Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c13795013-04**
EudraCT No.: **EU Trial No:**	2017-003101-17	
BI Trial No.:	1293-0013	
BI Investigational Product:	BI 655064	
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	
Lay Title:	An exploratory maintenance trial of BI 655064 in patients with lupus nephritis	
Clinical Phase:	II	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax:	
Coordinating Investigator:	[redacted] Phone: [redacted] Fax:	
Status:	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date:	**Version: 3.0**	**Date: 21 Dec 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Not applicable
Active ingredient name	BI 655064
Protocol date	14 September 2017
Revision date	21 Dec 2020
Trial number	1293-0013
Title of trial:	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
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial
Clinical phase:	II
Objectives:	To evaluate long term efficacy and safety of different doses of BI 655064 versus placebo as add-on therapy to standard of care during maintenance treatment for lupus nephritis. To study the effect of steroid tapering and steroid withdrawal during maintenance treatment.
Methodology:	Double blind, placebo-controlled, parallel design comparison of different dose groups over 52 weeks of maintenance treatment.
Number of patients entered:	Group 1: approximately 60 patients to roll over from 1293.10.
Number of patients per treatment arm:	Group 1: the number of patients in each treatment arm will vary depending on the total number of eligible patients rolling over from 1293.10.
Diagnosis:	Patients with Class III or IV lupus nephritis based on ISN/RPS 2003 classification.
Test product	BI 655064
Dose:	Group 1 – roll-over patients will continue to receive the same treatment allocation as previously assigned in 1293.10.
Mode of administration:	Subcutaneous injection
Comparator products	Placebo
Dose:	Not applicable

Company name	Boehringer Ingelheim
Finished product name	Not applicable
Active ingredient name	BI 655064
Protocol date	14 September 2017
Revision date	21 Dec 2020
Trial number	1293-0013
Main in- and exclusion **Main in- and exclusion criteria**	• Males or females, age 18 – 70 years (inclusive) • Males or females, age 18 – 70 years (inclusive) • Diagnosis of SLE according to 1997 ACR classification with at least 4 documented criteria, one of which must either be a positive ANA or a positive anti-dsDNA antibody confirmed at the start of induction therapy (historical data) • eGFR $\geq$ 30ml/min/1.73m^2 at screening • Group 1: achieved either a CRR or a PRR or proteinuria $\leq$ 1g/d (or UP/UC $\leq$ 1) at the end of 1293.10.
Mode of administration:	Subcutaneous injection
Duration of treatment	52 weeks
Endpoints	Primary endpoint: - Proportion of patients with CRR and without any renal flares at week 52. Secondary endpoints: - Proportion of patients with CRR at week 52 - 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 confirmed CRR (defined as CRR at both week 42 and week 52 using UP/UC from spot urine) - Change from baseline in SLEDAI at weeks 12, 26, 42 and 52.
Safety criteria:	Assessments include physical examination, vital signs, ECG, safety laboratory tests and adverse events.
Statistical methods:	Descriptive statistics, Kaplan-Meier analysis or other statistical methods appropriate for exploratory analyses.

FLOW CHART 1 – ROLL-OVER PATIENTS FROM 1293.10 (GROUP 1)

Trial Periods	Baseline	Treatment							End of treatment	Follow-up	End of Study
Visit	1[1]	2	3	4	5	6	7	8	EOT[3]	FUp	EOS
Week	0	4	8	12	18	26	34	42	52	EOT+4	EOT+12
Day (± time window)[2]	1	29±3	57±3	85±5	127±5	183±5	239±5	295±5	365±5	393±5	449±5
Informed consent[4]	X										
Demographics / Medical history[5]	X										
Review inclusion/exclusion criteria	X										
Physical examination[6]	X[c1]	X[t]	X[t]	X[t]	X[t]	X[c]	X[t]	X[t]	X[c]	X[t]	X[t]
12-lead ECG	X[1]			X		X			X		
Lupus PRO, SF-36, FACIT-F, SLEDAI[7]	X[1]			X		X		X	X		
2 x 24hr urine collection[8]	X[1]								X		
Pregnancy test[9]	X[1]	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests[10]	X[1]	X	X	X	X	X	X	X	X	X	X
Infection screening[11]	X										
Immunology tests[12]	X[1]			X		X		X	X		X
[redacted]				[redacted]		[redacted]			[redacted]		[redacted]
Exploratory biomarker sampling[14]	X[1]	X		X		X			X		
mRNA peripheral blood sampling[14]	X[1]					X			X		
miRNA urine sampling[14]	X[1]					X			X		
[redacted]	[redacted]			[redacted]		[redacted]			[redacted]		
Dispense trial medication and provide instructions for home administration	X	X	X	X	X	X	X	X			
Administer trial medication	X	X	X	X	X	X	X	X			
Continue SOC (MMF or AZA)	—	—	—	—	—	—	—	—	—	—	→
Glucocorticoids tapering[15]	—	—	—	—	—	—	—	—	→		
Compliance Check	X[1]	X	X	X	X	X	X	X	X		
Dispense new diary at baseline and review compliance of diary use	X	X	X	X	X	X	X	X	X		
Adverse events	X[16]	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy[17]	X[16]	X	X	X	X	X	X	X	X	X	X

FLOW CHART 1 – ROLL-OVER Patients from 1293.10 (Group 1) (CONT)

Vital status collection[18]											X
Completion of patient participation											X

1. Visit 1 must be performed on the same day as the 1293.10 end of treatment (EOT) visit. All assessments performed at the 1293.10 EOT visit will be used as baseline for this trial and should not be repeated. See Section 6.2.1.
2. Any deviation from the visit schedule is strongly discouraged and can only occur with the approval of CTL/CTM. See Section 6.1.
3. For prematurely discontinued patients, an EOT visit should be performed within 7 days of stopping the trial medication and these patients will be invited to attend a subset of follow-up visits. See Section 6.2.3.3
4. Re-consenting may be necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
5. Previously reported medical history data from 1293.10 will have to be be transcribed into 1293-0013 eCRF. Information on smoking and alcohol history will also be collected if status changed since Visit 1 of 1293.10 trial.
6. Includes height (at screening only), weight and vital signs. X^c is a complete physical examination. X^t is a targeted physical examination. See Section 5.2.1.
7. Questionnaires to be completed at the trial site by the patients before any trial related investigations or discussions. See Section 5.1.2.
8. See Section 5.1.1 for details on the 24-hour urine collection.
9. Pregnancy test will be performed at Baseline and then every 4 weeks in women of child bearing potential. See Section 5.2.3.
10. Routine safety laboratory tests include haematology, chemistry, coagulation and urinalysis. See Section 5.2.3.
11. Infectious screening will only be done in case of suspicion of a (re-) infection as this has been tested at screening in clinical trial 1293.10. If so, blood samples will be collected for assessing the presence of HIV, HBV and HCV. The QuantiFERON-TB Gold test will be also performed to assess the presence of TB infection. See Section 5.2.3.
12. Immunology tests: Blood samples for anti-dsDNA, anti-C1q antibodies, C3 and C4 complements will be collected at time-points indicated in the above Flow Chart. For ANA and Anti-phospholipid antibodies, these samples will be collected at visits 1 and EOT only. For C3/C4 and Anti-dsDNA these will be tested in addition at week 42 due to the SLEDAI questionnaire being completed. Refer to Table 5.2.3:1 for more information.
13. [redacted]
14. See Section 5.4.1 for details on exploratory biomarker, mRNA peripheral blood and miRNA urine sampling requirements.
15. For glucocorticoids tapering schedule, see Section 4.2.1.
16. All new and ongoing Adverse Events/Concomitant Therapy at the EOT of 1293.10 will need to be entered into the eCRF for 1293-0013 at Visit 1.
17. Compliance to lupus nephritis -concomitant therapy will be recorded by patients in e-diary provided and assessed by trial staff at every visit.
18. For prematurely discontinued patients who are unable to attend a subset of follow-up visits, their vital status should be assessed at Week 52, see Section 6.2.3.3. All patients to complete the trial until Week 52 and are not returning for FUp will have at least a vital status collection at Week 64.

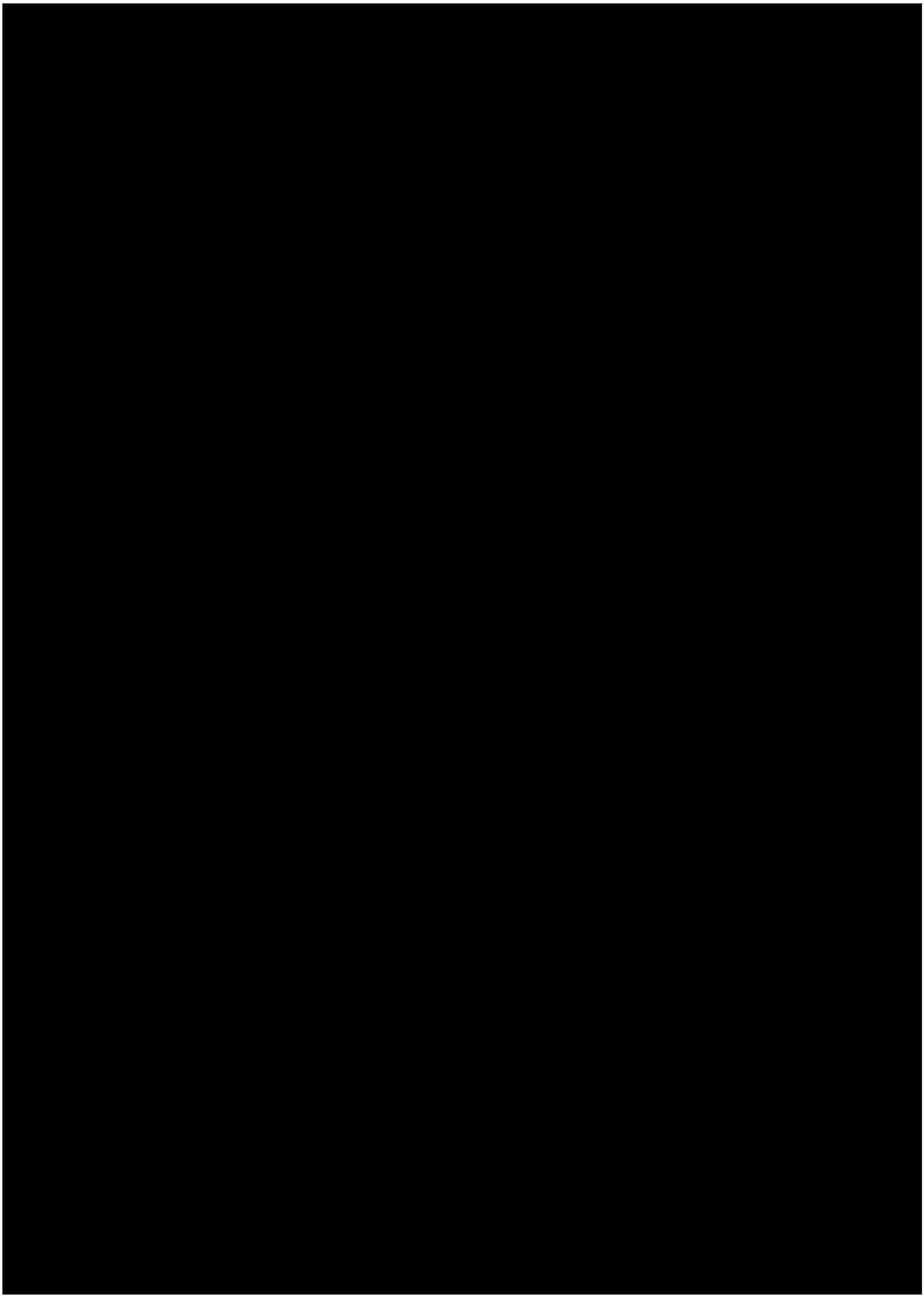
TABLE OF CONTENTS

ABBREVIATIONS

ACR	American College of Rheumatology
[redacted]	[redacted]
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANA	Antinuclear Antibody
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
AZA	Azathioprine
BI	Boehringer Ingelheim
CA	Competent Authority
CD	Cluster of Differentiation
[redacted]	[redacted]
CI	Confidence Interval
CK	Creatinine Kinase
[redacted]	[redacted]
CTM	Clinical Trial Manager
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CRR	Complete renal Response
CTCAE	Common Terminology Criteria for Adverse Events
CYC	Cyclophosphamide
DBL	Database Lock
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
dsDNA	double strand DeoxyriboNucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylendiaminetetraacetic acid
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
ESR	Erythrocyte sedimentation rate
ESRD	End Stage Renal Disease
EudraCT	European Clinical Trials Database
FACIT-F	Functional Assessment Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FC	Flow Chart
FUp	Follow Up
GC	Glucocorticoids
GCP	Good Clinical Practice

HA	Health Authorities
HPF	High Power Field
HRQoL	Health Related Quality of Life
HV	Healthy Volunteer
IB	Investigator's Brochure
IC	Inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ISN/RPS	International Society of Nephrology / Renal Pathology Society
ITP	Immune thrombocytopenia
ITT	Intention To Treat
i.v.	intravenous
LN	Lupus Nephritis
LPDD	Last Patient Drug Discontinuation
LupusPRO	Lupus patient-reported outcome
MCP1	Monocyte Chemoattractant Protein-1
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMF	Mycophenolate mofetil
MRD	Multiple Rising Dose
MRR	Major Renal Response
MTX	Methotrexate
[redacted]	[redacted]
NOAEL	No Observed Adverse Effect Level
[redacted]	
OPU	Operative Unit
[redacted]	[redacted]
PRR	Partial Renal Response
q1w	Once a week
q2w	Every 2 weeks
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
REP	Residual Effect Period
RNA	Ribonucleic Acid
RO	Receptor Occupancy
SAE.	Serious Adverse Event
s.c	subcutaneous
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SLE	Systemic Lupus Erythematosus
SLEDAI	SLE Disease Activity Index
SOC	Standard of Care
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SRD	Single Rising Dose

SUSAR	Suspected Unexpected Serious Adverse Reaction
CTL	Clinical Trial Leader
TDMAP	Trial Data Management and Analysis Plan
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
UP/UC	Urine protein/urine creatinine (ratio in mg/mg)
WBC	White Blood Cell



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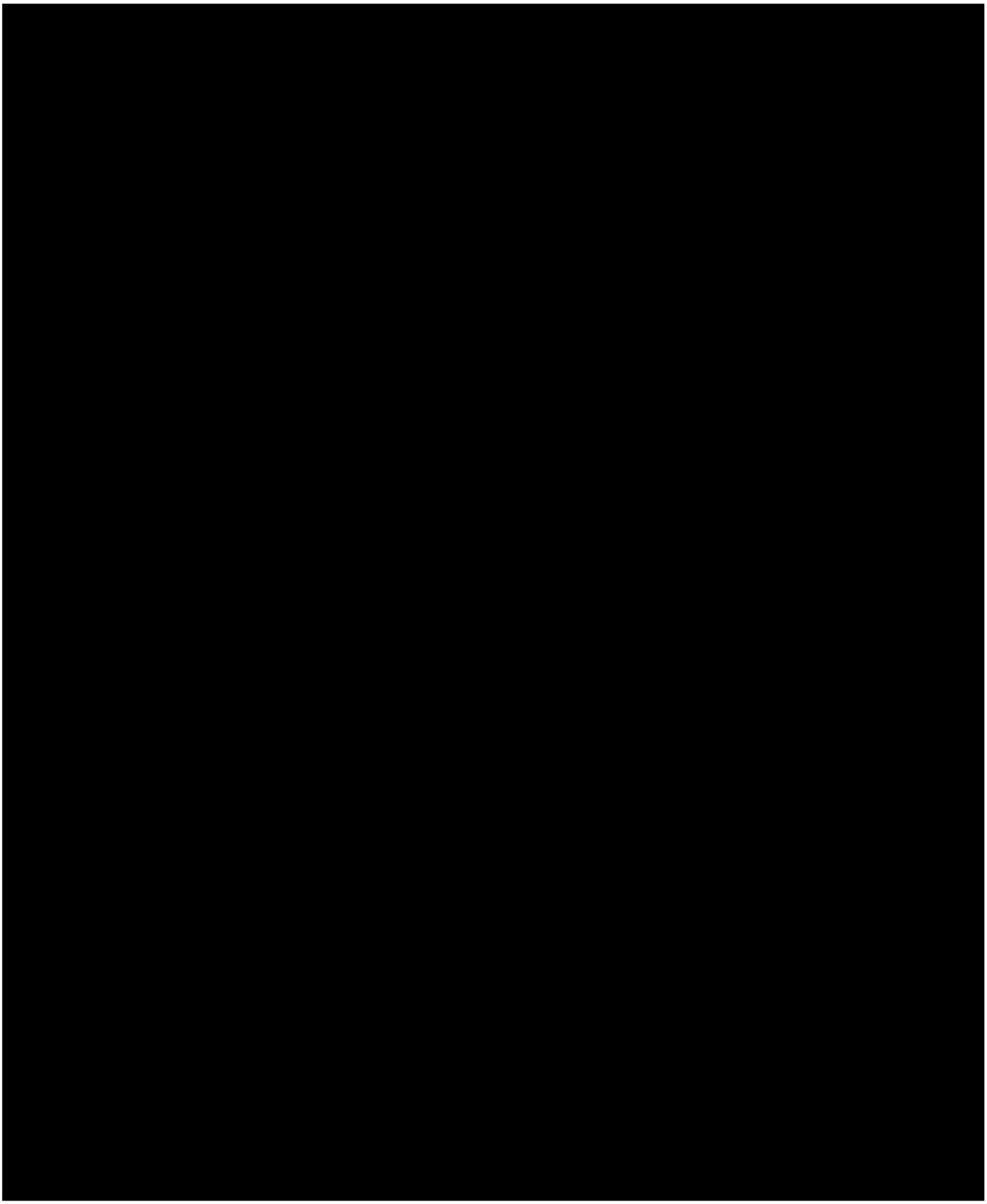


1.3 RATIONALE FOR PERFORMING THE TRIAL

Patients with LN class III-V are at high risk for irreversible kidney damage leading to ESRD, dialysis and death. Although not yet approved in most countries for the treatment of LN, the combination of either CYC or MMF with glucocorticoids is considered as current standard of care (SOC) for induction therapy in LN. The current SOC for maintenance therapy is a combination of low dose MMF or azathioprine (AZA) with low dose glucocorticoids. However, only 20-30% of LN patients treated with induction therapy achieved a complete renal response (CRR) within 1 year and another 20-30% with a partial renal response (PRR). Patients with a CRR, or PRR with proteinuria <0.8 g/d at 1 year after the start of induction therapy have the best long term prognosis (R15-4294). Therefore, the target for longer treatment of LN is to reduce proteinuria to <0.8 g/d. With the current maintenance therapy, there is a relevant risk of relapsing which justifies long-term maintenance therapy (R15-3724).

Furthermore, a large number of patients who achieved a renal response by induction therapy still require treatment with steroids at doses >5 mg/d. The European Medicines Agency (EMA) guideline recommends at least one year maintenance treatment after completion of induction therapy for LN (R15-3716). As a result, steroid-related side effects are frequently

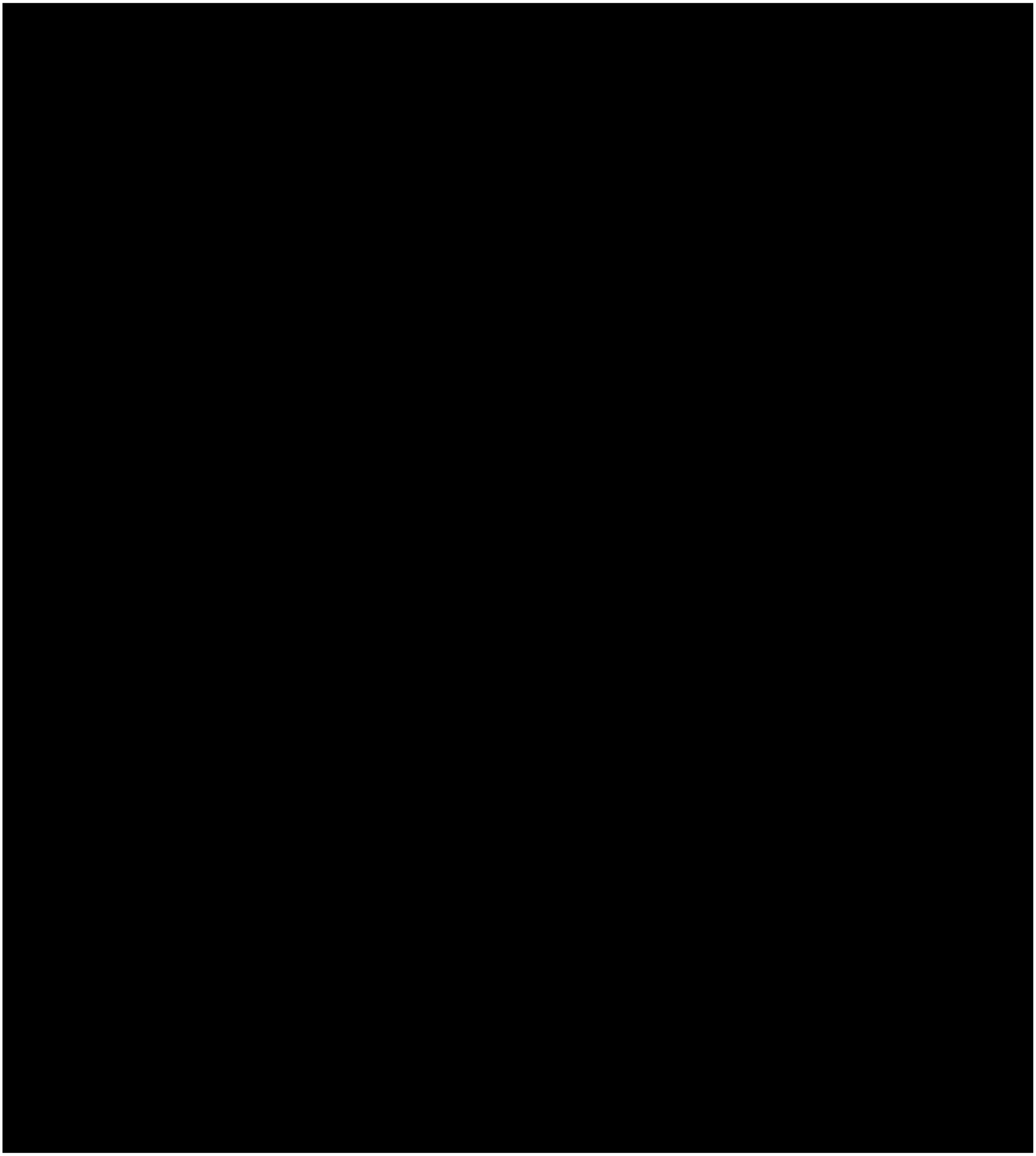
observed in LN patients, therefore reducing steroid dosage is a critical target in maintenance therapy for LN (P15-01916).

In addition, both immunosuppressants used for maintenance therapy of LN have associated side-effects, s.a. gastrointestinal related side effects and leucocytopenia for both MMF and AZA; amenorrhoea for MMF and liver damage for AZA. Thus, alternative immunosuppressant with a better safety and efficacy profile for LN maintenance therapy with the aim to reduce steroid doses should be explored.

Blocking the CD40-CD40L pathways will impact multiple mechanisms which involved in pathology of LN by inhibiting B-cell and T-cell responses as well as directly influence the inflammation in the kidney by decreasing CD40L induced MCP1 secretion of endothelial cells, mesangial cells and CD40L induced IL-6 secretion by proximal tubular epithelial cells. Therefore, targeting the CD40-CD40L pathway is considered a potential effective approach for the treatment of this disease.

The therapeutic benefit or specific adverse events in patients cannot always be anticipated during the trial setup. Later on there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug. In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking. If the patient agrees, banked samples may be used for future drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event, and thereby better match patients with therapies.

[redacted]



2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to evaluate the long-term efficacy and safety of different doses of BI 655064 versus placebo as add-on therapy to SOC during maintenance therapy for lupus nephritis. Since patients are randomized at the start of 1293.10 and on the same treatment in 1293-0013, the baseline of trial 1293.10 will be used as baseline for all assessments of change from baseline if not specified otherwise.

2.1.2 Primary endpoint

The primary endpoint is the proportion of patients with complete renal reponse (CRR) and without any renal flares at week 52.

2.1.3 Secondary endpoints

- Proportion of patients with CRR at week 52
- 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 confirmed CRR (defined as CRR at both week 42 and week 52 using UP/UC from spot urine)
- Change from baseline in SLEDAI at weeks 12, 26, 42 and 52.

Safety endpoints:

- Physical examination
- Vital signs
- Safety laboratory tests
- Electrocardiogram
- Adverse events (including drug-related AEs)
- Adverse events of special interest (AESI)
- Serious adverse events

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

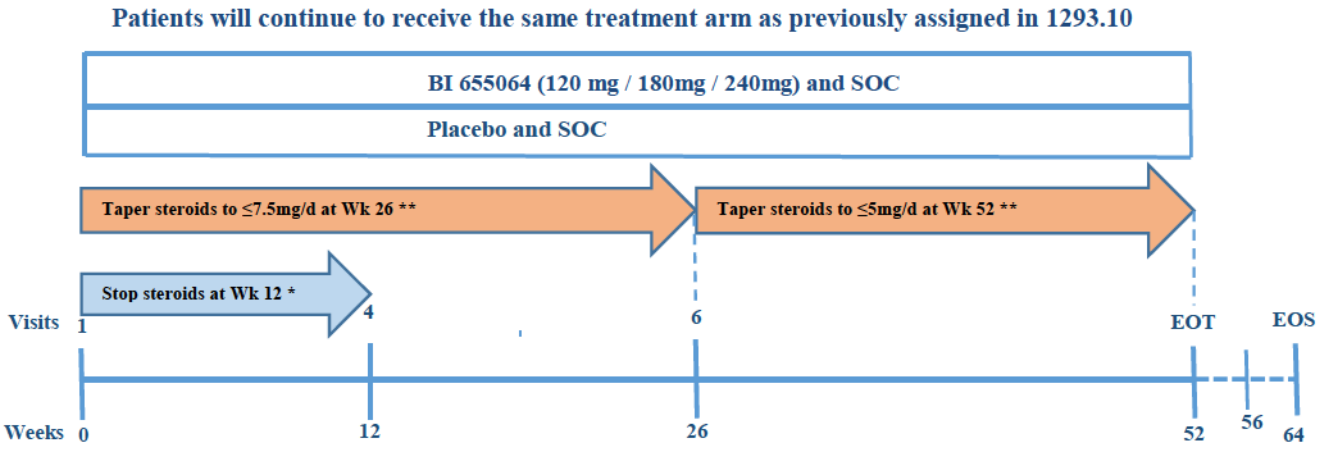
3.1 OVERALL TRIAL DESIGN AND PLAN

This is a phase II, double-blind, parallel-design, dose-ranging, placebo-controlled, exploratory maintenance trial. The trial is designed to evaluate the long term efficacy and safety of different doses of BI 655064 in patients with LN; and to study the effect of steroid tapering and steroid withdrawal during 52 weeks of maintenance treatment.

This trial is had been planned to include up to two groups of patients:
- Group 1 are roll-over patients that have achieved either a CRR or a PRR or proteinuria ≤1.0 g/d (or UP/UC ≤ 1) at the end of 1293.10.
- Group 2 was not started as the predefined criteria to start the group was not met (cf. Ch 1.2)

In addition to receiving either BI 655064 or placebo, all entered patients will continue to receive SOC treatment, and steroids tapering will be performed. Refer to Figure 3.1:1 below and section 4.2.1 for more information. This trial consists, and of a 52-week treatment period; followed by safety assessments at FUp and EOS visits (Flow Charts). The primary analysis will be performed in all treated patients to assess the proportion of patients with CRR after 52 weeks of treatment and without any renal flares.

Study Design: Patients from 1293.10 (Group 1)



* For patients with CRR or proteinuria <0.8g/d: steroids tapering should start immediately at Visit 1 and steroids should be stopped at Week 12.
** For patients with proteinuria ≥0.8g/d: steroids should be tapered down to ≤7.5mg/d at Week 26 and then to ≤5mg/d at Week 52.

Figure 3.1:1 Outline of trial design – Group 1

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

The design of this trial together with the 1293.10 (dose-finding, efficacy and safety of BI 655064 in patients with active LN) is intended to facilitate the selection of appropriate dose regimens for further confirmation in the Phase III trials.

The treatment duration of 52 weeks was selected based on feedback from external experts and recommendation in the currently available EMA guideline for at least one year maintenance treatment following induction therapy for LN (R15-3716).

Group 1 are patients that have achieved a renal response or proteinuria ≤1.0 g/d (or UP/UC ≤1) at the end of 1293.10; it is therefore justifiable for these patients to continue receiving the same treatment arm as previously assigned in 1293.10 during the maintenance phase. This is to ensure both patients and investigators remain blinded in order to allow comparisons of efficacy and safety of different doses in a population that appears to be able to safely receive the same dose as in the 1293.10 induction study. The patients will continue to receive one injection per week at Visit 1 of either BI 655064 (120mg/180mg/) or Placebo for up to 52 weeks (12 months). Patients on 240mg receive one injection of 120mg every week.

After topline data from trial 1293.10 became available, an independent DMC reviewed these topline data and unblinded safety and efficacy data of Group 1 patients in trial 1293-0013. The DMC recommended to continue trial 1293-0013 as planned.

The Boehringer Ingelheim Benefit Risk Committee (BRC) assessed the benefit-risk of BI 655064 for patients in Group 1 of trial 1293 13 (responders from trial 1293.10). The BRC took into consideration the recommendation to continue the trial given by the DMC and concluded that the benefit-risk for patients in Group 1 of trial 12930013 is unchanged for responders but decided that investigators should be informed about topline data and should receive treatment information for those patients remaining in Group 1 of trials 1293-0013. The investigator and the patient should thoroughly discuss treatment options and the patient's continuing participation in 1293-0013. Following this decision, a total of 29 patients (20 on treatment, 9 in follow-up) were unblinded.

As the majority of efficacy endpoints are based on laboratory parameters (serum creatinine, urine protein and urine creatinine) which should not be influenced by the knowledge of the treatment, the unblinded patients will be analyzed. Further details on analysis will be provided in the Trial Statistical Analysis Plan.

It was planned to initiate a second patient group depending on the final analysis of 1293.10, however as the primary endpoint in trial 1293.10 was not met, it was decided not to proceed with group 2. Therefore, all sections in the clinical trial protocol referring to group 2 were deleted.

Based on literature, patients who reached CRR have a good long term prognosis on renal outcome thus reducing steroid dosage is a major target to reduce side effects (R15-4294). Patients with proteinuria <0.8 g/d will also have a good long term prognosis (R15-4920); it is therefore justifiable to also start steroid tapering in these patients. Tapering of steroids may

increase the risk of renal flares and this risk might even be higher in those patients on Placebo. For steroid-related side effects, except effects on bone, a dose of 7.5 mg/d prednisone-equivalent is looked upon as threshold. For steroid-related effects on bone, it is arguable that even a dose <7.5 mg/d will have an effect if administered for a long period. Therefore, steroids should be tapered to as low as possible and ideally should be stopped.

In addition, once the 1293.10 trial results are available, BI 655064 doses might potentially be adjusted during 1293-0013 trial period and treatment arms might be modified accordingly via an amendment.

The primary endpoint selected for this trial is the proportion of patients with CRR after one year of maintenance treatment without any renal flares. The trial analysis will be exploratory. Patients with CRR and with steroids dose of ≤ 5mg/d prednisone equivalent after one year of maintenance treatment will be considered to have an optimal prognosis as these patients will have higher chance for a good long term renal outcome and a reduced risk of steroid-related side effects (R15-3157).

3.3 SELECTION OF TRIAL POPULATION

This extension trial is designed to offer continuous treatment to all eligible patients rolling over from 1293.10 (Group 1).

It is estimated that approximately 60 patients from 1293.10 will roll over into this multinational trial.

All sites rolling over patients from participating in the former trial, 1293.10, will be eligible to continue their participation in this study.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with the investigational drug or not.

3.3.1 Main diagnosis for trial entry

Patients with lupus nephritis who have achieved a renal response or reached a pre-defined proteinuria level; and met all eligibility criteria may qualify for inclusion in the trial.
Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

1. Male or female patients.
   - Women of childbearing potential* must be ready and able to use two reliable methods of birth control simultaneously, one of which must be highly effective. Highly effective birth control per ICH M3(R2) is a method that result in a low failure rate of less than 1% per year when used consistently and correctly. The reliable methods of birth control must be used before starting MMF/AZA and the trial drug; then continue during the trial

period; and for at least 50 days after the last dose of MMF and trial medication. In case a female patient is treated with AZA the contraception shall continue for 90 days after treatment with AZA. A list of contraception methods meeting these criteria is provided in the patient information.
- Sexually active men must be ready to use condoms ** during treatment with MMF/AZA and for at least 90 days after cessation of MMF/AZA.

* A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile.
- Permanent sterilisation methods include hysterectomy, bilateral oophorectomy and bilateral salpingectomy.
- Tubal ligation is NOT a method of permanent sterilisation.
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

** Condoms are applied for both reproductively competent and vasectomised men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients treated with MMF are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of MMF.

Definition of highly effective contraceptives:

- The use of hormonal methods of contraception associated with inhibition of ovulation (either combined oestrogen and progestogen containing hormonal contraception, or progestogen-only hormonal contraception)
- Placement of intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised sexual partner
- Complete sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

<u>For Group 1 patients only:</u>

3. Achieved either a CRR or a PRR or proteinuria ≤ 1g/d (or UP/UC ≤ 1) at the end of 1293.10.

3.3.3 Exclusion criteria

1. Evidence of current or previous clinically significant diseases or medical conditions other than lupus, or findings of the medical examination (including vital signs and ECG) that, in the opinion of the investigator, would compromise the safety of the patient or the quality of the data. This criterion provides an opportunity for the investigator to exclude patients based on clinical judgment, even if other eligibility criteria are satisfied.
2. Significant central nervous system symptoms related to SLE based on investigators assessment.

3. Clinically important acute or chronic infections including but not limited to HIV, hepatitis B or C.
4. Impaired hepatic function defined as serum AST/ALT, bilirubin or alkaline phosphatase > 2 x ULN.
5. Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2 at screening (using CKD-EPI formula).
6. Known hypersensitivity to any constituents of the trial medication; and/or contraindications to MMF or AZA or glucocorticoids.
7. The use of any restricted medications (see section 4.2.3.1) or any drug considered likely to interfere with the safe conduct of the trial.
8. Unable to comply with the protocol in the investigator's opinion.
9. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial.
10. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see sections 3.3.4.1 and 3.3.4.2 below.
Every effort should be made to keep patients in the trial if possible, on treatment or at least to collect important trial data. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements as well as the explanation of the safety follow up after a potential withdrawal.
It should be avoided that withdrawn patients would become lost to follow up, therefore safety visits or at least phone calls shall be conducted until 52 weeks after study start (V1 for group1 and V2 for group 2). See also 6.2.3.3.

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication (see section 4.2).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient develops an anaphylactic reaction (see section 4.2.2).
- In case of worsening or flare, if deemed appropriate by the investigator, the patient will be discontinued from the trial treatment to receive rescue therapy as per the available guidelines for the treatment of LN.

- The patient experiences an infection with SARS-CoV-2 (as confirmed by local PCR test). The patient may resume trial treatment following recovery from SARS-CoV-2 infection if a negative test for SARS-CoV2 was taken and the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor.

Please note that withdrawal from trial treatment should not necessarily lead to withdrawal from the study. Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Charts and section 6.2.3.

For all patients, the decision to withdraw from trial treatment (e.g. adverse events) or from the whole trial as well as the reason must be documented in the patient files and recorded in the eCRF. These data will be included in the trial database and reported.

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision. This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore, it may mean that further patient follow-up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent to trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk assessment that could significantly affect the continuation of the trial.
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
4. The sponsor decides to discontinue further development of BI 655064.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The trial medication will be provided by Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany.

4.1.1 Identity of the Investigational Medicinal Products

Details of the trial medication are provided below.

Table 4.1.1: 1 Investigational Medicinal Product 1

Substance:	BI 655064
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	120mg/pre-filled syringe and 180mg/pre-filled syringe
Posology	Group 1 patients: 1 injection per week.
Route of administration:	s.c.

Table 4.1.1: 2 Investigational Medicinal Product 2

Substance:	Placebo
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer-Ingelheim Pharma GmbH & Co. KG
Unit strength:	Placebo to match 120mg BI 655064 Placebo to match 180mg BI 655064
Posology:	Group 1 patients: 1 injection per week.
Route of administration:	s.c.

4.1.2 Selection of doses in the trial

The different doses of BI 655064 used in the induction trial, 1293.10, were selected based on the results of preclinical studies, the 1293.1 Caucasian SRD study, 1293.8 Asian SRD study and 1293.2 MRD study as well as the results from modelling of exposure in chronic treatment of LN. Treatment with BI 655064 has been well tolerated with no dose-dependent safety concerns identified so far (see section 1.3). Refer to the Investigator's Brochure (U11-1925) and section 4.1.3 below for further information on dosing in 1293-0013 trial.

4.1.3 Method of assigning patients to treatment groups

Group 1 patients will continue to receive the same treatment allocation as previously assigned in the 1293.10 trial (i.e., either 120mg or 180mg or 240mg or Placebo) at Visit 1.

The assignment will occur in a blinded fashion via Interactive Response Technology (IRT). Details regarding the use of IRT are described in the site IRT user manual available in the ISF.

4.1.4 Drug assignment and administration of doses for each patient

Each pre-filled syringe of trial medication will be labelled with the trial code and a unique medication identification number. At each applicable visit where trial medication is to be prescribed, the trial sites will be required to complete the medication (re)supply module in IRT. The IRT will then adequately assign enough medication kits for the weekly s.c injections administered by the patient at home until the next onsite visit.

BI 655064 / Placebo will be provided in sterile, preservative-free, non-pyrogenic, single-use pre-filled glass syringes for subcutaneous injection. Any unused product or waste material will be disposed of in accordance with local requirements.

The first dose of trial medication will be administered at the trial site for all eligible patients by the investigator (or a suitably qualified designee).

All subsequent doses shall be done by self-injection at the patient's home.
For group 1 patients is it acceptable to do the first study drug administration at home, as it is not considered to be a safety or compliance issue because these patients have injected themselves in the previous trial for one year already

After proper training on the administration technique for self-injection and if the investigator determines that it is appropriate with medical follow-up as necessary, the patients will be instructed to self-inject the trial medication at home in between onsite visits on the same day of each week (+/- 1 day). Further information on self-injection technique and instructions for use will be available in the ISF for providing to patients.
In case of missed dose, the patient should immediately contact the study investigator for guidance on further dosing.

Table 4.1.4: 1 Dosage and treatment schedule for patients in Groups 1 and 2

Patient Group	Treatment arm & Dose regimen	BI 655064 120mg	BI 655064 180mg	BI 655064 240mg	Placebo
Group 1	Baseline to EOT	**120mg q2w**	**180mg q2w**	**120mg q1w**	**Placebo**
	Syringes to be administered weekly	1 x 120mg BI 655064 syringe alternating with 1 x Placebo syringe	1 x 180mg BI 655064 syringe alternating with 1 x Placebo syringe	1 x 120mg BI 655064 syringe	1 x Placebo syringe

Dose modification is not permitted during the treatment period. In addition, dilution of the trial medication or the use of other syringes or other needles than those specifically provided by the sponsor is prohibited.

Group1 patients only: In case a patient cannot be rolled over (only for administrative issues) within the timeframe defined in section 6.2.1, but for ethical reasons the patient shall still be given the chance to continue into 1293-0013, approval must be obtain from CTL/TMM. It will be decided on a case by case basis how to overcome the prolonged treatment interruption between the trials, which may include changing the order in which the initial injections are given to the patient or which may include adding a loading dose at the beginning of the trial.

During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations (for more details see section 6.2.2).

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In this double-blind trial, all patients, investigators and sponsor staff (except those BI members independent of the trial team that will perform the primary analysis) will remain blinded with regard to the randomised treatment assignments.

After the final analysis of the preceeding trial 1293.10 it was revealed that the primary endpoint was not reached. An independent DMC reviewed the topline results of 1293.10 and unblinded efficacy and safety results of the ongoing Group 1 in trial 1293-0013 and recommended to continue trial 1293.0013. Taking this recommendation into consideration, a Benefit Risk Committee concluded that the benefit-risk for patients in Group 1 of trial 1293-0013 is unchanged but decided that treatment of patients remaining in the trial should be unblinded.
The unblinding step was taken on 20 Oct 2020 and communicated to the applicable investigators. All other patients who had already completed or early discontinued the trial at that timepoint and were no longer in follow up remain blinded.

For the remaining patients who were not unblinded, a limited number of sponsor personnel will have the potential to be unblinded a limited number of sponsor personnel will have the potential to be unblinded; however, sponsor personnel involved in the conduct of 1293-0013 (e.g.trial monitor and local monitors) will remain blinded until completion of 1293-0013. These investigators and patients will also remain blinded until completion of the trial.

For Group 1 IRT will used in 1293.10 for the assignment of patients to treatment groups and the randomisation sequence generated using validated software and verified by an independent BI statistician who is was not involved in the planning or performance of the trial. The randomisation code will be kept confidential by Clinical Trial Support up to DBL. For Group 1.

The randomisation codes will be provided to bioanalytics prior to last patient out to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo patients. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise to assure the safety of trial participants. The reason for unblinding must be documented in the source documents and/or on appropriate eCRF page along with the date and the initials of the person who broke the code; and the Sponsor must be informed immediately.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

4.1.6 Packaging, labelling, and re-supply

BI 655064 and Placebo supplies will be provided by BI or a designated CRO. Each prefilled syringe of trial medication will be packaged in individual carton and labelled in accordance with the principles of Good Manufacturing Practice. Refer to the ISF for details of packaging and description of the label.

Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of trial medication supplies available at the sites.

4.1.7 Storage conditions

Each prefilled syringe will be kept in its original packaging until administration in order to protect from light and stored according to the recommended storage conditions on the medication label at 2-8°C (36-46°F). It cannot be frozen. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor must be contacted immediately. For temperature deviations during shipping to sites and depots, refer to the ISF for instructions.

4.1.8 Drug accountability

The investigator, pharmacist, or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee,

- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator if applicable,
- Availability of FDA Form 1572 (for USA only).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator, pharmacist, or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The investigator / pharmacist / investigational drug storage manager will maintain records document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Standard of care (SOC) treatment

All patients will continue to receive SOC treatment for LN of either MMF or AZA in combination with glucocorticoids (if not tapered down to 0mg).

It is acceptable to switch a patient from mycophenolate mofetil to mycophenolate sodium as long as the dose is documented as to mycophenolate mofetil equivalent in the CRF. For simplicity reasons the entire protocol refers to MMF only.

The SOC treatment (MMF and/or AZA) will be procured locally and prescribed at the trial site by the investigator. The sponsor will reimburse the costs for SOC treatment during the trial period in accordance with local regulations.

- MMF and AZA will be considered auxiliary medicinal product (AMP) in this trial.MMF: a stable dose of 1 to 2 g/d. It is recommended not to increase MMF above 2g/d to reduce the risk of MMF related severe side effects. In case of side effects, MMF dose may be reduced to 1g/d; or in case of intolerance, switch to AZA at 2mg/kg/day.

- Patients deviating from the above mentioned dose ranges shall be pre-approved by the CTL/TMM whether they can be enrolled in the trial or not.
- Patients on less than 1g/d MMF before entering the trial may be eligible, if it is documented that the patient did not tolerate higher doses.
- Patients on more than 2g/d MMF before entering the trial may be eligible only if the patient did not suffer from any side effects considered possibly related to MMF in the past.

- AZA: 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.
- Glucocorticoids: At Visit 1 recommended ≤ 10mg/d prednisone-equivalent for group 1 patients (depending on actual dose at the end of 1293.10). The tapering of steroids should be performed as follows:

  ➢ Group 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 roll over. If this is 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.

In case of worsening or renal flare occurs at any time point, patients will be allowed treatment with higher dose of steroids; alternatively, the investigator may allow patients to receive rescue therapy in according to the available guidelines for LN treatment. For the study analysis, these patients will be considered treatment failures.
However, in any case, deviating from the tapering scheme due to medical reasons will not exclude the patient from the trial.

<u>Adjunctive treatments</u>

All patients should continue taking adjunctive treatments if started before screening such as:

- Hydroxychloroquine at 200 – 400 mg/day or other anti-malarial (such as chloroquine).
- Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker,
- Sstatins.

It is recommended that patients to remain on stable doses for these treatments during the duration of the study.

There are no special emergency procedures to be followed.

4.2.2 Management of Adverse Events

In case of emergency surgery or if patient develops a serious infection, opportunistic or mycobacterium tuberculosis infections treatment of the infection should be initiated promptly according to local standard of care, during the treatment period, treatment with BI 655064 and SOC will be temporarily interrupted and to be restarted once the patient has recovered as per the investigator's judgement. In addition, patients who develop recurrent infections should have their serum IgM and IgG measured according to investigator's assessment.

In case patient develops a thrombosis suspected to be related to immunosuppression during the treatment period, treatment with BI 655064 and SOC will be temporarily interrupted and anti-thrombotic therapy will be started. Treatment with BI 655064 and/or SOC may be restarted once the patient has recovered according to investigator's assessment.

In case of suspected hepatic injury (as defined in section 5.2.5.1) during the treatment period, treatment with BI 655064 has to be stopped. If the follow–up identifies a confounder (e.g. high dose of paracetamol) and the liver function has recovered, treatment with BI 655064 may be restarted according to the investigator's assessment after discussion with the sponsor.

In case of severe injection reactions, anaphylactic reactions, cytokine release syndrome, or occurrence of lymphoproliferative diseases, treatment with BI 655064 and SOC will be permanently discontinued and must not be re-introduced.

For side effects known to be related to higher doses of MMF or AZA, dose reduction of MMF or AZA should be considered and handled as per the investigator's judgement.

Malignancies
In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with BI655064. Diagnostics and treatment have to be initiated according to local standard of care.

-in case a patient develops neutropenia (< 1000 cells/µl) confirmed by a second measurement consider to reduce or suspend MMF, in case the neutropenia worsens

- In case of emergency surgery during treatment in the study, treatment with BI 655064 and MMF (respectively azathioprine) will be interrupted. Treatment with BI 655064 and SOC will be restarted when the patient has recovered according to investigator's assessment.

- In case of severe injection reactions, anaphylactic reactions or cytokine release syndrome, treatment with BI 655064 and SOC has to be stopped and must not be introduced again.

- In case of occurrence of lymphoproliferative diseases, treatment with BI 655064 and SOC has to be stopped and must not be introduced again.

4.2.3 Restrictions

4.2.3.1 Restrictions regarding concomitant treatment

Concomitant medications (or therapy) to provide adequate care may be given as clinically necessary. If a restricted concomitant therapy is required, treatment with trial medication should be permanently discontinued.

Table 4.2.3.1:1 Permitted and restricted medications

Therapy	Treatment Period	Follow up Period
MMF	Permitted if dose ≤1-2 g/d*	Permitted
Azathioprine	Permitted if dose ≤ 2 mg/kg	Permitted
Abatacept or Cyclophosphamide	Not permitted	Not Permitted
Cyclosporine / Tacrolimus / Mizoribine	Not permitted	Permitted if required as per investigator's decision
Belimumab or other "anti- BLyS" or another investigational drug	Not permitted	Not permitted
Biologic B-cell depleting therapy (e.g. anti-CD20)	Not permitted	Not permitted
IV glucocorticoids	Not Permitted	Permitted

[1]: for group 1 patients, the doses for MMF and AZA are given in 1293.10 are acceptable to be continued throughout 1293-0013 as long as the patient otherwise qualifies for roll over.
*exception see section 4.2.1.

4.2.3.2 Restrictions on diet and lifestyle

Patients should not donate blood during MMF treatment and for at least 6 weeks after the last dose of MMF.

In addition, men should not donate semen during MMF/AZA treatment and for at least 90 days after the last dose of MMF/AZA.

During the trial, all patients should avoid intensive physical activity and unprotected exposure to direct sunlight. Intensive physical activity is an activity that is considered as a higher intensity than usually performed by the individual. The use of tanning booths is forbidden.

4.3 TREATMENT COMPLIANCE

Patients must take all doses of trial medication and SOC background therapy according to the trial protocol unless medically indicated. Any temporary interruption should be discussed with the Sponsor and all patients are to be advised of the importance in adhering to the dosing schedule.

Each patient will be provided with a medication bag to store unused and empty cartons of trial medication and a sharp bin to store all used syringes. Patients are requested to bring all remaining trial medication including empty cartons with them when attending onsite visits for compliance checks. At the EOT visit, patients must return the sharp bin to the trial site for disposal in accordance with local requirements.

At each onsite visit, a compliance check of the trial medication will be performed to ensure the weekly injections are being administered correctly at both the trial site and by the patient at home. In case of non-compliance, the site staff will explain to patient the importance of treatment compliance and retrain patient on the injection technique for self-administration at home.

In addition, MMFdosing level will also be checked at the time points indicated in the Flow Charts to assess compliance. The last two intakes dates and time of MMF taken before the blood sampling will be recorded in eCRF, based on patient's interview.

Any discrepancies should be documented and explained in the eCRF by the investigator or the designee. Patients will also be provided with an e-diary to record the intake of trial medication and SOC background therapy.
The ediary is considered to be the primary tool for collecting compliance information to the trial medication.
Patients will be asked to enter date and time of injection as well as the kit number of any dose taken. If a dose was not injected the kit shall still be recorded in the ediary
SOC medication is tracked by responding whether the daily medication was taken.
In case the patient did not enter a dose in the ediary, the injection shall be entered in the eCRF by the site staff. Proper source documentation will be required for this data entry.
Every kit of investigational product dispensed to a patient should be accounted for (injected or not injected).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Assessment of renal response

For primary, secondary and further efficacy endpoints assessed at baseline and at week 52, the 24hr urine collections will be performed in duplicate (2 x 24hr collection). A detailed description for 24hr urine collection will be provided in the laboratory manual and further instructions will be provided to the patients. For other time points, proteinuria will be assessed by spot urine.

Complete and partial renal responses are defined as follows:

- Complete renal response (CRR) is defined as Uprot <0.5 g/day and **either** eGFR within normal range or decrease in eGFR < 20% from baseline if below normal range.
- Partial renal response (PRR) is defined as 50% reduction of proteinuria from baseline and **either** eGFR within normal range or decrease in eGFR < 20% from baseline if below normal range.

An alternative way to calculate CRR and PRR will be to use UP/UC from 24hr urine collections, which could compensate for incomplete urine collections. The decisions which calculation approach is selected for the primary endpoint will be based on review of blinded data before finalization of the TSAP.

A renal flare is defined as follows:

- If proteinuria ≤ 0.5 g/d at baseline: if increase to > 1g/d (or UP/UC >1) at anytime during the treatment period as confirmed by a repeat test within 2 weeks and if worsening of proteinuria cannot be explained by any other reasons
  Or
- If proteinuria > 0.5 g/d at baseline: if improving to ≤ 0.5 g/d (respectively UP/UC ≤ 0.5) during the treatment period in at least 2 consecutive visits but subsequently increase to > 1g/d (or UP/UC >1) as confirmed by a repeat test within 2 weeks and if worsening of proteinuria cannot be explained by any other reasons
  Or
- If proteinuria > 0.5 g/d at baseline: if increase to double (respectively UP/UC > 2x baseline) as confirmed by a repeat test within 2 weeks and if worsening of proteinuria cannot be explained by any other reasons
  Or
- Decrease in eGFR by >20% from baseline and eGFR < 90 ml/min as confirmed by a repeat test within 2 weeks and if worsening of eGFR can not be explained by any other reasons eg, infection or injury.

The primary endpoint is the proportion of patients with complete renal reponse (CRR) and without any renal flares at week 52.

5.1.2 Assessment of patient reported outcomes

Patients should complete all study questionnaires in the following order: LupusPRO, SF-36, FACIT-F at the trial site at each time point indicated in the Flow Charts in a quiet area/room prior to any assessments or treatments and, if possible, before any interactions with the investigator or any member of the study team. The trial site staff /investigator may record the study questionnaires on behalf of the patient only if the patient has difficulty in writing or unable to read. This must be clearly documented in the patient medical notes.

The questionnaires generally take about 5-10 minutes to complete. Refer to the ISF for a copy of the questionnaires. The SF-36 version 2 will be used in this trial.

5.1.3 Assessment of SLEDAI:

The SLEDAI assessment should take approximately 10 minutes to complete. The investigator will complete the SLEDAI assessments (version SELENA-SLEDAI) based on examination of the patient, their medical history including symptoms over the last 10 days and their laboratory results.

Laboratory tests may be considered for use in scoring the SLEDAI if they are drawn -10 to +7 days from the date of assessment and cannot be used to complete more than one assessment.

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Physical examination
- Vital signs
- Safety laboratory tests
- Electrocardiogram
- Adverse events (including drug-related AEs)
- Adverse events of special interest (AESI)
- Serious adverse events

5.2.1 Physical examination

Physical examinations will be performed at the time points specified in the flow charts. Complete physical examination will include general appearance, vital signs assessment and evaluation of organ systems (eyes, ears, nose, mouth, throat, neck and respiratory, cardiovascular, chest, gastrointestinal, lymphatic, musculoskeletal, skin, neurologic and psychiatric). Height (at screening only) and body weight will also be measured.

Targeted physical examination will include weight, vital sign assessment and evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

All abnormal findings at baseline will be recorded on the Medical History/Concomitant Diagnosis eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations will be recorded as adverse events on the appropriate eCRF page.

5.2.2 Vital signs

Vital signs evaluation includes temperature, pulse rate and systolic/diastolic blood pressure will be performed at the time points specified in the Flow Charts. Pulse rate and blood pressure will be measured after patients have been sitting comfortably for at least five minutes. Measurement of vital signs should precede blood sampling to avoid potential impact on vital measurements.

Any abnormal findings shall be evaluated by the investigator and confirmed whether they qualify to be documented as adverse event.

5.2.3 Safety and immunology laboratory parameters

The safety and immunology laboratory parameters to be assessed are listed in Table 5.2.3:1. Patients do not have to be fasted for the blood sampling. Refer to the flowcharts for blood sampling time points.

Table 5.2.3:1 Safety and immunology laboratory tests

Category	Test name	Frequency
Haematology	Haematocrit Haemoglobin Red Blood Cell Count / Erythrocytes White Blood Cells / Leukocytes Platelet Count / Thrombocytes	At every visit until EOT (inclusive), repeat after EOT only if clinically significant findings at the discretion of investigator.
	Erythrocyte sedimentation rate	Analysed locally at baseline, weeks 12, 26 and 52.
	Reticulocyte Count	At baseline, weeks 12, 26 and 52.
Diff. Automatic	Relative count: Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes	At every visit until EOT (inclusive), repeat after EOT only if clinically significant findings at the discretion of investigator.
Diff. Manual	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear Eosinophils, Basophils, Monocytes, Lymphocytes	Only if Diff. Automatic is abnormal (reflex test).

Table 5.2.3:1 Safety and immunology laboratory tests (Cont.)

Coagulation	Partial Thromboplastin Time Prothrombin time (Quick and INR)	At every visit until EOT (inclusive), repeat after EOT only if clinically significant findings at the discretion of investigator.
	Fibrinogen	At baseline, weeks 12, 26 and 52. Repeat after EOT only if clinically significant findings.
Enzymes	AST(GOT), ALT(GPT) Alkaline Phosphatase Creatine Kinase (CK) CK-MB (only if CK is elevated) Gamma-Glutamyl Transferase Lactate Dehydrogenase	At every visit until EOT (inclusive), repeat after EOT only if clinically significant findings at the discretion of investigator.
	Lipase, Amylase	At baseline, weeks 12, 26 and 52.
Electrolytes	Calcium, Sodium, Potassium, Chloride	At every visit until EOT (inclusive), repeat after EOT only if clinical significant findings at the discretion of investigator.
Substrates	Plasma Glucose, Creatinine and calculated Creatinine Clearance (CKD-EPI), Bilirubin Total, Bilirubin Direct and Indirect Albumin, Uric Acid, Urea Nitrogen	At every visit until EOT (inclusive), repeat after EOT only if clinically significant findings at the discretion of investigator.
	Cholesterol, triglycerides	At baseline, weeks 12, 26 and 52.
	hsC-Reactive Protein	At baseline, weeks 12, 26 and 52
	Haptoglobin	At baseline, weeks 12, 26 and 52
Serum Pregnancy test *	Human Serum Chorionic Gonadotropin	At screeningand anytime if urinary test is positive.
Urine Pregnancy test *	Human Chorionic Gonadotropin in the urine	At screening, baseline and then every 4 weeks thereafter.
Urinalysis - dipstick	Urine: Nitrite, Protein, Glucose, Ketone, Bilirubin, RBC/ Erythrocytes, WBC/ Leukocytes, pH, creatinine Urobilinogen	At every visit until EOT (inclusive), repeat after EOT only if clinically significant findings at the discretion of investigator.
Urine	Spot protein/creatinine ratio	At every visit for safety/efficacy measurement.

Table 5.2.3:1 Safety and immunology laboratory tests ° (Cont.)

Urine-Sediment (microscopic examination)	Urine: Sediment Bacteria, Cast in Sediment, Squamous Epithelial Cells, Sed. Crys., Unspecified, Sediment RBC/ Erythrocytes, Sediment WBC/ Leucocytes	At every visit or if urine analysis is abnormal according to investigator (reflex test).
Infections screening**	Hepatitis B Surface Antigen (qualitative) Hepatitis B core Antibody Hepatitis C Antibodies (qualitative) HIV-1 and HIV-2 Antibody (qualitative) QuantiFERON-TB Gold***	At screening only for group 2 patients. For group 1 patients only done if suspicion for an infection
Immunoglobulin	IgG, IgM	At baseline, weeks 12, 26 and 52.
Immunology testing	ANA Anti-phospholipid antibodies	At screening for Group 2 only. At baseline for Group 1 only For both groups:week 52.
	Anti-dsDNA,	At screening for Group 2 only. At baseline for Group 1 only For both groups: weeks 12, 26, 52 and EOS.
	Complements C3, C4, anti-C1q antibodies	At baseline for Group 1 and weeks 12, 26, 42(only complements C3 and 4), 52 and EOS.

° Baseline is referring to visit 1 of group 1-patients and visit 2 of group 2 patients. For group 1 patients any lab parameters for visit 1 are already taken during the end of treatment visit of clinical trial 1293-0010 and will not be repeated.

* Urine (dipstick) pregnancy test will be performed prior to study entry and then every 4 weeks in women of child bearing potential. If visit intervals are >4 weeks, dipsticks will be provided to patients to perform the pregnancy test at home. A serum pregnancy test will also be performed at Screening visit. Throughout the trial, if any dipstick test is positive or uncertain, a serum pregnancy test must be collected on the same day for confirmation. Only patients with a negative pregnancy test will be eligible and will continue with trial medication administration.

** Results of infections screening will not be captured in the sponsor's database. In case HB_C positive but HBs antigen negative then measure Hepatitis B DNA. If result positive, exclude patient; if result negative, patient can be included.

*** In case of an indeterminate result, test should be repeated; in case the result is indeterminate again, a PPD skin test should be performed.

[1] In case HBc positive but HBs antigen negative then measure Hepatitis B DNA: if positive exclude patient, if negative patient can be included.

If patient is positive for anti-HCV during the trial, the HCV-RNA test can be performed locally to exclude false positive results. If HCV-RNA test is negative, patient may continue (the result must be documented in eCRF).

All blood samples will be analysed at a designated central laboratory, and if necessary, by additional specialist laboratories, except erythrocyte sedimentation rate (ESR) which will be performed onsite or at a local accredited lab. The central laboratory will provide materials for

all blood sampling including ESR. Instructions for sample collection, handling, processing and shipping are provided in the Laboratory Manual in the ISF.

The central laboratory will send reports to the investigator and will transfer the results of the analysis to the sponsor. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (refer to Section 5.2.5); and should be repeated using an unscheduled visit lab kit until normalisation or stabilisation or until an alternative explanation has been established.

Mycophenolate blood levels will be collected at all timepoints indicated in the Flow Charts. Samples will be analysed for exploratory purposes after trial completion.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.5.1 and the DILI Checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

5.2.4 Electrocardiogram

The 12-lead ECGs will be recorded according to local standard procedures at the visits indicated in the Flow Charts. Automatically generated interval data (PR, QRS, QT) and heart rate on the printed ECG will be collected on the eCRF. QTcB and QTcF will be calculated with HR and QT interval.

Rate, rhythm and repolarisation changes have to be evaluated, compared to previous charts, and assessed for clinical relevance. Clinically relevant abnormal findings will be reported either as baseline conditions (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate. If necessary, additional ECGs may be repeated for quality or safety reasons and the repeated ECG will be used for analysis.

Dated and signed printouts of ECG with findings should be documented in patient's medical record.

5.2.5 Assessment of adverse events

5.2.5.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- results in death
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect, or
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

For Japan only: the following events will be handled as "deemed serious for any other reason". AEs which possibly lead to disability will be reported as SAEs.

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in Section 5.2.5.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

In accordance with the EMA initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the electronic data capture (eDC) system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class.

AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see above.

The following are considered as AESIs:

- Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided via the eDC system. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

➢ Injection reactions including anaphylactic reaction

Any suspicion of severe injection reaction and any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (R11-4890).

➢ Cytokine release syndrome

A cytokine release syndrome manifests when a large number of immune cells becomes activated and releases inflammatory cytokines. It is consistently associated with elevated TNFα, IFNγ, and IL-6 levels. The cytokine-release syndrome is clinically characterised by fever, chills, rigor and rash. Other symptoms are nausea, dyspnoea, tachycardia and hypotension. Potentially life-threatening complications of a cytokine release syndrome include cardiac dysfunction, respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. In case of suspicion of a cytokine release syndrome, it is recommended to measure IL-6 levels in the local laboratory if the assay is available.
In general therapy with BI 655064 is immunosuppressive and potentially could increase the risk for infections or lymphoproliferative diseases.

➢ Opportunistic infections and/or severe infections

Opportunistic infections include pneumocystis pneumonia, toxoplasmosa gondii encephalitis, cryptosporidiosis; microsporidiosis, mycobacterium tuberculosis, mycobacterium avium; bacterial respiratory disease, bacterial enteric infection, mucocutaneous candidiasis, invasive mycoses, CMV, EBV, herpes simplex (invasive only), varicella zoster, human herpesvirus 8, JC virus infection.
Any severe infection should also be reported as AESI.
Whenever a patient comes to a visit and reports of an (S)AE related to infections which occurred in the interval since the last visit, then he/she is routinely asked whether they have been seen/treated by a physician and whether blood samples had been taken in that context. Should this be answered in the affirmative then efforts should be undertaken to collect the respective information.

➢ Lymphoproliferative disorders (e.g. B- and T-cell lymphoma, Non-Hodgkin lymphoma and Hodgkin lymphoma, hepatosplenic T-cell lymphoma)

In case of adenopathy, hepato- or splenomegaly, fever of unclear origin, night sweats or loss of weight, occurrence of lymphoproliferative diseases should be evaluated. As the

occurrence of lymphoproliferative disorders is associated with active EBV-infection, patients suffering from active EBV infection should be carefully evaluated for the occurrence of lymphoproliferative diseases.

- Thrombosis and adjunct immunosuppression

Immunosuppression may favour a prothrombotic state. Therefore, patients should be carefully followed for early signs of peripheral or central thrombosis or thromboembolic events.

For countermeasures and management of the above mentioned Adverse Events please refer to section 4.2.2 of the protocol.

The specific therapy of the listed AESIs will be according to institutional standards.

Other adverse events

In case during the course of the trial a patient develops a neutropenia with a severity grade higher than 3, it is recommened to first decrease or stop MMF, then to check lab values and decide on the possible root cause of the neutropenia.

Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the eCRF according to the Rheumatology Common Terminology Criteria for Adverse Events (RCTC) Version 2.0 developed by [redacted] (R13-3515). Refer to the ISF for RCTC intensity/severity classification.
Intensity options are:

Grade 1	mild
Grade 2	moderate
Grade 3	severe
Grade 4	life-threatening

Causal relationship of AEs

Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).

- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.5.2 Adverse event collection and reporting

AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate eCRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of study:
  - All AEs (serious and non-serious) and all AESIs.
- Patients who discontinue trial medication prematurely and agree to be contacted further, should be followed up as described in section 3.3.4.1. From then on until the individual patient's end of the trial:
  - The investigator must report all deaths/fatal AEs regardless of relationship; related SAEs and related AESIs that the investigator becomes aware of.
- After the individual patient's end of study:
  - The investigator does not need to actively monitor the patient for AEs but should report related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the eCRF.

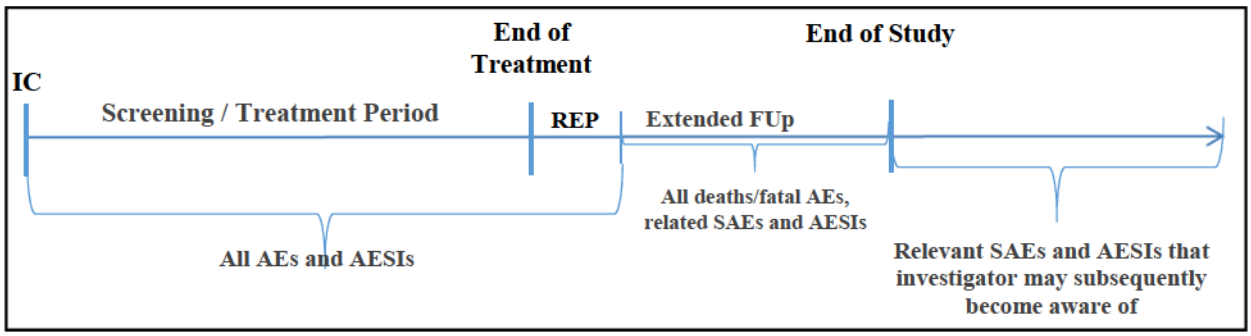


Figure 5.2.5.2: 1 AE Collection

The REP is defined as 50 days after the last trial drug administration. All AEs that occur during the treatment phase and throughout the REP will be considered as on treatment (see section 7.3.4). Events that occur after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication and any possible interactions between the trial medication and an Auxiliary Medicinal Product (AMP).

The following should also be recorded as an (S)AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only.

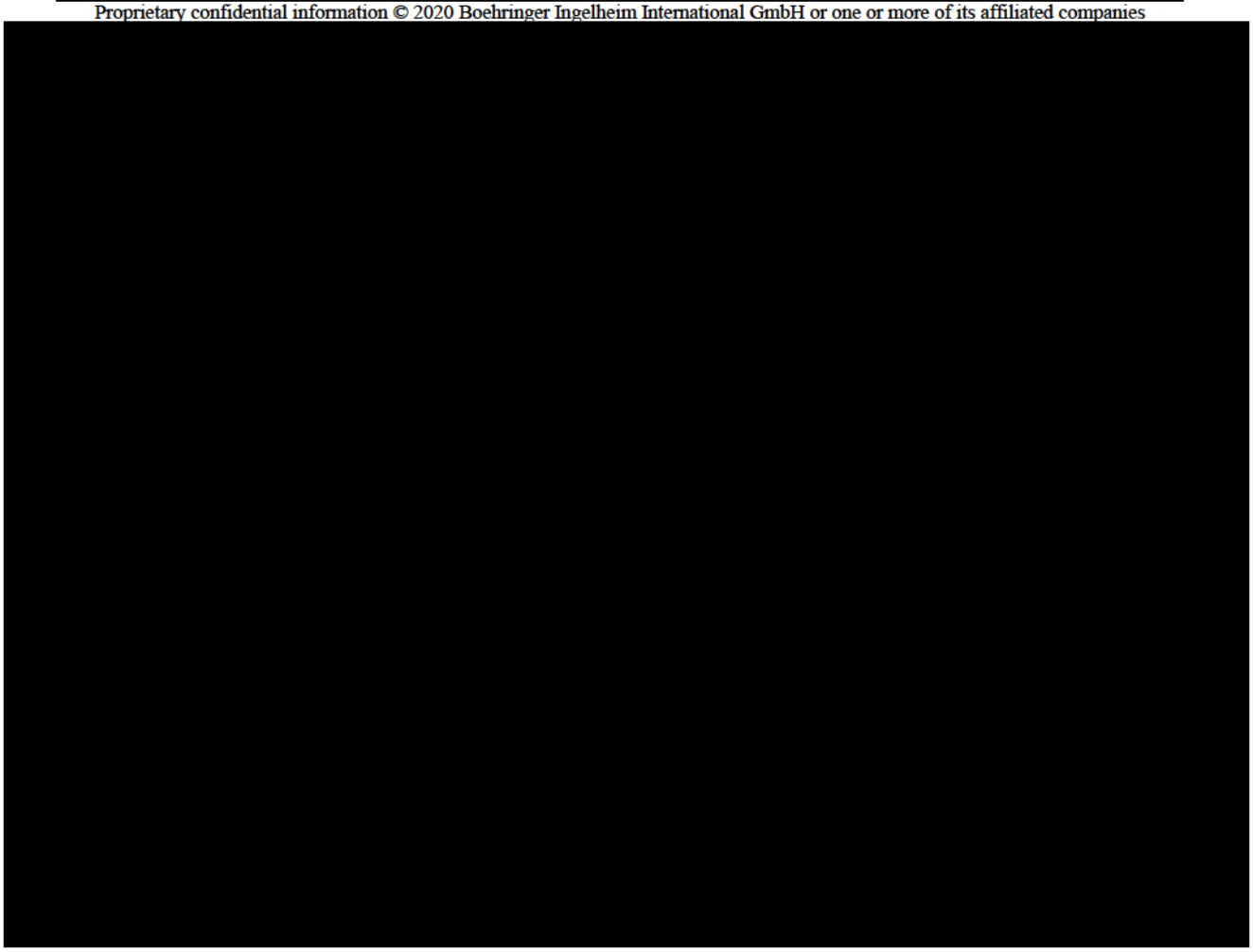
All (S)AEs, including those persisting after individual patient's end of study must be followed up until they have resolved, have been assessed as "chronic" or "stable" or no further information can be obtained.

Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point. Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Parts A and B) as well as information and consent form for the pregnant partner.

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



[redacted]

[redacted]

5.5 APPROPRIATENESS OF MEASUREMENTS

Standard methods will be used as measures conducted for both primary and secondary endpoints. Measures conducted for exploratory further endpoints might be new

methodologies that have already been used in clinical trials in LN but not yet validated for this rare disease. This includes measurements of patient reported outcomes e.g. Lupus Pro and Facit-F.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Charts. If any visit needs to be rescheduled outside of the protocol allowed window, approval must be obtained from the CTM/CTL and subsequent visits should follow the original visit schedule.

Additional unscheduled visits might be arranged at the discretion of the investigator (e.g, in case of relapses). For unscheduled visit, it is sufficient to record only the clinically relevant laboratory parameters and safety findings in the patients' medical records and on the adverse event eCRF. During or at the end of each visit, site must register the respective visit in IRT for each patient.

For a detailed overview of the trial procedures and the acceptable time windows for each visit, please refer to the Flow Charts.

In exceptional cases, if standard visits at the trial sites are impossible because of COVID-19 related safety risks or local restrictions, the following trial procedures may be performed remotely, e.g. via telephone and/or internet based means of communication, as locally allowed:

- Collection of information of existing or new adverse events
- Confirming current or new concomitant medication or dose changes
- SLE-disease state
- Compliance check, including study drug injections and the use of the ediary
- Outcome of home pregnancy test, if applicable

In addition the following alternatives to study procedures may be used

- Lab procedures: in case critical study visits such as week 12, 26, 42 and/or 52 cannot be done at the clinical site, the patient will be asked to have at least certain parameters (hematology, chemistry, urine tests, C3/C4 and Anti-dsDNA) tested in a local lab if possible. The results of the lab tests must be transferred to the investigator who ensures medical review and proper documentation in the eCRF.
- If a 24 hr urine sample will be required per protocol, the respective containers should be shipped to the patient and UP/UC-values measured in a local lab.
- If patients' questionnaires will be required per protocol, these should be sent to the patient's home and completed by the patient. It is considered to be an appropriate measure as all patients have previously completed such questionnaires at the site and are familiar with their use.
- The investigator may ask the patient to measure the body temperature and weight at home and verbally report to the investigator.If the patient is also not allowed to pick up re-supply of investigational product at the site, a direct to patient's home shipment may be arranged by using a BI-qualified courier service.

All of the above mentioned workarounds shall only be performed after prior approval by CTL or TMM and with the consent by the patient (preferred in writing, but verbal consent possible) and if local regulations do allow such exceptional measures.

All remote visits need to be discussed with and approved by the sponsor`s trial team. Local regulatory and legal requirements of the participating country still apply.

In case of strict movement restrictions in a certain region and no workarounds are possible, the following applies

- If a patient has to interrupt treatment with investigational product for more than 6 weeks the patient shall be discontinued from the trial.
- If no safety lab can be taken for more than 12 weeks, the patient shall be discontinued from the trial.

All COVID-19 related deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Refer to the study Flow Charts for a detailed description of trial procedures during the trial period. Only additional and critical information are outlined below.

6.2.1 Baseline (Group 1)

Written informed consent must be obtained prior to any study related procedures or assessments are being performed.

For roll-over patients (Group 1), the preliminary decision on renal response for participation in this trial will be based on laboratory results from visit 15 of the 1293.10 trial.
In case visit 15 of the 1293.10 trial cannot be used to come to a clear roll over decision, V16 /EOT-results can be used. It is preferred to use the results from the 24 hr urine collection, however UP/UC-results from spot urine are also acceptable.
The baseline visit must take place on the same day or at a maximum within 3 days from EOT visit of the 1293.10 trial. All assessments performed at the 1293.10 EOT visit will be used as baseline assessments for this trial and should not be repeated.
In case the baseline visit could not be performed on the same day or within 7 days from the 1293.10 EOT visit, approval must be obtained from the CTM/CTLprior to proceeding.

In case the baseline visit will be later than 7 days after EOT of 1293.10, selected lab values shall be repeated (biochemistry, hematology, Anti-dsDNA complement C3/C4 and serum creatinine and UP/UC).

In case the treatment interruption between the trials is longer than the above mentioned timefame, in exceptional cases patients can roll over for ethical reasons. Please refer to section 4.1.4.

For a detailed description of the trial procedures at the baseline (Group 1) visit, please refer to Flow Charts.

Baseline Conditions and Medical History

As a precaution, risk factors for thromboembolic disease (including medical history of DVT/TE) should be specifically checked. If clinically relevant, the case should be discussed with the CTL prior to enrollment.

History of antiphospholipid syndrome should be recorded and patients should be excluded from the study.

6.2.2 Treatment period

Patients from Group 1 will not be randomised as they will continue receiving the same treatment allocation as previously assigned in 1293.10. Patients will receive the first dose of study medication at Visit 1, after all eligibility criteria have been confirmed, to ensure no interruption to their current treatment.
Investigators will not be given access to the treatment information of roll over patients until the trial is completed.

The 24hr urine collections will be performed for endpoint assessments at the visits indicated in the Flow Charts. Patients will be given instructions and materials to allow the collection of 2 x 24hr urine samples during the week before the scheduled visit. At all other visits, proteinuria will be assessed by spot urine.

In general, if several procedures including venepuncture are scheduled at the same time point, venepuncture should be performed last due to its inconvenience and possible influence on subject's physiologic parameters.

At any visit, should a decision be made to discontinue the patient from study medication, please complete EOT visit instead.

For a detailed description of trial procedures during the treatment period, refer to Flow Charts.

Any treatment interruption of more than 2 consecutive missed injections shall be communicated to the CTL.

6.2.3 Follow up period and trial completion

6.2.3.1 End of Treatment (EOT) Visit

The EOT visit will be performed within 7 days after the last administration of trial medication in all patients who either complete the 52-week treatment period or prematurely discontinue the study medication for any reason.

For a detailed description of the trial procedures at EOT, refer to Flow Charts.

6.2.3.2 Follow-Up (FUp) and End of Study (EOS) Visits

After the EOT visit, patients who have completed the 52-week treatment period will return for a safety FUp visit 4 weeks later, followed by the EOS visit 12 weeks after EOT.
In case a patient has to discontinue the trial medication prior to having completed the 52-week treatment period, the patient will be invited to attend a subset of visits as per section 6.2.3.3 below.

The investigator will continue to record and follow-up on all AEs until the residual effect period (REP). Refer to section 5.2.5.2 for AE collection procedures after the REP. At EOS visit, the investigator needs to confirm whether the AEs are sufficiently followed up and provide documentation in the patient's medical records and on the eCRF.

For a detailed description of the trial procedures at FUp and EOS visits, refer to Flow Charts.

6.2.3.3 Additional follow-up for prematurely discontinued patients

For prematurely discontinued patients, it is important that their renal function parameters and safety assessments are performed and recorded until the end of the 52-week period.
Therefore, all early discontinued patients will be invited to attend a subset of FUp visits at the following time points: Week 12, Week 26, Week 42 and Week 52.

At these FUp visits, the following assessments will be performed: physical examination, AE and CT collection, serum creatinine and spot urine test to assess renal function. Other safety laboratory tests, PK, ADA, soluble protein biomarkers, anti-ds-DNA and complement levels will be collected at these visits.

If the next FUp visit is planned more than 12 weeks after EOT, all optional tests shall be performed at least once in the FUp period: i.e. if the patient EOT is at week 26 and the next visit will be only at week 42: optional tests must be done at week 42, even if the time between week 26 &42 is >12 weeks.

During the additional follow-up period, after the patients have discontinued the trial medication and have been followed-up for 4 weeks, the patients will be allowed to participate in another investigational study whilst continue to attend these additional study visits as described above.

In case the patient discontinued more than 12 weeks before week 52, no additional follow up visits would be required after week 52. In case the patient discontinued less than 12 weeks before week 52, the last follow-up visit will be 12 weeks +/- 5 days after discontinuation.

In case the patient was unable to attend these additional study visits, vital status information will be collected at - Week 52 or 64 depending on discontinuation date (see above).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This exploratory Phase II maintenance trial is designed to study the long term efficacy and safety of different doses of BI 655064 versus placebo as add-on therapy to standard of care; and the effect of steroid tapering and steroid withdrawal during the 52 weeks of maintenance treatment.

The trial is a parallel-design, dose-ranging, placebo-controlled, double-blind, multi-centre and multi-national. The trial will include patients who responded to either BI 655064 or placebo in the induction trial. Patients will remain on the treatment to which they were randomly assigned at the start of the induction trial.

Based on these design considerations, analyses will be exploratory and descriptive.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal statistical hypotheses will be tested. Inferential tests will be performed with nominal p-values and confidence intervals provided to describe the efficacy of BI 655064 versus placebo as add-on therapy to standard of care during and following 52 weeks of maintenance treatment.

7.3 PLANNED ANALYSES

As the objectives of the trial are to study long term efficacy and safety and all patients will have had add-on induction therapy with either BI 655064 or placebo, the analyses will incorporate data from 1293.10. This will allow comparison of treatment groups over the two-year treatment period. Unless otherwise noted, the baseline from 1293.10 will be used as the baseline for all change from baseline assessments.

Baseline characteristics of patients who enter the 1293-0013 trial will be compared to the baseline characteristics of patients who entered trial 1293.10. Any changes with respect to overall baseline characteristics or the distribution of relevant baseline characteristics across treatment groups will be noted.

The primary analysis will follow the intention to treat (ITT) principle thus it is based on the treated set, i.e., all patients treated in 1293-0013 Safety analysis will be based on all treated patients and the safety profile will be compared in a descriptive manner between the experimental arms and the control arm.

All individual data will be listed. Adherence to the protocol (e.g. inclusion/exclusion criteria, times of measurement, completeness and consistency of data etc.) will be checked using the data recorded. Important protocol violations will be described in the Trial Statistical Analysis Plan (TSAP). Standard statistical parameters (number of non-missing values, mean, standard

deviation, median, quartiles, minimum and maximum) or frequency tables will be calculated where appropriate. In general, these parameters or frequencies will be calculated separately for each treatment group.

7.3.1 Primary endpoint analyses

The primary endpoint is the proportion of patients with complete renal response after 52 weeks of treatment and without any renal flares. The primary analysis will be performed in all treated patients using ITT.

Comparisons between treatment groups will be exploratory in nature and based on numerical comparison of the respective response rates.

Statistical methods used in 1293.10 for pairwise comparisons will be used. Inferential tests are intended for informational and descriptive purposes.

Further details will be provided in the TSAP.

7.3.2 Secondary endpoint analyses

Secondary endpoints (Section 2.1.3) will be analysed in the same way as the primary endpoint. For the endpoint of time to first renal flare, a Kaplan Meier curve will be presented. Further details will be provided in the TSAP.

[redacted]

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 50 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation. Analysis will be performed based on randomised treatment.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Frequency, severity and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at the database lock.

AESIs will be summarized separately using a standard BI summary table. Note that there is one SAE definition specified in Section 5.2.5.1 for Japan only.
Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.4 INTERIM ANALYSES

No interim analysis is planned but DMC will be in place with tasks as described in Section 8.7.

7.5 HANDLING OF MISSING DATA

As an imputation technique to deal with missing data in this study, for the analysis of primary and CRR-related secondary endpoints, non-completers considered failure will be used.
Further details on the imputation approaches will be specified in the TSAP.

7.6 RANDOMISATION

Patients entering the trial from 1293.10 (Group 1) will remain on their assigned treatment.

BI will arrange for the packaging and the labelling of trial medication.

7.7 DETERMINATION OF SAMPLE SIZE

It is estimated that 60 responders from 1293.10 will be prepared to roll-over into 1293-0013.

There is no power calculation for this.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

For Japan only: The investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient

understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Electronic case report forms (eCRFs) for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the eCRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)

- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it)
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all eCRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH-GCP.

Due to Covid-19 pandemic restrictions), site access may be restricted thus limiting the ability to perform standard site monitoring activities on site such as on-site source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralized monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

8.3.3 Storage period of records

Trial sites:
The trial sites must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whichever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the World Health Organisation GCP handbook.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95).
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").

The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A Data Monitoring Committee (DMC), independent of the Sponsor, will be established. They are physicians experienced in the treatment of the disease under investigation and a statistician. Regular DMC meetings will be held at specified intervals to evaluate safety data and they will also receive urgent significant safety concerns including DILI for immediate evaluation. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate RAs/HAs, IRBs/ECs, and to investigators as requested by local law. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the Investigator Site File (ISF). The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Clinical Trial Leader, responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Local Clinical Trial Managers (CTMs), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. Data Management and Statistical Evaluation will be done by BI according to BI SOPs. Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the Central Laboratory and IRT manuals available in the ISF.

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		04 May 2018
EudraCT number EU number		2017-003101-17
BI Trial number		1293-0013
BI Investigational Product(s)		BI 655064
Title of protocol		An exploratory maintenance trial evaluating the effect of BI 655064 in Lupus Nephritis patients who have achieved ameaningful response either at the end of 1293.10 or after an induction treatment outside of 1293.10.
To be implemented only after approval of the IRB / IEC / Competent Authorities	☒	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve		

logistical or administrative aspects only		
Section to be changed		**Flowchart 1 and 2**
Description of change		1. Adding "end of treatment" 2. Adding that a line for dispensing/reviewing the ediary 3. Flowchart 1 ONLY: adapting the wording for infectious screening in roll-over patients 4. Change wording to complete compliance records for LN-concomitant medication 5. Adding a sentence concerning vital signs collection after the follow up period
Rationale for change		1. To clarify the abbreviation for EOT 2. To ensure that sites review the patient's compliance when using the ediary and consider re-training. 3. To clarify that infectious screening in roll over patients is not mandatory as they have been tested in the previous trial. 4. To clarify that only the compliance to LN-medication is to be recorded in the ediary (not dosing etc) 5. To ensure patients not returning for follow up visit shall not be lost and a vital status shall be collected as a minimum
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		**3.2. DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP**
Description of change		Adding the criteria for selecting a dose for treatment of group 2 patients
Rationale for change		Pre-define criteria for selecting a dose for group 2 patients following the interim analysis of the previous trial 1293.10
Section to be changed		**3.3.2. Inclusion criteria**
Description of change		-Removing inconsistencies -Adding contraception instructions for patients on Azathioprine
Rationale for change		-to clarify that two methods of contraception are not possible -adjust the contraception requirements for Azathioprine for female and male patients following the SPC of Azathioprine

Section to be changed		**3.3.3. Exclusion criteria**
Description of change		Adding that the investigator would judge whether the diabetes mellitus of the patient is well controlled
Rationale for change		To clarify that there is no trial procedure or lab parameter to determine whether the diabetes condition is under control. This would be left to the investigator's medical judgement
Section to be changed		**3.3.4 Withdrawal of patients from therapy or assessments**
Description of change		Adapting the wording for safety follow up of early withdrawn patients
Rationale for change		To clarify that if possible any effort should be made to follow up patients who withdrew early from the trial (either by follow up visit or phone call). It should be explained to the patient upfront during informed consent process.
Section to be changed		**4.1.5.1. Blinding**
Description of change		Adding a sentence regarding the potential unblinding of trial team members or site staff regarding group 1 patients
Rationale for change		To confirm that measures will be taken that team members and site staff of 1293-0013 will not be unblinded for group 1-patients when the 1293.10 trial will be analysed and unblinded
Section to be changed		**4.2.1 Other treatments and emergency procedures**
Description of change		1.define that MMF and AZA will be considered to be AMP 2. adding a sentence about rounding of AZA-doses 3. add wording on baseline doses for glucocorticoids for group1 and 2 patients 4. adding wordings that the tapering scheme can be deviated from
Rationale for change		1. formal definition of SOC medication 2. to ensure that the dosing of the patient shall be done per medical judgement of the investigator and what is locally feasible per size of single dose available 3.to support the tapering schedule as mentioned in figures 3.1.1 and 3.1.2 4. to clarify that for patient's safety the tapering scheme can be deviated from if needed for the medical condition of the patient. In such case the patient would not be excluded from the trial
Section to be changed		**4.2.3.1 Restrictions regarding concomitant treatment**
Description of		Deleting a sentence referring to AZA only being used in case MMF is

change		not tolerated.
Rationale for change		To clarify AZA is allowed as background medication in any case
Section to be changed		**5.1.3. Assessment of SLEDAI**
Description of change		Correct the version of SLEDAI-2K assessment to SELENA-SLEDAI
Rationale for change		To correct an error. The SLEDAI assessment used in the predecessor trial was SELENA-SLEDAI which is continued in this trial as well.
Section to be changed		**5.2.3 Safety and immunology laboratory parameters**
Description of change		Adding wordings for group 1 and group 2
Rationale for change		To match the flowcharts with table 5.2.3.1. and to clarify which parameters are taken for group 1 patients and which for group 2 patients. Also defining the visit naming for baseline. Baseline in group 1 is V1. Baseline for group 2 is V2.
Section to be changed		**5.2.5.1 Definition of AEs**
Description of change		Exchanging the reference to a version of the [redacted]-Terminology Criteria
Rationale for change		To adapt the reference to a newer version of the RCTCAE Criteria for rating of AE intensities.
Section to be changed		**5.2.5.2. Adverse event collection and reporting**
Description of change		Exchange “trial” by “study”
Rationale for change		To clarify EOT stands for “end of treatment” and EOS stands for “end of study”
Section to be changed		**5.3.3. MMF plasma concentrations**
Description of change		Adding a sentence that the MMF-sample is taken as listed in the flowcharts 1 and 2
Rationale for change		To be consistent with all other lab parameters which are mentioned in the flowcharts as well as section 5.

[redacted]

[redacted]

Section to be changed		**6.2.1 Baseline (Group 1) / Screening (Group 2) period**
Description of change		Change the time window between EOT of 1293.10 and V1 of 1293-0013 from 7 to 3 days
Rationale for change		The reduction of the time window was chosen, because the previous window of 7 days would already be considered a treatment interruption of the weekly injections. Treatment interruption in a roll over trial shall be avoided for medical reasons (treatment continuity)
Section to be changed		**6.2.2. Treatment peroid**
Description of change		Adding a sentence that investigators will remain blinded for group 1
Rationale for change		To be consistent throughout the protocol that group 1 patients will remain blinded even after final analysis and unblinding of the predecessor trial 1293.10.
Section to be changed		**6.2.3.3 Additional follow-up for prematurely discontinued patients**
Description of change		Changing the time window for follow up visits for early discontinued patients from 8 to 12 weeks before week 52
Rationale for change		To be consistent with the follow up period of 12 weeks for completing patients.
Section to be changed		**7.3.1. Primary endpoint analysis**
Description of change		Adding further details on stratification factors and other statistical parameters
Rationale for change		To be more precise on statistical analysis
Section to be changed		**9. References**
Description of change		Add a newer reference to assessment of advers events
Rationale for		To be consistent with section 5.2.5.1

change		

11.2 GLOBAL AMENDMENT 2

Date of amendment		21 Dec 2020
EudraCT number **EU number**		2017-003101-17
BI Trial number		1293-0013
BI Investigational Product(s)		BI655064
Title of protocol		An exploratory maintenance trial evaluating the effect of BI 655064 in Lupus Nephritis patients who have achieved ameaningful response either at the end of 1293.10 or after an induction treatment outside of 1293.10.
Global Amendment due to urgent safety reasons		☐
Global Amendment		**X**

Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Adding secondary endpoints
Rationale for change		To be consistent with section 2.1.3, for rationale for change see below
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		Removing reference to group 2 in sections "number of patients entered/per treatment arm", Main in- and exclusion criteria" and "dose"
Rationale for change		The start of group 2 was cancelled due to the outcome of clinical trial 1293.10
Section to be changed		**Flow Chart 1**
Description of change		1. Adding immunology tests (C3/C4 complement, Anti-dsDNA) to visit week 42 2. Re-phrasing the description of data transcription for roll over patients from the previous trial to 1293-0013 3. Changing role names of Clinical Trial Leader (previously called Trial Clinical Monitor) and Clinical Trial Manager (previously called Clinical Monitor Local)
Rationale for change		1. To be consistent with the SLEDAI-questionnaire which is taken at Week 42 which asks for C3/C4 and Anti-dsDNA-levels 2. For better clarity 3. To comply with BI's new role titles
Section to be changed		**Flow Chart 2**

Description of change		Deleted
Rationale for change		Group 2 was cancelled
Section to be changed		Abbreviations, also throughout the entire CTP
Description of change		New Abbreviations added
Rationale for change		To comply with BI's new role titles
Section to be changed		**1.2 Drug Profile**
Description of change		1. Adding unblinded safety data following the final analysis of 1293.10 2. Adding unblinded efficacy data following the final analysis of 1293.10
Rationale for change		To make more current data available
[redacted]		
Section to be changed		**2.1 Main Objectives, primary and secondary endpoints**
Description of change		1. Main Objectives: Baseline values are re-defined 2. Secondary endpoints: added primary endpoint from 1293.10 and confirmed CRR endpoint from 1293.10
Rationale for change		1. to be able to analyze the full two treatment years from 1293.10 and 1293-0013 2. to align with endpoints from 1293.10
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		**3.1 Overall trial design and Plan**
Description of change		1. Deleting the word "randomised" 2. Deleting references and descriptions related to group 2
Rationale for change		1. Group 1 patients were randomized to their treatment arm in the front running trial 1293.10 2. Group 2 was cancelled
Section to be changed		**3.3.2 Inclusion criteria**
Description of change		1. Specification of highly effective contraceptives 2. Removal of inclusion criteria for group 2
Rationale for change		1. To comply with the current BI standards 2. Group 2 was cancelled

Section to be changed		**3.3.3 Exclusion criteria**
Description of change		Removal of exclusion criteria for group 2
Rationale for change		Group 2 was cancelled
Section to be changed		**3.3.4.1 Withdrawal from trial treatment**
Description of change		Addition of a Sars CoV2-infection
Rationale for change		To clarify that an infection might not necessarily result in a permanent discontinuation, but re-start of trial medication is possible.

Section to be changed		**4.1.1 Identity of investigational medicinal products**
Description of change		Removal of any reference to group 2
Rationale for change		Group 2 was cancelled
Section to be changed		**4.1.3 Method of assigning patients to treatment groups**
Description of change		Removal of treatment assignments for group 2
Rationale for change		Group 2 was cancelled
Section to be changed		**4.1.4. Drug assignment and administration of doses for each patient**
Description of change		1. Deleted observation period for group 2 patients 2. Added permission for group1 to self-inject the first trial injection at home 3. Deleted loading dose for group 2 patients 4. Deleted dose and treatment schedule for group 2 5. Added that a deviation from roll over time window might be allowed 6. Adding IP supply measures during the Covid-19 pandemic restrictions
Rationale for change		1., 3., 4. Group 2 was cancelled 2. To allow more flexibility at roll over. 5. Due to ethical implications, as described in this section 6. Workaround to ensure continueous IP supply during Covid-19 related movement restrictions.
Section to be changed		**4.1.5.1. Blinding**
Description of change		1.Removing section on interim analysis 2.Adding the rationale for unblinding some group 1 patients
Rationale for change		1.Due to cancellation of group 2, only a final analysis will take place. 2.To describe the course of actions after the final analysis of 1293.10
Section to be changed		**4.2.1. other treatments and emergency procedures**
Description of change		1. Adding Mycophenolate sodium to the list of SOCs 2. Adding that deviations from SOC-dosages are possible

		3. Removing reference to group 2
Rationale for change		1. To clarify that there is no medical difference in these compounds 2. To clarify that only under certain circumstances a deviation is possible and to ask for preapproval 3. Group 2 was cancelled
Section to be changed		**4.2.2. Management of Adverse Events**
Description of change		1.Specifying infections, Malignancies, neutropenia, surgeries, injection reactions, lymphoproliferative diseases 2. Adding Azathioprine as SOC
Rationale for change		1.To provide guidance to investigators how to handle IP intake and SOC dosing in case these events occur. To align with instructions provided in 1293.10. 2. For consistency within the document. Azathioprine had been allowed SOC before
Section to be changed		**4.2.3.1 Restriction regarding concomitant treatment**
Description of change		1. Removing prior to study and screening period 2. Corrections of permitted SOC doses
Rationale for change		These phases are not applicable to group 1 patients as they roll over from 1293.10 To be consistent with section 4.2.1
Section to be changed		**4.3 Treatment compliance**
Description of change		1.Add the timepoint of documentation of MMF intake before MMF dosing lab sample is taken 2.Description of ediary use
Rationale for change		1. To add clarity to the process 2. To add clarity to the importance of compliance checks

Section to be changed		**5.1.1. Assessment of renal response**
Description of change		Adding methods of how to define CRR or PRR
Rationale for change		To add more clarity how to determine the CRR and PRR from lab values
Section to be changed		**5.2.2.Vital signs**
Description of change		Adding that abnormal findings might qualify as AE
Rationale for change		To clarify the importance of vital sign evaluation by the investigator.

Section to be changed		**Table 5.2.3.1 Safety and immunology laboratory tests**
Description of change		1. Removing sample time points for group2 2. Adding sample timepoint C3/C4 and Anti-dsDNA at week 42 for group 1 3.Adding arule how to handle ambigious Hep B and C test results
Rationale for change		1. Group 2 was cancelled 2. To be consistent with the Flowchart and for the investigator to be able to complete the SLEDAI questionnaire at week 42 3. To be consistent with instructions provided in 1292.10
Section to be changed		**5.2.5.1 Definitions of AEs**
Description of change		1. Adding invasive herpes simplex 2. Adding a wording for the investigators to request information on AEs related to infections 3. Adding neutropenia and instructions 4. Clarifying the severity grading of AEs 5. Adapting the SAE reporting process description 6. Adding a reference to the informed consent form for pregnant partners
Rationale for change		1. To add clarity for investigators 2., 3. To provide instructions to investigators, and to be consistent with 1293.10 4. To be consistent with the already used RCTC 5. To add a more flexible wording and accounting for the different reporting processes in the regions 6. To be consistent with the process to collect information also from pregnant partners of male study patients.

[redacted]

		starts
Section to be changed		**6.1. Visit schedule**
Description of change		Covid-19 pandemic work arounds were added
Rationale for change		To allow patients to remain on the trial during movement restrictions due to the Covid-19 pandemic. Also to ensure medical oversight by investigators and ensure critical safety and lab data can still be obtained

[redacted]

Section to be changed		**6.2.1 Baseline (group 1)**
Description of change		1. Adding a description of the timepoint when the roll over decision can be made 2. Adding a wording for cases when the interruption between the trial is longer than 7 days. 3. replace randomization by enrollment
Rationale for change		1. To clarify that the latest timepoint for roll over decision can also be EOT of 1293.10 2. To clarify that in case of longer interruption certain lab parameters shall be taken as baseline for 1293-0013 3. To adapt to group 1 (with no randomization)
Section to be changed		**6.2.2. Treatment period**
Description of change		1. Removing reference to group 2 2. Adding a wording on treatment interruptions
Rationale for change		1. Group 2 was cancelled 2. To clarfy that the CTL shall be informed about longer treatment interruptions.
Section to be changed		**6.2.3.3. Additional follow-up for prematurely discontinued patients**
Description of change		Adding a wording regarding follow up visit intervals
Rationale for change		To clarify when early discontinued patients shall come for follow up visits
Section to be changed		**7.1 Statical design - model**

Description of change		Modified design description to highlight important features of the Group 1-only trial
Rationale for change		Group 2 was cancelled
Section to be changed		**7.2 Null and Alternative Hypotheses**
Description of change		Further description/justification of statistical approach added.
Rationale for change		To more clearly describe how the statistical testing addresses the trial objectives.
Section to be changed		**7.3. Planned analysis**
Description of change		1. Analyses will incorporate data from 1293.10. 2. Baseline for 1293-0013 is defined as the baseline from 1293.10 unless otherwise indicated. 3. Baseline characteristics for pateints who enter 1293-0013 (Group 1) will be compared to baseline characteristics for the treated population of 1293.10. 4. Population data set defined as ITT.
Rationale for change		1 & 2. With cancellation of Group 2, the analysis focus can be the long term (two-year) efficacy and safety assessment for the Group 1 pateints. 3. Any relevant shifts in baseline characteristics could affect interpretation of results & should be noted. 4. Approach will be to consider discontinued patients as failures & include in analysis of the primary endpoint.
Section to be changed		**7.3.1 Primary endpoint analysis**
Description of change		1. Population data set defined as ITT. 2. Descriptions of Group 2 analyses removed. 3. Statistical methods in 1293.10 will be used in 1293-0013. 4. Removed analyses by ethnicity and race.
Rationale for change		1. Approach will be to consider discontinued patients as failures & include in analysis of the primary endpoint. 2. Group 2 cancelled. 3. For consistency/comparison with 1293.10 results 4. Small numbers of patients per treatment group.
Section to be changed		**7.3.2 Secondary endpoint analysis**
Description of change		Simplified analysis plan for time to first renal flare by removing hazard ratio & 95% confidence interval.

Rationale for change		Numbers of renal flares to date are small. Plan to present Kaplan Meier curve should be adequate.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		**7.3.4 Safety analyses**
Description of change		1. Added that analysis of AEs will be based on randomised treatment. 2. Analysis of AESIs and additional SAE rule for Japan mentioned.
Rationale for change		More complete specification of analysis and for consistency with Section 5.2.
Section to be changed		**7.4 Interim Analyses**
Description of change		Deleted reference to an interim analysis
Rationale for change		Due to cancellation of group 2, the previously specified interim analysis after completion of Group 1 is now the final analysis of the trial.
Section to be changed		**7.5 Handling of missing data**
Description of change		1. Added text to indicate that the 'non-completers considered failure' approach is only for CRR-related endpoints 2. Removed statement that no imputation will be performed for all other endpoints.
Rationale for change		1. Correction to previous specification 2. Need for imputation of other endpoints will be assessed during data review. If there are significant numbers of pateints with missing data, imputation techniques may be considered & specified in the TSAP.
Section to be changed		**7.6 Randomisation**
Description of change		Removed description of the randomisation of Group 2 patients.
Rationale for change		Group 2 is cancelled.
Section to be changed		**7.7 Determination of samples size**

Description of change		Removed references to Group 2 including references to sample size calculations, assumptions and expected power for Group 2. Also removed discussion of number(s) of doses to be studied in Group 2.
Rationale for change		Group 2 was cancelled
Section to be changed		**8.3.2. Direct access to source data and documents**
Description of change		Adding a wording to allow for remote source data verification
Rationale for change		Due to movement restriction during the Covid 19 pandemic, remote SDV might be possible in regions where permitted per local regulations.

Boehringer Ingelheim

APPROVAL / SIGNATURE PAGE

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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

Signatures (obtained electronically)

Since the re-organization, some job titles have changed, but I think we are not adapting anything here because this is CTP v3 from 2020. Am I right?

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area [redacted]	[redacted]	21 Dec 2020 18:38 CET
Approval-Team Member Medicine		21 Dec 2020 18:47 CET
Approval-Clinical Trial Leader		21 Dec 2020 19:51 CET
Approval-Team Member Drug Safety		22 Dec 2020 12:26 CET
Author-Trial Statistician		22 Dec 2020 14:55 CET
Approval-Clinical Trial Leader		23 Dec 2020 12:08 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed