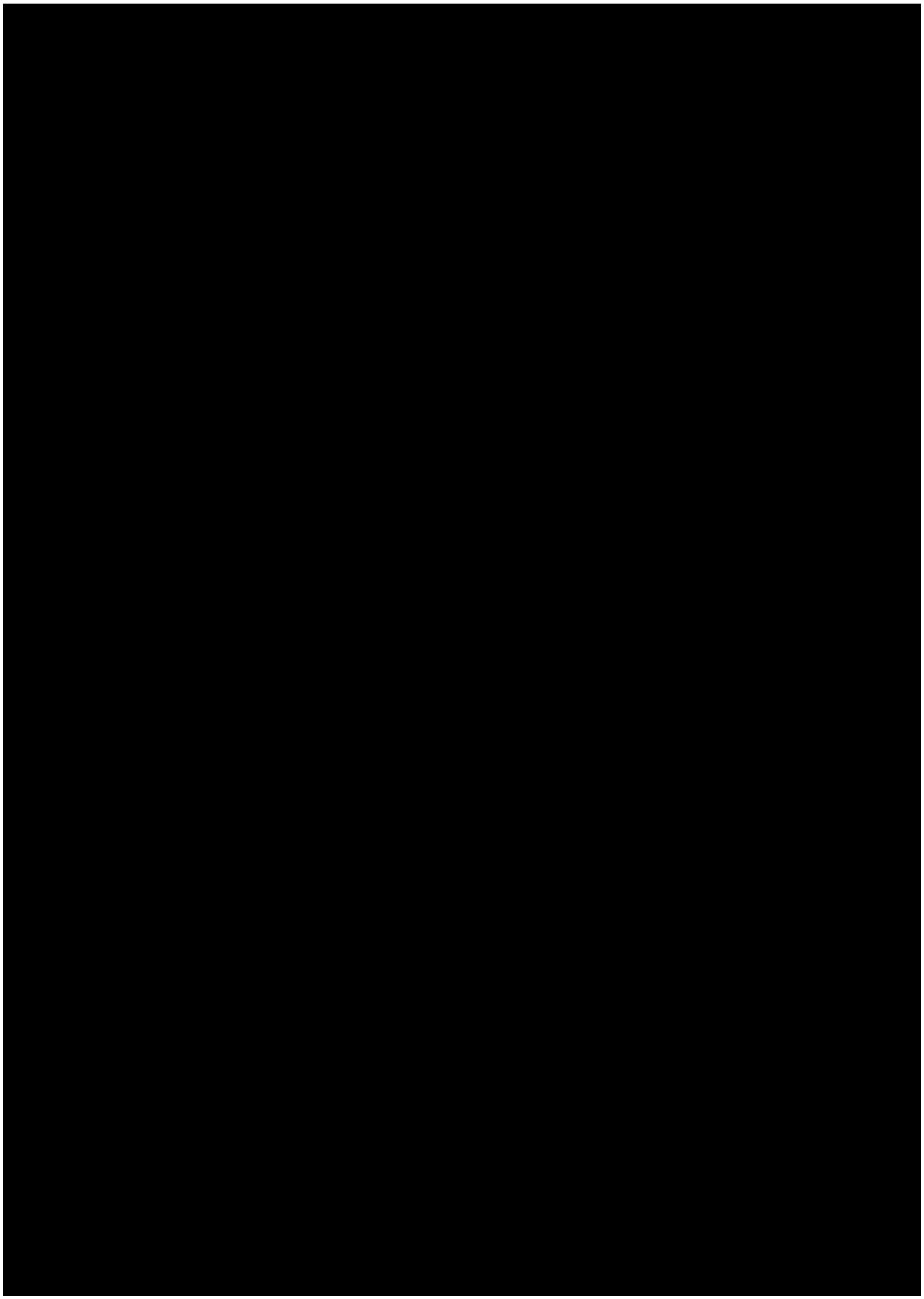
- Proportion of patients experiencing at least one renal flare during 52 weeks

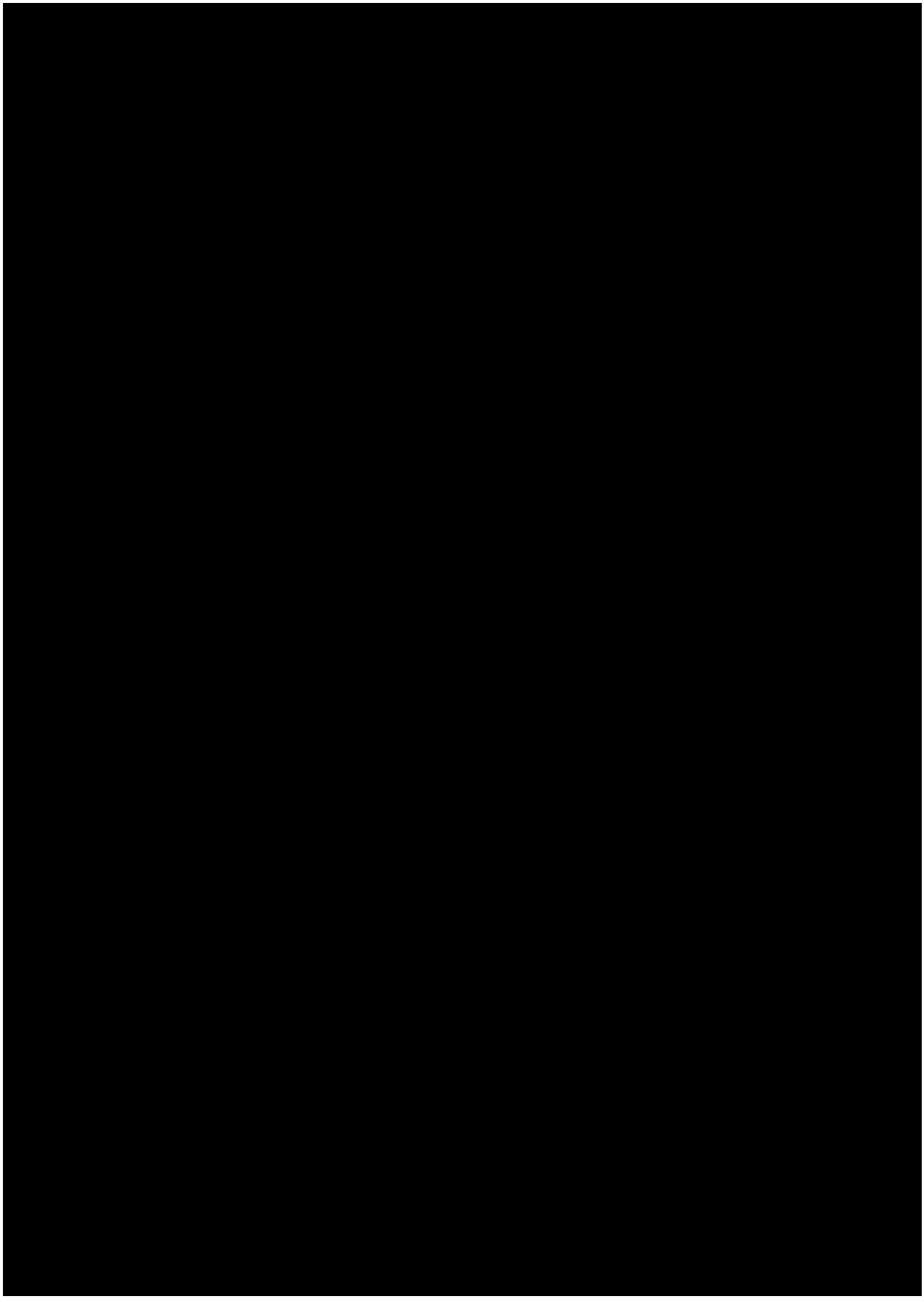
- Time to first renal flare over the course of 52 weeks.

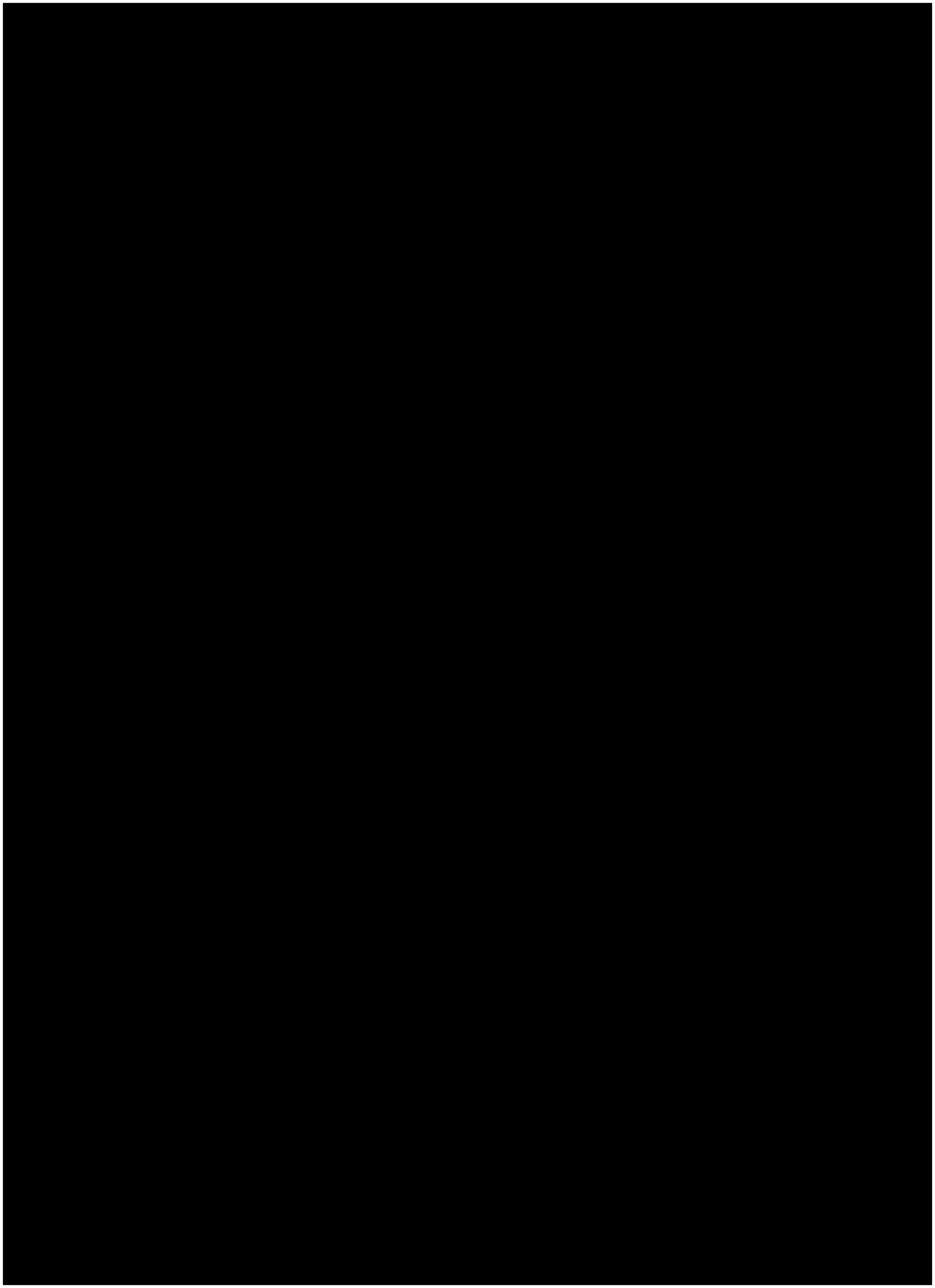
- Proportion of patients with PRR without renal flare derived from UP 24h collection at Week 52.
  Although not included in the list of endpoints in the CTP, PRR is defined in the CTR along with CRR as an assessment of renal response.
  It is defined as at least 50% reduction of proteinuria from baseline and **either** eGFR within normal range at time of assessment or decrease of eGFR < 20% from baseline if eGFR below normal range at time of assessment.

- Change from baseline in SLEDAI at weeks 12, 26, 42 and 52.

- Proportion of patients with CRR at Week 52.
  It was decided that CRR alone without consideration of whether a patient experienced a renal flare was not appropriate as the occurrence of a flare indicates the patient was not a responder. This endpoint will not be analysed.







6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For reporting purposes, all patients will be classified into one of the following treatment groups as determined by random treatment assignment at the start of 1293.10:

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:

Treatment: start date of randomised to double-blind medication in 1293.10 to date of last dose in 1293.13

Follow-up: day after the last dose of randomised double-blind medication in 1293.13 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.

Adverse events with onset on or after the 51st day after the last administration of trial medication will be considered ‘Follow-up’ events.

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 -**	**automatic PVs**	
	A1.1	Patient must have a CRR or a PRR or proteinuria ≤ 1g/d (or UP/UC ≤ 1)	Note: This can be at Week 46 or Week 52 of 1293.10.	PPS
	A1.2	Women of childbearing potential must be ready and able to use two reliable methods of birth control simultaneously; one must be highly effective. Sexually active men must be ready to use condoms during & following treatment with MMF		None
	A2.1	Clinically important acute or chronic infections including but not limited to HIV, hepatitis B or C.		PPS
	A2.2	Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2 at screening (using CKD-EPI formula).		
	A2.3	The use of any restricted medications (see CTP) or any drug considered likely to interfere with the safe conduct of the trial.		
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing **(automatic PV)**	All
	B2	Informed consent too late	Informed consent date <*actual consent date*> was after Visit 1date <*Visit 1 date*> **(automatic PV)**	None
C		**Trial medication and randomization**		
	C1	Randomization not followed	Patient was not assigned to the treatment group specified in BI's randomization schedule. (to be checked at time of DBL).	None (TBD at MQRM/ BRPM)

Table 6.2: 1 (continued) Handling of iPDs

	C2	Wrong dosage schedule	(1)Medication number dispensed was not the medication number assigned OR (2)syringes used in the wrong order	PPS/ (TBD at MQRM/ BRPM)
	C3	Non-compliance with study medication	Any evidence of gross non-compliance. (Patient meets the non-compliance criteria in Section 5.4) **(manual or automatic PV)**	PPS/ (TBD at MQRM/ BRPM)
	C4	Medication code broken inappropriately	Medication code broken inappropriately - reason for medication code break <reason> (manual PV)	PPS
D		**Concomitant medication**		
	D1	Prohibited medication use (as described in CTP, section 4).	• **Abatacept or Cyclophosphamide** during treatment period • **Cyclosporine / Tacrolimus / Mizoribine** during treatment period (permitted during follow up per investigator's decision) • **Belimumab or other "anti- BLyS" or another investigational drug** during treatment period • **Biologic B-cell depleting therapy (e.g. anti-CD20)** during treatment period • **IV glucocorticoids** during treatment period **(Automatic & Manual iPVs)**	PPS/ (TBD at MQRM/ BRPM)
	D2	Non-permitted oral steroid use (as described in CTP, section 4.2.1)	• Patients with a CRR or proteinuria of <0.8g/d at the end of 1293.10 should start steroid tapering immediately at Visit 1. If necessary, patients may remain on a certain level of steroids due to other symptoms of SLE based on investigator's judgement. Although the tapering schedule will allow some flexibility, however **steroids should be stopped at 3 months (Week 12)** after randomisation. If this this not possible due to the patient's medical condition, the patient can stay on the lowest possible dose with the best benefit. • Patients with proteinuria of ≥0.8g/d at the end of 1293.10 should taper steroids down to ≤7.5mg/d at **week 26** and then to ≤5mg/d at **week 52**.	PPS/ (TBD at MQRM/ BRPM)

Table 6.2: 1 (continued) Handling of iPDs

	D4	Non-permitted AZA dose	AZA is allowed at a stable dose of 2mg/kg/day. (In case of intolerance or the body weight <50kg, dose may be reduced to 1mg/kg/day or the dosage should be rounded to the nearest 50mg. In regions where only a fixed single dosage is available on the market, the rounding should be done according to the investigators judgment, not exceeding 2mg/kg/day.)	PPS/ (TBD at MQRM/ BRPM)
	D5	Non-stable dose of ACE inhibitors or ARBs	ACE inhibitors or ARBs allowed at stable dose.	PPS/ (TBD at MQRM/ BRPM)
G		**Trial specific**		
	G1	Failure to remove patient from therapy (=study medication)	As described in CTP section 3.3.4.1	PPS/ (TBD at MQRM/ BRPM
Z		**Other**		
	Z1	Other iPVs affecting efficacy and possibly safety		PPS/ (TBD at MQRM/ BRPM
	Z2	Other iPVs affecting safety only		None

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

[redacted]

The Per protocol set (PPS) was dropped with the second CTP amendment.

Table 6.3: 1 Subject sets analysed

	Patient set			
Class of endpoint	Treated set	ITT		
Primary endpoint: CRR at week 52		X		
Secondary endpoints		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

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 Primary, 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.

The following rule was applied to the baseline of 1293.10. 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 52, then UP from a 24h collection will be imputed as follows:

- For the week 52 UP, use the mean of UP/UC from the spot urines at weeks 42 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 18. If UP/UC from the spot is missing at 52; use 42.

If no serum creatinine value (to determine eGFR) was available at baseline in 1293.10, then it was imputed using the value at the screening visit. If no serum creatinine value is available at week 26 or week 52 in 1293.13, then it will be imputed using the value at week 18 or week 42, respectively.

For secondary and further 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 (not applicable to unblinded Placebo patients who obtained BI approval to stop injections)

The CTP specified that as an imputation technique to deal with missing data, for the analysis of primary and CRR-related secondary endpoints, non-completers considered failure will be used. To determine if this was a reasonable approach, the trial team reviewed the patients who discontinued early, including review of reasons for early treatment discontinuation, AEs, concomitant meds, renal labs. The following handling rules better fit the circumstances around treatment discontinuation & were adopted.

- (1) If the details around the early discontinuation of trial medication indicated that the patient discontinued due to worsening renal function, had a renal flare or needed rescue medication, then CRR & PRR will be defined as ‘Non-responder’.

- (2) If there was no discernable worsening of renal function & the patient had a reasonable treatment duration, renal tests at the time of treatment discontinuation will be used to derive CRR & PRR.

- (3) If neither of the above applies and if at the time of discontinuation, the patient could have been considered a responder, then the patient was considered censored or non-evaluable. If the patient discontinued before Week 26, then both Week 26 & Week 52 are non-evaluable. If the patient discontinued after Week 26, then CRR & PRR were derived for Week 26 & Week 52 is non-evaluable.

For patients who took study drug for < 42 weeks, continued to participate in the trial and have urine collections and serum creatinine determinations, their data will be displayed in a separate listing.

6.6.2 Other endpoints and safety endpoints

With respect to the SLEDAI, no missing item(s) will be imputed. If one item comprising the sub-score is missing, the sub-score will be set to missing. Other sub-scores will be derived and analysed. If one item is missing, the total score will be set to missing.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates"). (1)

[redacted]

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

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Since patients are randomized at the start of 1293.10 and on the same treatment in 1293.13, the baseline of trial 1293.10 will be used as baseline for all assessments of change from baseline if not specified otherwise. The 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) in 1293.10. 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.

Visit 1 of trial 1293.1 3 was to be performed on the same day as the 1293.10 end of treatment (EOT) visit. All assessments performed at the 1293.10 EOT visit were used as baseline for this 1293.13 and were not repeated.

The following visit labels will be used in 1293.13 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 who do not continue participation in the trial:

EOT = 'EOT'

For completed patients:

Week 52='Week 52/ EOT'

Follow-up visit at Week 56='FU'

End of study visit at Week 64='EOS'

Patient who discontinued treatment before week 40 & continued in trial:

EOT='EOT'

Visit 4='Visit 4/FU'

Visit 6='Visit 6/FU'

Visit 8='Visit 8/FU'

EOS='EOS/FU'

Patient who discontinued treatment after week 40 & continued in trial:

EOT='EOT'

Visit 8='Visit 8/FU'

Visit EOS='EOS/FU' This is the 'week 52' visit

Visit EOS='EOS + 12w/FU' This is the 'week 52' plus 12 weeks visit

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 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) at the time of entry to 1293.10, height, weight, smoking status, alcohol status, LN class, FACIT-F total score, anti-double stranded DexoxyriboNucleic Acid (anti-dsDNA), Complement Component C3 (C3) and Complement Component C4 (C4) counts 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, modified activity and chronicity index scores. Baseline is the baseline of 1293.10.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases 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, a separate display will be provided to characterize usage of ACEi (Angiotensin-converting enzyme inhibitors) and ARBs (Angiotensin receptor blockers) by treatment group as these therapies may impact renal response. A separate display will be provided to characterize usage of antimalarial therapies by treatment group as usage of antimalarial therapies may impact occurrence of renal flares.

For individual patients who experience renal flares, their usage of antimalarial therapies may be explored.

For the non-standard displays, it is of interest to capture the number of patients who use these meds at:

- Baseline
- On-treatment
  Including any changes such as: therapies newly started, dose increases, therapies stopped and dose decreases
- At week 52 (when patient is evaluated for the primary endpoint)

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.

Proportion of patients with CRR at Week 52 without renal flare (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) in 1293.10.

Pairwise comparisons of the *modelled* proportion of patients at each dose level who are CRRs without renal flare 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).

Pairwise comparisons of the *observed* proportion of patients at each dose level who are CRRs without renal flare will be compared to placebo. 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 who are CRRs without renal flare will be compared to placebo. 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.

For 1293.10 it was decided that for the pairwise comparisons, an alpha level of < 0.20 (two-sided) would be the cut-off for declaring statistical significance. This will be adopted for 1293.13. However, it is important when interpreting the p-values (and numerical comparisons) to keep the trial design with its inherent biases in mind. This is an extension trial with the requirement to entry that patients responded to treatment in 1293.10 and have

the desire to continue participation in a clinical trial. Treatment assignments were not randomized and numbers of patients per treatment group are not balanced.

The partial unblinding of treatment codes for the risk-benefit discussions between investigators and patients is not expected to have a meaningful impact on this primary endpoint derived from laboratory measurements.

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

Sensitivity analyses:

Pairwise comparisons of the *observed* proportions of patients at each dose level to placebo who are CRRs without renal flare 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 in 1293.10* (UP/UC < 3 vs. UP/UC ≥ 3) as per the lab results. These analyses will be performed for CRR derived using UP determined from the 24h collections, UP/UC determined from the 24h collections and confirmed CRR.

Exploratory analyses:

The *observed* proportion of patients who are CRRs without renal flare in the 180 mg and 240 mg dose groups combined will be compared to placebo, displaying the same confidence intervals and p-values as noted above. This is an exploratory analysis, based on unexpected findings/imbalances observed in the 120 mg group at the time of the interim analysis of 1293.10. Analyses will be performed for CRR derived using UP determined from the 24h collections and confirmed CRR. These analyses were added via this version of the TSAP.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

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 population.

For the secondary endpoints listed below, the pairwise comparison of observed proportion of patients at each dose level will be compared to placebo using the same methods outlined for the primary endpoint.

- Proportion of patients with confirmed CRR without renal flare
- Proportion of patients with proteinuria <0.8g/d and without any renal flares
- Proportion of patients with CRR and sustained steroid reduction to ≤5 mg/d without renal flare
- Proportion of patients experiencing at least one renal flare
- Proportion of patients with partial renal response (PRR) without renal flare

At the time this TSAP was prepared, 8 renal flares were known to have occurred. The secondary endpoint, time to renal flare, will be displayed using a Kaplan Meier curve across all treatment groups to explore the timing of renal flares with color-coding, symbols or an embedded table to indicate the treatment group in which they occurred.

For the secondary endpoint, change from baseline in the SLEDAI, descriptive statistics will be provided.

Due to the perceived importance of the secondary endpoint, confirmed CRR, the logistic analyses described for the primary analysis will be performed and the sensitivity analyses by race and by proteinuria at screening in 1293.10 will be performed.

The analysis of proportion of patients with CRR having sustained steroid reduction <= 5 mg from week 26 will be repeated for confirmed CRR. The proportion of patients with confirmed CRR or confirmed PRR will be analysed. The analysis of proportion of patients with CRR who were steroid free from week 26 will be repeated for confirmed CRR. The exploratory analysis combining 180mg and 240mg BI 655064 versus placebo will repeated for confirmed CRR.

At the time this TSAP was prepared, the expectation is that confirmed CRR will be more sensitive than the primary endpoint for detecting treatment effects within subgroups. For this reason, the secondary endpoint, confirmed CRR, will be used for exploring treatment effects within subgroups.

Time since diagnosis (of LN) was identified in trial 1293.10 as prognostic of obtaining CRR. A subgroup analysis of confirmed CRR will be performed based on the ITT, defined by time since diagnosis at the time of entry to 1293.10. One group will include those patients with time of diagnosis from 0- < 6 months. The second group will include patients with time of diagnosis >=6 months.

A subgroup analysis of confirmed CRR at week 52 will be performed based on the ITT data set, defined by proteinuria at baseline. An important CTP inclusion criterion in 1293.10 was active renal disease evidenced by proteinuria ≥ 1.0 g/day [(UP/UC) ≥ 1] at screening. However, by baseline, there were patients for whom UP and/or UP/UC determined from 24h

urine collections were < 1.0 g/day. Subgroups will be created based on the UP from the 24h collections at baseline. One group will include patients with UP < 1.0 g/day. The second group will include all other patients.

Subgroup analyses of confirmed CRR at week 52 will be performed based on the ITT data set stratified using biopsy-derived disease activity index and chronicity index scores. The scoring was performed by a renal pathologist who evaluated biopsy slides submitted by the sites. Subgroup analyses will be performed based on the activity score and on the chronicity score. The median score will be used as the cut-point to split the patients into one group with scores less than the median versus the group with scores greater than or equal to the median.

Graphical displays will be used to explore relationships between biomarkers and clinical endpoints. The biomarkers were determined from samples obtained at Week 26 of 1293.10. Five biomarkers were selected for this exploratory analysis based on meaningful post-treatment decreases from baseline distinguishing these biomarkers from other biomarkers observed. Individual patient change from baseline for the biomarker, change from baseline in SLEDAI score and confirmed CRR status will be displayed. The biomarkers from 1293.10 will be displayed with SLEDAI scores and confirmed CRR status. In each figure, the clinical endpoints will be from the same time points with separate figures for 1293.10 - Weeks 26, 1293.10 – Week 52 and 1293.13- Week 52.

7.7 EXTENT OF EXPOSURE

Duration of time on treatment starting with the first injection in 1293.10 to the last injection in 1293.13 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' (3).

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' (4).

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 (5), 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 (5), 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 (6).

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.

Possibly 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-dsDNA, C3 and 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

No analysis of ECG data is planned. Mean heart rate, PR interval, QRS duration and QT interval will be listed by treatment group by patient.

7.8.5 Others

Not applicable.

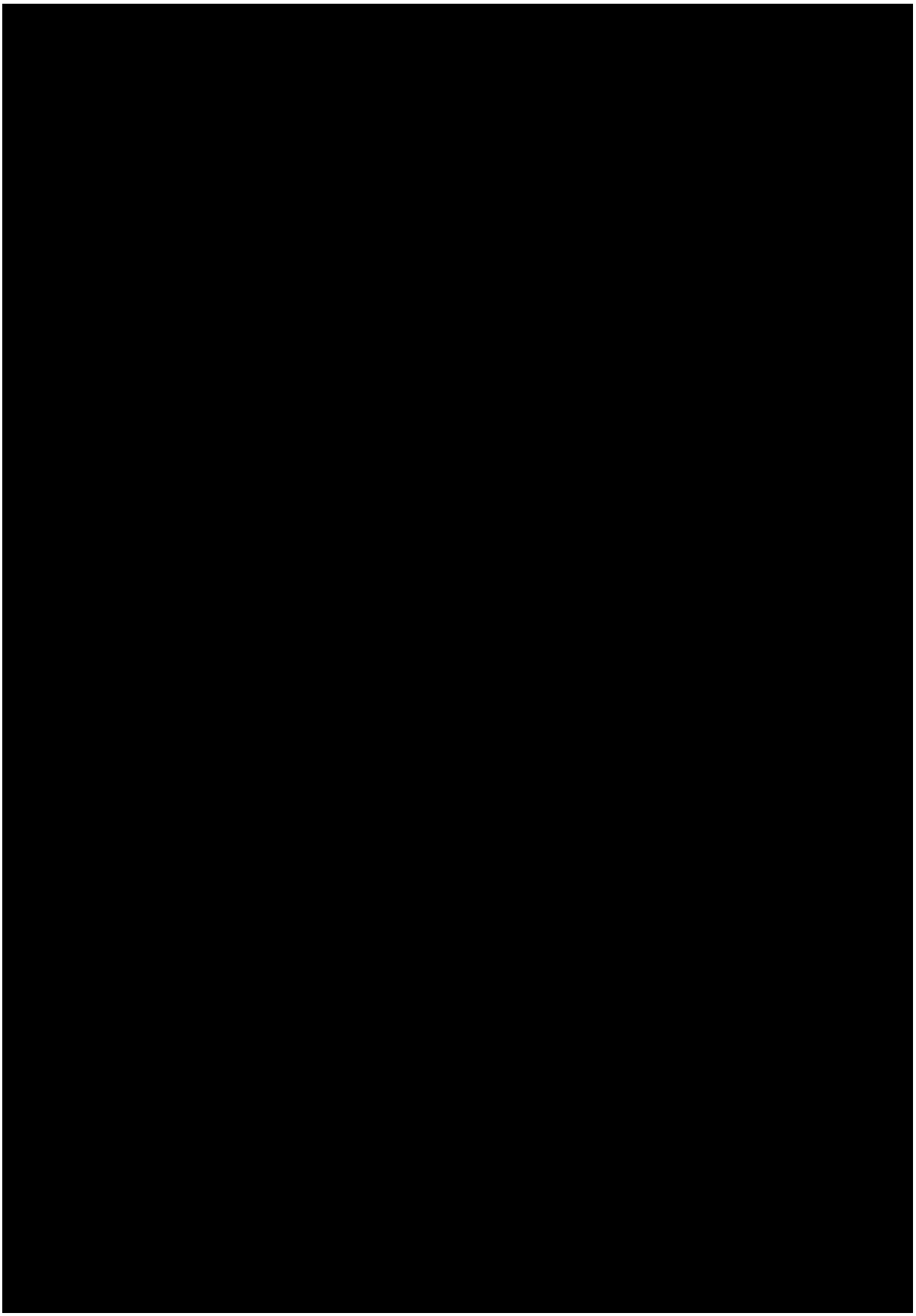
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Once the last patient has completed their End-of-Treatment (EOT) visit and all corresponding data has been entered and cleaned to the level documented in the "Data Delivery Request" (DDR) form, the data will be declared ready to be unblinded via the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form. Then the treatment information will be released for analysis.

The data collection for the off-treatment residual effect period until the End-of-Study (EoS)/ Follow-Up visit will continue into the unblinded trial database. Once trial data collection has been completed and all data has been entered and cleaned as documented on the RUN form, a final data lock will be performed.

9. REFERENCES

1	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED platform.
[redacted]	
3	*BI-KMED-BDS-HTG-0045:* "Reporting of clinical trials and project summaries", current version, KMED platform.
4	*BI-KMED-BDS-HTG-0041:* "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; KMED platform.
5	*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.
6	*BI-KMED-BDS-HTG-0042:* "Display and Analysis of Laboratory Data", current version, KMED platform.



11. HISTORY TABLE

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

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	14-DEC-17	[redacted]	None	This is the final TSAP
2	17-JUN-21	[redacted]	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. Updates based on CTP Amendment #2 are also included.