Clinical Trial Protocol

	Document Number:	**c03085195-07**
EudraCT No.:	2015-001750-15	
BI Trial No.:	1293.10	
BI Investigational Product(s):	BI 655064	
Title:	A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year of treatment, in patients with active lupus nephritis	
Brief Title:	Dose-finding, efficacy and safety of BI 655064 in patients with active lupus nephritis	
Clinical Phase:	II	
Trial Clinical Monitor:	Tel. : / fax :	
Coordinating Investigator:	Tel: / Fax:	
Status:	Final Protocol (Revised Protocol based on Global Amendment 6)	
Version and Date:	**Version:7.0**	**Date: 07 SEP 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 655064	
Protocol date: **29 Oct 2015**	**Trial number:** **1293.10**		**Revision date:** 07 SEP 2018

Title of trial:	A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year of treatment, in patients with active lupus nephritis
Coordinating Investigator:	
Trial site(s):	Multi-centre trial in approximately 22 countries
Clinical phase:	II
Objective(s):	To characterize the dose-response relationship, identify the target dose and investigate the safety, tolerability and efficacy of three doses of BI655064 given s.c. for 52 weeks in patients with Lupus Nephritis
Methodology:	Multi-national, randomized, double-blind, placebo-controlled, 4 parallel group in patients with Lupus Nephritis
No. of patients:	
total entered:	120 randomised
each treatment:	20 pat in group 1 (120mg) 20 pat in group 2 (180 mg) 40 pat in group 3 (240 mg) 40 patients in placebo group
Diagnosis :	Lupus Nephritis (Class III or IV (ISN/RPS 2003 classification)

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Main criteria for inclusion:	1. Males and females, age 18 –70 (inclusive) years at visit 1 2. Diagnosis of systemic lupus erythematosus (SLE) by ACR criteria 1997, at least 4 criteria must be documented, one of which must be a positive anti-dsDNA antibody OR a positive antinuclear antibody (ANA) at screening or around time of start of induction therapy 3. Lupus Nephritis Class III or IV (ISN/RPS 2003 classification) with either active or active/chronic disease, co-existing class V permitted, proven by renal biopsy within 3 months prior to screening or during screening in case induction therapy for LN has not yet been started 4. Active renal disease evidenced by proteinuria ≥ 1.0 g/day (Uprot/Ucrea ≥ 1)
Test product(s):	BI 655064
dose:	Dose group 1: 120 mg once a week for 3 weeks followed by 120 mg once every two weeks Dose group 2: 180 mg once a week for 3 weeks followed by 180 mg once every two weeks Dose group 3: 240 mg once a week for 3 weeks followed by 120 mg once a week
mode of administration:	Subcutaneous injection
Comparator products:	Placebo
dose:	Not applicable
mode of administration:	Subcutaneous injection
Duration of treatment:	52 weeks

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Endpoints	Primary endpoint : Proportion of patients with Complete Renal Response at week 52 Secondary endpoints : Proportion of patients with Complete renal response at week 26 Proportion of patients with Partial renal response at week 26 and 52 Proportion of patients with Major renal response at week 26 and 52
Safety criteria:	Physical examination, vital signs (BP, PR), weight, 12-lead ECG, laboratory tests, adverse events and tolerability
Statistical methods:	The primary objective is to define a suitable dose for BI 655064 regarding efficacy and safety for further pivotal testing in Phase III. For this purpose, a multiple comparison procedure with modelling (MCPmod) approach is considered. The primary endpoint is Complete Renal Response after 52 weeks of treatment. Comparisons between treatment groups will be exploratory in nature and based on the numerical comparison of the respective response rates including confidence intervals when appropriate.

FLOW CHART

Trial Periods	**Screening**	**Randomised Treatment Period (week 0 – 26)**											
Visit	**1**	**2**	**2.1**	**2.2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Day	**-28 to -**	**1**	**2[1]**	**3[1]**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**148**	**18**
Week	**-4 to -1**	**0**			**1**	**2**	**4**	**6**	**8**	**12**	**16**	**21**	**26**
Time window for visits (days)	**N.A.**	**±0**	**±0**	**±0**	**±1**	**±1**	**±2**	**±2**	**±3**	**±3**	**±5**	**±5**	**±3**
Check of Eligibility	X	X											
Informed Consent	X												
Med. History / Demographics	X												
Physical Examination[2]	X[c]	X[c]			X[t]	X[t]	X[t]	X[t]	X[t]	X[c]	X[t]	X[t]	X[c]
12-Lead Resting ECG		X					X			X			X
Inclusion/Exclusion Criteria	X	X											
Randomisation		X											
Administer BI 655064/placebo[3]		X			X	X	X	X	X	X	X	X	X
Administer Methylprednisolone 500mg i.v. (SOC I) [1]		X	X	X									
Start oral glucocorticoids [4]				X →									→
Administer MMF 2-3g/day		→											→
Dispense treatment and instructions for home admin [5]						X	X	X	X	X	X	X	X
Assess compliance							X	X	X	X	X	X	X
Assess for Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
Safety Laboratory Tests [6]	X	X			X	X	X	X	X	X	X	X	X
2 x 24h collection of urine		X											X
Uprot/Ucrea spot urine	X	X			X	X	X	X	X	X	X	X	X
Serum pregnancy test [7] (only female subjects)	X												
Urine Pregnancy Test[7]		X					X		X	X	X	X	X

Trial Periods	**Screening Period**	**Randomised Treatment Period (week 0 – 26)**											
Visit	**1**	**2**	**2.1**	**2.2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Day	**-28 to -7**	**1**	**2[1]**	**3[1]**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**148**	**183**
Week	**-4 to -1**	**0**			**1**	**2**	**4**	**6**	**8**	**12**	**16**	**21**	**26**
Time window for visits (days)	**N.A.**	**±0**	**±0**	**±0**	**±1**	**±1**	**±2**	**±2**	**±3**	**±3**	**±5**	**±5**	**±3**
Infectious Serology, TB Screening	X												

Trial Periods	**Randomised Treatment Period (week 27 – 52)**					**Follow-up Period[11]**	
Visit	**12**	**13**	**14**	**15**	**16-EOT[10]**	**17**	**18-EOS**
Day	**211**	**246**	**281**	**323**	**365**	**393**	**421**
Week	**30**	**35**	**40**	**46**	**52**	**56**	**60**
Time window for visits (days)	**±5**	**±5**	**±5**	**±5**	**±3**	**±5**	**±5**
Physical Examination[2]	X[t]	X[t]	X[c]	X[t]	X[c]	X[t]	X[t]
12-Lead Resting ECG			X		X		
Administer BI 655064/placebo[3]	X	X	X	X			
Assess compliance	X	X	X	X	X		
Continue oral glucocorticoids[4]	→	→	→	→	→	→	→
Continue MMF 1-2g/day	→	→	→	→	→	→	→
MMF level					X		
Dispense treatment and instructions for home admin [5]	X	X	X	X			
Assess for Adverse Events	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X
Safety Laboratory Tests[6]	X	X	X	X	X	X	X
2 x 24h collection of urine					X		
Uprot/Ucrea spot urine	X	X	X	X	X	X	X
Urine Pregnancy Test[7]	X	X	X	X	X	X	X

Trial Periods	**Randomised Treatment Period (week 27 – 52)**					**Follow-up Period[11]**	
Visit	**12**	**13**	**14**	**15**	**16-EOT[10]**	**17**	**18-EOS**
Day	**211**	**246**	**281**	**323**	**365**	**393**	**421**
Week	**30**	**35**	**40**	**46**	**52**	**56**	**60**
Time window for visits (days)	**±5**	**±5**	**±5**	**±5**	**±3**	**±5**	**±5**
Optional renal biopsy					X		
Vital status collection							X[12]
Conclusion of patient participation							X

Footnotes:

1. Visit 2.1 and 2.2 are necessary for IV steroids injections only. Refer to section 4.2.1. IV methylprednisolone injections to be done only to reach 1.5 g total dose if not reached within 6 weeks prior to randomisation. If a higher dose of IV steroid is considered necessary by the investigator a total dose of up to 3g is acceptable.
2. Physical exam includes height (at screening only), vital signs and weight. x^c is a complete physical examination, x^t is a targeted physical examination. See section 5.3.1 for description.
3. PK samples will be collected before study medication administration on these days if the visit date coincides with a day of injection; therefore study medication should be administered on site in that case. If the visit does not correspond to an injection day, the PK sample will be taken at anytime during the visit. Exact date and time of sampling should be recorded. See Section 5.4
4. Oral glucocorticoids have to be started on day 4 (or day 1 if IV steroids were already received) and tapered to 10mg prednisone equivalent within 12 weeks.
5. Starting from week 2, patients have to administer the injections with BI 655064/placebo by themselves always 7 days after the previous dose.
6. Safety lab tests : details of tests is given in section 5.3.3
7. Pregnancy test will be performed in women of childbearing potential every 4 weeks. A serum pregnancy test will be performed at screening visit. Urine dipstick tests will be done during the screening phase (8-10 days after the first test) and immediately before starting medication. It will be repeated at visits every 4 weeks and will be provided for at home pregnancy testing as soon as visit intervals are > 4 weeks,. In case of a positive urine pregnancy test result, a blood sample for serum pregnancy test will be drawn for confirmation. Only those females with a negative pregnancy test will receive study medication and will be allowed to start treatment with MMF
8. Will be measured in serum and urine
9. Questionnaires should be completed in the following order: LupusPRO, SF-36, FACIT-F, before any other visit assessment
10. EOT visit has to be carried-out for all patients when they stop treatment. At week 52, patients who reach at least partial response (based on values obtained at week 46) will be offered to enter a maintenance trial (trial 1293.13). Patients who stopped treatment before week 52 will not be allowed to participate in the maintenance trial.
11. Follow up visits to be performed after end of treatment except for patients entering the maintenance trial 1293.13 and patients who have withdrawn drug prematurely
12. For randomized patients leaving the study before the planned EOS, their vital status should be collected at week 60

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ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANA	Antinuclear Antibody
ASAT or AST	Aspartate Transferase
ALAT or ALT	Alanine Transferase
AUC	Area under the Curve
AZA	Azathioprine
BI	Boehringer Ingelheim
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
CD	Cluster of Differenciation
CD40L	Ligand of CD40
Cmax	Maximum Concentration in plasma
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CRR	complete renal Response
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYC	Cyclophosphamide
DBL	Data Base Lock
DEDP	Drug Exposure During Pregnancy
DILI	Drug Induced Liver Injury
dsDNA	double strand DexoxyriboNucleic Acid
EC	Effective concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
ESRD	End Stage Renal Disease
EudraCT	European Clinical Trials Database
EULAR/ERA-EDTA	European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association
EMA	European Medecines Agency
FAS	Full Analysis Set
FDA	Food and Drug Association
FU	Follow Up
FC	Flow Chart
GC	GlucoCorticoids
GCP	Good Clinical Practice

eGFR	(estimated) Glomerular Filtration Rate
HA	health Authorities
HPF	High Power Field
HRQoL	Health related Quality of Life
HV	Healthy Volunteer
i.v.	intravenous
IB	Investigator's Brochure
IC	Inhibitory concentration
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITP	Immune thrombocytopenia
ITT	Intention to Treat
LupusPRO	Lupus patient-reported outcome
LN	Lupus Nephritis
MCP1	Monocyte Chemoattractant Protein-1
MCPmod	Multiple Comparison Procedure with modelling
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMF	Mycofenolate
MRD	Multiple Rising Dose
MRR	Major Renal Response
MTX	Methotrexate
NOAEL	No Observed Adverse Effect Level
p.o.	per os (oral)
PD	Pharmacodynamics
PK	Pharmacokinetics
PRR	Partial renal Response
q1w	once a week
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
RCTCAE	Rheumatology Common Terminology Criteria for Adverse Events
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RNA	Ribonucleic Acid
RO	Receptor Occupancy
s.c.	subcutaneous
SAE	Serious Adverse Event
SLE	Systemic Lupus Erythematosus
SOC	Standard of Care
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SRD	Single Rising Dose

SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TCM	Trial Clinical Monitor
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WBC	White Blood cell

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Lupus nephritis (LN) i.e. kidney involvement (mainly glomerulonephritis) is defined by persistent proteinuria >0.5 g/day (or a spot urine protein / creatinine ratio >0.5) and active urinary sediment (>5 red blood cells/high power field (RBC/HPF), >5 white blood cells (WBC)/HPF, or cellular casts limited to RBC or WBC casts (R12-4273). LN in SLE varies with ethnic background ranging from about 35% in Caucasians to about 46% in Hispanics or Asians and to about 50% in African Americans. Survival in patients with SLE is approximately 92% at 10 years after diagnosis but significantly reduced to 88% after 10 years in the presence of lupus nephritis (R12-4273). Among the different ethnicities, African-Americans show the worst clinical outcome and the lowest response to current therapy. In addition, poor socio-economic status is associated with lower outcome. Persistent active and long-lasting lupus nephritis causes end-stage renal disease (ESRD) and death.

Renal biopsies from SLE patients with LN show a spectrum of vascular, glomerular, and tubulointerstitial lesions. The glomerular injury is determined by immune-complex localization on mesangial, endothelial and epithelial cells. Depending on these changes lupus nephritis can be classified by the current ISN/RPS classification (R12-5040). In this classification, LN is divided into 6 classes ranging from relatively mild impairment (class I and II) to global sclerosis in >90% of the glomerula (class VI). Patients with LN class III-V show clinical signs of haematuria, symptomatic proteinuria and loss of Glomerular Filtration Rate (GFR). These patients are at high risk for irreversible kidney damage leading to ESRD. Therefore, these patients are the primary target population for immunosuppressive therapy.

Within patients suffering from LN, about 25% are class III, 40% class IV and 10% class V. About 1/6 of class III and IV will also have class 5 (overlap).

Although not approved for LN, cyclophosphamide (CYC) and mycophenolate mofetil (MMF) each in combination with glucocorticoids (GC) have been shown to improve clinical symptoms of active LN and to reduce the risk of progression to ESRD (e.g. R12-4322, R12-4326, R12-4285, R12-4284, P12-11005). However, the complete response rates remain low and there is a relevant risk of relapse. Furthermore, both treatments for LN may be associated with significant toxicity (for example, infertility, infection, malignancy). As a consequence, there is a high unmet medical need for treatments in LN.

The generation of the auto antibodies is dependent on T cell-B cell interactions within the lymph node and requires CD40-CD40L (CD40 Ligand) to drive B cell proliferation and formation of germinal centres. Based on current knowledge (refer to section 2.3) there is a stronger evidence for a critical role of the CD40-CD40L in LN class III and class IV than LN class V (R12-3090). Therefore, the clinical development for BI 655064 will focus on LN patients with class III and IV including overlap with class V.

1.2 DRUG PROFILE

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 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 being not approved for therapy of LN, CYC or MMF, each in combination with glucocorticoids have been shown to improve clinical symptoms of active LN and to reduce the risk of progression to ESRD. Therefore, the combination of one of these two agents with glucocorticoids is considered as current standard of care for LN. However, only about 20-30% of patients treated with MMF or CYC show a complete renal response and another about 20% show at least a partial response. There is a high risk of relapse justifying long-term maintenance therapy. Both treatments for LN may be associated with significant toxicity (for example, amenorrhoea, infertility, infection, malignancy).

Thus, there is high unmet need for improvement in clinical efficacy and treatment alternatives for LN should be explored. Blocking the CD40-CD40L pathways will impact multiple mechanisms which are 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 as well as 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 primary objective of this study is to investigate efficacy of BI 655064 as add-on therapy to Standard of Care (SOC) in patients with active lupus nephritis in order to establish proof of concept, and characterize the dose-response relationship within the therapeutic range, and select the target dose for phase III development. To achieve this, the statistical design is based on the multiple comparison and modelling (MCPmod) approach for dose finding that combines multiple comparison procedures and modelling techniques.

Rationale for SOC selection

There is no approved treatment for LN but the ACR (R12-4273) and the EULAR/ERA-EDTA guidelines (R12-4921) recommend the use of MMF or CYC in combination with glucocorticoids, starting with three consecutive pulses of intravenous (i.v.) methylprednisolone, and followed by oral glucocorticoids. The efficacy of MMF- and CYC-based induction therapy in LN is quite comparable (R15-3723 and R15-5330). For this trial, MMF-based SOC in combination with glucocorticoids with initial i.v. methylprednisolone pulse was selected based on feedback from international experts who in the majority

presently recommend MMF. MMF and i.v. methylprednisolone are non investigational products in this trial.

2.2 TRIAL OBJECTIVES

The overall purpose of this trial is to assess the efficacy of three different doses of BI 655064 against placebo as add-on therapy to standard of care (SOC) treatment for active lupus nephritis (See section 4.2.1) in order to characterize the dose-response relationship within the therapeutic range, and select the target dose for phase III development.

Other objectives of this study are safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 655064.

Study endpoints are listed in Section 5.

2.3 BENEFIT - RISK ASSESSMENT

Potential benefit

Patients with LN class III-V are at considerable risk for irreversible kidney damage leading to ESRD, dialysis and death. CYC or MMF, each in combination with glucocorticoids are looked upon as current standard of care for LN.

However, only about 20-30% of patients treated with induction treatment either combining MMF or CYC with steroids show a complete renal response and another about 20% show at least a partial response within a year. Both treatments for LN may be associated with significant toxicity (for example, amenorrhoea, infertility, infection, malignancy). Taken together, there is a high unmet need for a better therapy.

Anti-CD40 therapy offers clear differentiation compared to current therapies with respect to mechanism by targeting humoral responses and inflammatory responses amplified locally in the kidney (in LN). Although clinical proof of concept remains to be established directly with anti-CD40, effective blockade of CD40-CD40L pathway using CD40L antibodies has been shown in many pre-clinical LN studies. Preclinical studies demonstrated direct effects of CD40L on immune (B cells, monocytes) and non-immune resident kidney cells (proximal tubular epithelial cells, mesangial cells) which secrete inflammatory cytokines that are inhibited by BI 655064. A small subset independent analysis of LN patients treated with anti-CD40L ab, ruplizumab by two investigators (R12-4866 and R15-4206) showed a decrease in auto-antibody titers, decreased proteinuria and decrease in disease scores thus underscoring the importance of CD40 pathway inhibition. Therefore, targeting CD40 pathway with BI 655064 shows high promise as an effective for treatment of LN.

Potential risks

Treatment with MMF is associated with higher risk of infections, blood and lymphatic system, gastrointestinal side effects, and teratogenicity. For further details please refer to the current prescribing information

Treatment with i.v. glucocorticoids is associated with higher risk of side effects. For further details please refer to the current prescribing information

It is important to note that all patients in this study will receive standard of care treatment for lupus nephritis. The majority of patients (2/3) will be randomized to add-on treatment of BI 655064 to SOC and even the lower dose of BI 655064 is expected to show some additional clinical benefit based on modelling of PK and PD. Patients in the placebo group will receive placebo to BI 655064 as add-on to standard of care treatment for lupus nephritis.

In conclusion, the sponsor believes that the activity demonstrated in patients with RA and positive trends in biomarker data from patients with RA and ITP, coupled with an acceptable safety profile generated to date, support initiation of a trial in patients with lupus nephritis and that the potential clinical benefit could surpass the potential risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This study will be randomized, parallel-design, dose-ranging, placebo-controlled, double-blind, multi-centre and multi-national. A total of up to approx. 120 male and female patients with active lupus nephritis will be randomized in this trial in about 22 countries. There will be three parallel BI 655064 dose groups (approx. 20, 20 and 40 patients) and one placebo dose group (approx. 40 patients). The patients will be randomized 1:1:2:2 to these dose groups. Randomisation will be done with stratification by ethnicity (Asians vs Non- Asian) and proteinuria at screening <3g/day or ≥ 3g/day (respectively UP/UC<3 or UP/UC≥3. All patients will receive standard of care (SOC) treatment for lupus nephritis, consisting of a 6 month initial phase with 2-3 g MMF/day starting with high dose steroids which will be tapered down to 10 mg prednisone equivalent within 12 weeks after randomization (Refer to section 4.2.1), followed by a second phase (from week 26 on) with 1-2 g MMF/day in combination with steroids <=10 mg prednisone equivalent/day. BI 655064 will be administered subcutaneously at 3 different doses. For the first 3 weeks the patients will receive two parallel injections/week on the same day of BI 655064 and/or placebo. Then the patients will receive one injection/week of BI 655064 or placebo for up to 52 weeks (12 months). Patients in the placebo dose group will receive only injections of placebo to BI 655064.

The primary endpoint (complete renal response as defined in section 5.2) will be assessed at 52 weeks. Patients with at least a partial response at week 52 will be offered to enter a maintenance trial (1293.13).

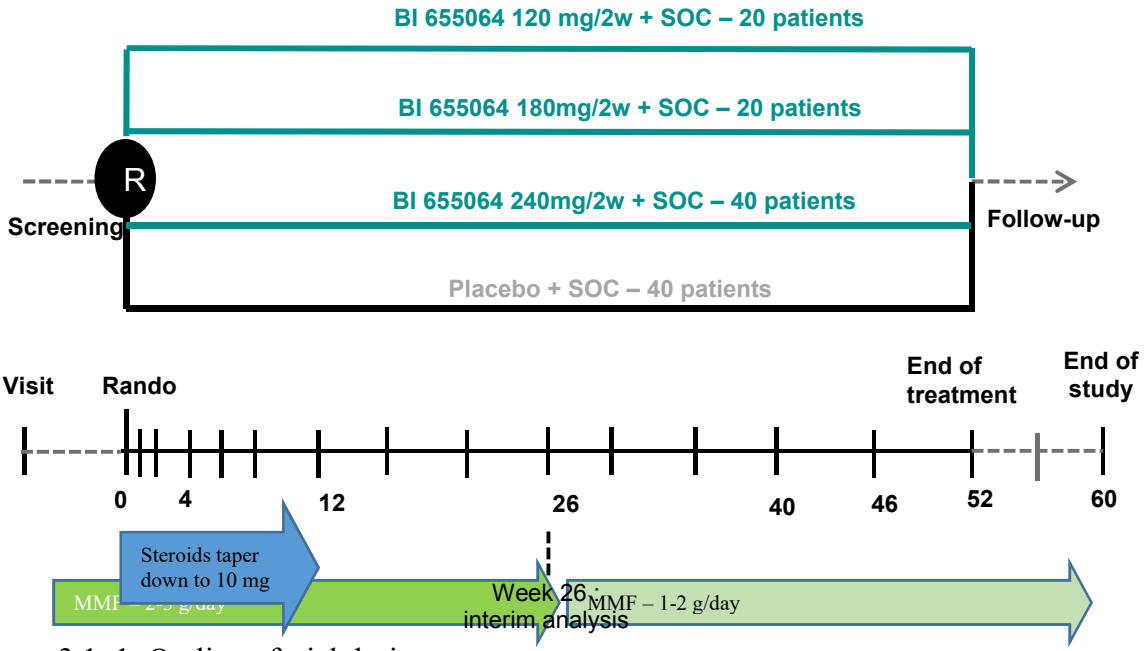

Figure 3.1: 1: Outline of trial design

3.1.1 Administrative structure of the trial

The trial will include the review of safety data by an internal, independent DMC with the support of an independent statistician. The purpose of the DMC is to ensure the welfare of subjects participating in the trial is maintained by monitoring the trial for possible, untoward harmful effects or inappropriate frequency of adverse events.
The DMC will evaluate and analyse accrued, unblinded data in order to recommend whether the trials should continue, be modified or stopped due to safety or ethical concerns.
Further details are specified in the Data monitoring Committee operating Charter. The DMC charter will be available before the start of patient recruitment.

Boehringer Ingelheim has appointed a Trial Clinical Monitor, 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,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organize, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A Coordinating Investigator will be nominated and will be responsible to coordinate Investigators at different centers participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in BIRDS.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

Study 1293.10 is a double-blind, randomized, parallel-design, dose-ranging, placebo-controlled clinical trial.

The trial design has been chosen to allow proof-of concept and selecting appropriate dose regimens for subsequent Phase III trials. The treatment duration of 52 weeks was selected, based on literature (e.g. R15-4294; R15-3157) and feedback from external experts, some patients improve further between 6 and 12 months and the 12 month time point may provide a better differentiation vs. the control group (R15-3718).

The study is aimed to evaluate the effects of the drug on renal activity. Study outcomes will focus on renal function endpoints. The primary endpoint is complete renal response at 52 weeks (12 months) as defined in section 5.2. Secondary endpoints assessing the response level at 26 and 52 weeks will complete the picture. Treatment of placebo as add-on to SOC

has been selected as control group as a placebo treatment add-on to SOC is recommended by Health Authorities (HA) as comparisons for dose finding in phase II trials. In addition there is no approved active comparator. MMF-based SOC was selected based on feedback from international experts who in the majority presently recommend MMF. For reasonable comparison and analysis, harmonization of steroid treatment is needed and a tapering schedule is provided which is followed by all patients. ACR and EULAR/ERA-EDTA guidelines recommend to taper steroids down to lowest effective dose. The 10 mg prednisone equivalent target was selected based on external expert recommendation. This amount is looked upon as balance between side effects induced by long-term steroid-treatment and efficacy. The 12 week time point to reach the 10 mg is selected as immunosuppressive therapy is expected to have reached full effect at that time. BI 655064 is expected to be at steady state for some weeks at that time too.. Ideally, patients entering the trial would not have started an induction therapy before randomization; however, it is anticipated that some patients who might have already started a short term induction therapy with SOC might benefit from the combination treatment with BI 655064. According to feedback from external experts, it's not expected that short term induction treatment before randomization will have a major impact on the outcome of a 1 year endpoint. An analysis on the effect of prior treatment with abatacept showed that patients who are naïve to induction treatment had the best response, whereas those who had received >3 months induction showed the poorest response (R15-3717).

In this trial (1293.10) start of induction treatment prior to randomization is limited to 6 weeks as this will allow for some prior treatment with MMF while maintaining a level of homogeneity to better assess treatment effect in this Phase 2 study. High dose steroids have significant impact on the short term response and have potentially relevant side effects. To keep the population included in the trial more homogenous and to avoid increased risk of side-effects, the total amount of i.v. steroids has to be limited. A total amount of 1.5 g of i.v. steroids is recommended by ACR (R12-4273) and EULAR/ERA-EDTA (R12-4921) for induction therapy (3x500 mg i.v.). For severe cases a maximal total amount of 3 g of iv steroids may be considered (3x1000 mg i.v.).

Thus, patients who had started induction with high i.v. dose steroids but ≤ 3g total i.v. within 6 weeks prior to randomisation (D1) will be eligible for the trial. Dose finding and proof of clinical concept are combined within this single trial. In order to achieve both aims in an efficient fashion, i.e. with a comparably large success probability, the generalized MCPmod approach (R10-1424) has been implemented as the statistical design. This approach is able to incorporate potential relationships between the different doses into the evaluations via optimal test contrasts which increases the probability of success compared to classical multiple comparison procedures. MCPMod has been evaluated by the EMA recently and is considered to be an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty (EMA qualification opinion). As a second step for designing the trial efficiently the allocation ratio has been chosen to be 2:1:1:2 for placebo, 120mg, 180mg, and 240mg respectively. Thereby the success probability of the trial is increased further compared to a balanced allocation ratio whilst keeping the risk of a false positive outcome at the same level. A sufficiently broad set of candidate shapes for

the dose-response relationship has been chosen including monotonic and non-monotonic options.

Details of the statistical approach including the set of candidate models as well as a sample size justification are given in section 7.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients with active lupus nephritis will be screened to ensure that an adequate number of patients will be randomized. It is planned that 120 male and female patients who meet the eligibility criteria will be randomized in the study. The planned number of randomized patients per site is 1 – 2 (approx. 80 to 100 sites). Enrolment will be competitive and will be closed when the total number of randomized patients has been reached, regardless of total enrolment at individual centres.

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 investigational drug or not.

3.3.1 Main diagnosis for trial entry

Patients diagnosed with active Lupus Nephritis and who comply with all inclusion and exclusion criteria may qualify for participation in the trial.

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Male or female patients. Women of childbearing potential* must be ready and able (as assessed by investigator) to use simultaneously two reliable methods of birth control, one of which must be highly effective. Highly effective method, 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 contraception should be used before starting MMF therapy and the study drug, during the treatment and until 50 days after stopping MMF and the study drug.
   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 and for at least 90 days after cessation of MMF treatment.

2. Age 18 –70 (inclusive) years at visit 1; For patients in Japan age 20-70 is applicable at visit 1

3. Diagnosis of systemic lupus erythematosus (SLE) by ACR criteria 1997, at least 4 criteria must be documented, one of which must be a positive anti-dsDNA antibody OR a positive antinuclear antibody (ANA) at screening or around time of start of induction therapy.

4. Lupus Nephritis Class III or IV (ISN/RPS 2003 classification) with either **active or active/chronic** disease, co-existing class V permitted, proven by renal biopsy within 3 months prior to screening or during screening in case induction therapy for LN has not yet been started

5. Active renal disease evidenced by proteinuria $\geq$ 1.0 g/day [(Uprot/Ucrea) $\geq$ 1] at screening

6. Signed and dated written informed consent must be obtained from each patient prior to participation to the trial in accordance with GCP and local legislation

*Women of childbearing potential are defined as:
Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below.
Women not of childbearing potential are defined as:
Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

$ Condom use applies for both reproductively competent and vasectomized 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/AZA are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of MMF/AZA.

3.3.3 Exclusion criteria

1. Clinically significant current other renal diseases, based on investigator's judgement. E.g.: post-infectious glomerulonephritis, pyelonephritis, interstitial nephritis, glomerulosclerosis

2. GFR < 30 ml/min/1.73m^2 at screening

3. Dialysis within 12 months of screening

4. Antiphospholipid syndrome, defined as positive antiphospholipid antibodies and either history of any thrombotic event or history of miscarriage

5. Diabetes mellitus if poorly controlled according to investigator or known diabetic retinopathy or diabetic nephropathy

6. Evidence of current or previous clinically significant disease, medical condition other than lupus, or finding 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.

7. With regards to previous treatments the following applies.

- Any induction therapy for LN within the last 6 months prior to randomization except induction with MMF and high dose steroids (maximal amount of i.v. steroids 1.5g prednisone equivalent) started within 6 weeks prior to randomization. If a higher dose of iv steroids is considered necessary by the investigator a total dose of up to 3g is acceptable.

- Treatment with any biologic B-cell depleting therapy (e.g. anti-CD20, anti-CD22,) within *12 months* prior to randomisation

- Treatment with Belimumab or other anti BLyS: when used for treatment of non-renal SLE 3 months or 5 half-lives whichever is longer, prior to randomisation ; when used for treatment of Lupus nephrits: 12 months prior to randomisation

- Treatment with abatacept within *12 months* prior to randomisation

- Treatment with tacrolimus or cyclosporin within 4 weeks prior to randomisation

- Treatment with cyclophosphamid within *6 months* prior to randomisation

- Treatment with investigational drug within 6 months or 5 half-lives, whichever is greater before randomisation

8. Contraindications for SOC medication used in this trial : mycophenolate mofetil or corticosteroids and/or known hypersensitivity to any constituents of the study drug.

9. Live vaccination within 6 weeks before randomisation

10. Clinically important as assessed by investigator acute or chronic infections including but not limited to HIV, hepatitis B or C.

11. Patients who are not eligible according to the following tuberculosis screening criteria

    - Have signs or symptoms suggestive of current active or latent TB upon medical history, physical examination and/or a chest radiograph (both posterior-anterior and lateral views, taken within 3 months prior to the first administration of study drug and read by a qualified radiologist).

    - Have history of latent or active TB prior to screening, except for patients who have documentation of having completed an adequate treatment regimen according to local guidelines within the past 3 years at least 6 months prior to the first administration of study agent.

    - Have positive QuantiFERON-TB Gold In-Tube test within 2 months prior to or during screening, in which latent or active TB has not been ruled out,

except for patients with history of TB and documentation of having completed an adequate treatment regimen at least 6 months prior to the first administration of study agent.

12. Any active or suspected malignancy or history of documented malignancy within the last 5 years before screening, except appropriately treated carcinoma in situ and treated basal and squamous cell carcinomas

13. Patients unable to comply with the protocol in the investigator's opinion.

14. Alcohol abuse or active drug abuse in the opinion of the investigator.

15. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

16. Impaired hepatic function, defined as serum AST/ALT, bilirubin or alkaline phosphatase levels > 2 x ULN

17. Patients with significant central nervous system (CNS) symptoms related to SLE based on investigators assessment

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

Removal of individual patients from therapy:

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

- The patient withdraws consent for study treatment or study participation, 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 4.2.2).
- Patient becomes pregnant during the trial. Patient will be followed up until birth or otherwise termination of the pregnancy.
- The patient is no longer able to participate for other medical reasons (e.g. surgery, AEs, or other diseases or finding of the medical examination including safety laboratory tests, vital signs and ECG) based on the opinion of the investigator.
- The patient develops an anaphylactic reaction (cf. section 4.2.1 and 5.3.5.1).
- In case of worsening or flare at any time point, the investigator may allow patients to discontinue and start rescue therapy according to the available guidelines for treatment of LN

In case a patient withdraws drug prematurely, it is important that his/her renal function parameters and safety data are recorded until the end of the 52 weeks period. Thus, all patients will be asked to follow some visits until 52 weeks. The patient will undergo the procedures for early treatment discontinuation and continue visits as described in section 6.2.3 until week 52.

For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the (e)CRF. These data will be included in the trial database and reported.

3.3.4.2 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 new toxicological findings /efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial
4. Other significant safety concerns across all patients
5. The sponsor decides to discontinue the 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 TREATMENTS TO BE ADMINISTERED

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

SOC will be prescribed by investigator and re-imbursed by the sponsor.

4.1.1 Identity of BI investigational product(s) and comparator product(s)

The characteristics of the test product for s.c. administration are below.

Substance:	BI 655064
Pharmaceutical formulation:	Solution for s.c. injection
Source:	Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany
Unit Strength:	120 mg BI 655064 in a pre-filled syringe and 180 mg BI 655064 in a pre-filled syringe
Posology:	2 injections per week for the first 3 weeks, then 1 injection per week.
Route of administration:	s.c. injection

The characteristics of the reference product for s.c. administration are below.

Substance:	Placebo
Pharmaceutical form:	Solution for s.c. injection
Source:	Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany
Unit Strength:	Placebo to match 120 mg BI655064 and placebo to match 180 mg BI 655064
Posology:	2 injections per week for the first 3 weeks, then 1 injection per week
Route of administration:	s.c. injection

4.1.2 Method of assigning patients to treatment groups

During Visit 2 and after the patient's eligibility has been confirmed, the treatment will be assigned via Interactive Response Technology (IRT). Patients will be randomized to receive 3 doses of BI655064 or placebo in a ratio of 1:1:2:2. Each pre-filled syringe of trial

medication will be labelled with the trial code and a unique medication identification number. At each applicable visit, the IRT will assign each patient medication numbers for each weekly drug administration. To facilitate the use of the IRT, the Investigator will receive all necessary instructions and the site-user manual available in the ISF.

4.1.3 Selection of doses in the trial

The doses of BI 655064 and weekly administration were selected based on the results of

(Refer to the Investigator's Brochure (U11-1925) for further information.).

4.1.4 Drug assignment and administration of doses for each patient

IRT will be used to allocate medication to patients throughout the study. At visits where study medication is to be prescribed, study sites will be required to complete the medication (re)supply module in the IRT. (Detailed information is provided in the Flow Chart). From week 2 on, there will be injections dispensation of syringes for home administration on the following week(s). It will be necessary for the investigator to instruct the patient on the proper administration technique for injections at home. If needed, injections could also be done by qualified persons e.g. a nurse.

BI 655064/placebo will be provided in sterile, preservative-free, non-pyrogenic, single-use pre-filled glass syringes. Prefilled syringe will be administered by 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 patients by the investigator (or a suitably qualified designee). The patient will be required to stay at the study site for observation for about 1 hour following the first dosing and 30 min after dose 2 and 3 (or more if locally required). After proper training on subcutaneous injection technique and if the investigator determines that it is appropriate with medical follow-up as necessary, patients will self-inject the weekly study medication at home (between two visits) on the same day (+/- 1 day) of each week. Further information regarding the self-injection technique and the instructions for use will be available in the ISF for providing to the patients. In case of missed dose, the patient should call his investigator to decide about further dosing as soon as possible.
All dose-regiments will start with a loading dose to reach the target mean exposure of each dose within 3 weeks: for the first 3 weeks (week 0, 1 and 2) the patients will receive two parallel injections per week (on the same day). From week 3 to end of treatment the patients will receive one injection per week.

Schedule of drug dispensations:

Visits 2 and 3 (week 0 and 1): syringes for the visit injection will be received

Visits 4-5-6 (from week 2): syringes for the visit injection plus next week (home) injection

Visits 7-8 (from week 8): syringes for the visit injection plus next 3 weeks (home) injections

Visit 9-10 (from week 16): syringes for the visit injection plus next 4 weeks (home) injections

Visit 11 (week 26): syringes for the visit injection plus next 3 weeks (home) injections

Visit 12-13 (from week 30): syringes for the visit injection plus next 4 weeks (home) injections

Visit 14-15 (from week 40): syringes for the visit injection plus next 5 weeks (home) injections

An additional syringe could be requested to accommodate for the time window when needed.

The different dose groups of BI 655064 will be double-blinded. Therefore, the patients will receive injections of BI 655064 and/or placebo to BI 655064.

Table 4.1.4: 1 Dose groups

Dose group	BI 655064 (Dose group 1)	BI 655064 (Dose group 2)	BI 655064 (Dose group 3)	Placebo (Placebo)
Dose received	120 mg weekly week 0-1-2 120 mg every two weeks week 3 to 51	180 mg weekly week 0-1-2 180 mg every two weeks week 3 to 51	240 mg weekly week 0-1-2 120 mg weekly week 3 to 51	
Syringes to be administered weekly Week 0-1- 2	120 mg BI 655064 + placebo	180 mg BI 655064 + placebo	120 mg BI 655064 + 120 mg BI 655064	Placebo to BI 655064 + Placebo to BI 655064
Syringes to be administered weekly Week 3 to 51	120 mg BI 655064 or/alternating placebo	180 mg BI 655064 or/alternating placebo	120 mg BI 655064	Placebo to BI 655064
No. of patients	20	20	40	40

No dose modification for BI 655064/placebo is permitted.

Please note that dilution of the study medication or the use of other syringes or needles than those specifically provided by the sponsor is not allowed.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This study has a double-blind design. From the time of randomisation at Day 1 the subjects, investigators and sponsor staff will not be aware of the treatment allocation until database lock.

After all patient have completed 26 weeks treatments a BI internal interim analysis will be performed for the purpose of facilitating further substance development and project planning. This analysis will be performed by a BI internal team independent of the trial team in order to prevent potential introduction of operational bias. An interim analysis trial statistical plan prepared and approved in accordance with sponsor's specific procedures will detail procedures used to ensure that some members of the trial team remain blinded. The plan will also contain a detailed list of functions that need to be unblinded for performing this analysis.

In order to ensure appropriate blinding, an IRT will be used for the assignment of patients to treatment groups and the randomization sequence will be generated using validated software and verified by an independent BI statistician who is not involved in the planning or performance of the trial. The randomization code will be kept secret by Clinical Trial Support up to database lock.

The randomization 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 randomization code or the results of their measurements until the trial is officially unblinded.

4.1.5.2 Unblinding and breaking the code

In this blinded trial, an emergency code break will be available to the Investigator / the sub-Investigators via the IRT system. This code break may only be accessed in emergency situations when the identity of the trial drug must be known to the Investigator /the sub-Investigators in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the Sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page. In case third party needs to break the code, however, when the Investigator cannot be reached, the code can be opened by calling emergency code manager.

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF.

BI 655064 and Placebo supplies will be provided by Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany. Syringes of study medication will be provided in individual

boxes identified with the trial number, batch number, medication number, contents, and sponsor. The outer carton will contain a Multilanguage booklet label that will contain the following (as needed):

- For clinical trial use only
- Keep out of the reach of children
- Trial number
- Contents/ batch number and strength
- Route and mode of administration
- Storage conditions
- Use by date
- Sponsor address
- Investigator
- Patient number
- Visit number

Supply of study medication will be managed by the IRT

4.1.7 Storage conditions

Syringes will be kept in its original packaging in order to protect from light until administration, and stored according to the recommended storage conditions on the medication label (2-8°C). It cannot be frozen. A temperature log must be maintained for documentation. If the storage temperature deviates from the required range, contact the local clinical monitor immediately. For temperature deviations during shipping to sites and depots, refer to Section 4 of the ISF for instructions. Study medication may only be dispensed to trial subjects according to the protocol by authorised personnel as documented on the Trial Staff List in the ISF.

4.1.8 Drug accountability

The Investigator or pharmacist or investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of 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
- If applicable, availability of the proof of a medical license for the principal Investigator
- For USA, availability of Form 1572

For Japan, the Investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the Sponsor after IRB / ethics committee approval of the trial and completion of a clinical trial contract between the Sponsor and the Head of Trial Center.

The Investigator or 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 alternative disposal of unused products.

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 that document adequately that the patients were provided the doses specified by the CTP 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 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

There are no special emergency procedures to be followed.

Background medication:

All patients will receive standard of care (SOC) treatment for lupus nephritis based on MMF:

SOC Initial phase (week 1 – 26):

- MMF: patients who are already on MMF of 2 g/day or a maximum of 3 g/day should stay at same MMF dose, provided that they have tolerated it well. Patients who start treatment with MMF or patients with a dose <2g/day should be increased to a stable MMF dose of 2g/day. It is recommended not to increase MMF above 2g/day to reduce the risk of severe side-effects of MMF. In case of side effects related to MMF, a MMF dose < 2g/day is allowed.
- AND glucocorticosteroids (GC) (methylprednisolone, recommended 500mg pulse IV for 3 days) followed by oral glucocorticosteroids, tapering to 10mg prednisone equivalent/day within 12 weeks. Tapering of steroids should follow the tapering schedule in Appendix 10.1. Patients who have had already a course of IV steroids (up to a total dose of maximum 3g if it had been considered necessary by the investigator) within 6 weeks prior to randomization should not necessarily repeat it depending on what they received. They should only have necessary pulses to reach a total of 1.5g IV steroids. E.g : if they have already received 2 pulses of 500mg, they will just receive one additional pulse. If they have already had 3 *500 mg, they simply do not repeat any IV pulse. If considered necessary by the investigator, a maximal dose of 1000 mg methylprednisolone per day for up to 3 days (maximal 3000mg) is acceptable.

SOC week 26 – 52:

- Mycophenolate mofetil (MMF) 1 to 2 g/day stable + low-dose (<= 10 mg/day) prednisone-equivalent

From week 26 only, in case of side effects: MMF may be reduced to 1g/day or in case of non tolerability, patients could be switched to Azathioprine (AZA) 2mg/kg/day + (<= 10 mg/day) prednisone-equivalent low-dose daily.

In patients who experience a worsening or a flare, the investigator is allowed to increase the steroid dose for the patient. These patients are allowed to continue treatment with BI 655064 until week 52..

During the participation in the trial, SOC medication has to be prescribed by the investigator. Boehringer-Ingelheim will reimburse costs for SOC for this period according to local regulations, or will provide the drugs according to local regulations.

Adjunctive treatments:

All patients should stay on their respective treatment if started before screening such as:

- Hydroxychloroquine (HCQ) 200 – 400 mg/day or other anti-malarial
- Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
- Statins.

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

There are no special emergency procedures to be followed.

Management of Adverse Events:

- In case a patient develops a serious infection during the treatment in the study, treatment with BI 655064 and MMF (respectively azathioprine) will be interrupted. Treatment with BI 655064 and MMF will be restarted when the patient has recovered according to investigator's assessment. In addition, patients who develop recurrent infections should have their serum IgM and IgG measured according to investigator's assessment.

- In case a patient develops a thrombosis suspected to be related to immunosuppression during the treatment in the study, treatment with BI 655064 and MMF (respectively azathioprine) will be interrupted and antithrombotic therapy has to be started. Treatment with BI 655064 and/or MMF(respectively azathioprine) may be restarted when the patient has recovered according to investigator's assessment.

- In case of suspected hepatic injury (refer to section 5.3.5.1 for definition of hepatic injury) during the treatment in the study, treatment with BI 655064 has to be stopped. In case 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 emergency surgery during treatment in the study, treatment with BI 655064 and MMF (respectively azathioprine) will be interrupted. Treatment with BI 655064 and MMF (respectively azathioprine) 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 MMF (respectively azathioprine) has to be stopped and must not be introduced again.

- In case of occurrence of lymphoproliferative diseases, treatment with BI 655064 and MMF (respectively azathioprine) has to be stopped and must not be introduced again.

- In case of side effects known to be related to higher doses of MMF (respectively azathioprine), dose reduction of MMF (respectively azathioprine) should be considered according to investigator's judgement.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

The Table 4.2.2.1: 1 specifies periods before randomization and for the whole duration of the study including the Follow-up, when specific drugs are allowed or restricted.

Table 4.2.2.1: 1 Permitted and Restricted medications

Therapy	**Prior to Study**	**Screening Period**	**Randomized Treatment Period**		**Follow up Period**
			SOC Initial phase week 0-26	**SOC week 26-52**	
Azathioprine	Permitted on maintenance therapy	Permitted on maintenance therapy	Not permitted	Permitted if MMF not tolerated or not authorised	Permitted
Cyclophosphamide	Not permitted (6 m prior to randomisation)	Not permitted	Not permitted	Not permitted	Not Permitted
MMF	Permitted if dose ≤2 g/day; doses≤ 3g/day permitted within 6 weeks prior randomisation	Permitted within 6 weeks prior randomisation	Permitted max 3g/day	Permitted Max 2g/day	Permitted
Cyclosporine - Tacrolimus	Not permitted 4 weeks before randomisation	Not permitted	Not permitted	Not permitted	Permitted if needed based on inv decision
Treatment with any biologic B-cell depleting therapy (e.g. anti-CD20,antiCD22) or abatacept*	Not permitted (12 m prior to visit 2)	Not permitted	Not permitted	Not permitted	Not permitted
Belimumab, antiBLyS	Not Permitted (3 months or 5 half-lives whichever is longer when used for non renal SLE, 12 months when used for renal SLE)	Not permitted	Not permitted	Not permitted	Not permitted
Investigational Medication	Not permitted (6m or 5 half-lives prior to visit 2)	Not permitted	Not permitted	Not permitted	Not permitted
IV glucocorticoids	Allow 3 g IV total max within 6 weeks prior randomisation; a single pulse should not be >1000 mg		Permitted as part of the trial regimen, according to the protocol	Not permitted	Permitted

4.2.2.2 Restrictions on diet and life style

Patients should not donate blood during MMF therapy and for at least 6 weeks following discontinuation of MMF.

Men should not donate semen during MMF therapy and for at least 90 days following discontinuation of MMF

During the trial, all patients should avoid intensive physical activity and unprotected exposure to direct sunlight. The use of tanning booths is forbidden. Intensive physical activity is considered activity that is of a higher intensity than usually performed by the individual. Fasting is not required for this study.

4.3 TREATMENT COMPLIANCE

It is recommended that patients take all doses of study 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 should be advised of the importance in adhering to the dosing schedule.

From Visit 4 onwards, a compliance check of the trial medication will be performed at each clinic visit to ensure the weekly injection is being administered correctly at both the trial site and by the patient at home. A MMF dosing will be performed at weeks 12, 26 and 52 to assess compliance to background medication a posteriori. The last two intakes dates and time of MMF taken before the blood sampling will be recorded in RDC, based on patient's interview.

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 unused trial medication and empty cartons with them to their next scheduled visit for compliance check. Any discrepancies should be documented and explained in the eCRF by the investigator or the designee. In addition, patients will be provided with a diary to record the intake of trial medication

At the EOT visit as a minimum, patients are requested to return the sharp bin to the trial site for disposal in accordance with local requirements.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

The primary efficacy endpoint is the proportion of patients with complete renal response at week 52.

5.1.2 Secondary Endpoint(s)

- Proportion of patients with complete renal response at week 26
- Proportion of patients with partial renal response at week 26 and 52
- Proportion of patients with major renal response at week 26 and 52

5.2 ASSESSMENT OF EFFICACY

Assessment of Renal Response:

For primary and secondary efficacy endpoints at baseline (week 0), week 26 and 52, 24h collection of urine will be performed in duplicates (2 times 24 h collection).

A detailed description for urine collection will be provided in the laboratory manual and instructions provided to the patients. At 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 eGFR within normal range; or decrease <20% from baseline if below normal range. Non responder patients withdrawn at 6 months are considered non responders for the 26 and 52 week timepoint for the primary endpoint.
- Partial renal response (PRR) is defined as 50% reduction of proteinuria from baseline and eGFR within normal range or decrease< 20% from baseline if below normal range.
- Major renal response (MRR) is defined as :
    - if baseline proteinuria<3 g/day : CRR at week 52
    - if baseline proteinuria >= 3 g/day : proteinuria <1g/day at week 52.

Renal biopsies:

Renal biopsies slides or electronic files used for the diagnosis as described in inclusion criterion have to be available as biopsies are planned to be re-assessed centrally by one pathologist for retrospective analysis. An additional renal biopsy at the end of treatment is voluntary. The renal biopsy at the end of treatment may provide additional information on remaining activity or chronicity of the renal damage despite clinically low disease activity (R15-3725). Change in renal biopsy at week 52 compared to screening biopsy (only for patients with a biopsy at the end of treatment (See section 5.2)) will be evaluated.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

Physical examinations will be performed as described in the Flow Chart.

Complete physical examination will include weight, vital sign assessment and general appearance as well as evaluation of all organ systems (eyes, ears, nose, mouth, and throat, neck, respiratory, cardiovascular, chest, gastrointestinal, lymphatic, musculoskeletal, skin, neurologic and psychiatric).

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

Height will be measured at screening visit only.

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

5.3.2 Vital Signs

Systolic and diastolic blood pressure and pulse rate will be measured with the patient seated after having rested for at least 5 minutes. All abnormal findings at screening visit will be recorded on the Medical History/Concomitant Diagnosis e-CRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations will be recorded as adverse events on the appropriate e-CRF page

5.3.3 Safety laboratory parameters

The laboratory tests will be performed at a designated central laboratory, and if necessary by additional specialist laboratories. Instructions for sample collection, processing and shipping are provided in the Laboratory Manual in the ISF.

The safety laboratory tests will include:

Table 5.3.3: 1: safety lab parameters

Category	Test name	Frequency
Haematology	Haematocrit (Hct), Haemoglobin (Hb) Red Blood Cell Count/ Erythrocytes White Blood Cells / Leukocytes Platelet Count/ Thrombocytes	Day 1/8 then every visit until EOT (included), repeat after EOT only if clinical significant findings at discretion of investigator
	Erythrocyte sedimentation rate (ESR)	ESR analysed locally day 1/ week 12/26/52
	Reticulocyte Count	Reticulocytes count : day 1/8 then week 4/8/12/26/35/52, repeat after EOT only if clinical significant findings at discretion of investigator
Diff. Automatic	Relative count: Neutrophils, Eosinophil, Basophils, Monocytes, Lymphocytes	Day 1/8 then every visit until EOT (included), repeat after EOT only if clinical significant findings at discretion of investigator
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophil, Basophils, Monocytes,Lymphocytes	Only when diff auto is abnormal (reflex test)
Coagulation	Partial Thromboplastin Time (=aPTT) Prothrombin time (Quick and INR)[2]	PTT and INR Day 1/8 then every visit until EOT (included), repeat after EOT only if clinical significant findings at discretion of investigator
	Fibrinogen	Fibrinogen day 1/8 then week 4/8/12/26/35/52 (after EOT only if findings)
Enzymes	AST(GOT), ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH)	Screening + day 1/8 then every visit until EOT (included), repeat after EOT only if clinical significant findings at discretion of investigator
	Lipase, Amylase	Lipase and amylase : baseline + week 12/26/52
Electrolytes	Calcium, Sodium, Potassium, Chloride	Screening + Day 1/8 then every visit until EOT (included), repeat after EOT only if clinical significant findings at discretion of investigator

Table 5.3.3: 1: safety lab parameters (cont'd)

Category	Test name	Frequency
Substrates	Plasma Glucose	Day 1/8 then every visit until EOT (included), repeat after EOT only if clinical significant findings at discretion of investigator
	Creatinine and calculated Creatinine Clearance (CKD-EPI) Bilirubin Total, Bilirubin Direct and indirect Albumin, Uric Acid, Urea nitrogen	Screening, Day 1/8 then every visit until EOT (included), repeat after EOT only if clinical significant findings at discretion of investigator.
	Cholesterol, triglycerides	baseline + every 4 weeks §
	hsC-Reactive Protein	baseline /w4/8/12/26/35/52
	Haptoglobin	baseline + week 12/26/52
Serum Pregnancy test *	Human Serum Chorionic Gonadotropin	Screening + anytime if urinary test positive
Urine Pregnancy test (only for females of childbearing potential)*	Human Chorionic Gonadotropin in the urine	Screening phase + baseline + every 4 weeks
Urinalysis - dipstick	Urine: Nitrite, Protein, Glucose, Ketone, Bilirubin, RBC/ Erythrocytes, WBC/ Leukocytes, pH, creatinine Urobilinogen	Screening, Day 1/8 then every visit until EOT (included), repeat after EOT only if clinical significant findings at discretion of investigator
Urine	Spot protein/creatinine ratio £	Every visit
Urine-Sediment (microscopic examination,)	Urine: Sediment Bacteria, Cast in Sediment, Squamous Epithel Cells, Sed. Crys., Unspecified, Sediment RBC/ Erythrocytes, Sediment WBC/ Leucocytes	baseline + week 4, 8 and every visit until EOS or if urine analysis abnormal according to investigator (reflex test)
Immunology testing	Total IgG and IgM	baseline + week 12/26/40/52
	ANA,	Screening, Baseline, week 26 and 52
	Anti-ds-DNA, complement C3, C4 anti-C1q antibodies Anti-phospholipid antibodies	Screening, Baseline + week 4/8/12/16/26/30/40/52/EOS
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[#]	Screening only

* Urine (dipstick) pregnancy test will be conducted prior to first study medication administration. In case of a positive urine pregnancy test result, a blood sample for serum pregnancy test will be drawn for confirmation. Only those females with a negative pregnancy test will receive study medication.
** Results of infections screening will not be captured in the sponsor's database
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 screening, the HCV-RNA test can be performed locally to exclude false positive results. If HCV-RNA test is negative, patient may be enrolled (the result must be documented in RDC).
§ or every visit when interval between visits is > 4 weeks
£ is safety/efficacy measurement
in case of an indeterminate result, test could be repeated, in case the result is indeterminate again, a PPD skin test should be performed

Mycophenolate blood levels will be collected at week 12, week 26 and 52. Samples will be analyzed for exploratory reasons after trial completion.

In addition, for primary endpoint assessment, 24h collections of urine (in duplicates) for proteinuria will be done at baseline (week 0), week 26 and 52.

5.3.4 Electrocardiogram

Regular 12-lead Electrocardiograms (ECGs) are conducted during the trial at the visits indicated in the Flow chart. Rate, rhythm and repolarization changes have to be looked at, compared to previous one, and assessed for clinical relevance. Clinically relevant findings must be entered as adverse events and if necessary additional ECGs for control may be performed. Automatically generated interval data (PR, QRS, QT interval) and heart rate on the printed ECG will be collected on the eCRF. QTcB and QTcF will be calculated with HR and QT interval. Signed and dated printouts of either ECG tracings or electronic ECG reports will be kept in the patient's medical file.

5.3.5 Assessment of adverse events

5.3.5.1 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 pharmaceutical 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:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,

- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context 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.

For Japan: The following events will be handled as "deemed serious for any other reason". An AE which possibly leads to disability will be reported as an SAE.

Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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 given above.

The latest list of "Always Serious AEs" can be found in the RDC system. These events should always be reported as SAEs.

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. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.6.

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 $\geq$3 fold ULN combined with an elevation of total bilirubin $\geq$2 fold ULN measured in the same blood draw sample, and/or
- Marked peak aminotransferase (ALT, and/or AST) elevations $\geq$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" via the RDC-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 of 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 characterized 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, 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 4.2.1 of the protocol.

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

Intensity of AEs

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities”

The intensity of adverse events should be classified and recorded in the (e)CRF according to the Rheumatology Common Terminology Criteria for Adverse Events (RCTCAE) version 2.0 developed by OMERACT (R13-3515). Refer to paper version filed in the ISF for RCTCAE intensity/severity classification.
Causal relationship of AEs

Medical judgment 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.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

No: There is no reasonable causal relationship between the investigational product administered and the AE.

The causal relationship must be provided by the Investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (such as any active comparator or placebo).

for japan The reason for the decision on causal relationship for unlisted AEs needs to be provided in the (e)CRF and on the SAE form (if applicable)

5.3.6 Adverse event collection and reporting

AE Collection

The following must be collected and documented on the appropriate eCRF by the Investigator:

- From signing the informed consent onwards through the Residual Effect period (REP), until trial completion, all AEs (serious and non-serious), and all AESIs.

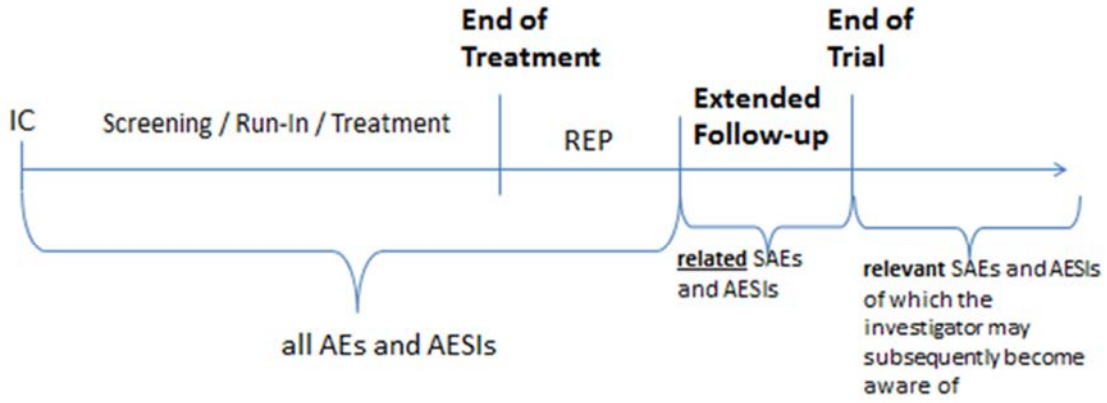

Figure 5.3.6:1 AE collection

The REP is defined as 50 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

After the last per protocol contact the Investigator does not need to actively monitor patients for AEs. However, if the Investigator becomes aware of SAEs or AESIs that occurred after the last per protocol contact, the SAEs and AESIs should be reported by the Investigator to the Sponsor if considered relevant by the Investigator.

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 via fax immediately (within 24 hours) to the Sponsor's unique entry point (country specific contact details will be provided in the ISF). In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

For Japan: All SAEs and AESIs must be reported immediately to the head of the trial site. 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 (e)CRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication, and any possible interactions between the investigational drug and a Non-Investigational Medicinal Product.

The following should also be recorded as an (S)AE in the (e)CRF and 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 trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

SAEs which occurred during the screening period are to be reported according to standard procedures.

Pregnancy

Due to the teratogenic potential of MMF/AZA, highly effective contraception has to be performed. The reliable contraception should be used in female patient before starting MMF therapy and the study drug, during the treatment and until 50 days after stopping MMF and the study drug (and until 90 days after stopping AZA in case of AZA is used).
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 treatment.

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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).

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

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 ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B), as well as information and consent form for the pregnant partner.
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5.6 OTHER ASSESSMENTS

5.7 APPROPRIATENESS OF MEASUREMENTS

The measures conducted for primary and secondary endpoints are using standard methods. Measures conducted for exploratory further endpoints might be new methodologies already used in clinical trials in LN but not yet validated for this rare disease.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

For a detailed overview of the trial procedures and time windows for visits, please refer to the Flow Chart.

The trial consists of a screening visit followed by a one year treatment period and 2 follow-up visits.

The study will last until every evaluable entered patient has completed the last follow-up visit.

After giving his/her Informed Consent, the patient will be screened for inclusion and exclusion criteria for the study at visit 1. Visit 2 will be scheduled after visit 1, after results from central laboratory are obtained (a minimum of 7 days to be planned). The screening phase must not be longer than 4 weeks (from visit 1 to visit 2). The patient will be randomised at visit 2 if all inclusion and none of the exclusion criteria are fulfilled.

Windows of ±1 to ±5 days is allowed for a majority of visits, to accommodate scheduling problems. If a delay is observed for a particular visit, the original calendar schedule should be kept for subsequent visits (delays should not accumulate). If a visit is missed the patient should be instructed to come for a visit as soon as possible. Investigator should contact the BI monitor to discuss further schedule.

Follow up visits have to be organized at 4 and 8 weeks after End of treatment

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period

Written informed consent must be obtained before any protocol specific screening assessments are performed.

The screening visit should take place within 7-28 days prior to randomization (Visit 2). All study procedures and assessments including the repeated tests in determining the patient's eligibility must be available prior to Visit 2.

Patients must satisfy all inclusion and exclusion criteria prior to randomization (Visit 2).

Details of any patient who is screened for the study but is found ineligible must be entered in an enrolment log (see ISF) and documented in the eCRF.

It is allowed to re-test (once) a lab parameter that is found abnormal at visit 1 if it is thought to be a measurement error (i.e. there was no abnormal result of this test in the recent history of the patient and there is no related clinical sign)".

It is allowed to re-test the proteinuria if the result from spot ratio at screening visit does not correspond to recent measurements done at site. In that case it is preferred to do a 24h measurement.

For a detailed description of the trial procedures at the screening visit, refer to Flow Chart.

Baseline Conditions/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 TCM/TMM prior to randomization. History of antiphospholipid syndrome should be recorded and patients should be excluded from the study.

Pregancy tests:

Serum pregnancy test will be perfomed at screening visit. A urine dipstick test will be done during the screening phase and immediately before starting medication. In case of a positive urine pregnancy test result, a blood sample for serum pregnancy test will be drawn for confirmation. Only those females with a negative pregnancy test will start treatment with MMF and will receive study medication.

6.2.2 Treatment period(s)

For details description of trial procedures during the treatment period, refer to Flow Chart. Only additional critical information is listed below.

Eligible patients will be randomised to receive the first dose of study medication at Visit 2. Each patient can only be randomised once in the trial via IRT.

Visit 2, 2.1, 2.2: drug administration:

The induction phase with SOC might have started for some patients already before the randomisation in the trial.

- MMF: if the patient is naïve with MMF or has received a dose < 2g/day, he will start receiving 2-3g/day MMF at visit 2

- Intravenous Glucocorticoids: patients who have not yet received any high dose pulse IV steroids will receive 500 mg methylprednisolone for 3 days (visits 2, 2.1, 2.2). If considered necessary by the investigator, a maximal dose of 1000 mg methylprednisolone for 3 days is acceptable. In case the patient had already received pulse steroids (max 3g total within last 6 weeks) he will receive additional IV steroids only to reach 1.5g total. If the 1.5 g is reached the visit 2.1 and 2.2 are not necessary.

The investigator will prescribe daily oral steroids starting the day after the last IV steroids. Refer to section 4.2.1. This should be tapered down to 10 mg prednisone equivalent within 12 weeks.

drug injection:

For all other weekly injection, this can either be administered on-site or at home by the patient.

Urine collection:

At visit 2 and 11 and 16, 2 times 24h collection of urine will be performed. The patient will be given instructions and material to allow collection of urine during 2 days in the week preceding the visit. At other time points, proteinuria will be assessed by spot urine.

Drug administration:

According to the Flow Chart the patients will be receiving the syringes necessary for the next week(s) injection at home between two visits. The patients will be given instructions for injection and treatment number, and a diary to record the exact date and time of injection

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

6.2.3 Follow Up Period and Trial Completion

6.2.3.1 End of Treatment (EOT) Visit:

All patients will be asked to return for the EOT visit within 7 days from the last dose of study medication (either at week 52 for completers, or when a patient prematurely discontinues the drug). For details description of the trial procedures at EOT, refer to the Flow Chart. 2 times 24h collection of urine has to be organized for this visit.

For patients that are eligible to participate in the extension trial 1293.13, the EOT visit will occur on the same day as the Visit 1 of the roll-over trial.

6.2.3.2 Follow-Up (FU) and End of Study (EOS) Visit:

After the end of treatment visit, patients who completed the 52 weeks treatment but are not eligible for the extension trial will return for a follow-up visit (after 4 weeks) and an EOS visit, 8 weeks after EOT.

Patients who are eligible for the extension trial will not have to complete the FU visit nor the EOS visit, but only the trial completion page will have to be completed.

During FU and EOS visits, the investigator will continue to follow-up on AEs that are not yet recovered. 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 details description of the trial procedures at FU and EOS visits, refer to the Flow Chart.

6.2.3.3 Continuation of the study for patients who withdrew drug prematurely (before completion of the 52 weeks treatment):

In case a patient has to discontinue the trial drug, prior to having completed the 52 weeks treatment (i.e., prior to visit 16), he will be invited to attend a subset of visits as originally planned until and including visit 16: visit 5 (week 4), visit 8 (week 12), visit 11 (week 26), visit 14 (week 40) and an end of study visit at 52 weeks. During these visits, the patient should undergo selected examinations: physical examination, AE and CT collection, serum creatinine and spot urine test to assess the renal function. Other safety laboratory tests, PK sample, ADA, soluble protein biomarkers and anti-ds-DNA and complement will be collected at all visits until up to 12 weeks after End of Treatment. If the next FUP visit is planned more than 12 weeks after EOT, please have all optional tests performed at least once in the FUP period: i.e. if the patient EOT is V11 (W26), the next visit will be V14 (week 40): optional tests must be done at week 40, even if the time between week 26 &40 is >12 weeks.

The visits may continue even though the patient will be allowed to participate in another investigational study after his withdrawal (discontinuation plus 28 days). The need for visits in case of premature drug withdrawal will be explained to the patients. In case the patient discontinued more than 8 weeks before week 52, no further follow up would be needed after week 52. In case the patient discontinued less than 8 weeks before week 52, the last follow-up visit will be 8 weeks +/- 5 days after discontinuation. In case the patient does not show-up at these visits, vital status information will be sought at planned EOS visit.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial is a study of proof of concept in patients with lupus nephritis. It is designed as a randomized, double-blind and placebo-controlled trial with 4 parallel groups (3 active vs. placebo).

The primary objective of this trial is to define one or more suitable doses regarding efficacy and safety for further pivotal testing in Phase III. For this purpose a multiple comparison procedure with modelling (MCPmod) approach is considered (R10-1424, R15-1961).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The primary endpoint is proportion of patients with complete renal response at week 52. The null hypothesis is that there is a flat dose response curve looking at the proportion of patients with complete renal response at week 52 in the placebo and the three BI 655064 dosage groups. The alternative hypothesis is that there is a non-flat dose response curve. Additionally it will be investigated whether at least one dose shows a modelled absolute benefit compared to placebo of at least 10%.

The MCPMod procedure allows for the simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of type I error of 20%. The pre-specified models and their parameters used for this test are outlined in Section 7.3.1 and Section 7.7.

This is an exploratory trial and no formal statistical testing will be performed. Any p-values or confidence intervals provided are to be interpreted in an exploratory sense.

7.3 PLANNED ANALYSES

All the analyses will be performed in an exploratory fashion to better-understand the efficacy and safety profile of the drug under study in the selected patient population. The primary analysis will follow the intention to treat principle (ITT), thus it is based on the FAS (Full Analysis Set) and analysis will be performed as randomised. The FAS contains all treated patients who have a valid baseline value and at least one valid value in at least one primary or secondary efficacy endpoint on treatment.

Safety analysis will be based on all treated patients and the safety profile will be compared in a descriptive manner between the three 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 I the TSAP. Standard statistical parameters (number of non-missing values, mean, standard deviation (SD), 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.

Data from subjects who are screened but not randomised will be listed but not included in any summary statistics.

7.3.1 Primary endpoint analyses

The primary endpoint is the proportion of patients with complete renal response after 52 weeks of treatment. Patients withdrawn due to non-response are considered non-responders for the analyses at 52 weeks.

The analyses for PoC and dose-finding will be performed using MCPMod techniques (R10-1424, R15-1961)for binary data whereby several possible dose response models (patterns) will be evaluated (while keeping full control of the type I error) to identify the best-fitting model or subset of models. Due to the rareness of the disease and in order to have a feasible resulting sample size the global α-level has been chosen to be 20% one-sided.

A non-flat dose-response relationship is established if the null hypothesis of no dose effect (i.e. a flat dose response curve) is rejected for at least one of the pre-specified models with respect to the global alpha chosen.

For the sample size calculation, the maximum effect size is assumed to be 45% with the placebo effect size assumed to be 25%. Further details are given in Section 7.7.

The following models shapes have been selected as the candidate set of possible dose response patterns:

Emax : E0+Emax *d/(ED50 + d)]

Exponential : E0 + E1 * (exp(d/delta) - 1)

Quadratic : E0 + beta1 * d + beta2*d^2

Sigmoid Emax : E0 + Emax * d^h / (ED50^h + d^h)Model shapes are illustrated in figure 7-3-1: 1. Note that the actual shapes are applied on the parameter scale (logit for binary data) according to Pinheiro et al. (R15-4293).

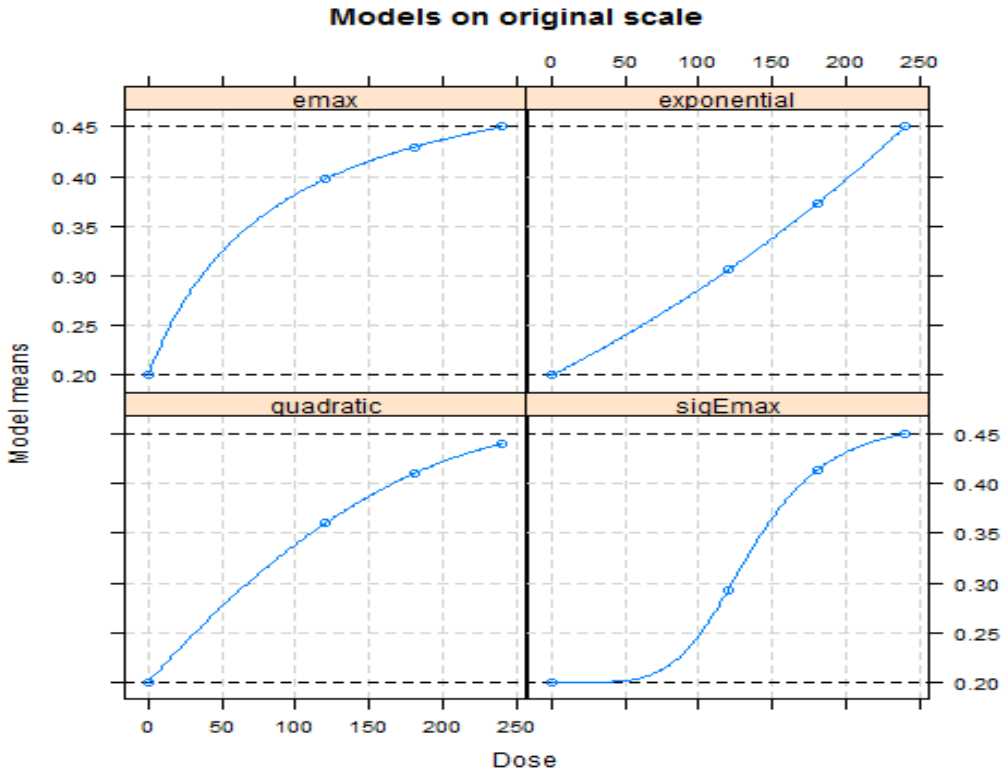

Figure 7.3.1 : 1: Shape of the models within the candidate set

If a non-flat dose response relationship is established, the significant model(s) from the above candidate set are refitted to the data without any parameter assumptions to generate new estimates of the model parameters from the data. The final model will be obtained via model averaging across the significant models based on Akaike Information Criterion (AIC). The target dose(s) can then be determined from that model by any incorporating information on the minimum clinically relevant effect as well as safety information. The target dose to be chosen should show a benefit of at least 10% in complete renal response rate at week 52 compared to the placebo. This will be measured on the modelled efficacy and only doses within the dose range investigated (0mg-240mg) will be considered although the actual modelling will be performed on a broader range of doses including extrapolation.

If considered necessary and for the purpose of further model refinement, MCPMod might be repeated on the primary endpoint but with an extended set of shapes including the original candidates. Additionally to that covariates may be taken into account in a sensitivity analysis. Finally the approach described by Klingenberg et al (R15-0407) will be taken into account to show robustness of the primary analysis. Details of these analyses will be described in the TSAP.

Comparisons between treatment groups will be exploratory in nature and based on the numerical comparison of the respective response rates. In addition, unadjusted absolute risk differences of the complete renal response at week 52 between the BI 655064 arms and the placebo group will be analysed. The proportion of responders in each arm, the risk difference

between each arm and placebo and 95% exact confidence intervals will be displayed. Finally, a logistic regression model on the proportion of patients with complete renal response at week 52 with factors treatment and race as strata will be applied. More details on the above analyses as well as additional sensitivity analyses will be given in the TSAP.

7.3.2 Secondary endpoint analyses

If considered necessary an MCPMod approach will also be applied to selected secondary endpoints.

Comparisons between treatment groups will be exploratory in nature and based on the numerical comparison of the respective response rates. In addition, unadjusted absolute risk differences of the response rates at week 52 between the BI 655064 arms and the placebo group will be analysed. The proportion of responders in each arm, the risk difference between each arm and placebo and 95% exact confidence intervals will be displayed.

Further details will be given in the TSAP.

7.3.4 Safety analyses

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. 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 treatment period for evaluation. Analysis will be performed based on randomised treatment.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The residual effect period is defined as 50 days. 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 Medical Dictionary for Drug Regulatory Activities (MedDRA).

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 highlighted in the

listings. 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

An interim analysis via an internal but independent team will be performed after all patients, complete 26 weeks of treatment. Alpha adjustments will not be made due to the exploratory nature of the assessment. At that timepoint, a preliminary database lock will be performed.

The independent team will review all available unblinded safety, efficacy This review is for internal planning purposes to facilitate further substance development. An interim analysis trial statistical plan will be written to define which functions will have access to the unblinded data.

7.5 HANDLING OF MISSING DATA

As an imputation technique to deal with the missing data in this study, for the analysis of primary and secondary endpoints, non-completers considered failure (NCF) will be used. All other endpoints will be analysed without imputing for any missing data.

7.6 RANDOMISATION

An IRT will be used for the assignment of subjects to treatment groups. Randomisation will be done with stratification by ethnicity (Asians vs Non- Asian) and proteinuria at screening <3g/day or ≥ 3g/day (respectively UP/UC<3 or UP/UC≥3)
. The influence of covariates (in particular with regard to Hispanics and Black / African-Americans) will be analyzed in a sensitivity analyses.

Patients will be randomized in blocks to double-blind treatment. Patients will be randomized to placebo and each treatment group in the following ratio 2:1:1:2 (approx. 40 patients allocated to placebo and 240mg, approx. 20 patients each to 120mg and 180mg). BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

The aims of this study are two-fold. A first aim is to show a significant non-flat dose-response curve across the different doses and placebo. Additionally to that at least one modelled dose within the dose range considered [0mg, 240mg] should show a benefit of at least 10% compared to placebo.

Assumptions for the efficacy of the different doses are provided in the table below.

Based on these assumptions and the planned sample size of 120 (=40:20:20:40) the success probability is approximately 82% for the base case of approximately 20% treatment benefit compared to placebo (45% vs 25% complete renal response rate at week 52). In case that there is only a minor treatment benefit the false success probability is basically limited by the α-level for the significance testing of the non-flat dose-response curve that is 20%.

Table 7.7:1: Success probabilities under different efficacy assumptions

Dose/ Scenario	0	120	180	240	Max. Effect	Sample Size	Alpha	Delta	Simulated power
Expected A	**0.25**	**0.30**	**0.38**	**0.44**	**0.45**	**40:20:20:40**	**20%**	**10%**	**82%**
Expected B	0.25	0.30	0.38	0.44	0.45	35:35:35:35	20%	10%	81%
Type I	**0.25**	**0.255**	**0.26**	**0.265**	**0.27**	**40:20:20:40**	**20%**	**10%**	**21%**
Shift	0.45	0.5	0.58	0.64	0.65	40:20:20:40	20%	10%	80%
Bad	0.25	0.275	0.30	0.34	0.35	40:20:20:40	20%	10%	49%
Type I Shift	0.45	0.455	0.46	0.465	0.47	40:20:20:40	20%	10%	22%

Success probabilities under different efficacy assumptions for the defined success criteria of 1) Significant non-flat dose-response AND 2) Treatment benefit of at least delta compared to placebo for at least one modelled dose within the considered dose range

Scenarios considered:

- Expected A: Main scenario reflecting assumptions for efficacy of 25% (placebo), 30% (low dose), 38% (medium dose), 44% (high dose) and 45% (maximum efficacy). Sample size considered is 40:20:20:40=120 patients with a 2:1:1:2 allocation.
- Expected B: Same scenario as A but for equal allocation and a larger sample size of 140 total. Shows that 'Expected A' (unequal allocation) with 120 patients provides approximately the same success probability with 120 patients as 'Expected B' (equal allocation) with 140 patients.
- Type I: Scenario reflecting almost no treatment benefit. Difference between maximum efficacy and placebo is 2% only (27%-25%). Shows that error probability is approx. 20% in such a case which is driven by the alpha for dose-response curve testing.
- Shift: Same benefit of treatment to placebo in efficacy but with a shift of 20% in all assumed response rates. Shows that success probability is robust if actual response rates are quite different from 'guesstimates' given by 'Expected A' scenario.
- Type 1 Shift: Shift scenario for very small treatment benefit of 2% only. Shows that still alpha drives error probability if actual response rates are quite different from 'guesstimates'.
- Bad: Scenario with a low treatment benefit of 10% maximum compared to placebo. Represents a 'worse-case' scenario of treatment where treatment benefit is in a region where it is borderline efficacious.

Calculations were performed using R version 3.1.3.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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) and relevant BI Standard Operating Procedures (SOPs) and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in 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 subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP*.

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 finalization of the Clinical Trial Report.

For japan: The rights of the investigator / trial site and of the sponsor with regard to publication of the results of this trial are described in the investigator contract / trial site's contract. As a general 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 (Investigator Site File)."

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND 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: The Investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is 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.

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

eCRFfor 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

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

All data must be derived from source documents

8.3.2 Direct access to source data and documents

The Investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in section 8.3.1.

8.3.3 Storage period of records

For Japan:

Trial site(s):
The trial site(s) must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and trial site's contract with the sponsor.

Sponsor:
The Sponsor must retain the essential documents according to the Sponsor's SOPs. When it is no longer necessary for the trial site to retain the source documents and essential documents, the Sponsor must notify the head of trial site.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For the BI655064 this is the current version of the Investigator's Brochure (U11-1925)

For non-investigational medicinal products the reference document are the SmPC for MMF and a representative SmPC for methylprednisolone (UK SmPC). The current versions of these reference documents are provided in the ISF. No AE are classified as listed for matching placebo, trial design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, will be done according to local regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

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

8.6 END OF TRIAL

The end of the trial is defined as last patient out, which is when the last patient will have completed his/her 52 weeks treatment and the follow-up period (or has entered the extension trial). See section 6.2.3.

The IEC / competent authority in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.

For japan: When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and Sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

For Japan:

The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

For Japan: In the event of health injury associated with this trial, the Sponsor is responsible for compensation based on the contract signed by the trial site.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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9.2 UNPUBLISHED REFERENCES

U11-1925 Investigator’s Brochure, BI 655064

10. APPENDICES

10.1 STEROIDS TAPERING SCHEDULE 1293.10

Doses should be based on body weight at baseline (week 0) and tapering schedule should be according the respective body weight class.

mg reference is to prednisone equivalent

Body weight below 60 kg (reference 50 kg):
Week1-2: 25 mg
Week 3-4: 20 mg
Week 5-6: 17.5 mg
Week 7-8: 15 mg
Week 9-10: 12.5 mg
Week 11-12: 10 mg
Week 13 onwards: ≤ 10 mg

Body weight 60 -80 kg (reference 70kg):
Week 1-2: 35 mg
Week 3-4: 30 mg
Week 5-6: 25 mg
Week 7-8: 20 mg
Week 9-10: 15 mg
Week 11-12: 12.5 mg
Week 13 onwards: ≤ 10 mg

Body weight above 80 kg (reference 90 kg):
Week1: 45 mg
Week 2: 40 mg
Week 3-4: 35 mg
Week 5-6: 30 mg
Week 7-8: 25 mg
Week 9-10: 20 mg
Week 11 15 mg
Week -12: 12.5 mg
Week 13 onwards: ≤ 10 mg

It is allowed to increase the steroid dose once during these 12 weeks but patients should reach the 10 mg at week 12. In case tapering of steroids is already started before randomization, the tapering schedule can be adapted but should not exceed to dose recommended in the schedule for the respective week. Latest from week 13 onwards, the dose should be 10 mg prednisone equivalent or less.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		24-NOV-2015
EudraCT number		2015-001750-15
BI Trial number		1293.10
BI Investigational Product(s)		BI 655064
Title of protocol		A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year of treatment, in patients with active lupus nephritis
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		3.3.2
Description of change		3.Diagnosis of systemic lupus erythematosus (SLE) by ACR criteria 1997, at least 4 criteria must be documented, one of which must be a positive anti-dsDNA antibody at screening was changed to 3.Diagnosis of systemic lupus erythematosus (SLE) by ACR criteria 1997, at least 4 criteria must be documented, one of which must be a positive anti-dsDNA antibody at screening or around time of start of induction therapy
Rationale for change		Initial information from central lab was that time needed to obtain results of anti ds-DNA would be up to 10 days. Revised information was that it

		could be up to 21 days. Many patients may start induction therapy already before screening and the protocol allows up to 4 weeks between start of induction therapy and randomization. With a turnaround time of up to 21 days for the anti ds-DNA test, patients who started induction therapy 2 to 3 weeks before screening would not be able to participate in the trial. The criterion has been revised to allow more flexibility so that patients with positive anti ds-DNA diagnosed near the start of induction therapy can be included in the trial.
Section to be changed		3.3.3
Description of change		Addition of one exclusion criterion : Live vaccination within 6 weeks before randomisation
Rationale for change		To avoid inclusion of patients who received live vaccination in order to improve patient safety

Number of global amendment		2
Date of CTP revision		02-FEB-2016
EudraCT number		2015-001750-15
BI Trial number		1293.10
BI Investigational Product(s)		BI 655064
Title of protocol		A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year of treatment, in patients with active lupus nephritis
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		SYNOPSIS: Section main criteria for inclusion
Description of change		4. Active renal disease evidenced by proteinuria ≥ 1.0 g/day (Uprot/Ucrea > 100 mg/mmol) was changed to: 4. Active renal disease evidenced by proteinuria ≥ 1.0 g/day (Uprot/Ucrea ≥ 100 mg/mmol)
Rationale for change		Typo
Section to be changed		FLOW CHART
Description of change		24h collection of urine – duplicate Was changed to 2 x 24h urine collection
Rationale for change		Consistency with first page of flow chart

Number of global amendment		2
Section to be changed		FLOW CHART Foot note 7
Description of change		In case of a positive urine pregnancy test result, a blood sample for serum pregnancy test will be drawn for confirmation. Only those females with a negative pregnancy test will receive study medication Was changed to Pregnancy test will be performed in women of childbearing potential every 4 weeks. A serum pregnancy test will be performed at screening visit. Urine dipstick tests will be done during the screening phase (8-10 days after the first test) and immediately before starting medication. It will be repeated at visits every 4 weeks and will be provided for at home pregnancy testing as soon as visit intervals are > 4 weeks. In case of a positive urine pregnancy test result, a blood sample for serum pregnancy test will be drawn for confirmation. Only those females with a negative pregnancy test will receive study medication and will be allowed to start treatment with MMF
Rationale for change		Additional requirements for pregnancy tests due to MMF new SmPC
Section to be changed		1.2 DRUG PROFILE
Description of change		For a more detailed description of the drug profile refer to the current Investigator's Brochure (IB) (U11-1925) which is included in the Investigator Site File (ISF). Was changed to For a more detailed description of the drug profile refer to the current Investigator's Brochure (IB) (U11-1925) which is included in the Investigator Site File (ISF). In the trial MMF and glucocorticoids are used as background medication, please refer to the current prescribing information for a more detailed description of these drugs.

Rationale for change		Provide reference to background information for MMF and glucocorticoids
Number of global amendment		2
Section to be changed		2.1 RATIONAL FOR PERFORMING THE TRIAL
Description of change		Rationale for SOC selection There is no approved treatment for LN but the off-label use of MMF or CYC is recommended by the ACR (R12-4273) and the EULAR/ERA-EDTA guidelines (R12-4921) and are therefore considered standard of care treatments. The efficacy of MMF- and CYC-based induction therapy in LN is quite comparable (R15-3723 and R15-5330). For this trial, MMF-based SOC was selected based on feedback from international experts who in the majority presently recommend MMF. MMF is a non investigational product in this trial. Was changed to Rationale for SOC selection There is no approved treatment for LN but the ACR (R12-4273) and the EULAR/ERA-EDTA guidelines (R12-4921) recommend the use of MMF or CYC in combination with glucocorticoids, starting with three consecutive pulses of intravenous (i.v.) methylprednisolone, and followed by oral glucocorticoids. The efficacy of MMF- and CYC-based induction therapy in LN is quite comparable (R15-3723 and R15-5330). For this trial, MMF-based SOC in combination with glucocorticoids with initial i.v. methylprednisolone pulse was selected based on feedback from international experts who in the majority presently recommend MMF. MMF and i.v. methylprednisolone are non investigational products in this trial.
Rationale for change		To clarify that the complete treatment regimen used as background medication is standard of care and not only MMF ; To clarify that IV methylprednisolone is also a Non Investigational Product in the trial

Number of global amendment		2
Section to be changed		2.3 BENEFIT-RISK ASSESSMENT
Description of change		The following was added : Treatment with MMF is associated with higher risk of infections, blood and lymphatic system, gastrointestinal side effects, and teratogenicity. For further details please refer to the current prescribing information Treatment with i.v. glucocorticoids is associated with higher risk of infections. For further details please refer to the current prescribing information
Rationale for change		Addition of main risks of treatment with MMF and i.v. glucocorticoids

Number of global amendment		2
Section to be changed		3.3.2 Inclusion criteria
Description of change		Male or female patients. Women of childbearing potential* must be ready and able (as assessed by investigator) to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. Was changed to Male or female patients. Women of childbearing potential* must be ready and able (as assessed by investigator) to use simultaneously two highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. The contraception should be used before starting MMF therapy and the study drug, during the treatment and until 6 weeks after stopping MMF and the study drug. 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 and for at least 90 days after cessation of MMF treatment. Foot note was added : $ Condom use applies for both reproductively competent and vasectomized 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
Rationale for change		CTP changed to reflect updated SmPC for MMF with more restrictive contraception rules

Number of global amendment		2
Section to be changed		4.2.1 Rescue medication, emergency procedures, and additional treatment(s)
Description of change		AND glucocorticosteroids (GC) (methylprednisolone 500mg) pulse IV for 3 days followed by oral prednisone, tapering to 10mg prednisone equivalent/day within 12 weeks. Was changed to AND glucocorticosteroids (GC) (methylprednisolone 500mg) pulse IV for 3 days followed by oral glucocorticosteroids, tapering to 10mg prednisone equivalent/day within 12 weeks.
Rationale for change		The type of oral glucocorticosteroid to be used is not specified.
Section to be changed		4.2.2.2.Restrictions on diet and life style
Description of change		The following was added: Patients should not donate blood during MMF therapy and for at least 6 weeks following discontinuation of MMF. Men should not donate semen during MMF therapy and for at least 90 days following discontinuation of MMF
Rationale for change		CTP changed to reflect updated SmPC for MMF with new recommendations regarding blood and semen donation.

Number of global amendment		2
Section to be changed		Table 5.3.3.1 : Frequency of urinary pregnancy tests
Description of change		Baseline + Visit 5, 7 (week 4 and 8) and then every visit Was changed to Screening phase + baseline + every 4 weeks
Rationale for change		Additional requirements for pregnancy tests due to MMF new SmPC
Section to be changed		5.3.6
Description of change		Pregnancy In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used. Was changed to Pregnancy Due to the teratogenic potential of MMF, highly effective contraception has to be performed In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.
Rationale for change		Additional requirements for pregnancy tests due to MMF new SmPC

Number of global amendment		2
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		The following was added : Pregancy tests : Serum pregnancy test will be perfomed at screening visit. A urine dipstick test will be done during the screening phase and immediately before starting medication. In case of a positive urine pregnancy test result, a blood sample for serum pregnancy test will be drawn for confirmation. Only those females with a negative pregnancy test will start treatment with MMF and will receive study medication.
Rationale for change		Additional requirements for pregnancy tests due to MMF new SmPC
Section to be changed		8.4.1 Listedness
Description of change		For a non-investigational medicinal product the reference document is the SmPC. The current versions of these reference documents are provided in the ISF. No AE are classified as listed for matching placebo, trial design, or invasive procedures. Was changed to For non-investigational medicinal products the reference document are the SmPC for MMF and a representative SmPC for methylprednisolone (UK SmPC). The current versions of these reference documents are provided in the ISF. No AE are classified as listed for matching placebo, trial design, or invasive procedures.
Rationale for change		Reference document for non investigational products are clarified

Number of global amendment		3
Date of CTP revision		24-Nov-2016
EudraCT number		2015-001750-15
BI Trial number		1293.10
BI Investigational Product(s)		BI 655064
Title of protocol		A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year of treatment, in patients with active lupus nephritis
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		Flow Chart
Description of change		Addition of measurement of - Neutralising anti BI655064 antibody measurement at same timepoints than ADA - Urine mi-RNA
Rationale for change		This measurement was in the text (sections 5.4.1 and 5.4.2 for nAB and 5.5 for miRNA) but missing in the flow chart
Section to be changed		Flow Chart
Description of change		Addition of Vital status collection at End of Study Addition of foot note 12 : For randomized patients leaving the study before

		the planned EOS, their vital status should be collected at week 60
Rationale for change		In order to have as much information as possible on vital status of patients after one year and avoid missing information.
Section to be changed		1.2 DRUG PROFILE Clinical Profile
Description of change		

Rationale for change		Updated according to the new Investigator Brochure.
Section to be changed		2.3 BENEFIT - RISK ASSESSMENT
Description of change		

Rationale for change		Updated according to the new Investigator Brochure.
Section to be changed		2.3 BENEFIT - RISK ASSESSMENT
Description of change		It is important to note that all patients in this study will receive standard of care treatment for lupus nephritis. The majority of patients (2/3) will be randomized to add-on treatment of BI 655064 to

		SOC and even the lower dose of BI 655064 is expected to show some additional clinical benefit based on modelling of PK and PD. Patients in the placebo group will receive placebo to BI 655064 as add-on to standard of care treatment for lupus nephritis. After 6 months of treatment, the patient's response will be assessed, and patients who do not respond will be recommended to consider other therapeutic options. Was changed to It is important to note that all patients in this study will receive standard of care treatment for lupus nephritis. The majority of patients (2/3) will be randomized to add-on treatment of BI 655064 to SOC and even the lower dose of BI 655064 is expected to show some additional clinical benefit based on modelling of PK and PD. Patients in the placebo group will receive placebo to BI 655064 as add-on to standard of care treatment for lupus nephritis.
Rationale for change		During all duration of the study there is the possibility to withdraw patient and this sentence if found to be confusing
Section to be changed		3.3.2 Inclusion criteria
Description of change		1. Male or female patients. Women of childbearing potential* must be ready and able (as assessed by investigator) to use simultaneously two highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. The contraception should be used before starting MMF therapy and the study drug, during the treatment and until 6 weeks after stopping MMF and the study drug. 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 and for at least 90 days after cessation of MMF

		treatment. Was changed to 1. Male or female patients. Women of childbearing potential* must be ready and able (as assessed by investigator) to use simultaneously two reliable methods of birth control, one of which should be highly effective. Highly effective method, 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 contraception should be used before starting MMF therapy and the study drug, during the treatment and until 50 days after stopping MMF and the study drug. 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 and for at least 90 days after cessation of MMF treatment.
Rationale for change		Cellcept recommendations are to have effective contraception by using two reliable methods. Highly effective methods as described by ICH are quite limited and it is found inadequate to ask women to have two methods of Highly effective contraception
Section to be changed		Foot note definition of WOCBP
Description of change		*Women of childbearing potential are defined as: Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below. Women not of childbearing potential are defined as: Women who are postmenopausal (12 months with

		no menses without an alternative medical cause) or who are permanently sterilized (e.g, tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy). Was changed to *Women of childbearing potential are defined as: Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below. Women not of childbearing potential are defined as: Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).
Rationale for change		Tubal occlusion is not acknowledged as a sterilisation procedure anymore and is instead considered a contraception measure
Section to be changed		3.3.2 Exclusion criteria
Description of change		5. Antiphospholipid syndrome, defined as history of any thrombotic event and positive antiphospholipid antibodies Was changed to 5. Antiphospholipid syndrome, defined as positive antiphospholipid antibodies and either history of any thrombotic event or history of miscarriage
Rationale for change		Requested by some authorities
Section to be changed		3.3.3. Exclusion criteria #8
Description of change		• Treatment with any biologic B-cell depleting therapy (e.g. anti-CD20, anti-CD22, antiBLys,) within *12 months* prior to randomisation Was changed to • Treatment with any biologic B-cell depleting therapy (e.g. anti-CD20, anti-

		CD22,) within *12 months* prior to randomisation • Treatment with Belimumab or other anti BLyS: when used for treatment of non-renal SLE 3 months or 5 half.lives whichever is longer, when used for treatment of Lupus nephrits: 12 months prior to randomisation
Rationale for change		To allow faster participation of patients who were treated with Belimumab or other anit-Blys therapy for non-renal SLE before developing lupus nephritis
Section to be changed		3.3.3 Exclusion criteria Ex criterion 9
Description of change		Contraindications for SOC medication used in this trial : mycophenolate mofetil or corticosteroids Was changed to Contraindications for SOC medication used in this trial : mycophenolate mofetil or corticosteroids and/or known hypersensitivity to any constituents of the study drug
Rationale for change		Requested by some authorities
Section to be changed		3.3.3 Exclusion criteria Ex criterion 12, bullet point 2
Description of change		Have history of latent or active TB prior to screening, except for patients who have documentation of having completed an adequate treatment regimen at least 6 months prior to the first administration of study agent. Was changed toHave history of latent or active TB prior to screening, except for patients who have documentation of having completed an adequate treatment regimen according to local guidelines within the past 3 years at least 6 months prior to

		the first administration of study agent.
Rationale for change		Was requested by some local authotities
Section to be changed		3.3.3 Exclusion criteria
Description of change		Addition of one exclusion criterion #18 : Patients with significant central nervous system (CNS) symptoms related to SLE based on investigators assessment
Rationale for change		Requested by some authorities
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		Addition of two cases for removal of individual patients from therapy : …/… • The patient develops an anaphylactic reaction (cf section 4.2.1 and 5.3.5.1). • In case of worsening or flare at any time point, the investigator may allow patients to discontinue and start rescue therapy according to the available guidelines for treatment of LN
Rationale for change		These reasons were implicit from other paragraphs but it was requested to clarify here by addition I this paragraph too.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		The first dose of trial medication will be administered at the trial site for all patients by the investigator (or a suitably qualified designee). Was changed to The first dose of trial medication will be administered at the trial site for all patients by the

		investigator (or a suitably qualified designee). The patient will be required to stay at the study site for observation for about 1 hour following the first dosing and 30 min after dose 2 and 3 (or more if locally required)
Rationale for change		To ensure an appropriate time of follow up after first doses injections
Section to be changed		4.1.5
Description of change		4.1.5.1 Blinding …/… After all patient have completed 26 weeks treatments a BI internal interim analysis will be performed for the purpose of facilitating further substance development and project planning. This analysis will be performed by a BI internal team independent of the trial team in order to prevent potential introduction of operational bias. A logistics plan prepared and approved in accordance with sponsor's specific procedures will detail procedures used to ensure that all members of the trial team remain blinded. The logistics plan will also contain a detailed list of functions that need to be unblinded for performing this analysis. Actual unblinding for the trial team will take place for the fast track analysis after the last patient has performed the EOT visit and not at DBL. Was changed to …/… After all patient have completed 26 weeks treatments a BI internal interim analysis will be performed for the purpose of facilitating further substance development and project planning. This analysis will be performed by a BI internal team independent of the trial team in order to prevent potential introduction of operational bias. A logistics plan prepared and approved in accordance with sponsor's specific procedures will detail procedures used to ensure that all members of the

		trial team remain blinded. The logistics plan will also contain a detailed list of functions that need to be unblinded for performing this analysis.
Rationale for change		There is no fast track analysis planned
Section to be changed		4.2.1 Rescue medication, emergency procedures, and additional treatment(s)
Description of change		During the participation in the trial, SOC medication has to be prescribed by the investigator. Boehringer-Ingelheim will reimburse costs for SOC for this period according to local regulations. Was changed to During the participation in the trial, SOC medication has to be prescribed by the investigator. Boehringer-Ingelheim will reimburse costs for SOC for this period according to local regulations, or will provide the drugs according to local regulations.
Rationale for change		In some countries the SOC will be directly supplied by sponsor
Section to be changed		4.2.1 Rescue medication, emergency procedures, and additional treatment(s)
Description of change		There are no special emergency procedures to be followed. In case of worsening or flare at any timepoint, the investigator may allow patients to escape to rescue therapy Was changed to In case of worsening or flare at any timepoint, the investigator may allow patients to escape to rescue therapy according to the available guidelines for treatment of LN <u>Management of Adverse Events:</u>

		- In case a patient develops a serious infection during the treatment in the study, treatment with BI 655064 and MMF will be interrupted. Treatment with BI 655064 and MMF will be restarted when the patient has recovered according to investigator's assessment. In addition, patients who develop recurrent infections should have their serum IgM and IgG measured according to investigator's assessment. - In case a patient develops a thrombosis suspected to be related to immunosuppression during the treatment in the study, treatment with BI 655064 and MMF will be interrupted and antithrombotic therapy has to be started. Treatment with BI 655064 and/or MMF may be restarted when the patient has recovered according to investigator's assessment. - In case of suspected hepatic injury (refer to section 5.3.5.1 for definition of hepatic injury) during the treatment in the study, treatment with BI 655064 has to be stopped. In case 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 emergency surgery during treatment in the study, treatment with BI 655064 and MMF will be interrupted. Treatment with BI 655064 and MMF 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 MMF has to be stopped and must not be introduced again. - In case of occurrence of lymphoproliferative diseases, treatment with BI 655064 and MMF has

		to be stopped and must not be introduced again. - In case of anaphylactic reactions treatment with BI 655064 and MMF will be stopped and must not be introduced again. - In case of side effects known to be related to higher doses of MMF, dose reduction ofMMF should be considered according to investigator's judgement.
Rationale for change		Some authorities requested to include measures to be taken in case of adverse events
Section to be changed		Section 4.4.1, Table 4.2.2.1:1
Description of change		Treatment with any biologic B-cell depleting therapy (e.g. anti-CD20, anti CD22, anti-Blyss) or abatacept* Was changed to Treatment with any biologic B-cell depleting therapy (e.g. anti-CD20, antiDC CD22) or abatacept* Belimumab, antiBLyS were added in the table: <u>Therapy</u>: Belimumab, antiBLyS <u>Prior to Study</u>: Not permitted (3 months or 5 halflives whichever is longer when used for non-renal SLE, 12 months when used for renal SLE) Screening Period: Not permitted Randomized Treatment Period: SOC Initial phase week 0-26: Not permitted <u>SOC week 26-52</u>: Not permitted Follow up Period: Not permitted
Rationale for change		To allow faster participation of patients who were treated with Belimumab or other anit-Blys therapy

		for non-renal SLE before developing lupus nephritis
Section to be changed		Table 5.3.3.1 safety lab parameters
Description of change		Addition of screening measurements Addition of Total IgG and Total IgM measures at baseline + week 12/26/40/52
Rationale for change		The screening measurements were missing in this table although mentioned in the text earlier The total IgG and total IgM are added to detect an increased risk of infection
Section to be changed		5.3.5.1 Definitions of AEs
Description of change		The following Adverse events of special interest are added : ✓ Injection reactions including anaphylactic reaction Any suspicion of severe injection reaction and of 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 characterized 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, varicella zoster, human herpesvirus 8, JC virus infection. Any severe infection should also be reported as AESI. ✓ 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 4.2.1 of the protocol. The specific therapy of the listed AESIs will be according to institutional standards.
Rationale for change		As per requested by some local authorities
Section to be changed		
Description of change		
Rationale for change		It is not mandatory to have the urine refrigerated
Section to be changed		6.2.2 Treatment period(s)
Description of change		At visit 2 and 11 and 16, 2 times 24h collection of urine will be performed. The patient will be given instructions and material to allow collection of urine in the 2 days preceding the visit. At other time points, proteinuria will be assessed by spot urine. Was changed to

		At visit 2 and 11 and 16, 2 times 24h collection of urine will be performed. The patient will be given instructions and material to allow collection of urine during 2 days in the week preceding the visit. At other time points, proteinuria will be assessed by spot urine.
Rationale for change		Some flexibility for urine collection is given to make this procedure easier to perform
Section to be changed		6.2.3.3 Continuation of the study for patients who withdrew drug prematurely
Description of change		The following was added : In case the patient does not show-up at these visits, vital status information will be sought at planned EOS visit.
Rationale for change		To make sure that missing data about vital status at 1 year for withdrawn patients are reduced to a minimum
Section to be changed		7.4 Interim analysis
Description of change		This paragraph was deleted : After last patient had passed the week 52 visit, a preliminary DBL will be performed for a fast track analysis of primary and secondary endpoints and safety. Details and the amount of analyses performed for fast track will be specified in the TSAP.
Rationale for change		There is no fast track analysis

Number of global amendment		4
Date of CTP revision		17-FEB-2017
EudraCT number		2015-001750-15
BI Trial number		1293.10
BI Investigational Product(s)		BI 655064
Title of protocol		A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year of treatment, in patients with active lupus nephritis
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		Flow chart weeks 27-52
Description of change		
Rationale for change		
Section to be changed		Flow chart inclusion criteria and 3.3.2 Inclusion criteria
Description of change		4. Active renal disease evidenced by proteinuria ≥ 1.0 g/day [(Uprot/Ucrea) ≥ 100 mg/mmol] at screening Was changed to 4. Active renal disease evidenced by proteinuria ≥ 1.0 g/day [(Uprot/Ucrea) ≥ 1] at screening
Rationale for change		Clarification: The Uprot/Ucreat ratio is expressed

		without unit in central lab results. This is in line with most publications and easier to interprete by investigators
Section to be changed		Flow chart foot note 1
Description of change		Visit 2.1 and 2.2 are necessary for IV steroids injections only. Refer to section 4.2.1. IV methylprednisolone injections to be done only to reach 1.5 g total dose within 4 weeks. Was changed to Visit 2.1 and 2.2 are necessary for IV steroids injections only. Refer to section 4.2.1. IV methylprednisolone injections to be done only to reach 1.5 g total dose within 6 weeks. If a higher dose of IV steroid is considered necessary by the investigator a total dose of up to 3g is acceptable.
Rationale for change		Based on feedback from some investigators, a higher dose of iv steroids is sometimes considered to be necessary for initial induction treatment. This is in line with the ACR guideline for treatment of Lupus Nephritis which recommends iv pulses of 500 mg to 1000 mg. In addition it was realized that the time window of 4 weeks is sometimes too narrow to allow participation of patients who otherwise would fulfill all In-and Exclusion criteria. Based on feedback from the Coordinating investigator, it is not expected that neither the extension to 6 weeks not the higher iv. steroid dose will have an impact safety or on the response at week 52 weeks which is the primary endpoint of the study.
Section to be changed		3.2 Discussion of trial design, including the choice of control groups
Description of change		In this trial (1293.10) start of induction treatment prior to randomization is limited to 4 weeks as this will allow for some prior treatment with MMF while maintaining a level of homogeneity to better assess treatment effect in this Phase 2 study. High dose steroids have significant impact on the short term response and have potentially relevant side effects. To keep the population included in the trial more homogenous and to avoid increased risk of side-effects, the total amount of i.v. steroids has to be limited. A total amount of 1.5 g is the maximum

		amount of i.v. steroids is recommended by ACR (R12-4273) and EULAR/ERA-EDTA (R12-4921) for induction therapy (3x500 mg i.v). Thus, patients who had started induction with high i.v. dose steroids but < 1.5g total i.v. within 4 weeks will be eligible for the trial. Was changed to In this trial (1293.10) start of induction treatment prior to randomization is limited to 6 weeks as this will allow for some prior treatment with MMF while maintaining a level of homogeneity to better assess treatment effect in this Phase 2 study. High dose steroids have significant impact on the short term response and have potentially relevant side effects. To keep the population included in the trial more homogenous and to avoid increased risk of side-effects, the total amount of i.v. steroids has to be limited. A total amount of 1.5 g of i.v. steroids is recommended by ACR (R12-4273) and EULAR/ERA-EDTA (R12-4921) for induction therapy (3x500 mg i.v.). For severe cases a maximal total amount of 3 g of iv steroids may be considered (3x1000 mg i.v.). Thus, patients who had started induction with high i.v. dose steroids but ≤ 3g total i.v. within 6 weeks will be eligible for the trial.
Rationale for change		Same as above
Section to be changed		3.3.3 exclusion 8, first bullet point
Description of change		Any induction therapy for LN within the last 6 months prior to randomization except induction with MMF and high dose steroids (maximal amount of i.v. steroids 1.5g prednisone equivalent) started within 4 weeks prior to randomization. Was changed to Any induction therapy for LN within the last 6 months prior to randomization except induction with MMF and high dose steroids (maximal amount of i.v. steroids g prednisone equivalent) started within 6 weeks prior to randomization. If a higher dose of iv steroids is considered necessary by the investigator a total dose of up to 3g is

		acceptable.
Rationale for change		Same as above
Section to be changed		4.1.1 Identity of BI investigational product(s) and comparator product(s) And 4.1.4:1 dose groups
Description of change		Volume is omitted in 4.1.1 and 4.1.4:1 when syringes are described, only the dose is given.
Rationale for change		New clinical trial supplies are being provided that utilize only one concentration, rather than two concentrations, necessitating a change in volume in the syringes. There is no change in the dose administered to patients, administration schedule or dose groups in the study.
Section to be changed		4.2.1
Description of change		Patients who have had already a course of IV steroids (up to a total dose of maximum 1.5g if it had been considered necessary by investigator) within 4 weeks prior to randomization should not necessarily repeat it depending on what they received. Was changed to: Patients who have had already a course of IV steroids (up to a total dose of maximum 3g if it had been considered necessary by investigator) within 6 weeks prior to randomization should not necessarily repeat it depending on what they received
Rationale for change		Same as above
Section to be changed		Table 4.2.2:1
Description of change		MMF Prior to screening: Permitted if dose ≤2 g/d; doses≤ 3g/d permitted within 4 weeks from randomisation. Screening period: Permitted within 4 weeks from randomisation IV Glucocorticoids Prior to screening Allow 1.5 g IV total max within 4 weeks prior randomisation; a single pulse should not be >500 mg Was changed to MMF Prior to screening: Permitted if dose ≤2 g/d; doses≤ 3g/d permitted within 6 weeks from randomisation. Screening period: Permitted within 6 weeks from randomisation IV Glucocorticoids Prior to screening: Allow 3 g IV total max within 6 weeks prior

		randomisation; a single pulse should not be >1000 mg
Rationale for change		Same as above
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		Addition of "It is allowed to re-test the proteinuria if the result from spot ratio at screening visit does not correspond to recent measurements done at site. In that case it is preferred to do a 24h measurement"
Rationale for change		24h collection of protein is considered to be more precise than the measurement by spot urine.
Section to be changed		6.2.2
Description of change		Intravenous Glucocorticoids: patients who have not yet received any high dose pulse IV steroids will receive 500 mg methylprednisolone for 3 days (visits 2, 2.1, 2.2). In case the patient had already received pulse steroids (max 1.5g total within last 4 weeks) he will receive additional IV steroids only to reach 1.5g total. If the 1.5 g is reached the visit 2.1 and 2.2 are not necessary. Was changed to: Intravenous Glucocorticoids: patients who have not yet received any high dose pulse IV steroids will receive 500 mg methylprednisolone for 3 days (visits 2, 2.1, 2.2). If considered necessary by the investigator, a maximal dose of 1000 mg methyl prednisolone for 3 days is acceptable. In case the patient had already received pulse steroids (max 3g total within last 6 weeks) he will receive additional IV steroids only to reach 1.5g total. If the 1.5 g is reached the visit 2.1 and 2.2 are not necessary.
Rationale for change		Same as above

Number of global amendment		5
Date of CTP revision		06-Oct-2017
EudraCT number		2015-001750-15
BI Trial number		1293.10
BI Investigational Product(s)		BI 655064
Title of protocol		A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year of treatment, in patients with active lupus nephritis
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		3.1 Overall trial design and plan
Description of change		Randomisation will be done with stratification by ethnicity (Asians vs Non- Asian) and proteinuria at screening <3g/d or ≥ 3g/d. Was changed to The patients will be randomized 1:1:2:2 to these dose groups. Randomisation will be done with stratification by ethnicity (Asians vs Non- Asian) and proteinuria at screening <3g/d or ≥ 3g/d (respectively UP/UC<3 or UP/UC≥3.
Rationale for change		Proteinuria at screening is evaluated through the urine protein/creatinin ratio in most cases
Section to be changed		Synopsis and Section 3.3.2 Inclusion criteria #3
Description of change		3. Diagnosis of systemic lupus erythematosus (SLE) by ACR criteria 1997, at least 4 criteria must be documented, one of which must be a positive anti-dsDNA antibody at screening or around time of start of induction therapy.

		Was changed to 3. Diagnosis of systemic lupus erythematosus (SLE) by ACR criteria 1997, at least 4 criteria must be documented, one of which must be a positive anti-dsDNA antibody OR a positive antinuclear antibody (ANA) at screening or around time of start of induction therapy.
Rationale for change		To allow selection in the trial of the proportion of patients who do not have positive anti dsDNA but are still diagnosed with LN
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		Exclusion criteria #3 has been deleted 3. Acute presence of oliguria (<500mL/day)
Rationale for change		To avoid excluding patients who may have oliguria for other reason than LN. Renal diseases that might interfere with the trial are already covered by exclusion 1
Section to be changed		Ch 4.2.1
Description of change		AND glucocorticosteroids (GC) (methylprednisolone, 500mg pulse IV for 3 days) followed by oral glucocorticosteroids, tapering to 10mg prednisone equivalent/day within 12 weeks Was changed to: AND glucocorticosteroids (GC) (methylprednisolone, recommended 500mg pulse IV for 3 days) followed by oral glucocorticosteroids, tapering to 10mg prednisone equivalent/day within 12 weeks
Rationale for change		To allow some flexibility in steroid dosing in case investigator used a lower dose of methylprednisolone e.g. 250 mg IV
Section to be changed		Table 5.3.3: 1: safety lab parameters
Description of change		The footnote # has been added in QuantiFERON-TB Gold # in case of an indeterminate result, test could be repeated, in case the result is indeterminate again, a PPD skin test should be performed
Rationale for change		To give instructions to investigators in case the test

		is indeterminate
Section to be changed		
Description of change		

Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		7.6 Randomisation
Description of change		Randomisation will be done with stratification by ethnicity (Asians vs Non- Asian) and proteinuria at screening <3g/d or >3g/d Was changed to Randomisation will be done with stratification by ethnicity (Asians vs Non- Asian) and proteinuria at screening <3g/d or ≥ 3g/d (respectively UP/UC<3 or UP/UC≥3
Rationale for change		To make clear that proteinuria at screening is evaluated through the urine protein/creatinin ratio in most cases. Also to correct the sign typo.
Section to be changed		Appendix 10.1 STEROIDS TAPERING SCHEDULE 1293.10
Description of change		It is allowed to increase the steroid dose once

		during these 12 weeks but patients should reach the 10 mg at week 12. Was changed to: It is allowed to increase the steroid dose once during these 12 weeks but patients should reach the 10 mg at week 12. In case tapering of steroids is already started before randomization, the tapering schedule can be adapted but should not exceed to dose recommended in the schedule for the respective week. Latest from week 13 onwards, the dose should be 10 mg prednisone equivalent or less.
Rationale for change		To give further instructions with regards to tapering steroids in case the patient had already started tapering before randomization

Number of global amendment		6
Date of CTP revision		07 Sep. 2018
EudraCT number		2015-001750-15
BI Trial number		1293.10
BI Investigational Product(s)		BI 655064
Title of protocol		A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year of treatment, in patients with active lupus nephritis
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		Front page & Synopsis
Description of change		Change of TCM name and typo corrections
Rationale for change		
Section to be changed		Flowchart
Description of change		Typo correction & Clarifications
Rationale for change		
Section to be changed		3.2
Description of change		Sentence moved to section 4.2.1: In patients who experience a worsening or a flare, the investigator is allowed to increase the steroid dose for the patient. These patients are allowed to continue treatment with BI 655064 until week 52
Rationale for change		Clarity
Section to be changed		4.1.5 & 7.4
Description of change		Rewording of “logistic plan” into “interim analysis trial statistical plan”
Rationale for change		Matching with the title of the referred document
Section to be changed		4.2.1
Description of change		Addition of sentence: In patients who experience a worsening or a flare, the investigator is allowed to

		increase the steroid dose for the patient. These patients are allowed to continue treatment with BI 655064 until week 52
Rationale for change		Clarify the use of glucocorticosteroids
Section to be changed		4.2.1
Description of change		Sentence deleted: "For the primary analysis, these patients will be looked upon as failures"
Rationale for change		The protocol allows some flexibility for the use of glucocorticosteroids, in no place addition of glucocorticosteroids to the recommeneded dose would lead to discontinuation. This drug can be administrated for other reason than treatment of lupus nephritis. Therefore for patient'safety, consistencies, and to avoid misunderstandings, the sentence is deleted.
Section to be changed		4.2.1
Description of change		Sentence deleted: " In case of worsening or flare at any timepoint, the investigator may allow patients to escape to rescue therapy according to the available guidleines for treatment of LN."
Rationale for change		Delete as mentioned in 3.3.4.1
Section to be changed		4.2.1
Description of change		Addition of Azathioprine when mention done on MMF.
Rationale for change		Clarification
Section to be changed		4.3
Description of change		Addition of the sentence: "The last two intakes dates and time of MMF taken before the blood sampling will be recorded in RDC, based on patient's interview."
Rationale for change		
Section to be changed		5.2
Description of change		Deletion of the sentence: "Patients who did not reach 10 mg prednisone-equivalent within 12 weeks or needed an increase in steroid dose above 10 mg after the 12 weeks, will be considered as Non- Responder for the primary analysis"

Rationale for change		The reason of deletion of the sentence is that it was misleading. This restriction is not included in the primary endpoint definition. It is also not included in the statistical part (section 7). During the trial, patients could need steroids for other reason than Lupus Nephritis (including emergency situation), therefore some flexibility must be possible for the investigator to treat adequately the patient. This is also done in other trials in this field. Details on how to handle steroid dosing and responder's patients will be clarified in TSAP.
Section to be changed		5.2 & 5.3
Description of change		Clarification of the baseline in screening biopsy
Rationale for change		Clarification
Section to be changed		5.3.5.1
Description of change		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
Rationale for change		On DMC request, meeting 15 May 2018.
Section to be changed		5.3.6
Description of change		Sentence added: "The reliable contraception should be used in female patient before starting MMF therapy and the study drug, during the treatment and until 50 days after stopping MMF and the study drug (and until 90 days after stopping AZA in case of AZA is used). 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 treatment"
Rationale for change		Clarification on contraception recommendations, with the use of MMF/ AZA.
Section to be changed		5.3.6
Description of change		Addition of the sentence: "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”
Rationale for change		Information about pregnant partner displayed.
Section to be changed		6.2.3.3
Description of change		Clarification of follow up visits to be performed when discontinuation
Rationale for change		Clarification

APPROVAL / SIGNATURE PAGE

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Title: A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year of treatment, in patients with active lupus nephritis

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		07 Sep 2018 16:20 CEST
Author-Trial Clinical Pharmacokineticist		07 Sep 2018 20:31 CEST
Verification-Paper Signature Completion		10 Sep 2018 13:53 CEST
Approval-Biostatistics		11 Sep 2018 17:25 CEST
Approval-Team Member Medicine		12 Sep 2018 10:17 CEST
Approval-Therapeutic Area		12 Sep 2018 10:59 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**