Clinical Study Protocol

Biotest AG

Title: *A Prospective, Double-blind, Randomized, Placebo-controlled, Repeated dose, Multicentre Phase IIa Proof-of-Concept Study with BT063 in Subjects with Systemic Lupus Erythematosus (BT063 in SLE)*

Clinical Phase:	**IIa**
Version; incl. date:	**1.0; 19 Mar 2015**
EudraCT Number:	**2014-005526-35**
Study No.:	**990**

Coordinating Investigator:

[redacted]

Sponsor:

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Manager Corporate Clinical Research

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Confidentiality Statement

1 SIGNATURE PAGE

This clinical study is carried out in accordance with the international guidelines on Good Clinical Practice (ICH-GCP) and in compliance with applicable regulatory authority requirements. It is confirmed that the clinical study will be carried out and documented in accordance with this study protocol.

Coordinating Investigator

[redacted]

26/MAR/2015

Date, signature

[redacted]

Head Corporate Clinical Research

[redacted]

Biotest AG

23.03.15

Date, signature

[redacted]

Statistician

[redacted]

Principal Statistician

[redacted]

Mar. 24/2015

Date, signature

[redacted]

1.1 Signature Page for Investigators

Declaration of the Principal Investigator

I have read and understood this clinical study protocol and agree to the following:

- To adhere to the ethical and scientific principles of good clinical practice, and the principles of the Declaration of Helsinki, the local laws and regulations, and the applicable regulatory requirements.
- To conduct the clinical study as set out in the protocol.
  This includes:
  - To wait until I have received approval from the appropriate Independent Ethics Committee / Institutional Review Board (IEC/IRB) before enrolling any subject in this study.
  - To obtain informed consent for all subjects prior to any study-related measure performed.
  - To permit study-related monitoring, audits, IEC/IRB review, and regulatory authority inspections.
  - To provide direct access to all study-related records, source documents, and subject files for the monitor, auditor, IEC/IRB, or regulatory authority upon request.
  - To use the IMP and all study materials only within the framework of this clinical study protocol.
  - To understand that changes to the clinical study protocol must be made in the form of an amendment that has the prior written approval of Biotest and, as applicable, of the appropriate IEC/IRB and regulatory authority.
  - To comply with the reporting obligations for Adverse Events / Serious Adverse Events (AE/SAE).

I understand that all documentation that has not been previously published will be kept in the strictest confidence. This documentation includes the Clinical Study Protocol, investigator's brochure, case report forms, and other scientific data.

Principal Investigator

<Name>

_____

Date, signature

Investigator stamp:

2 STUDY SYNOPSIS

Title	*A Prospective, Double-blind, Randomized, Placebo-controlled, Repeated dose, Multicentre Phase IIa Proof-of-Concept Study with BT063 in Subjects with Systemic Lupus Erythematosus (BT063 in SLE)*
Clinical Phase	IIa
Coordinating Investigator	[redacted]
Study Objectives	This study has 2 parts. The primary objective of Part I of this study is to evaluate the safety and tolerability of 3 months of treatment with 50 mg BT063 versus placebo in subjects with systemic lupus erythematosus (SLE). The primary objective of Part II of this study is to evaluate the safety and tolerability of either 25 mg, 50 mg or 100 mg BT063 versus placebo in subjects with SLE. The dose level for Part II will be determined based on an interim analysis conducted after Part I. Secondary objectives for both parts of the study are to: • Evaluate the efficacy of 3 months of treatment with BT063 versus placebo as assessed by various disease activity indices including subject-reported outcomes • Determine the pharmacokinetics (PK) of BT063 • Compare the pharmacodynamics (PD) of BT063 and placebo on various PD markers including biomarkers • Determine the immunogenicity of BT063
Study Design	Prospective, double-blind, randomized, placebo-controlled, multicentre, proof-of-concept study conducted in 2 parts; including an interim analysis at the end of Part I. Subjects who participate in Part I of the study cannot participate in Part II
Study Population	Subjects with active SLE disease
Inclusion Criteria	• Able to provide written informed consent and/or consent obtained from a legally acceptable representative (as required by Institutional Review Board/Independent Ethics Committee) prior to the initiation of any protocol-required procedures • Diagnosis of SLE as defined by American College of Rheumatology (ACR) criteria such that ≥ 4 of the 11 criteria are met for ≥ 3 months before screening • Moderate to severe SLE disease activity at screening and baseline demonstrated by SLEDAI-2K total score

	≥ 6, including skin **and** joint involvement • Regarding skin and joints, both need to be involved, and either skin should be involved according to CLASI Activity score ≥ 5 **or** at least 5 of 66/68 joints with pain and signs of inflammation present at screening and baseline (joints suspected or known to have ischemic osteonecrosis are not to be taken into consideration) • No change in concomitant medication for SLE activity maintenance and symptom control (e.g., azathioprine, methotrexate, leflunomide, mycophenolate mofetil, cyclosporine, antimalarials such as chloroquine or hydroxychloroquine, glucocorticosteroids, pain medication, e.g. nonsteroidal anti-inflammatory drugs [NSAIDs] or paracetamol) regarding type of medication and dose level for at least 8 weeks prior to baseline (for steroids and NSAIDs/pain medication 2 weeks) and with the expectation that there will be no need for change in concomitant medication until the End-of-Treatment visit (ideally throughout the whole study); however, if the subject is taking an oral glucocorticosteroid at a dose higher than equivalent to 20 mg prednisone/day, and planning to reduce dose of glucocorticosteroid, the dose can be titrated down during the screening period so that the subject has been on, at most, a dose equivalent to 20 mg prednisone/day for 2 weeks by day 0 (baseline; i.e., first BT063 dose) • The dose of concomitant medication for SLE activity maintenance and symptom control (e.g., azathioprine, methotrexate, leflunomide, mycophenolate mofetil, cyclosporine, antimalarials such as chloroquine or hydroxychloroquine, glucocorticosteroids, pain medication, e.g. nonsteroidal anti-inflammatory drugs [NSAIDs] or paracetamol) should not exceed the doses outlined in the summary of product characteristics (SPC) or standards for SLE management. For oral glucocorticosteroids maximal allowed dose is limited to a dose equivalent to 20 mg prednisone/day. NSAIDs should not be taken within 24 hours, paracetamol not within 12 hours prior to study visits • Positive anti-nuclear antibodies (ANA) test at screening (as per central laboratory results). • Age ≥ 18 and ≤ 75 years at screening • Body mass index ≥ 18 and ≤ 35 kg/m^2 • Normal electrocardiogram (ECG), i.e., no acute and clinically relevant abnormalities

Exclusion Criteria	• Has active, severe SLE disease activity which involves the renal system and/or active, severe, neuropsychiatric SLE, defined as any neuropsychiatric element scoring BILAG level A disease • Diagnosed psoriasis • Presence or history of malignancy within the previous 5 years (except successfully treated non-metastatic cutaneous squamous or basal cell carcinoma and/or localized carcinoma in situ of the cervix) • Received any vaccination within 8 weeks prior to screening (except for influenza or tetanus booster) • History of more than 3 infections during the last 12 months, requiring intravenous (IV) antibiotic treatment • Systemic antibiotic treatment within 2 weeks before baseline visit • A positive diagnosis for any of the following: o Acute or chronic viral hepatitis B (isolated positivity to hepatitis B surface antibody [anti-HBs] is allowed as an indicator of a previous vaccination that will be confirmed in subject's notes) or acute or chronic hepatitis C (positive to anti-hepatitis C antibodies or hepatitis C viral RNA) o Human immunodeficiency virus (HIV) or tested positive for tuberculosis as assessed by QuantiFERON® TB gold test (if the result is inconclusive it may be repeated once) o Acute, clinically relevant, or potentially recent infection with Herpes Zoster or Herpes Simplex (Type 1 and Type 2), Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infection or reactivation at screening • Clinically significant hematologic abnormalities attributed to SLE: o Haemoglobin < 8 g/dL o Platelets < 50×10^9/L o Leucocytes < 2.0×10^9/L • Active or history of inflammatory bowel disease (including active or history of colitis) • Received the following medications: o Rituximab within the last 48 weeks before screening o Belimumab within the last 12 weeks before screening o IV immunoglobulin (Ig) within the last 12 weeks before screening

	○ Intramuscular (IM) or intra-articular glucocorticosteroids within the last 4 weeks before screening ○ IV cyclophosphamide within the last 6 months before screening ○ IV glucocorticosteroids (pulse therapy) within the last 6 months before screening • Participation in another clinical study in the 90 days prior to baseline or within 5 half-lives of the investigated compound, whichever is longer; Participation in another clinical study during this study and/or previous participation in this study • Pregnant or nursing women or women who intend to become pregnant • Men or women not willing to use effective contraception excluding women not of childbearing potential (Subjects who are sexually active women of childbearing potential or sexually active men who are not practicing 2 different methods of birth control with their partner during the trial and for 4 months after the last dose of IMP or who will not remain abstinent during the trial and for 4 months after the last dose. If using birth control, each couple must use 2 of the following precautions: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injections, condom, or sponge with spermicide. Women who are not of childbearing potential include those who are at least 1 year post-menopausal confirmed by follicle-stimulating hormone levels or women who are surgically sterile) • Known intolerance to immunoglobulins or comparable substances (e.g., significant vaccination reaction) • Known intolerance to proteins of human origin • Employee or direct relative of an employee of the contract research organization (CRO), the study site, or Biotest • History of clinically significant drug or alcohol abuse within the last 12 months • Any other significant acute or chronic illness or laboratory abnormality, which, in the opinion of the investigator, might compromise the safety of the subject or influence the outcome of the study and its objectives

Number of Subjects	Part I: Placebo, n= 6 BT063, n=12 Part II (depending on interim analysis): Placebo, n= 6 BT063, n=12
Countries/Number of Study Sites	3 to 4 countries, 12 to 15 sites
Investigational Medicinal Product (IMP)	BT063 and matching placebo administered as IV infusion
Dosage and Mode of Administration	Part I: Placebo, or BT063 (50 mg) at week 0 (baseline), week 1, 2, 4, 6, 8, 10, and 12 Part II (depending on interim analysis results of Part I): Placebo, or BT063 (either 25 mg, 50 mg or 100 mg) at week 0 (baseline), week 1, 2, 4, 6, 8, 10, and 12
Duration of Treatment	3 months of treatment with 4 months of Follow-Up
Criteria for Evaluation ***Safety Assessments***	• Adverse events (AEs), serious AEs (SAEs), and withdrawals due to AEs • Physical examinations • Vital signs • ECGs • Safety laboratory parameters (full blood count including white differential count, clinical chemistry, thyroid hormones, urinalysis, and faecal occult blood test) • Auto-antibodies against double-stranded DNA (anti-dsDNA) and nucleus (ANA), thyroid gland (thyroid peroxidase [TPO], thyroid stimulating hormone receptor [TSHR]), anti-islet cells, anti-cyclic citrullinated peptide (CCP), Coombs test • Anti-drug antibodies against BT063 (anti-BT063) • Immunological status of potential viral and bacterial infections (HBV, HCV, HIV, tetanus, diphtheria tuberculosis as well as EBV / CMV serology)

Efficacy Assessments	• Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) • Cutaneous Lupus Erythematosus Disease Area and Sensitivity Index (CLASI) • British Isles Lupus Assessment Group (BILAG) assessments • Tender/swollen joint counts • Physician's Assessment of Disease Activity (Physician's Global Assessment, PGA) • Subject Reported Outcomes using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F), and SF-36v2 Physical Component Score (PCS) • European Consensus Lupus Activity Measurement (ECLAM)
Pharmacokinetics and Pharmacodynamics	• Pharmacokinetics: BT063 serum concentration - Maximum serum concentration (C_{max}) - Time to maximum serum concentration (t_{max}) - Area under the concentration-time curve from time 0 to the last observable concentration at time t (AUC_{0-t}) - Elimination half-life ($t_{1/2}$) - Apparent terminal-phase disposition rate constant (λ_Z) - Total body clearance from serum (CL) - Apparent volume of distribution during the terminal phase (V_Z). • Pharmacodynamics: - T- and B-lymphocytes (CD3, CD4, CD8, CD19, CD20, CD27, CD38, CD69, CD62L, HLA DR, CD45RA) - Complement activity CH50, C3, and C4 - Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) - Cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-α, IFN-γ) - Immunoglobulins (IgG, IgM, IgA, IgE) - Free IL-10 • Biomarkers related to IL-10 biology and expected safety, efficacy, and mechanism of action of BT063 • Immunological parameters
Endpoints ***- Primary - Safety***	• Incidence of Adverse events (Including SAEs and AEs leading to discontinuation) from Baseline through End of Trial Visit (Week 14)

	• Changes from baseline through End of Trial Visit (Week 14) in:
	  ○ Physical examinations
	  ○ Vital signs
	  ○ ECGs
	  ○ Safety laboratory parameters (full blood count including white differential count, clinical chemistry, thyroid hormones, urinalysis, and faecal occult blood test)
	  ○ Development of anti-drug antibodies against BT063 (anti-BT063)
	  ○ Immunological status of potential viral and bacterial infections (HBV, HCV, HIV, tetanus, diphtheria tuberculosis)
	  ○ EBV / CMV Serology
	  ○ Premature withdrawals

- Secondary – Efficacy	• 50% improvement of swollen/tender joints or 50% improvement in CLASI Activity score at week14 and week 28, depending on which was the more severe manifestation at baseline. • Percent changes in SLEDAI-2K scores from baseline to week 14 and at week 28 • Flare rate and severity at week 14 and week 28 based on BILAG index A or B (flare is defined as the presence of 1 or more new BILAG A scores or 2 or more new BILAG B scores.) • Time to first flare • Number of patients requiring an increase in oral glucocorticosteroid dose before week 14 • Physician's Global Assessment, Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) and SF-36v2 Physical Component Score (PCS) at week 14 and week 28 • ECLAM at week 14 and week 28

Pharmacokinetics and Pharmacodynamics	Based on PK/PD findings at protocol-defined time points:
	• Pharmacokinetics:
	  - BT063 serum concentration
	  - Maximum serum concentration (C_{max})
	  - Time to maximum serum concentration (t_{max})
	  - Area under the concentration-time curve from time 0 to the last observable concentration at time t (AUC_{0-t})
	  - Elimination half-life ($t_{1/2}$)
	  - Apparent terminal-phase disposition rate constant (λ_Z)
	  - Total body clearance from serum (CL)

	- Apparent volume of distribution during the terminal phase (V_Z). • Pharmacodynamics: - T- and B-lymphocytes (CD3, CD4, CD8, CD19, CD20, CD27, CD38, CD69, CD62L, HLA DR, CD45RA) - Complement activity CH50, C3, and C4 - Erythrocyte sedimentation rate (ESR) and C-reactive protein - Cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-α, IFN-γ) - Immunoglobulins (IgG, IgM, IgA, IgE) - Free IL-10 • Biomarkers related to IL-10 biology and expected safety, efficacy, and mechanism of action of BT063 • Immunological parameters
Concomitant Medication ***Allowed***	Stable background therapy with standard SLE medication (e.g. e.g., steroids, azathioprine, antimalarials such as chloroquine or hydroxychloroquine, methotrexate, leflunomide, mycophenolate mofetil, cyclosporine) should not exceed the doses outlined in the summary of product characteristics (SPC) or standards for SLE management. Stable dose of oral glucocorticosteroids up to 20 mg/day. Topical non-steroidal treatment of skin lesions and analgesic treatment of joint pain is allowed; however, not within 24 hours before assessment
Prohibited	Prohibited within protocol-specified time frames • IV cyclophosphamide • IV glucocorticosteroids • Rituximab, belimumab • Investigational agents • IM or intra-articular administration of glucocorticosteroids • Plasmapheresis and/or IVIg therapy
Biometrical Concept	Explorative descriptive statistics will be used for all variables. No statistical tests will be performed.
Data and Safety Monitoring Board	An independent Data and Safety Monitoring Board (DSMB) will be established.
First Subject First Visit *(planned)*	May 2015
Last Subject Last Visit *(planned)*	Q3 2017

Confidentiality Statement

3 FLOWCHART OF THE STUDY

Study 990 Part I and II	**Visit**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V 11**	**V 12**	**V 13**	**V 14**
	Week	**W -4 to -1**	**W 0**	**W 1**	**W 1**	**W 2**	**W 4**	**W 6**	**W 8**	**W 10**	**W 12**	**W 13**	**W 14**	**W 20**	**W 28**
	Day	**D -28 to -7**	**D0**	**D4 or 5**	**D7 ±1**	**D14 ±1**	**D28 ±2**	**D42 ±2**	**D56 ±2**	**D70 ±2**	**D84 ±2**	**D91 ±2[g]**	**D98 ±2**	**D140 ±7**	**D196 ±7**
Assessments	**Phase**	**Screening**	**Baseline**		**Treatment**								**EoT**	**Follow-up**	
Informed consent		•	•c												
Medical history incl. previous/current medication, vaccination status, risk factors, and demography		•													
Eligibility criteria (inclusion / exclusion)		•	•												
Safety Assessments															
Adverse events			•	•	•	•	•	•	•	•	•	•	•	•	•
Physical examination (full at screening and baseline and targeted afterwards)		•	•		•	•	•	•	•	•	•		•	•	•
Vital signs (pulse, blood pressure, temperature)		•	•		•	•	•	•	•	•	•		•	•	•
ECG (12 lead)		•											•		
Body weight and height (at screening only)		•											•		
Safety laboratory [e]		•f	•f		•	•	•		•		•		•f	•	•
Auto-antibodies (ANA, anti-dsDNA, thyroid gland [TPO, TSHR], anti-islet cells, anti-CCP, Coombs test)		•	•			•	•		•		•		•	•	•
Anti-BT063 antibodies			•				•		•				•	•	•
Immunological status (HBV, HCV, HIV, tetanus, diphtheria, tuberculosis)		•	•a										•		•a

Study 990 Part I and II	**Visit**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V 11**	**V 12**	**V 13**	**V 14**
	Week	**W -4 to -1**	**W 0**	**W 1**	**W 1**	**W 2**	**W 4**	**W 6**	**W 8**	**W 10**	**W 12**	**W 13**	**W 14**	**W 20**	**W 28**
	Day	**D -28 to -7**	**D0**	**D4 or 5**	**D7 ±1**	**D14 ±1**	**D28 ±2**	**D42 ±2**	**D56 ±2**	**D70 ±2**	**D84 ±2**	**D91 ±2[g]**	**D98 ±2**	**D140 ±7**	**D196 ±7**
Assessments	**Phase**	**Screening**	**Baseline**		**Treatment**								**EoT**	**Follow-up**	
EBV and CMV serology		•	•a										•		•a
Pregnancy test (in women of childbearing potential) or FSH assessment (in women not of childbearing potential) [b]		•	•				•		•		•		•		
Concomitant medications			•	•	•	•	•	•	•	•	•	•	•	•	•
Efficacy Assessments															
SLEDAI-2K score		•	•			•	•		•		•		•	•	•
CLASI Activity score		•	•			•	•		•		•		•	•	•
BILAG score		•	•				•		•		•		•	•	•
Tender joint count, swollen joint count		•	•			•	•		•		•		•	•	•
Physician's Global Assessment of Disease Activity		•	•			•	•		•		•		•	•	•
Subject Reported Outcomes (SF-36v2, FACIT-F)			•			•	•		•		•		•	•	•
ECLAM			•				•		•		•		•	•	•
PK Assessments															
BT063 serum level [d]			••	•	••	••	••	••	••	••	••	•g	•	•	•
PD Assessments															
T- and B-lymphocytes (CD3, CD4, CD8, CD19, CD20, CD27, CD38, CD69, CD62L, HLA DR,			•		•			•			•				•

Study 990 Part I and II	Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V 11	V 12	V 13	V 14
	Week	W -4 to -1	W 0	W 1	W 1	W 2	W 4	W 6	W 8	W 10	W 12	W 13	W 14	W 20	W 28
	Day	D -28 to -7	D0	D4 or 5	D7 ±1	D14 ±1	D28 ±2	D42 ±2	D56 ±2	D70 ±2	D84 ±2	D91 ±2[g]	D98 ±2	D140 ±7	D196 ±7
Assessments	**Phase**	**Screening**	**Baseline**		**Treatment**								**EoT**	**Follow-up**	
CD45RA)															
Complement activity CH50, C3, and C4		•	•			•	•		•		•		•	•	•
ESR and CRP			•			•	•		•		•		•	•	•
Cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-α, IFN-γ)			•	•		•		•			•		•		•
Immunological parameters			•					•			•				
Immunoglobulins (IgG, IgM, IgA, IgE)			•			•	•	•			•		•		
Free IL-10 [h]			••			••	••	•			•		•	•	•
Biomarker			•			•		•					•		•
IMP															
Randomization			•												
Administration of study drug			•		•	•	•	•	•	•	•				

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BILAG = British Isles Lupus Assessment Group; CCP = cyclic citrullinated peptide; CLASI = Cutaneous Lupus Erythematosus Disease Area and Sensitivity Index; CMV = cytomegalovirus; D = day; EBV = Epstein-Barr virus; ECG = electrocardiogram; ECLAM = European Consensus Lupus Activity Measurement; EoT = end of treatment; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FSH = follicle-stimulating hormone; fT3 = free triiodothyronine; fT4 = free thyroxine; GGT = gamma glutamyl transferase; HBV = hepatitis b virus; HBC = hepatitis C virus; IMP = investigational medicinal product; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; RBC = red blood cells; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; V = visit; W = week; WBC = white blood cells

a) Retention sample only.

b) Urine pregnancy test at all scheduled visits; FSH at screening only.

c) Availability of a signed and dated informed consent is to be confirmed baseline.

d) Sampling for BT063 serum levels before and after IMP infusion at each dosing visit.

e) Potential subjects will be notified prior to V1 to fast for at least 12 hours before the scheduled visit. Laboratory assessments include: haematology (haematocrit, haemoglobin, RBC, WBC, differential WBC, platelets), coagulation (fibrinogen, prothrombin time, partial thromboplastin time), clinical chemistry (ALT, AST, GGT, AP, LDH, lipase, bilirubin, total protein, albumin, creatinine, urea, sodium, chloride, potassium, calcium), urinalysis: dipstick (pH, qualitative for blood, leucocytes, protein, glucose, ketone bodies, bilirubin, urobilinogen, nitrites, specific gravity) and microscopy, and faecal occult blood test. Faecal occult blood will be assessed at V2, V6 and V12 only.

   In addition, the following will be assessed at Visits V1, V2, and V12 only: thyroid stimulating hormone, fT3 and fT4, fasting glucose, fasting triglycerides, fasting cholesterol, fasting high-density lipoprotein, and fasting low-density lipoprotein.

f) Subjects should not eat or drink anything except water for 12 hours before the fasting glucose and fasting lipid tests at Visits V1, V2, and V12.

g) BT063 serum level sampling at Visit 11 at least 5 days after last dosing (Visit 10).

h) Free IL-10 sampling before and after IMP infusion at V2, V5 and V6; at all other visits before IMP infusion only.

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5 LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
anti-dsDNA	Auto-antibodies against double-stranded DNA
AP	Alkaline phosphatase
APC	Antigen-presenting cell
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-t}	Area under the concentration-time curve from time 0 to the last observable concentration at time t
BDRM	Blind data review meeting
BILAG	British Isles Lupus Assessment Group
CCP-Ab	Cyclic citrullinated peptide antibody
CL	Total body clearance
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
C_{max}	Maximum plasma/serum concentration
CMV	Cytomegalovirus
CRO	Contract research organization
CRP	C-reactive protein
D	Day
DNA	Deoxyribose nucleic acid
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECLAM	European Consensus Lupus Activity Measurement
eCRF	Electronic case report form
EDC	Electronic data capture

EoT	End of Treatment
ESR	Erythrocyte sedimentation rate
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FSH	Follicle-stimulating hormone
fT3	Free triiodothyronine
fT4	Free thyroxine
FU	Follow-up
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
Ig	Immunoglobulin
IL	Interleukin (e.g., IL-1, IL-6, IL-8, etc.)
IM	Intramuscular
IMP	Investigational medicinal product
IRAE	Immediately reportable adverse event
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-treat (population)
IV	Intravenous
IWRS	Interactive web response system
LOCF	Last observation carried forward
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities

MHC-II	Major histocompatibility class II
NaCl	Sodium chloride
NSAIDs	Non-steroidal anti-inflammatory drugs
PCS	Physical Component Score (of the SF-36v2)
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol (population)
RBC	Red blood cell (count)
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SF-36v2	36-item short form health survey, version 2
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
$t_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum plasma/serum concentration
TMF	Trial Master File
TNF-α	Tumour-necrosis factor alpha
TPO	Thyroid peroxidase
TSH	Thyroid-stimulating hormone
TSHR	Thyroid-stimulating hormone receptor
UK	United Kingdom
US	United States
VAS	Visual analogue scale
V_z	Apparent volume of distribution during the terminal phase
W	Week
WBC	White blood cell (count)
λ_z	Apparent terminal-phase disposition rate constant (also called K_{el})

6 INTRODUCTION

The clinical development of BT063, a monoclonal humanised anti-IL10 antibody, targets the autoimmune disease systemic lupus erythematosus (SLE). Systemic lupus erythematosus is a systemic inflammatory autoimmune disease predominantly affecting women with peak age of onset between 15 and 40 years (Pisetsky et al 2001, Rus et al 2001).

Based on published prevalence rates approximately 250,000 people in the United States (US), 64,000 people in Japan and 125,000 people in Germany, Italy, France, Spain and the United Kingdom (UK) are suffering from SLE. Assuming a mean prevalence rate of 40 per 100,000, the European Union (EU) with its 500 million inhabitants has around 200,000 people who are affected by this disease. Recent studies of SLE conclude that the SLE population will experience a slight growth over the next decade (Danchenko et al 2006, Hannon et al 2009, Reynolds and Bruce 2013).

Regardless of the unknown aetiology of SLE, it is accepted that ethnic origin, genetics, and environmental factors contribute to SLE susceptibility and outcome. Women, African-Americans, and Hispanics are more likely to develop SLE (Bertsias et al 2012).

Various cytokines are elevated in patients with SLE. Evidence suggests that interleukin (IL)-10 could be a strong candidate gene influencing SLE susceptibility. IL-10 is an important immunoregulatory cytokine that inhibits T-cell function by suppressing the expression of pro-inflammatory cytokines such as tumour necrosis factor (TNF), IL-1, IL-6, IL-8, and IL-12 (López et al 2010). It also inhibits antigen presenting cells by down-regulating major histocompatibility complex class II (MHC-II) and B7 expression (López et al 2010). In addition to these inhibitory actions, IL-10 promotes B-cell-mediated functions, enhancing survival, proliferation, differentiation, and antibody production (Emilie 2002). Hence, increased production of IL-10 could explain B-cell hyperactivity and autoantibody production, two main features of the immune dysregulation in SLE.

The hyperactivity of B-lymphocytes plays a key role with massive abnormal production of immunoglobulin (Ig) G auto-antibodies (95% of patients with anti-nuclear auto-antibodies [ANA], 70% with auto-antibodies against double-stranded DNA [anti-dsDNA]). This pathological process results in sequestration and destruction of Ig-coated cells, fixation and cleaving of complement proteins, and release of chemotaxins, vasoactive peptides, and destructive enzymes into tissues. Most of the auto-antibody profiles/types are characteristic for each person at the time of clinical manifestations (Hahn 2005).

In the course of the entire disease, the vast majority (95%) of patients suffer from systemic symptoms such as fatigue, malaise, fever, anorexia, and weight loss, which are present most of the time. During the course of SLE, a total of 95% of patients complain of musculoskeletal disease (symptoms of arthralgia and myalgia, non-erosive polyarthritis, and myositis), 80% have cutaneous lesions (photosensitivity, malar rash, alopecia, and discoid rash), 85% report haematological disease (chronic anaemia, leukopenia, and lymphopenia), 60% have neurological disorders (cognitive, mood, and headache), 60% experience cardiopulmonary disease (pleurisy, pericarditis, and

effusions), 30 to 50% have renal disease, 40% report gastrointestinal disease, 15% report thrombosis and 15% experience ocular disease (Bertsias et al 2012).

Most patients experience periods of flares alternating with remissions. Permanent remissions (absence of symptoms with no treatment) are very rare. Nowadays, 10-year survival is over 90% mainly based on earlier diagnoses, as well as symptomatic treatment with anti-inflammatory and immune-suppressive medications.

Despite improvements in short-term survival, SLE remains a potentially fatal disease. The most common causes of death include infections, atherosclerotic disease, and active SLE or organ failure resulting from active SLE (Trager et al 2001). However, there is no causative treatment available to cure SLE or improve patients' quality of life on a long term basis. A favourable approach to treat SLE would be a specific treatment interacting or correcting the pathological immune response, resulting in the massive overproduction of polyclonal auto-antibodies. IL-10, IL-1ra, IL-12 (Capper et al 2004), and IL-6 (Chun et al 2007) are important cytokines in regulating immune response and are especially raised during flares in SLE patients. Plasma levels of IL-10 and anti-dsDNA often mirror disease activity in patients with SLE. Elevated IL-10 levels correlate with disease activity in SLE patients (Park et al 1998).

The spontaneous amount of the Th2 cytokine IL-10 produced spontaneously by SLE monocytes and B-cells is 33 times higher than that produced by normal cells (Llorente et al 1993).

IL-6 and IL-10 are both potent inducers of B-lymphocyte proliferation, differentiation into plasma cells, and up-regulation of MHC II expression.

Thus the immunological imbalance of SLE may be related to an abnormally high production of IL-6 and/or IL-10, or hypersensitivity of immune cells to these cytokines in vivo. This might explain the correlation of disease activity and plasma IL-10 levels that is found for most patients (Park et al 1998). Another main characteristic of immune dysregulation in SLE is the impaired cell-mediated immunity resulting from both, T-cell and antigen-presenting cell (APC) abnormalities. As IL-10 acts as powerful inhibitor of APC and T-cell functions, neutralisation of increased IL-10 levels leads to a partial restoration of T-lymphocyte function (Lauwerys et al 2000). In an investigator-initiated trial, Llorente and colleagues demonstrated that treatment of SLE subjects with daily IV doses of an IL-10 mAb over 21 days led to clinical improvement of symptoms (Llorente et al 2000).

Based on these pathological mechanisms, BT063 is in development for treatment of SLE.

Currently, treatment choices depend on: (a) whether disease manifestations are life-threatening or likely to cause organ damage justifying aggressive therapy; (b) whether manifestations are potentially reversible; and (c) the best approaches to preventing complications of disease and its treatment. Non-life threatening disease in SLE patients with fatigue, pain, and auto-antibodies, but without major organ involvement, can be treated symptomatically with analgesics and antimalarials. Non-steroidal anti-inflammatory drugs (NSAIDs) are useful particularly for arthritis/arthralgia. The mainstays for life-threatening SLE treatment (i.e., proliferative forms of lupus nephritis) are systemic glucocorticoids and cytotoxic agents (Hahn 2005).

Several new biologics are in various phases of clinical development targeting (activated) T- or B-cells or pro-inflammatory cytokines. Monoclonal antibodies (mAbs)

currently being investigated are ocrelizumab, infliximab, etanercept, efalizumab, tocilizumab, and the recombinant fusion proteins abatacept and atacicept (US National Institutes of Health).

7 STUDY OBJECTIVES

This study has 2 parts. The primary objective of Part I of this study is to evaluate the safety and tolerability of 3 months of treatment with 50 mg BT063 versus placebo in subjects with SLE.

The primary objective of Part II of this study is to evaluate the safety and tolerability of either 25 mg, 50, mg or 100 mg BT063 versus placebo in subjects with SLE. The dose level for Part II will be determined based on an interim analysis conducted after the last subject of Part I has completed the treatment.

Secondary objectives for both parts of the study are to:

- Evaluate the efficacy of 3 months of treatment with BT063 versus placebo as assessed by various disease activity indices including subject-reported outcomes
- Determine the pharmacokinetics (PK) of BT063
- Compare the pharmacodynamics (PD) of BT063 and placebo on various PD markers including biomarkers
- Determine the immunogenicity of BT063

8 ETHICAL AND REGULATORY CONSIDERATIONS

This clinical study protocol and any amendments will be submitted to a properly constituted Independent Ethics Committee (IEC) / Institutional Review Board (IRB) and/or Regulatory Authorities, in agreement with applicable regulatory requirements, for formal approval of the study conduct. A copy of these approvals must be submitted to Biotest before initiation of the clinical study and each site needs to keep a copy of these documents.

Changes to the clinical study protocol must be made in the form of an amendment that has the prior written approval of Biotest and – as applicable – of the appropriate IEC/IRB and Regulatory Authority.

The clinical study will be performed according to the applicable regulatory requirements taking into account the principles of Good Clinical Practice (GCP) and the latest version of the Declaration of Helsinki.

8.1 Data Safety Monitoring Board

Efficacy and safety data from the study will be evaluated by a Data Safety Monitoring Board (DSMB) at predetermined points in time, to ensure that the continuation of the study is appropriate and to make recommendations to the Sponsor. Unblinded data for the closed session of each DSMB meeting will be provided to the DSMB members by the unblinded CRO (POI) statistician, prior to the scheduled DSMB meetings. At each meeting, the DSMB will review the available safety and efficacy data to make

recommendations to Biotest about study continuation. The meetings for Part I of the study will be scheduled after the 3rd, the 9th and the 18th subject has completed the End-of-Treatment/Early Termination Visit. After the last subject in Part I is enrolled, there will be a hold on recruitment.

As soon as the last subject in Part I has completed the End-of-Treatment/Early Termination Visit an interim analysis of the available data (including follow-up visits of previous subjects) will be performed. The DSMB will review the safety and efficacy data and make a recommendation about the dose to be used in Part II of the study. Based on the overall conduct of the study and the DSMB's recommendation, Biotest will determine whether to continue the study and the dose to be used in Part II. During Part II of the study, the DSMB will meet to review and discuss available safety and efficacy data after the 3rd and 9th subject has completed the End-of-Treatment/Early Termination Visit to make recommendations to Biotest about study continuation.

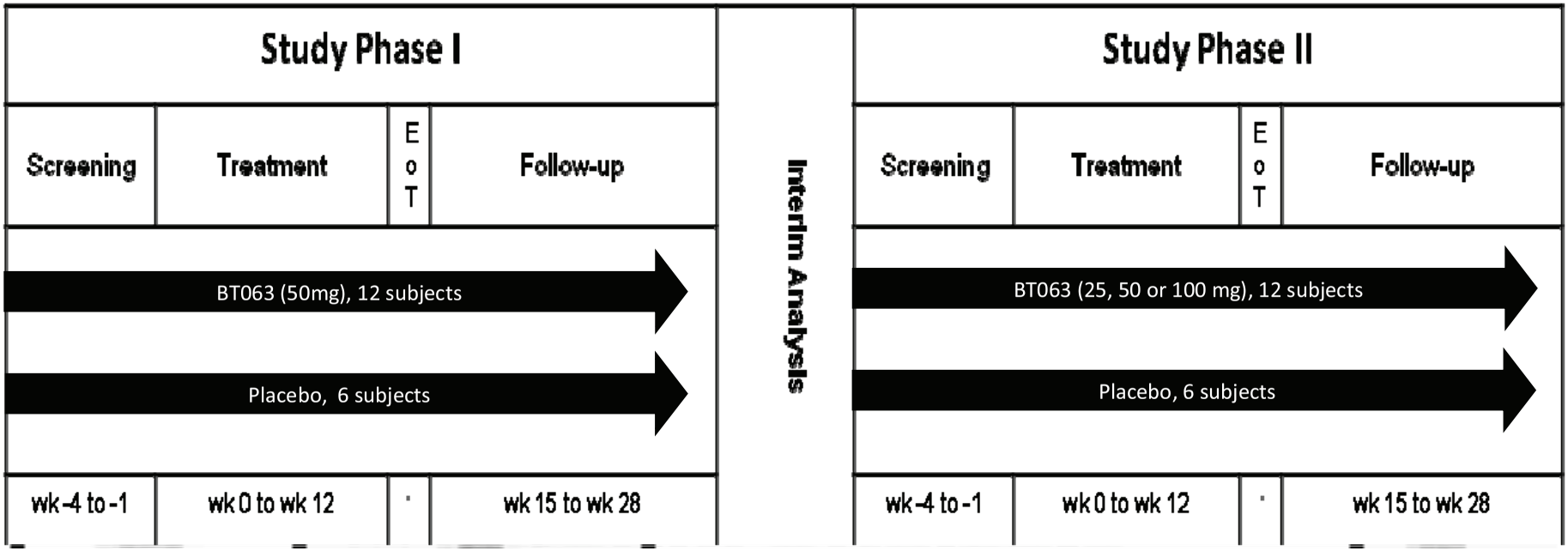
The DSMB will consist of permanent members who are not associated with the Sponsor or with the operative conduct of the study. A description of the scope of work and operating procedures for the DSMB is provided in a separate DSMB Charter, together with details of the composition of the DSMB.

9 STUDY DESIGN

This is a Phase IIa, double-blind, randomized, placebo-controlled, proof-of-concept study of BT063 in subjects with SLE. Subjects between 18 and 75 years, inclusive, must have a diagnosis of SLE by American College of Rheumatology Criteria (ACR; ≥ 4 of the 11 criteria must be met for ≥ 3 months prior to screening), moderate to severe SLE disease activity demonstrated by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) of at least 6 (joint and skin component must be positive). Also, at least 5 joints with pain and signs of inflammation (66/68 joint count) or Cutaneous Lupus Erythematosus Disease Area and Sensitivity Index (CLASI) Activity score ≥ 5 must be present.

This study is divided into 2 parts. Subjects will be randomly assigned to receive BT063 or placebo in a 2:1 ratio (BT063:placebo) for both parts. Part I will enrol 18 subjects: 12 subjects to 50 mg BT063 administered by intravenous (IV) infusion 8 times and 6 subjects to matching placebo administered by IV infusion 8 times (week 0 [baseline], and then at weeks 1, 2, 4, 6, 8 10, and 12). After the last subject in Part I has completed week 14 of the study, an interim analysis of the available data (including follow up visits of previous subjects) will be performed and the DSMB will review the safety and efficacy data. Depending upon the results of that review, the DSMB will recommend that Part II be started at a higher dose of BT063 (100 mg), a lower dose of BT063 (25 mg), or at the same dose (50 mg). After reviewing the DSMB recommendation, Biotest will determine whether to continue the study and if so, which dose will be used in Part II. Part II will enrol 18 subjects: 12 subjects to BT063 administered by IV infusion 8 times and 6 subjects to matching placebo administered by IV infusion 8 times (week 0 [baseline], and then at weeks 1, 2, 4, 6, 8, 10, and 12). For both Part I and Part II, subjects will be followed for 4 months after their last dose of BT063. In both Part I and Part II, subjects will not be replaced after receiving the first dose of BT063.

Figure 9.1. Schematic of Study Design



* End of Treatment visit: 2 weeks after last drug application

10 INVESTIGATIONAL MEDICINAL PRODUCT(S)

10.1 Investigational Medicinal Product – BT063

BT063 will be provided as a sterile solution containing the IL-10 binding monoclonal antibody (mAb) BT063 [redacted].

BT063 solution is a clear to slightly opalescent, colourless or slightly yellow liquid, free from visible particles, [redacted] A dose strength of 50.0 ± 5.0 mg/mL will be used in this study. Each glass vial contains an extractable volume of 1.0 mL solution.

BT063 will be diluted for infusion [redacted]

10.1.1 Description of Investigational Medicinal Product – BT063

Substance code:	BT063
Active ingredients:	BT063
Composition:	[redacted]
Dosage form:	1 mL solution to be diluted for infusion
Concentration:	50.0 mg/mL
Container:	glass vial (2 mL)
Manufacturer:	Biotest AG, D-63303 Dreieich, Germany

Batch number and expiry date are provided on the applicable certificates of analysis.

10.1.2 Packaging and Labelling

BT063 will be labelled according to local requirements. A sample label will be included in the Trial Master File (TMF).

An appropriate identification code will be used. This code will include the study number (990), the vial number, the kit number, and the lot number. The vial number, the kit number, and the lot number must be documented in the electronic Case Report Form (eCRF) and the drug accountability log. The extracted vial volume and the infusion volume will be recorded as well. Instead of prefixed identification numbers on the IMP,

the kit numbers (code of identification) will be allocated to the subjects and recorded in the study documents.

Packaging and labelling of BT063 will comply with Good Manufacturing Practice (GMP), GCP rules, Annex 13, and country specific regulatory requirements. Information on labels will be available in the local language.

10.1.3 Storage Conditions

BT063 will be stored at the study site in a cabinet or other enclosure which is locked securely. Access should be restricted to the investigator and authorized personnel.

BT063 will be stored at a temperature of +2°C to +8°C and must not be frozen. The storage temperature during shipment and at site will be documented on a temperature log. Any temperature excursion at the site must be reported to the Contract Research Organization (CRO, [redacted]). Deviations from the required storage conditions will be evaluated.

Investigational medicinal product that has been stored improperly must be quarantined at the site and must not be dispensed to any subject before it has been re-evaluated and approved for use by the Sponsor.

10.1.4 Preparation of BT063 Solution for IV Infusion

BT063 solution for IV infusion will be prepared under sterile conditions at the study site or a pharmacy associated with the study site.

During study Part I, 1.0 mL BT063 will be withdrawn from the vial and diluted in [redacted] During study Part II either 0.5 mL, 1.0 mL or 2.0 mL IMP (depending on the results of the interim analysis) will be diluted in [redacted].

BT063 and the diluent should be brought to room temperature (+15°C to +25°C) before use. The resulting final solution of BT063 will be filled in a perfusor syringe and administered via continuous IV infusion.

The infusion should be started immediately after dilution. Only clear to slightly opalescent, colourless or slightly yellow solutions without visible particles are to be administered.

10.2 Investigational Medicinal Product – Placebo

The placebo formulation consists of the identical volume in an identical container, and includes an identical end formulation buffer, but no BT063 drug product is included.

Placebo will be diluted for infusion in 20 mL of a physiological sodium chloride solution (0.9 % NaCl solution).

10.2.1 Description of Investigational Medicinal Product – Placebo

Substance code: Placebo

Active ingredients: Placebo

Composition: [redacted]

[redacted]

Dosage form:	1 mL solution to be diluted for infusion
Concentration:	[redacted])
Container:	glass vial (2 mL)
Manufacturer:	Biotest AG, D-63303 Dreieich, Germany

10.2.2 Packaging and Labelling

Placebo will be packaged and labelled in the same way as the active drug (Section 10.1.2).

10.2.3 Storage Conditions

Placebo will be stored in the same way as the active drug (Section 10.1.3).

10.2.4 Preparation of Placebo Solution for IV Infusion

Placebo will be diluted in the same way as the active drug (Section 10.1.4).

11 STUDY TREATMENT

11.1 Dosage Regimen

The IMP will be administered by site personnel over 8 visits within a period of 12 weeks. The visits take place in weekly or fortnightly intervals according to the visit schedule and within the visit windows specified in the Flowchart of the Study (Section 3) and Section 13 "Course of the Study." The IMP (BT063 or placebo) will be administered via an IV continuous infusion for approximately 2 hours. The 12-week IMP administration period will be followed by and End of Treatment Visit 2 weeks after the last dose of IMP and then a 14-week follow-up period.

11.1.1 Dosage and Administration

The IMP will be available in single-use vials containing 1.0 mL placebo or BT063 (50 mg/mL). During Part I of the study, 1.0 mL IMP (placebo or BT063) will be diluted in [redacted]). During Part II, either 0.5 mL, 1.0 mL, or 2.0 mL IMP (25 mg, 50 mg, or 100 mg BT063) will be used. The decision on the final dose for Part II will be made after the interim analysis.

The diluted IMP will be infused completely via a perfusor pump at an infusion rate of 10 mL/h. Before the infusion starts, the perfusor tubing is to be primed with diluted IMP

so that it is completely filled. After infusion of the diluted IMP the tubing will be flushed with physiological sodium chloride solution (at least one dead space volume of the tubing) at the same infusion rate. Further details are provided in the IMP handling manual.

After the end of the first 2-hour infusion of IMP (D0 [baseline]), the subject must stay at the investigational site for at least an additional 2 hours to enable monitoring for a type I hypersensitivity reaction. At all subsequent visits the subject should be observed for at least half an hour after the infusion of IMP.

11.1.2 Compliance with Dosage Regimens

The IMP will be administered by study personnel during visits. Therefore 100% compliance is expected. The investigator or a designee is responsible for ensuring that the IMP is prepared properly and that accurate records are maintained. Further details are provided in the IMP handling manual.

11.1.3 Dose Justification

The dosing regimen for Study 990 is based on the results of the investigator-initiated trial with B-N10 (the murine predecessor of BT063) in subjects with SLE (Llorente et al 2000), a single-dose escalation Phase I study (Study 977) with BT063 in healthy subjects, a repeated-dose toxicity study in monkeys (Study BE-092-43/00), extrapolation of PD effects from *in vitro* whole blood assay, and the modelling and simulation of kinetic of plasma concentrations based on PK data from Study 977.

Llorente et al demonstrated that treatment of SLE subjects with daily IV doses of 20 mg B-N10 over 21 days led to an improvement of skin lesions and joint symptoms (Llorente et al 2000). Signs and symptoms started to improve by day 10 to 12, and optimal improvement was reached at month 2. At the end of the follow-up period of 6 months, the disease was clinically inactive in 5 of 6 subjects. The mean steady state plasma concentration of B-N10 during the treatment phase was 20 µg/mL (range: 14 to 27 µg/mL on day 9 to 11). Similarly, in this proof-of-concept study (Study 990), one objective is to demonstrate improvement of skin and/or joint symptoms by maintaining an average plasma concentration close to 20 µg/mL during 12 weeks IMP treatment. Signs and symptoms of SLE will be recorded for 16 weeks after treatment is completed (at an End of Treatment Visit 2 weeks after the last dose of IMP and then for an additional 14 weeks).

In Study 977, single IV doses of 0.175, 0.75, 3.5, 7.5, 15, 30, 60, and 100 mg BT063 were given to healthy subjects (12 male, 11 female). Overall, BT063 was well tolerated during this study. Most of the observed AEs were consistent to those seen in a healthy population, although mouth ulcers occurred in subjects starting at the 15 mg dose group. After recurrence of mouth ulcers 43 days after the 100 mg BT063 dose in the first subject of the 100 mg cohort, the Sponsor determined that the risks outweighed the benefits in healthy subjects, so the last subject of the 100 mg cohort was not dosed.

In addition to preliminary safety data, pharmacokinetic behaviour of BT063 was also examined in Study 977. The data showed that the maximum plasma concentration (C_{max}) was reached in humans 1 to 2 hours after IV dosing. The total exposure as

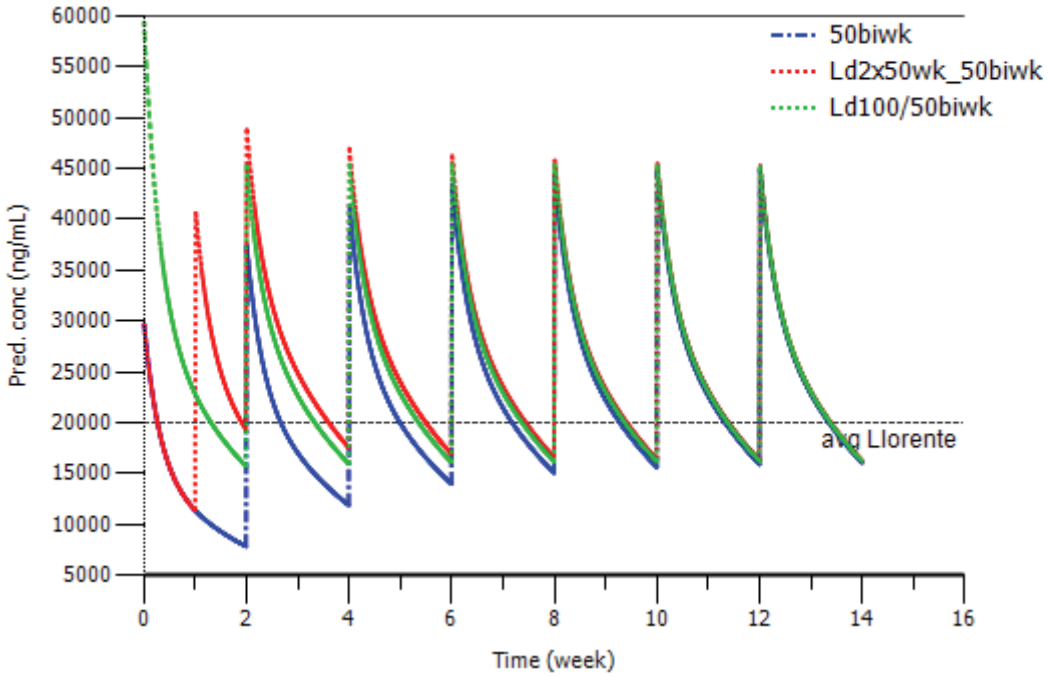
represented by the area under the concentration-time curve (AUC) and C_{max} were approximately dose proportional. The mean BT063 half-life ranged between 20 days and 26 days. A transient mild IL-10 dose-dependent increase was observed at doses above 7.5 mg. This increase might be caused by prolonged circulation of IL-10 neutralized by BT063. Apart from IL-10, no BT063-related effects on cytokine levels and lymphocyte values were observed during Study 977.

Cynomolgus monkey is regarded as a relevant animal model due to cross reaction of BT063 with monkey IL-10. In a multiple dose toxicity study (Study BE-092-43/00), cynomolgus monkeys received 7 fortnightly doses of 1, 7, or 50 mg/kg BT063 by IV for a total of 13 weeks. The low dose level of 1 mg/kg is comparable to a human equivalent dose of ~330 µg/kg, resulting in a total human dose of 20 mg (60 kg body weight) assuming equivalency on the basis of mg/m^2. For the high level dose of 50 mg/kg, the equivalent total human dose would be 1000 mg/kg. No clinical signs considered to be related to BT063 were observed up to the highest dose administered, except minimal transient platelet rises observed at 50 mg/kg. No signs of mouth ulcers were evident. Also no difference between male and female cynomolgus monkeys could be detected.

Finally, the total exposure (AUC) and maximal concentration over a 13-week treatment with the highest dose in monkey were several fold (>10-fold) above those predicted for humans treated with a dose up to 200 mg biweekly.

The level of IL-10 neutralization by BT063 required to demonstrate beneficial effects in SLE subjects in the clinic is still not known. Therefore, in order to select a safe and effective dose, modelling and simulation were also performed to predict maximal concentrations, total exposure (measured by AUC), average concentrations, and trough levels. Predicted BT063 plasma levels for different dose schedules were simulated based on population PK modelling of Study 977 plasma concentrations. According to these predictions (Figure 11.1), bi-weekly (every 2nd week) dosing of 50 mg BT063 would lead to trough levels similar to the average level reached with B-N10 in the Llorente study (Llorente et al 2000) only after the fourth administration. To avoid a long accumulation period, either a higher initial loading dose of 100 mg BT063, or alternatively an initial weekly dosing of 50 mg was considered. Simulations of both scenarios indicated a C_{max} of about 59 µg/mL with a 100 mg loading dose and of 49 µg/mL with an initial weekly dosing of 50 mg (Figure 11.1). In both cases, the predicted trough levels were closer to the desired level already after the second week.

Figure 11.1. Predicted BT063 Plasma Concentrations in Humans



Note: Plasma concentrations following bi-weekly dosing of 50 mg IV and different loading dose options (no loading dose [50biwk], 100 mg loading dose [Ld100/50biwk], or twice 50 mg at 1 week interval [Ld2x50wk_50biwk]) were simulated.

Although, the 100 mg dose has been already administrated in a Phase I study with healthy subjects (Study 977), a progressive loading with 50 mg dosing at baseline, followed by 50 mg at weeks 1, 2, 4, 6, 8, 10, and 12 was chosen for Part I of this study. After 18 of 36 planned subjects have been treated through study week 12 (12 with BT063 and 6 with placebo), an interim analysis of safety and efficacy data will be performed to decide on the dosing schedule for Part II. Currently it is expected that the dose level will be either 25, 50, or 100 mg using the same dosing intervals as in Part I.

11.1.4 Treatment of Overdose

BT063 has been administered to healthy subjects as IV infusions of doses up to 100 mg in 20 mL solution.

No experience with overdose of BT063 in humans exists. In case of an overdose of IMP, treatment should be suspended and the subject should receive appropriate medical treatment according to the clinical condition.

11.2 Randomization Code / Emergency Unblinding Procedures

11.2.1 Randomization

This is a double-blind study, therefore subjects, investigators, and study personnel will remain blinded with regard to the randomized treatment assignment until after database

lock. Database lock for interim analysis of study Part I will comprise data including End-of-Treatment visit (Visit 12)/Early Termination Visit of the 18th subject and all available Follow-up visit data of previous subjects.

An interactive web response system (IWRS) will be implemented and used for randomization and IMP re-supply. The randomization is thereby balanced for the entire study but not necessarily for each study site. Detailed instructions for the use of the IWRS system are provided in the IWRS User Manual that will be filed in the Investigator Site File (ISF).

11.2.2 Procedures for Unblinding

In the event of an emergency, each study site will be able to unblind subject treatment allocation via IWRS (either the Principal Investigator or a designated medic sub investigator at the study site). Unblinding shall be carried out only if a medical emergency requires the identification of the IMP for that particular subject. If possible, and time allows, investigators should make every effort to discuss the subject's case with the Sponsor or representative prior to breaking the blind. If the code is broken for a subject (via the IWRS), the Sponsor must be informed immediately. When the qualified study site personnel executes an unblind request within the system, the IWRS will prompt the requestor for information relating to the unblind request prior to releasing the code. The reason for breaking the code must be documented on the appropriate eCRF page along with the date and the system user ID of the person who broke the code.

Any subject for whom the blind is broken will be discontinued from the study.

Instructions for breaking the blind via IWRS will be described in the IWRS User Manual that will be provided to each site.

If emergency unblinding via IWRS is not possible due to a technical error or failed internet connectivity, the site must contact [redacted] Once the identity of the caller is authenticated, the unblinding details will be provided over the telephone.

11.3 Drug Accountability

The investigator or his/her designee must maintain records to document adequately that the subjects were provided the IMP as specified in the protocol and to reconcile all IMPs received for the study. The investigator must ensure that consignments of IMP are received, and that the IMP is safely and appropriately handled and stored.

Drug re-supply will be managed by the IWRS system.

The investigator or designee must keep sufficient documentation of the delivery, use, and destruction or return of unused, used, or partially used packages of IMP. The documentation must include dates, quantities, subject numbers, batch numbers or other identification numbers, and expiry dates.

After drug accountability procedures are complete, used and unused IMPs are to be destroyed at the site in accordance with local procedures, or returned to the Sponsor or its representative for destruction.

The investigator must allow the Clinical Research Monitor (monitor) to perform drug reconciliation. The entries in the eCRF as well as the documentation kept in the ISF will

be compared with the returned and residual IMPs, with clarification of any discrepancies or inconsistencies.

11.4 Previous and Concomitant Medication or Treatment

Subjects should be on stable doses of concomitant medication for SLE activity maintenance and symptom control (e.g., azathioprine, methotrexate, leflunomide, mycophenolate mofetil, cyclosporine, antimalarials such as chloroquine or hydroxychloroquine, steroids, NSAIDS/pain medication), without change in the type or dose of the drug used during the 8 weeks prior to baseline (for steroids and NSAIDs/pain medication 2 weeks) with the expectation that there will be no need for change in concomitant medication until the End of Treatment visit (ideally throughout the whole study); however, if the subject is taking an oral glucocorticosteroid at a dose higher than equivalent to 20 mg prednisone/day, and planning to reduce the dose of glucocorticosteroid, the dose can be titrated during the screening period so that the subject has been on at most, a 20 mg/day dose of 2 weeks by day 0 (baseline; i.e., first BT063 dose).

Concomitant medications should not exceed the doses outlined in the summary of product characteristics (SPC) or standards for SLE management; except for oral glucocorticosteroids which are limited to a dose equivalent to 20 mg prednisone/day.

All previous and concomitant medications will be recorded in the appropriate sections of the eCRF.

11.5 Prohibited Medication or Treatment

Medication other than allowed SLE treatments that is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF. Investigators are encouraged to discuss the introduction of any restricted medications with the Sponsor or its representative.

Medications that are restricted or have special allowances during the study are listed in Table 11.1. These restrictions begin at screening and are to be followed through the End of Treatment Visit at W14. During the 14-week follow-up period, certain medications may be administered at the investigator's discretion. However, no new medications for SLE should be started at any time during the study.

Table 11.1: Treatment Restrictions

Treatment	Restriction or Allowance
Glucocorticosteroids:	Oral Glucocorticosteroids: stable dose ≤ 20.0 mg prednisone daily or equivalent for at least 2 weeks prior to baseline and through the End of Treatment Visit at week 14. At most two short courses of an increased dose of oral glucocorticosteroids (i.e., 5 days) are allowed between week 4 and week 12 for management of flares. During the follow-up period these medications may be administered at the investigators discretion. Intramuscular or intra-articular Glucocorticosteroids: not permitted in the 4 weeks prior to screening and during the entire study. If necessary, 1 intra-articular steroid injection is allowed, but the treated joints cannot be assessed within 4 weeks. Intravenous Glucocorticosteroids (pulse therapy): not allowed within the 6 months before screening and during the entire study. Inhaled and topical Glucocorticosteroids: use of topical steroids is allowed, but not within 24 hours before assessment.
Antimalarial drugs: hydroxychloroquine/ chloroquine	Stable dose levels up to the highest dose defined by the SPC for treatment of SLE are allowed during the 8 weeks prior to baseline and through the End of Treatment Visit at week 14. During the follow-up period these medications may be administered at the investigators discretion.
Immunosuppressive drugs: azathioprine, methotrexate, leflunomide, cyclophosphamide (oral), mycophenolate mofetil, cyclosporine	Stable dose levels up to the highest dose defined by the SPC for treatment of SLE are allowed during 8 weeks prior to baseline and through the End of Treatment Visit at week 14. During the follow-up period these medications may be administered at the investigators discretion. Intravenous cyclophosphamide is not allowed within the 6 months before screening and during the entire study.
Biological therapies: Rituximab, Belimumab	Rituximab is not allowed within the last 48 weeks before screening and during the entire study. Belimumab is not allowed within the last 12 weeks before screening and during the entire study.
Non-steroidal treatments:	Non-steroidal topical treatments of skin lesions are allowed; however, not within 24 hours before assessments. Stable dose levels of the following NSAIDs and -Coxibs are allowed up to the maximum daily doses stated during the 2 weeks prior to baseline and through the End of Treatment Visit at week 14; however, not within 24 hours before assessments: diclofenac (150 mg); ibuprofen (2400 mg), naproxen (750 mg), meloxicam (15 mg), etoricoxib (90 mg), celecoxib (200 mg). During the follow-up period these medications may be administered at the investigators discretion.
'Rescue' pain/analgesic treatment on demand:	Paracetamol/acetaminophen: can be taken during the study up to a maximum of 4000 mg per day; maximum 2000 mg per day on the day before joint assessment. Not to be taken within 12 hours prior

Treatment	Restriction or Allowance
	to joint assessment.
Folic acid:	Folic or folinic acid supplementation may be administered at the discretion of the investigator and in accordance with any local guidelines. If applicable, dose should remain stable from ≥8 weeks prior to baseline and where possible, throughout the entire study.
Vaccinations:	Any vaccination within 8 weeks prior to screening and throughout the entire study is not allowed, except for influenza and a tetanus booster.
Anti-retrovirals:	Anti-retroviral therapy is prohibited throughout the entire duration of the study.
Antibiotic or antiviral therapy:	Subjects who have infections requiring antibiotic or antiviral therapy (by any route of administration) in the 2 weeks prior to baseline are not eligible for the study. IV antibiotics are not allowed during the entire study, however oral antibiotics are allowed.
Investigational agents:	Subjects cannot have received any investigational agent within 90 days or within 5 half-lives of the investigated compound, whichever is longer, prior to baseline and during the entire study.
Plasmapheresis, IVIg	Plasmapheresis and or IVIg therapy are not allowed during the entire study; IVIg is not allowed within 12 weeks before screening.
Others:	All other medications including over-the-counter self-administered medications, herbal remedies and traditional medicines (including single doses) administered in the 6 weeks prior to screening and during the study period are to be recorded in the source documents and the eCRF. Doses, route of applications, duration of treatment, and reasons for prescription are also to be recorded.

11.6 Risks and Precautions

Detailed information about the risks and precautions are described in the Investigator's Brochure (IB). Further information is given in Section 13.5, Benefit-Risk Evaluation.

12 STUDY POPULATION

12.1 Study Population, Diagnosis and Number of Subjects

12.1.1 Sex Distribution

Since SLE affects women more than men, it is expected that approximately 90% of enrolled study subjects will be women and approximately 10% will be men. A total of 36 subjects will be enrolled in Study 990 (18 each in Part I and Part II) No specific measures will be taken to control the distribution of sex in the enrolled population.

12.1.2 Diagnosis

Adult subjects of both sexes with a diagnosis of SLE as defined by the ACR criteria (Appendix B) are eligible for inclusion in this study if at least 4 of the 11 criteria are met during the 3 months before screening.

Subjects must have moderate to severe SLE disease defined by a SLEDAI-2K total score of at least 6. Skin and joints must be affected by the disease and contribute to SLEDAI-2K scoring.

Skin involvement measured by CLASI score must reach at least 5 or alternatively at least 5 of 66/68 joints must have pain and signs of inflammation present (i.e., swelling and/or specific tenderness at the joint lining).

For further definition of the study populations please refer to the inclusion and exclusion criteria in Section 12.2 and Section 12.3.

12.2 Inclusion Criteria

Only subjects meeting all of the following inclusion criteria will be considered for study inclusion:

Inclusion Criteria	Rationale	Screening	Baseline
1. Able to provide written informed consent and/or consent obtained from a legally acceptable representative (as required by IRB/IEC) prior to the initiation of any protocol-required procedures.	Administrative	•	
2. Diagnosis of SLE as defined by ACR criteria (Appendix B) such that ≥ 4 of the 11 criteria are met for ≥ 3 months before screening	Medical	•	
3. Moderate to severe SLE disease activity at screening and baseline demonstrated by SLEDAI-2K total score ≥ 6, including skin **and** joint involvement	Medical	•	•
4. Regarding skin and joints, both need to be involved, and either skin should be involved according to CLASI Activity score ≥ 5 **or** at least 5 of 66/68 joints with pain and signs of inflammation present at screening and baseline (joints suspected or known to have ischemic osteonecrosis are not to be taken into consideration)	Medical	•	•
5. No change in concomitant medication for SLE activity maintenance and symptom control (e.g., azathioprine, methotrexate, leflunomide, mycophenolate mofetil, cyclosporine, antimalarials such as chloroquine or hydroxychloroquine, glucocorticosteroids, pain medication, e.g. nonsteroidal anti-inflammatory drugs [NSAIDs] or paracetamol) regarding type of medication and dose level for at least 8 weeks prior to baseline (for steroids and NSAIDs/pain medication 2 weeks) and with the expectation that there will be no need for change in concomitant medication until the End-of-Treatment visit (ideally throughout the whole study);	Medical	•	•

Inclusion Criteria		Rationale	Screening	Baseline
	however, if the subject is taking an oral glucocorticosteroid at a dose higher than equivalent to 20 mg prednisone/day, and planning to reduce dose of glucocorticosteroid, the dose can be titrated down during the screening period so that the subject has been on, at most, a dose equivalent to 20 mg prednisone/day for 2 weeks by day 0 (baseline; i.e., first BT063 dose)			
6.	The dose of concomitant medication for SLE activity maintenance and symptom control (e.g., azathioprine, methotrexate, leflunomide, mycophenolate mofetil, cyclosporine, antimalarials such as chloroquine or hydroxychloroquine, glucocorticosteroids, pain medication, e.g. nonsteroidal anti-inflammatory drugs [NSAIDs] or paracetamol) should not exceed the doses outlined in the summary of product characteristics (SPC) or standards for SLE management. For oral glucocorticosteroids maximal allowed dose is limited to a dose equivalent to 20 mg prednisone/day. NSAIDs should not be taken within 24 hours, paracetamol not within 12 hours prior to study visits	Medical	•	•
7.	Positive ANA at screening (as per central laboratory results)	Medical	•	
8.	Age ≥ 18 and ≤ 75 years at screening	Medical	•	
9.	Body mass index ≥ 18 and ≤ 35 kg/m^2	Medical	•	
10.	Normal ECG, i.e., no acute and clinically relevant abnormalities	Medical	•	

12.3 Exclusion Criteria

Subjects having any of the following criteria, either at screening or at baseline, will not be included in the study:

Exclusion Criteria		Rationale	Screening	Baseline
1.	Has active, severe SLE disease activity which involves the renal system and/or active, severe, neuropsychiatric SLE, defined as any neuropsychiatric element scoring BILAG level A disease.	Medical	•	•
2.	Diagnosed psoriasis	Medical	•	
3.	Presence or history of malignancy within the previous 5 years (except for successfully treated non-metastatic cutaneous squamous or basal cell carcinoma and/or localized carcinoma in situ of the cervix)	Medical	•	
4.	Received any vaccination within 8 weeks prior to screening (except for influenza or tetanus booster)	Medical	•	

Exclusion Criteria	Rationale	Screening	Baseline
5. History of more than 3 infections during the last 12 months requiring IV antibiotic treatment	Medical	•	
6. Systemic antibiotic treatment within 2 weeks before the baseline visit	Medical		•
7. A positive diagnosis for any of the following: • Acute or chronic viral hepatitis B (isolated positivity to hepatitis B surface antibody [anti-HBs] is allowed as an indicator of a previous vaccination that will be confirmed in the subject's notes) or acute or chronic hepatitis C (positive to anti-hepatitis C antibodies or hepatitis C viral RNA) • Human immunodeficiency virus (HIV) or tested positive for tuberculosis as assessed by QuantiFERON® TB gold test (if the result is inconclusive it may be repeated once) • Acute, clinically relevant, or potentially recent infection with Herpes Zoster or Herpes Simplex (Type 1 and Type 2), EBV or CMV infection or reactivation at screening	Medical	•	
8. Clinically significant hematologic abnormalities attributed to SLE: • Haemoglobin < 8 g/dL • Platelets 50 × 10^9/L • Leucocytes < 2 × 10^9/L	Medical	•	
9. Active or history of inflammatory bowel disease (including active or history of colitis)	Medical	•	
10. Received the following medications: • Rituximab within the last 48 weeks before screening • Belimumab within the last 12 weeks before screening • IV immunoglobulin within the last 12 weeks before screening • Intramuscular (IM) or intra-articular glucocorticosteroids within the last 4 weeks before screening • IV cyclophosphamide within the last 6 months before screening • IV glucocorticosteroids (pulse therapy) within the last 6 months before screening	Medical	•	
11. Participation in another clinical study in the 90 days prior to baseline or within 5 half-lives of the investigated compound, whichever is longer; Participation in another clinical study during this study and/or previous participation in this study	Medical		•

Exclusion Criteria	Rationale	Screening	Baseline
12. Pregnant or nursing women or women who intend to become pregnant	Medical	•	•
13. Men or women not will to use effective contraception excluding women not of childbearing potential (Subjects who are sexually active women of childbearing potential or sexually active men who are not practicing 2 different methods of birth control with their partner during the study and for 4 months after the last dose of IMP or who will not remain abstinent during the study and for 4 months after the last dose. If using birth control, each couple must use 2 of the following precautions: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injections, condom, or sponge with spermicide. Women who are not of childbearing potential include those who are at least 1 year post-menopausal confirmed by follicle-stimulating hormone [FSH] levels or women who are surgically sterile.)	Medical	•	•
14. Known intolerance to immunoglobulins or comparable substances (e.g., significant vaccination reaction)	Medical	•	
15. Known intolerance to proteins of human origin	Medical	•	
16. Employee or direct relative of an employee of the CRO, the study site, or Biotest	Administrative	•	•
17. History of clinically significant drug or alcohol abuse within the last 12 months	Medical	•	
18. Any other significant acute or chronic illness or laboratory abnormality, which, in the opinion of the investigator, might compromise the safety of the subject or influence the outcome of the study and its objectives.	Medical	•	

12.4 Subject Withdrawal Criteria and Procedures

In both Part I and Part II, subjects will not be replaced after receiving the first dose of BT063.

The participation of an individual subject may be discontinued prematurely for reasons such as:

- Withdrawal of written informed consent
- Required treatment with any medication known or suspected to interfere with the IMP
- Adverse reactions during administration of the IMP
- Lack of study compliance

- Treatment unblinding (see Section 11.2.2)
- Any other condition which in the opinion of the investigator no longer permits safe participation in the study

A subject may discontinue participation in the clinical study at his/her own request at any time without stating a reason.

The investigator can stop a subject's participation in the study at any time if continuation could lead to disadvantages for the subject which cannot be justified by the investigator.

The reason for withdrawal of the subject must be documented by the investigator together with all data collected until the day of premature study discontinuation including laboratory results and assessment of AEs. All assessments for the End of Treatment/Early Termination Visit (Visit 12) should be performed 2 weeks after the last IMP dosing.

If a subject withdraws due to an AE or serious adverse event (SAE) please follow the instructions given in Section 14.3.4.1 of this protocol.

12.5 Subject Information

The subject or his/her legally acceptable representative will be informed about the study according to the requirements of GCP and the legal requirements of the country in which the subject is recruited.

The study, its objectives, possible benefits and risks, and its consequences will be explained. Additionally, written information about the study will be provided. The subject or his/her legally acceptable representative will have sufficient time to read the information and ask questions. The subject or his/her legally acceptable representative must be told that refusal to participate in the study will not cause any disadvantages to the subject's treatment and that the subject or his/her legally acceptable representative may withdraw informed consent at any time, without stating a reason, and without prejudice to further medical management.

Subjects or their legally acceptable representatives must be informed and agree that their medical data may be reviewed by authorized persons during monitoring and during an audit or an inspection by the appointed Regulatory Authority or IEC/IRB, but that personal data will be treated with absolute confidentiality.

Upon request, the subject or his/her legally acceptable representative must be granted access to the insurance terms and conditions.

Any new and relevant information that evolves during the course of the study concerning the IMP, alternative treatments, or the benefit/risk ratio will be communicated.

12.6 Declaration of Informed Consent

The subject or his/her legally acceptable representative must provide written informed consent to participate in the study by signing and personally dating the informed consent form (ICF). Informed consent to the proposed data handling and to data inspection must also be documented on the ICF. Written informed consent must be

obtained from each subject or legally acceptable representative before any study-related procedures are performed. The subject's or his/her legally acceptable representative's signed and dated ICF will be filed at the investigator's site and a copy must be given to the subject or his/her legally acceptable representative.

13 COURSE OF THE STUDY

13.1 Visit Schedule

A signed and dated IEC/IRB-approved ICF must be obtained from each subject or his/her legally acceptable representative before any study-specific procedures can be performed. Screening procedures will be performed between 28 and 7 days (Visit 1) prior to IMP administration (Baseline, Visit 2). Potential subjects will be notified prior to Visit 1 to fast for at least 12 hours before the scheduled visit.

During the study, every effort should be made to perform study procedures as indicated in the Flowchart of the Study (Section 3). Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the investigator's discretion.

13.1.1 Screening - Visit 1, Days -28 to -7 (Week -4 to -1)

The following procedures are to be completed during the screening period at time points designated on the Flowchart of the Study (Section 3).

- Provide informed consent and request ICF signature
- Record demographic data including sex, age, race, and ethnicity
- Record medical/surgical history (including any risk factors)
- Record previous and current medications as well as history of vaccinations
- Verify eligibility (inclusion/exclusion criteria)
- Complete full physical examination (including weight and height)
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Perform 12-lead ECG
- Draw blood for safety and eligibility laboratory assessments (haematology, coagulation, and clinical chemistry), auto-antibodies (ANA, anti-dsDNA, thyroid gland [TPO and TSHR], anti-islet cells, anti-CCP, and Coombs test); immunological status (HBV, HCV, HIV, tetanus, diphtheria, tuberculosis); and EBV and CMV serology
- Draw additional blood for the following tests: thyroid-stimulating hormone (TSH), fT3, fT4, fasting glucose, fasting triglycerides, fasting cholesterol, fasting high-density lipoprotein, and fasting low-density lipoprotein (fasting must be for at least 12 hours)

- Obtain sample for urinalysis
- Urine pregnancy test for women of childbearing potential, FSH assessment for women not of childbearing potential
- Perform and record the following assessments:
    - SLEDAI-2K
    - CLASI Activity score
    - BILAG score
    - Tender joint count and swollen joint count
    - Physician's Global Assessment of Disease Activity
- Draw blood for PD assessment: complement activity (CH50, C3, and C4)

13.1.2 Baseline – Visit 2, Day 0 (Week 0)

Baseline procedures will be performed on Day 0, the first day of IMP administration. The following procedures are to be completed at time points designated on the Flowchart of the Study (Section 3).

- Confirm that the ICF has been signed
- Confirm eligibility (inclusion/exclusion criteria)
- Record AEs
- Perform full physical examination
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Draw blood for safety laboratory assessments (haematology, coagulation, and clinical chemistry), auto-antibodies (ANA, anti-dsDNA, thyroid gland [TPO and TSHR], anti-islet cells, anti-CCP, and Coombs test), and anti-BT063 antibodies; as well as retention samples for immunological status and EBV and CMV serology
- Draw blood for the following additional tests: TSH, fT3, fT4, fasting glucose, fasting triglycerides, fasting cholesterol, fasting high-density lipoprotein, and fasting low-density lipoprotein (fasting must be for at least 12 hours)
- Obtain samples for urinalysis and faecal occult blood test
- Urine pregnancy test for women of childbearing potential
- Record concomitant medications
- Perform and record the following assessments:
    - Subject Reported Outcomes: FACIT-F and SF-36v2
    - SLEDAI-2K
    - CLASI Activity score
    - BILAG score
    - Tender joint count and swollen joint count
    - Physician's Global Assessment of Disease Activity
    - ECLAM
- Draw blood for PD assessments: T- and B-lymphocytes (CD3, CD4, CD8, CD19, CD20, CD27, CD38, CD69, CD62L, HLA DR, CD45RA), complement activity, ESR and CRP, cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-α, and

INF-$_{\gamma}$), immunological parameters, immunoglobulins (IgG, IgM, IgA, and IgE), and biomarkers
- Draw blood before IMP administration for serum BT063 level and Free IL-10
- Randomize subject and administer IMP
- Draw blood after IMP administration for serum BT063 level and Free IL-10
- Ask the subject to stay at the investigational site for at least an additional 2 hours and monitor for a type I hypersensitivity reaction

13.1.3 Treatment – Visit 3, Day 4 or 5 (Week 1)

The following procedures will be completed at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Record concomitant medications
- Draw blood for PK and PD assessment: serum level of BT063 and cytokines

13.1.4 Treatment – Visit 4, Day 7±1 (Week 1)

The following procedures will be completed at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Perform targeted physical examination
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Draw blood for safety laboratory assessments (haematology, coagulation, and clinical chemistry)
- Obtain sample for urinalysis
- Record concomitant medications
- Draw blood for PD assessment: T- and B-lymphocytes
- Draw blood before IMP administration for serum BT063 level
- Administer IMP
- Draw blood after IMP administration for serum BT063 level
- Monitor the subject for at least half an hour after the infusion of IMP

13.1.5 Treatment – Visit 5, Day 14±1 (Week 2)

The following procedures will be completed at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Perform targeted physical examination
- Measure and record vital signs (pulse, blood pressure, and body temperature)

- Draw blood for safety laboratory assessments (haematology, coagulation, and clinical chemistry), and auto-antibodies (ANA, anti-dsDNA, thyroid gland [TPO and TSHR], anti-islet cells, anti-CCP, and Coombs test)
- Obtain samples for urinalysis and faecal occult blood test
- Record concomitant medication
- Perform and record the following assessments:
    - Subject Reported Outcomes: FACIT-F and SF-36v2
    - SLEDAI-2K
    - CLASI Activity score
    - Tender joint count and swollen joint count
    - Physician's Global Assessment of Disease Activity
- Draw blood for PD assessments: complement activity, ESR and CRP, cytokines, immunoglobulins, and biomarkers
- Draw blood before IMP administration for serum BT063 level and Free IL-10
- Administer IMP
- Draw blood after IMP administration for serum BT063 level and Free IL-10
- Monitor the subject for at least half an hour after the infusion of IMP

13.1.6 Treatment – Visit 6, Day 28±2 (Week 4)

The following procedures will be completed at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Perform targeted physical examination
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Draw blood for safety laboratory assessments (haematology, coagulation, and clinical chemistry) and auto-antibodies (ANA, anti-dsDNA, thyroid gland [TPO and TSHR], anti-islet cells, anti-CCP, and Coombs test), and anti-BT063 antibodies
- Obtain samples for urinalysis and faecal occult blood
- Urine pregnancy test for women of childbearing potential
- Record concomitant medication
- Perform and record the following assessments:
    - Subject Reported Outcomes: FACIT-F and SF-36v2
    - SLEDAI-2K
    - CLASI Activity score
    - BILAG score
    - Tender joint count and swollen joint count
    - Physician's Global Assessment of Disease Activity
    - ECLAM
- Draw blood for PD assessments: complement activity, ESR and CRP, immunoglobulins

- Draw blood before IMP administration for serum BT063 level and Free IL-10
- Administer IMP
- Draw blood after IMP administration for serum BT063 level and Free IL-10
- Monitor the subject for at least half an hour after the infusion of IMP

13.1.7 Treatment - Visit 7, Day 42±2 (Week 6)

The following procedures will be completed at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Perform targeted physical examination
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Record concomitant medications
- Draw blood for PD assessments: T- and B-lymphocytes, cytokines, immunological parameters, immunoglobulins, Free IL-10, and biomarkers
- Draw blood before IMP administration for serum BT063 level
- Administer IMP
- Draw blood after IMP administration for serum BT063 level
- Monitor the subject for at least half an hour after the infusion of IMP

13.1.8 Treatment – Visit 8, Day 56±2 (Week 8)

The following procedures will be completed at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Perform targeted physical examination
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Draw blood for safety laboratory assessments (haematology, coagulation, and clinical chemistry) and auto-antibodies (ANA, anti-dsDNA, thyroid gland [TPO and TSHR], anti-islet cells, anti-CCP, and Coombs test), and anti-BT063 antibodies
- Obtain sample for urinalysis
- Urine pregnancy test for women of childbearing potential
- Record concomitant medications
- Perform and record the following assessments:
    - Subject Reported Outcomes: FACIT-F and SF-36v2
    - SLEDAI-2K
    - CLASI Activity score
    - BILAG score
    - Tender joint count and swollen joint count
    - Physician’s Global Assessment of Disease Activity
    - ECLAM

- Draw blood for PD assessments: complement activity and ESR and CRP
- Draw blood before IMP administration for serum BT063 level
- Administer IMP
- Draw blood after IMP administration for serum BT063 level
- Monitor the subject for at least half an hour after the infusion of IMP

13.1.9 Treatment – Visit 9, Day 70±2 (Week 10)

The following procedures will be completed at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Perform targeted physical examination
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Record concomitant medication
- Draw blood before IMP administration for serum BT063 level
- Administer IMP
- Draw blood after IMP administration for serum BT063 level
- Monitor the subject for at least half an hour after the infusion of IMP

13.1.10 Treatment – Visit 10, Day 84±2 (Week 12)

The following procedures will be completed at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Perform targeted physical examination
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Draw blood for safety laboratory assessments (haematology, coagulation, and clinical chemistry) and auto-antibodies (ANA, anti-dsDNA, thyroid gland [TPO and TSHR], anti-islet cells, anti-CCP, and Coombs test)
- Obtain sample for urinalysis
- Urine pregnancy test for women of childbearing potential
- Record concomitant medication
- Perform and record the following assessments:
    - Subject Reported Outcomes: FACIT-F and SF-36v2
    - SLEDAI-2K
    - CLASI Activity score
    - BILAG score
    - Tender joint count and swollen joint count
    - Physician's Global Assessment of Disease Activity
    - ECLAM

- Draw blood for PD assessments: T- and B-lymphocytes, complement activity, ESR and CRP, cytokines, immunological parameters, immunoglobulins, and Free IL-10
- Draw blood before IMP administration for serum BT063 level
- Administer IMP
- Draw blood after IMP administration for serum BT063 level
- Monitor the subject for at least half an hour after the infusion of IMP

13.1.11 Treatment – Visit 11, Day 91±2 (Week 13, at least 5 days after Visit 10)

The following procedures will be completed at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Record concomitant medications
- Draw blood at least 5 days after Visit 10 to measure serum BT063 level

13.1.12 End of Treatment/Early Termination – Visit 12, Day 98±2 (Week 14)

The following procedures will be completed at the End of Treatment/Early Termination Visit at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Perform targeted physical examination (including weight)
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Perform 12-lead ECG
- Draw blood for safety laboratory assessments (haematology, coagulation, clinical chemistry), auto-antibodies (ANA, anti-dsDNA, thyroid gland [TPO and TSHR], anti-islet cells, anti-CCP, and Coombs test), anti-BT063 antibodies, immunological status, and EBV and CMV serology
- Draw additional blood for the following tests: TSH, fT3, fT4, fasting glucose, fasting triglycerides, fasting cholesterol, fasting high-density lipoprotein, and fasting low-density lipoprotein (fasting must be for at least 12 hours)
- Obtain sample for urinalysis and faecal occult blood
- Urine pregnancy test in women of childbearing potential
- Record concomitant medications
- Perform and record the following assessments:
    - Subject Reported Outcomes: FACIT-F and SF-36v2
    - SLEDAI-2K
    - CLASI Activity score
    - BILAG score
    - Tender joint count and swollen joint count
    - Physician's Global Assessment of Disease Activity
    - ECLAM

- Draw blood for PK and PD assessments: serum level of BT063, complement activity, ESR and CRP, cytokines, immunoglobulins, Free IL-10, and biomarkers

13.1.13 Follow-up – Visit 13, Day 140±7 (Week 20)

The following procedures will be completed at the first Follow-up Visit at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Perform targeted physical examination
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Draw blood for safety laboratory assessments (haematology, coagulation, and clinical chemistry), auto-antibodies (ANA, anti-dsDNA, thyroid gland [TPO and TSHR], anti-islet cells, anti-CCP, and Coombs test), and anti-BT063 antibodies
- Obtain sample for urinalysis
- Record concomitant medications
- Perform and record the following assessments:
    - Subject Reported Outcomes: FACIT-F and SF-36v2
    - SLEDAI-2K
    - CLASI Activity score
    - BILAG score
    - Tender joint count and swollen joint count
    - Physician's Global Assessment of Disease Activity
    - ECLAM
- Draw blood for PK and PD assessments: serum level of BT063, complement activity, ESR and CRP, Free IL-10.

13.1.14 Follow-up - Visit 14, Day 196±7 (Week 28)

The following procedures will be completed at the second Follow-up Visit at the times designated on the Flowchart of the Study (Section 3).

- Record AEs
- Perform targeted physical examination
- Measure and record vital signs (pulse, blood pressure, and body temperature)
- Draw blood for safety laboratory assessments (haematology, coagulation, clinical chemistry), auto-antibodies (ANA, anti-dsDNA, thyroid gland [TPO and TSHR], anti-islet cells, anti-CCP, and Coombs test), and anti-BT063 antibodies; as well as retention samples for immunological status and EBV and CMV serology
- Obtain sample for urinalysis
- Record concomitant medications
- Perform and record the following assessments:
    - Subject Reported Outcomes: FACIT-F and SF-36v2
    - SLEDAI-2K
    - CLASI Activity score

- BILAG score
- Tender joint count and swollen joint count
- Physician's Global Assessment of Disease Activity
- ECLAM

- Draw blood for PK and PD assessments: serum level of BT063, T- and B-lymphocytes, complement activity, ESR and CRP, cytokines, Free IL-10, and biomarkers

13.2 Duration of the Study

First Subject First Visit *(planned)*	May 2015
Last Subject Last Visit *(planned)*	Q3 2017

Individual Subject Study Participation

It is anticipated that each subject will participate in the study for up to 32 weeks including up to 4 weeks for screening, 12 weeks of treatment, and 16 weeks of follow-up (including an End of Treatment Visit 2 weeks after the last dose of IMP and then a follow-up period of 14 weeks).

13.2.1 End of Study

The end of study will be defined as the Last Visit of the Last Subject (= Last Subject Last Visit [LSLV]).

13.3 Criteria for Premature Termination

13.3.1 Premature Termination of the Entire Clinical Study

The study as a whole may be stopped by Biotest after consultation with the Coordinating Investigator for reasons such as:

- Unacceptable delay of study completion
- Low recruitment rate
- A large number of subjects with premature discontinuation
- Changed benefit-risk ratio according to the efficacy and/or safety results from this or parallel studies
- Lack of efficacy

In case of premature termination of the entire study, the Sponsor must notify the appropriate Regulatory Authorities within the timeframe required for the countries participating in this study.

13.3.2 Premature Termination of an Individual Study Site

The study may be stopped at an individual study site for reasons such as:

- Low recruitment rate
- Lack of co-operation
- Severe deviations from study protocol
- Manipulation of study data
- Violation of other ethical or legal principles

13.4 Treatment and Care after the End of the Study

The investigator is responsible for choosing the adequate SLE treatment for subjects who have finished the study or who have discontinued the study prematurely.

13.5 Benefit-Risk Evaluation

13.5.1 Benefit

Systemic lupus erythematosus is a multisystem autoimmune disorder associated with significant morbidity that can be fatal if not treated early in some patients.

Despite some progress in understanding the nature of SLE, the heterogeneous nature of this disease has made clinical investigation more difficult compared with other rheumatic diseases.

There is a clear unmet medical need for novel options in SLE treatment. BT063 is an anti-IL-10 antibody that has the potential to address this unmet need in SLE as there is reasonable evidence that the regulatory cytokine IL-10 plays a role in the pathogenesis of SLE. However, IL-10 is a pleiotropic cytokine and the many underlying mechanisms of IL-10 or IL-10R need to be further clarified. Clinical studies investigating the effect of drugs on IL-10 or IL-10R are highly desired (Gorski et al 2000).

That BT063 may address an unmet need is supported by clinical data with the murine predecessor of BT063 (Llorente et al 2000). All 6 subjects showed improvement in cutaneous and musculoskeletal manifestations of lupus, and 5 out of 6 subjects had clinically inactive disease at the end of the follow-up period. In addition, only 1 relatively mild AE was reported.

13.5.2 Foreseeable Risk and Discomfort Related to BT063

13.5.2.1 Potential risks

- Uncertain effect on the mucous membrane of the gastrointestinal tract (GI)
- Hypersensitivity reactions
- Interactions with other drugs
- Interaction with live vaccines or induction of immune system overreactions in vaccinated subjects
- Infections

13.5.2.2 Identified risks

Based on the results of the completed Phase I study in healthy subjects the following risks were classified as identified for BT063:

- Mouth ulcers/aphthous stomatitis

13.5.2.3 Important missing information

- Lack of knowledge about potential influence on pregnant women and embryonic development

13.5.3 Other Sources of Possible Risk and Discomfort

Puncture of a vein and/or placement of indwelling catheters for blood withdrawal may cause pain and occasionally results in thrombosis or thrombophlebitis.

Discomfort may be caused by any study procedure such as pre- and post-study examination (including drug and virological HIV tests), sampling (blood, urine) etc.

13.5.4 Summary of Possible Risk and Discomfort

The risks subjects have encountered from administration of single doses of IMP are mouth ulcers/aphthous stomatitis.

The major effect of IMP is as an immunomodulatory drug; therefore, the rate of infections may increase in subjects administered BT063. Infections will be closely monitored.

The Sponsor does not anticipate that AEs other than those outlined in Section 13.5.2 and Section 13.5.3 may occur from the IMP or study procedures; however, such AEs cannot be excluded.

Although risks cannot entirely be excluded, they can be minimized by the careful selection of the subjects and by their close surveillance by experienced investigators who recognize safety issues by carefully surveying warning signs and taking appropriate medical action.

Considering the

- Unmet medical need in SLE,
- Reasonable assumption that BT063 as anti-IL-10 antibody has the potential to address this unmet medical need,
- Encouraging clinical data with the murine predecessor of BT063,
- Positive results from the toxicology studies in animals which showed the good tolerability and safety of BT063, and
- Proposed mitigation strategies for identified or potential risks and important missing information,

the benefits of BT063 for use in a well-designed Phase II study outweigh the risks described.

14 ASSESSMENT OF OBJECTIVES / CRITERIA FOR EVALUATION

14.1 Safety Assessments

14.1.1 Specification of Safety Parameters

Safety will be assessed by reported AEs, physical examinations and vital signs (pulse, blood pressure, and temperature), laboratory measurements (haematology including coagulation, clinical chemistry, urinalysis, and faecal occult blood test), 12-lead ECGs, anti-dsDNA and ANA, thyroid gland (TPO, TSHR), anti-islet cells, anti-CCP, and Coombs test, anti-drug antibodies against BT063, and immunological status of potential viral and bacterial infections (hepatitis B and C virus, HIV, tetanus, diphtheria, tuberculosis as well as EBV/CMV serology).

14.1.2 Methods for Assessing, Recording and Analysing Safety Parameter(s)

14.1.2.1 Adverse Events

Safety and tolerability will be addressed by occurrence, frequency, nature, and severity of AEs. Adverse event and SAE assessments will be made throughout the study and will be evaluated and recorded in the source documents and on the eCRF as specified in Section 14.3.2.

The seriousness, severity, and causality of each AE or SAE will be evaluated by the investigator in accordance with the definitions in Section 14.3.1.

Subjects will be asked about AEs that occurred during the IV infusion or since the last visit by the use of non-leading questions.

Adverse Events of Special Interest

Adverse Events of special interest (AESI; serious or nonserious) are events that are of scientific and medical concern specific to the Sponsor's product for which close monitoring and rapid communication by the investigator to the Sponsor is appropriate. For this study, the following AEs of special interest will be recorded:

- Aphthous mouth ulcers (new, recurrent or aggravation of pre-existing lesions)
- Any other GI ulcers or significant GI symptoms (e.g., pain, blood in stool, dyspepsia or similar)

14.1.2.2 Physical Examination and Vital Signs

The investigator or qualified designee will perform a complete physical examination (genitourinary examination not required) at screening and baseline and then targeted physical examinations at the time points designated on the Flowchart of the Study (Section 3). Pre-dose abnormal findings will be recorded on the medical history eCRF. Any adverse change from the baseline physical examination (day 0 examination) will be documented on the AE eCRF. Weight will be measured at screening and the End of Treatment Visit only and height at screening only.

A full physical examination will include inspection of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, musculoskeletal system, and nervous system.

Vital signs will be measured and recorded at the time points designated on the Flowchart of the Study (Section 3). The following measurements must be performed: systolic/diastolic blood pressure, pulse, and body temperature. Vital signs will be measured after the subject has been in the supine position for at least 5 minutes. All measurements will be recorded on the vital signs eCRF. Tests with abnormal results may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF. When vital signs, ECGs, and/or blood sample collection occur at the same time, vital signs should be performed before ECGs and/or blood sample collection.

14.1.2.3 Laboratory Parameters

The tests listed in Table 14.1 will be conducted on samples collected and analysed by standard laboratory procedures at the time points designated on the Flowchart of the Study (Section 3). Tests that are not done must be reported as such on the eCRFs. Subjects should not eat or drink anything except water for 12 hours before the fasting glucose and fasting lipid tests at Visits 1, 2, and 12.

Sample handling, shipment, and assessment methods are described in the laboratory manual.

Table 14.1: Clinical Laboratory Tests

Haematology		
Haematocrit Haemoglobin Red blood cell count Platelets	White blood cell count with differential (neutrophils, eosinophils, lymphocytes, basophils, monocytes)	Coagulation (fibrinogen, prothrombin time, partial thromboplastin time)
Clinical Chemistry		
Alanine aminotransferase Aspartate aminotransferase Gamma glutamyl transferase Alkaline phosphatase Lactic dehydrogenase ESR	Lipase Bilirubin Total protein Albumin Creatinine CRP	Urea Sodium Chloride Potassium Calcium
Urinalysis		
pH Blood Leucocytes Protein	Glucose Ketones Bilirubin	Urobilinogen Nitrites Specific gravity Microscopy

Table 14.1: Clinical Laboratory Tests

Other tests		
Thyroid stimulating hormone Free triiodothyronine Free thyroxine Fasting glucose Fasting triglycerides Fasting total cholesterol Fasting high-density lipoprotein Fasting low-density lipoprotein	Hepatitis B virus (hepatitis B virus polymerase chain reaction, hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody) Hepatitis C (hepatitis C polymerase chain reaction, hepatitis C viral RNA) HIV (anti-HIV1, anti-HIV2)	Tetanus (tetanus IgG antibodies, QuantiFERON®-TB Gold in-tube assay) Diphtheria (IgG) Epstein-Barr virus Cytomegalovirus Faecal occult blood test Pregnancy test or FSH assessment (females only)

All laboratory results have to be evaluated and results reported on the eCRF according to the following pattern:

- Outside reference range but not clinically relevant (e.g., due to already known conditions, due to sampling conditions, only marginal deviation, due to underlying diseases in the study population)
- Outside reference range and clinically relevant.

Laboratory values which are outside the reference range and assessed as clinically relevant) must be documented as AEs if they occur for the first time after administration of IMP.

If abnormal laboratory values are signs of an AE (e.g., an infection) that has already been reported during the study, that AE and not the laboratory value is all that should be reported.

14.1.2.4 Electrocardiograms

During the study, 12-lead ECGs will be performed at the time points designated on the Flowchart of the Study (Section 3).

The subject must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible. All ECGs should be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, corrected QT, RR, and PR intervals.

The Principal Investigator or designated site physician will review and sign all ECGs. Results must be summarized in writing and classified as normal; abnormal; abnormal, clinically relevant; or abnormal, not clinically relevant. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the Sponsor, a copy of the original ECG will be made available.

14.1.2.5 Auto-antibodies

The following auto-antibody titres will be determined from samples collected at the time points specified in the Flowchart of the Study (Section 3).

- Anti-dsDNA
- ANA
- TPO, THSR
- Anti-islet cells
- Anti-CCP
- Coombs test

Sample handling, shipment, and assessment methods are described the laboratory manual.

14.1.2.6 Anti-drug Antibodies

Antibodies to BT063 will be assessed from samples collected at the time points specified in the Flowchart of the Study (Section 3).

14.1.2.7 Immunological Status

The status of the following infections will be assessed from samples collected at the time points specified in the Flowchart of the Study (Section 3).

- Hepatitis B and C virus
- HIV
- Tetanus
- Diphtheria
- Tuberculosis (QuantiFERON® TB gold test)
- EBV/CMV serology

Sample handling, shipment, and assessment methods are described the laboratory manual.

14.1.2.8 Retention samples

The blood samples for immunological status of HBV, HCV, HIV, tetanus, diphtheria, tuberculosis, as well as EBV and CMV serology will be taken at baseline (V2, W0) and for follow-up (V14, W28) and stored at -20 °C or below, preferably below -65 °C, for up to 12 months after the end of the study for possible future testing.

Sample handling, shipment, and assessment methods are described in the laboratory manual.

14.2 Efficacy, Pharmacodynamic, and Pharmacokinetic Assessments

14.2.1 Specification of Efficacy Parameter(s)

Efficacy will be assessed at the times designated on the Flowchart of the Study (Section 3) using the following assessments:

- SLEDAI-2K
- CLASI
- BILAG score
- Tender joint count and swollen joint count
- Physician's Assessment of Disease Activity
- Subject Reported Outcomes: FACIT-F and SF-36v2 PCS
- ECLAM

14.2.2 Methods for Assessing, Recording and Analysing Efficacy Parameter(s)

Disease activity assessments for a particular subject should be performed (if at all possible) by the same assessor throughout the study to minimize inter-observer variation.

14.2.2.1 Systemic Lupus Erythematosus Disease Activity Index 2000

The SLEDAI-2K is a global index that measures SLE disease activity. It includes 24 items for the 9 organs/systems. Scores range from 0 to 105; a score of 6 is considered clinically important. The index measures disease activity within the last 10 days. The following activity categories and outcomes have been defined based on SLEDAI-2K scores:

SLEDAI-2K Score	**SLE Activity**
0	No activity
1 to 5	Mild activity
6 to 10	Moderate activity
11 to 19	High activity
20	Very high activity
Outcomes	
Reduction > 3 points	Improvement in SLE
Change of 1 to 3 points	Persistently active disease
Score of 0	Remission
Flares	
Increase > 3 points	Mild to moderate flare

Increase > 12 points	Severe flare

The SLEDAI-2K will be administered at the time points designated on the Flowchart of the Study (Section 3). A sample SLEDAI-2K data collection sheet is presented in Appendix C.

14.2.2.2 Cutaneous Lupus Erythematosus Disease Area and Sensitivity Index

The CLASI is an assessment over 13 body regions (scalp, ears, nose – incl. malar area, rest of the face, V-area neck – frontal, post. neck & shoulders, chest, abdomen, back and buttocks, arms, hands, legs, feet) and consists of 2 scores: total activity score and total damage score. Only the activity score will be used in this study. The activity score assesses erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and non-scarring alopecia for each of body regions and the damage score assesses dyspigmentation and scarring, including scarring alopecia for each of regions. Higher scores indicate more disease activity. The grades associated with the CLASI are as follows:

Assessment	**Score**	**Activity**
Erythema	0	Absent
	1	Pink, faint erythema
	2	Red
	3	Dark red; purple/violaceous/crusted; haemorrhagic
Scale/Hypertrophy	0	Absent
	1	Scale
	2	Verrucous/hypertrophic
Dyspigmentation	0	Absent
	1	Dyspigmentation
Scarring/Atrophy/ Panniculitus	0	Absent
	1	Scarring
	2	Severely atrophic scarring or panniculitus

The CLASI will be administered at the time points designated on the Flowchart of the Study (Section 3). A sample of the CLASI is presented in Appendix D.

14.2.2.3 British Isles Lupus Assessment Group Score

The BILAG 2004 index assesses lupus activity based on the physician's intent to treat. The index assesses conditions in 9 systems: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal,

and haematological. The use of the BILAG 2004 helps assess whether or not disease activity has resolved in 1 or more systems and whether or not there is new activity on other systems.

The index consists of 97 items. Some are rated as follows: 1 (improving), 2 (same), 3 (worse), and 4 (new). Others are recorded as values (e.g., blood pressure) or as Yes/No (e.g., accelerated hypertension). A graded score combining severity and perceived seriousness of the manifestation can be calculated manually or by a computer program. Overall scores per system are calculated as follows (the weighted numerical scores also make it possible to calculate a global score covering all 9 systems):

Score	Weighted Numerical Score	Findings and Treatments
A	12	Very active disease; treatment would include immunosuppressive drugs and/or an increased dose of prednisone > 20 mg/day or equivalent (including IV pulse methylprednisolone > 500 mg) or systemic immunomodulators (including biologicals, immunoglobulins, and plasmapheresis)
B	8	Moderate disease activity; use of lower dose corticosteroids, topical steroids, topical immunosuppressive drugs, antimalarials, or non-steroidal anti-inflammatory drugs - including low does prednisone, intramuscular or intra-articular methylprednisolone, topical glucocorticoids or immunomodulators, antimalarials, thalidomide, prasterone, or acitretin
C	1	Mild stable disease; requires symptomatic therapy like simple analgesics
D	0	No disease activity but the system had been affected previously
E	0	No current or previous disease activity

A severe flare is defined as an increase of a previous score to an “A” and a moderate flare is an increase to a “B” score from C, D or E in any organ system.

Response is defined as loss of “A” and “B” scores in all systems without the development of any new “A” or “B” scores. Partial response is defined as a loss of “A” scores but with “B” scores persisting or developing while in a treatment.

The BILAG 2004 will be administered at the time points designated on the Flowchart of the Study (Section 3). A sample of the BILAG 2004 index is presented in Appendix E.

14.2.2.4 Tender/Swollen Joint Count

A total of 66/68 joints will be assessed for the tender/swollen joint count. A joint that is normal (no tenderness or swelling) will be graded as 0. A joint with tenderness or swelling will graded as 1. Higher scores indicate more disease activity.

The tender/swollen joint count will be assessed at the time points designated on the Flowchart of the Study (Section 3). A graphical presentation of the joints to be assessed is provided in Appendix F.

14.2.2.5 Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of disease activity is based on a 100 mm visual analogue scale (VAS) with the following range and increments (Appendix A):

Score	**Definition**
0	No disease activity
1	Mild disease activity
2	Moderate disease activity
3	Severe disease activity

The 100-mm scale will be provided to investigators who will make a vertical mark on the VAS indicating their assessment of the subject's disease activity. The distance along the line from 0 (no disease activity) to the mark will be measured and the number in mm will be recorded in the eCRF. Higher scores indicate more disease activity. The Physician's Global Assessment will be done at the time points designated on the Flowchart of the Study (Section 3).

14.2.2.6 Subject Reported Outcomes

Questionnaires on subject reported outcomes must be completed by the subject before any investigations or discussions about their disease with the study personnel.

<u>SF-36v2 Physical Component Score</u>

The SF-36v2 assesses the function status and well-being of subjects. The composite index includes 8 subscales: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, emotional role functioning, social role functioning, and mental health. For this study, the summary measure of the physical components (physical functioning, physical role functioning, bodily pain, and general health perceptions) will be used. Scores for each concept and overall scores for the physical and mental components are calculated according to the SF-36v2 manual. Higher scores indicate better quality of life.

The SF-36v2 will be administered at the time points designated on the Flowchart of the Study (Section 3). A sample SF-36v2 health questionnaire is presented in Appendix G.

<u>Functional Assessment of Chronic Illness Therapy-Fatigue</u>

The FACIT system is a collection of quality of life measurements targeted to assess chronic illness. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) will be used in this study.

The FACIT-F consists of 5 areas: physical well-being, social/family well-being, emotional well-being, functional well-being, and additional concerns (fatigue).

The FACIT-F will be administered at the time points designated on the Flowchart of the Study (Section 3). A sample of the FACIT-F is presented in Appendix H.

14.2.2.7 European Consensus Lupus Activity Measurement

The purpose of the ECLAM is to assess SLE disease activity within the past month. The measurement consists of 12 categories: generalised manifestations, articular manifestations, mucocutaneous manifestations, myositis, pericarditis, intestinal manifestations, pulmonary manifestations, neuropsychiatric manifestations, renal manifestations, haematologic features, erythrocyte sedimentation rate, and hypocomplementaemia. Scores range from 0 to 10 (scores higher than 10 are rounded off to 10) with lower scores indicating less disease activity.

The ECLAM will be administered at the time points designated on the Flowchart of the Study (Section 3). A sample of the ECLAM is presented in Appendix I.

14.2.3 Pharmacodynamic and Pharmacokinetic Assessments

The analyses for PK and PD markers will be performed by a central laboratory or by central specialised laboratories.

14.2.3.1 Pharmacodynamic Assessments

The PD measurements will be analysed by standard procedures at the central laboratory or by central specialized laboratories. All final laboratory results from the central laboratory will be delivered electronically to [redacted] and loaded into the clinical database.

- Complement activity: C3, C4, CH50
- ESR and CRP
- Immunoglobulins: IgG, IgM, IgA, IgE
- Cytokines: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-α, IFN-$_{\gamma}$
- T- and B-lymphocytes: CD3, CD4, CD8, CD19, CD20, CD27, CD38, CD69, CD62L, HLA DR, CD45RA
- Free IL-10

<u>Biomarkers</u>

In order to explore systemic and local biological effects of BT063, biomarkers related to IL-10 biology and expected safety, efficacy, and mechanism of action of BT063 will be explored.

A quantitative, multiplex immunoassay for measurement of cytokines, chemokines, metabolic markers, hormones, growth factors, tissue remodeling proteins, angiogenesis

markers, acute phase reactants, cancer markers, kidney damage markers, central nervous system biomarkers and other important circulating proteins will be used.

Immunological Parameters

The following analyses are planned:

- Analysis of spontaneous dendritic cell maturation
- Analysis of IL-10 production by regulatory T-cells
- IL-10R expression and frequency of Th17 cell subsets
- Analysis of T cell homeostasis
- Cytokine concentrations in serum

14.2.3.2 Pharmacokinetic Assessments

To assess the serum level of BT063 over the course of the study, blood will be drawn pre-infusion and within 5 to 30 minutes after the 2-hour infusion on the following days: Day 0, Day 7, Day 14, Day 28, Day 42, Day 56, Day 70, and Day 84. In addition, blood will be drawn for PK assessments on Days 4 or 5, 91 (at least 5 days after last dosing), 98, 140, and 196. The actual PK sampling times will be captured in the eCRF.

The following PK measurements will be determined:

- Maximum serum concentration (C_{max})
- Time to maximum serum concentration (t_{max})
- Area under the concentration-time curve from time 0 to the last observable concentration at time t (AUC_{0-t})
- Elimination half-life ($t_{1/2}$)
- Apparent terminal-phase disposition rate constant (λ_Z)
- Total body clearance from serum (CL)
- Apparent volume of distribution during the terminal phase (V_Z).

14.2.4 Anticipated Blood Volumes

All subjects will provide blood for eligibility confirmation, safety, PK testing, and biomarker development throughout the study. The total anticipated blood volume to be collected is approximately 555 mL for each subject.

14.3 Adverse Events

14.3.1 Definitions

Adverse Event (AE)

Per ICH, an 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 a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The AE may be any of the following:

- A new illness
- An exacerbation of a sign or symptom or the underlying condition or of a concomitant illness under treatment
- Unrelated to participation in the clinical study or an effect of the study medication or comparator drug
- A combination of 1 or more of the above factors

No causal relationship with the study medication is implied by the use of the term "adverse event."

Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. Conditions leading to unplanned surgical procedures may be AEs.

When an AE occurs after written consent has been obtained but before the first dose of study drug, the AE will be considered a non-treatment emergent AE. An AE that occurs from the time the subject receives his/her first dose of study drug until his/her last study visit will be considered a treatment-emergent AE regardless of the assessed relationship to the administration of the IMP.

For the recording of pregnancy and relevant laboratory data see Section 14.3.2.

Immediately Reportable Adverse Event

Immediately reportable AEs (IRAEs) are AEs that must be reported to the Sponsor within 24 hours of the study site being informed of the IRAE (reporting requirements are detailed in Section 14.3.2.1).

Immediately reportable AEs include:

- All SAEs
- Overdose
- Pregnancy
- AEs that result in a subject's withdrawal from the study
- All AESIs (Section 14.1.2.1)

Serious adverse event (SAE)

An SAE is any untoward medical occurrence or effect that at any dose:

- Results in death

- *Death is an outcome of an AE and not an AE in itself. All deaths, regardless of cause or relationship must be reported for subjects on study.*

- Is life-threatening
  - *Life-threatening means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it were more severe.*
- Requires hospitalization or prolongation of existing hospitalization
  - *Complications that occur during hospitalizations are AEs. However, if a complication prolongs hospitalization or requires new hospitalization, it is an SAE. In-patient hospitalization means the subject has been formally admitted to a hospital for medical reasons, for any length of time, which may or may not be overnight. It does not include presentation and care within an emergency department. If a subject experiences an AE during dosing and remains in hospital until the AE resolves, this is not considered an SAE unless the investigator considers that the event would have required hospitalization.*
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is another medically important condition

An important medical event that is not immediately life threatening or will result in death or hospitalization, but which may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above, should be reported as “serious” as well.

Medical and scientific judgment should be exercised in deciding whether a case is serious.

“Occurring at any dose” does not imply that the subject is receiving study drug at the time of the event.

Severity of Adverse Event:

Refers to the extent to which an AE affects the subject's daily activities. Severity will be categorized according to the following criteria:

Mild:	The AE does not interfere with the subject’s routine activities.
Moderate:	The AE interferes with the subject’s daily routine, but usual routine activities can still be carried out.
Severe:	The AE results in the inability to perform routine activities.

The term "severity" is used to describe the intensity of an event. This is not the same as "serious". Seriousness, not severity, serves as the guide for defining regulatory reporting obligations. The highest severity grade attained should be reported, for AEs with divergent severities.

Causality of Adverse Event:

Refers to the relationship of the AE to the study drug. Causality will be categorized according to the following criteria:

Not related:	Adverse events for which a reasonable explanation for an alternative cause is considered plausible, e.g., no study drug taken, plausible clinical alternative like accidental injury, expected progression of underlying or concomitant disease, pharmacologically incompatible temporal relationship, or intercurrent illness.
Related:	Adverse events for which a reasonably possible clinical and/or pharmacological relationship to study drug cannot be excluded, e.g., lacking plausible alternatives.

14.3.2 Recording Adverse Events

Period: Subject Enrolment to the First Administration of Study Drug: Non-treatment emergent AEs will be recorded from the time when the subject is enrolled into the study (date of signature of the informed consent) until first administration of study drug.

Period: First Administration of Study Drug to Subject's last study visit: Thereafter all AEs are treatment-emergent AEs (TEAEs, see Definitions, Section 14.3.1) and will be recorded until the final follow-up visit has been performed.

Period after last study visit: Any SAE occurring after the subject's last study visit but considered by the investigator to be related to the study drug will be recorded.

If an AE (serious or not) started during the study but did not end before the final follow-up visit, the investigator should make a reasonable effort to establish the outcome and the end date. If this is not possible, the outcome recorded at the final follow-up visit will be assumed to be the final outcome.

If an event stops and later restarts, all the occurrences must be reported. Adverse events assessed as related to study medication by the investigator and all SAEs must be followed up until resolution.

Signs/symptoms should be documented if a definite diagnosis cannot be established. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms. If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the symptoms have to be reported separately.

In addition to the definition as given, the following special types of events should be recorded:

a) **Pregnancy -** Although not an AE per se, occurrence of pregnancy in a subject during a clinical study must be recorded.

b) **Laboratory values that are outside the normal range** and if, in the opinion of the investigator, these values represent a clinically relevant change versus pre-treatment values are also defined as AEs.

If abnormal laboratory values are signs of an AE (e.g., an infection) that has already been recorded, the respective abnormal laboratory value does not constitute a separate AE.

Wherever reasonable the reporting investigator will use the clinical term rather than the laboratory term (e.g., anaemia versus low haemoglobin value).

14.3.2.1 Responsibilities of Investigator

Adverse event data should be obtained through observation of the subject, from any information volunteered by the subject, or through subject questioning. The general type of question asked could be similar to: “Do you have any health problems?” or “Have you had any health problems since your last clinic visit?”

Adverse events are to be recorded accurately and completely on the AE pages of the respective CRF and in the subject's source data.

All non-treatment and treatment-emergent AEs will be recorded.

This is true even if the IMP was not administered according to the study protocol.

For conditions leading to unplanned surgical procedures the underlying condition, should be documented as an AE, but not the procedure.

Reporting IRAEs:

For AEs that are "serious" (SAEs) and AESIs (Section 14.1.2.1 additional separate documentation is required using the electronic SAE/AESI Forms.

The following variables will be recorded on the electronic SAE/AESI Form and on the eCRFs provided in accordance to the eCRF completion guidelines:

- Description of the event, including its duration (date of onset and resolution),
- Whether the event constitutes a SAE/AESI or not (if yes, see event seriousness criteria in Section 14.3.1)
- Any action taken *(e.g., changes to study treatment, other treatment given and follow up tests*
- Outcome of the event
- Investigator’s assessment of causality *(the relationship to the study treatment[s] and study procedures)*
- Severity.

For all SAEs where important or relevant information is missing, follow-up should be undertaken to ensure that all information is reported.

Whether or not a causal relationship exists between the study medication/study conduct and the AE is not relevant. The investigator is obligated to record AEs and notifying IRAEs to the Sponsor.

For withdrawals due to AEs the eCRF page "Study completion / Study termination Form" and a copy of the eCRF AE page needs to be completed and forwarded to [redacted] Drug Safety Department.

Pregnancy Reporting: Each pregnancy that starts during the study must be reported by the investigator to [redacted] Drug Safety Department within 24 hours of the investigator's knowledge of the pregnancy by using the SAE Form. Any adverse outcome of the pregnancy must be recorded and notified on the "Drug Exposure via Parent Report Form". The investigator should make any reasonable effort to follow any pregnancy until birth of the child.

Overdose (as defined in Section 11.1.4) needs to be reported to [redacted] Drug Safety Department following the criteria for SAE reporting.

If additional information is required by the [redacted] Drug Safety department, then as a representative of the Sponsor [redacted] must be granted access to the medical records.

After subject's last study visit:

The investigator records and forwards to the Sponsor all SAEs that she or he becomes aware of and she or he considers related to the IMP.

14.3.2.2 Responsibilities of Sponsor

For purposes of safety analyses all AEs will be recorded in the clinical database. To ensure expedited and periodic notification of authorities, SAEs will also be recorded in the drug safety database.

14.3.3 Evaluation of Adverse Events

14.3.3.1 Responsibilities of Investigator

The investigator will assess the seriousness, severity, and causality of each AE in accordance with the definitions in Section 14.3.1. Notification of IRAEs must follow the procedure described in Section 14.3.2.1.

Causality of AE:

For all AEs a causality assessment must be provided and documented on the respective form (eCRF AE page for all AEs, SAE form for SAEs and eCRF page "Study completion / termination form" for withdrawals due to AEs.

14.3.3.2 Responsibility of Sponsor

The Sponsor will not downgrade the causality assessment provided by the investigator. If the Sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the Sponsor will be recorded.

14.3.4 Notifying of Adverse Events

14.3.4.1 Responsibility of Investigator

For IRAEs (SAEs, AEs leading to withdrawal, and AESIs) the investigator must inform the [redacted] Drug Safety department via e-mail or fax using the SAE report/ eCRF page within 24 hours of the study site being informed of the IRAE. At a later date, the [redacted] Safety Contact will report to Biotest Corporate Drug Safety, the Clinical Study Manager, and the Clinical Research Physician.

Adverse Event Reporting Contact:

[redacted] Drug Safety

E-mail: [redacted]

Fax: [redacted]

For questions regarding IRAEs, or to provide information that cannot be provided electronically, or to notify the Sponsor of an IRAE in the event of technical failure, the investigator should contact [redacted]

Investigators or other site personnel should inform [redacted] Drug Safety department of any follow-up information that becomes available for a previously reported SAE immediately but no later than 24 hours of becoming aware of the information. Follow-up reports (as many as required) should be completed and faxed or e-mailed following the same procedure above. Any requested supporting documentation (e.g., ECG, laboratory results, autopsy report) should be sent to the [redacted] Drug Safety department.

Prior to forwarding any personal data for safety reporting, the documents need to be coded in a way that keeps the subject's identity confidential (e.g., by using the subject's identification code, randomization number, etc.).

For fatal and life-threatening SAEs, [redacted] Drug Safety department will work with the investigator to ensure that any additional information is provided by the investigator within 1 business day. The investigator will ensure that all the necessary information for all other SAEs will be provided within the timelines stipulated by the Sponsor when the request for information is made.

If required, the investigator is responsible for informing local IECs/IRBs of safety reports in compliance with applicable regulatory requirements. Copies of all correspondence relating to reporting of any safety reports to the IEC/IRB should be maintained in the ISF / Regulatory Binder.

Subject Enrolment to the First Administration of Study Drug:

Only serious procedure-related AEs will be reported to the Sponsor using the IRAE reporting process (SAE report form) as described above.

After subject's last study visit:

The investigator will notify [redacted] Drug Safety department of any SAE that she or he becomes aware of and considers related to the study drug.

Following-up AEs / SAEs:

At the subject's last study visit (including the Early Termination Visit), a Safety Follow-up Visit should be scheduled up to 2 weeks after the final examination only for those subjects who experienced not resolved related AEs or laboratory parameters showing not normalized clinical relevant changes or SAEs. The assessments measured will be determined by the investigator. All data must be documented in the eCRF.

14.3.4.2 Responsibility of Sponsor

Biotest's Corporate Drug Safety department is responsible for fulfilling all obligations regarding notification of Regulatory Authorities and IECs/IRBs according to applicable regulatory requirements (expedited and periodic reporting, e.g., serious unexpected suspected adverse reactions, Development Safety Update Report). In addition, the Sponsor will provide safety information to investigators according to the current regulations.

15 STATISTICS

The statistical planning and evaluation of the study will be carried out by a qualified statistician in accordance with the International Conference on Harmonisation (ICH) guidelines and adequate biostatistics standard operating procedures (SOPs). A detailed Statistical Analysis Plan (SAP) will be prepared prior to database closure and unblinding.

15.1 Calculation of Sample Size

Sample size was not based on any statistical assumptions, as no formal statistical tests are planned. Approximately 36 subjects will be treated in the study and provide sufficient efficacy and safety information of study medication.

15.2 Statistical Methods

15.2.1 Populations for Analysis

Three analysis sets will be defined for analysis:

Safety set:

The safety set comprises all subjects who have received the study medication at least once.

Intention-to-treat set:

The intention-to treat (ITT) set consists of all subjects who have received any study medication and have at least 1 post-baseline efficacy measurement.

Per-protocol set:

The per-protocol (PP) set consists of all subjects of the ITT set who finish the study without major protocol deviations or who discontinue the trial prematurely due to an event which could be possibly related to the study medication. Subjects with major protocol deviations will be excluded from the PP population. Classification of protocol deviations as major or minor will be agreed upon between Sponsor and study statistician prior to the analysis.

Pharmacokinetic set:

The pharmacokinetic (PK) set will include all subjects who have at least one dose of study drug without major protocol deviations and for whom the serum concentrations of BT063 are interpretable. It will be used for the pharmacokinetic analysis.

15.2.2 General Methodology

Descriptive statistics will be presented for all parameters of interest. Continuous variables will be summarized using the n, mean, standard deviation (SD), median, minimum value, and maximum value. Categorical variables will be summarized using the sample size (N), frequency count (n), and percentage (%). All summary tables will be presented by treatment group, unless otherwise specified. For all parameters of interest, the value that was obtained just prior to the first dose of study drug will be used as the baseline.

No formal statistical tests will be performed. Last observation carried forward (LOCF) imputations for efficacy analysis may be used to impute missing data, if appropriate.

15.2.3 Demographic Data and other Baseline Characteristics

The demographic data such as age, sex, race, ethnic origin, height, and weight will be summarised by treatment group using summary statistics. Other baseline disease characteristics will be tabulated and summarized as well.

15.2.4 Safety Analysis

The safety assessments for this study are the following:

- Adverse events (Including SAEs and AEs leading to discontinuation due to AEs)
- Physical examinations
- Vital signs
- ECGs
- Safety laboratory parameters (full blood count including white differential count, clinical chemistry, thyroid hormones, urinalysis, and faecal occult blood test)
- Development of anti-drug antibodies against BT063 (anti-BT063)
- Immunological status of potential viral and bacterial infections (HBV, HCV, HIV, tetanus, diphtheria tuberculosis)
- EBV / CMV Serology
- Premature withdrawals

Adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Incidence rates (i.e., number and percentage of affected subjects) will be calculated for the coding levels system organ class and preferred term. Further analyses of AEs will focus on seriousness, intensity, causal relationship to study medication, and outcome. Serious adverse events will be displayed in detail.

Safety laboratory assessments will be categorized with respect to the laboratory specific reference ranges as normal/abnormal. Abnormal values will be further classified with respect to clinical relevance. Changes over time will be described by means of "shift-tables".

Observed values and change from baseline in 12-lead ECG parameters will be presented by treatment group. The number and percentage of subjects who had an overall impression status in category of normal, abnormal not significant, or abnormal significant will be summarized by treatment group.

Vitals signs parameters (systolic blood pressure, diastolic pressure, heart rate, and temperature) will be presented as a summary of observed and change from baseline values. Summaries for vital signs will be presented by visit and treatment group.

Safety analysis will be based on the safety population.

15.2.5 Efficacy Analysis

The efficacy endpoints in this study are as below:

- 50% improvement of swollen/tender joints or 50% improvement in CLASI score at week 14 and at week 28, depending on which endpoint was the more severe manifestation at baseline.
- Percent changes in SLEDAI-2K scores from baseline to week 14 and at week 28
- Flare rate and severity at week 14 and week 28 based on BILAG index A or B (flare is defined as the presence of 1 or more new BILAG A scores or 2 or more new BILAG B scores.)
- Time to first flare
- Number of patients requiring an increase in oral glucocorticosteroid dose before week 14
- Physician's Global Assessment at week 14 and week 28
- Fatigue (FACIT-F) and SF-36v2 Physical Component Score (PCS) at week 14 and week 28
- ECLAM at week 14 and week 28

Efficacy endpoints will be summarized using descriptive statistics by visit and treatment group. Change from baseline will be calculated as post-baseline value minus baseline value. Percentage change from baseline will be calculated as (post-baseline value – baseline value)/baseline value ×100(%). Efficacy analysis will be performed on the ITT and PP populations.

15.2.6 Pharmacokinetic (PK) and Pharmacodynamics (PD) Analysis

15.2.6.1 Pharmacokinetic Analysis

Pharmacokinetic parameters will be determined using WinNonlin based on BT063 serum concentrations by non-compartmental procedures. The following pharmacokinetic variables will be derived from serum BT063 concentrations for analysis:

- Maximum serum concentration (C_{max})
- Time to maximum serum concentration (t_{max})
- Area under the concentration-time curve from time 0 to the last observable concentration at time t (AUC_{0-t})
- Elimination half-life ($t_{1/2}$)
- Apparent terminal-phase disposition rate constant (λ_Z)
- Total body clearance from serum (CL)
- Apparent volume of distribution during the terminal phase (V_Z).

Pharmacokinetic parameters will be evaluated before and after investigational medicinal product BT063 (IMP) infusion (if an infusion is scheduled at that time) on the following days: day 0, day 4 or 5, day 7, day 14, day 28, day 42, day 56, day 70, day 84, day 91, day 98, and day 196.

All PK parameters will be presented using descriptive statistics for the respective visits and protocol scheduled times based on PK population. These statistics include arithmetic mean, arithmetic standard deviation, geometric mean, geometric standard deviation, coefficient of variation, minimum, median, and maximum.

15.2.6.2 Pharmacodynamic Analysis

The following pharmacodynamic (PD) variables will be analysed for the study:

- T- and B-lymphocytes (CD3, CD4, CD8, CD19, CD20, CD27, CD38, CD69, CD62L, HLA DR, CD45RA)
- Complement activity CH50, C3, and C4
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-α, IFN-γ)
- Immunoglobulins (IgG, IgM, IgA, IgE)
- Free IL-10

PD variables will be presented using descriptive statistics for the respective visits and protocol scheduled times based on the ITT and PP populations.

15.2.7 Other Measures of Interest

Other measures of interest such as biomarkers specified in the protocol will be analysed as exploratory parameters using descriptive statistics.

15.2.8 Interim Analysis

After the last subject in Part I has completed week 14 of the study, an interim analysis will be performed and the DSMB will review the safety and efficacy data. Depending upon the results of that review, the DSMB may recommend that Part II be started at a higher dose of BT063 (100 mg), a lower dose of BT063 (25 mg), or at the same dose (50 mg). After reviewing the DSMB recommendation, Biotest will determine whether to continue the study and if so, which dose will be used in Part II.

The interim analysis will consist of the descriptive safety and efficacy summary tables as well as individual listings.

15.2.9 Further Statistical Issues

A detailed description of statistical analyses will be provided in the SAP which will be finalized prior to database closure and unblinding.

16 DATA MANAGEMENT

16.1 Data Collection

Study data will be entered into the study database on a central server via eCRF by authorized investigators and/or study personnel or uploaded directly. The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined in advance within a data handling plan/ data management plan together with a description of the personnel responsible for data entry.

16.2 Correction of Data

Automatic and manual queries will be defined according to the data validation plan. These queries will be generated by the [redacted] Data Management Department and sent through the electronic data capture (EDC) system for clarification. Corrections will be entered directly into the system. This procedure will be repeated until all queries are resolved. All query forms will be linked to the eCRF in the EDC system.

16.3 Data Handling

The final data will be transferred to the SAS-system for data analyses in accordance with the SAP.

The MedDRA dictionary will be used for coding of AEs and concomitant diseases. Concomitant medication will be coded using the World Health Organization Drug Dictionary **A**(natomical) **T**(herapeutical **C**(hemical) code.

16.3.1 Deviations from the Study Protocol

Deviations from the protocol will be listed during the study and/or when an individual subject's eCRF is completed (monitored).

Before unblinding the data for interim and final analysis, a blinded data review meeting (BDRM) will take place where protocol deviations will be classified (major/minor protocol deviations) for statistical analysis.

17 QUALITY CONTROL AND QUALITY ASSURANCE

17.1 Study Initiation Activities

The investigator(s) are informed about study objectives and methods, the inclusion and exclusion criteria, the time-schedule, and study procedures at a Pre-Study Visit by the monitor (if necessary), an investigators' meeting, and during the Site Initiation Visit by the monitor.

17.2 Training of Site Staff

The Principal Investigator will ensure that everyone assisting with the clinical study is adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions. Investigators will be adequately trained to perform the individual scores (e.g., BILAG) in order to standardize the assessments. Furthermore, the Principal Investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated study-related duties.

17.3 Documentation and Filing

<u>eCRF System</u>

All data recorded according to this study protocol must be documented in an eCRF. The investigator and persons authorized by the investigator will be instructed about how to complete the eCRF. Entries in the eCRF must only be made by the investigator or persons authorized by the investigator. A list of all persons who are allowed to make entries in the eCRF must be available in each study site.

The investigator must verify that all data entries in the eCRF are accurate and correct. Entries will be checked against appropriate source documentation by the monitor.

<u>List of subjects (subject identification log)</u>

The investigator will keep a confidential list of names of all subjects participating in the study, so that the subjects' records can be identified if necessary.

In addition, the investigator will keep a list of all subjects screened on a screening log to document identification of subjects who entered pre-study screening. If someone is not eligible to participate in the study, a reason must be provided.

<u>Source data</u>

Per ICH, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are

contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

Investigator Site File / Regulatory Binder

Before site initiation [redacted] will provide an ISF/ Regulatory Binder to each site. The ISF will include essential documents as defined by the ICH GCP guideline and applicable local requirements.

The investigator will be responsible for the update and maintenance of the ISF, which will be reviewed periodically by the monitor(s). These documents will be reviewed during an audit by the Sponsor or an inspection by the Regulatory Authorities.

All study-related documents are to be archived and stored according to legal requirements.

Prior to destruction of study-related documents, the investigator will contact Biotest AG for approval and confirmation.

17.4 Monitoring

The monitor is responsible for checking the quality of data and ensuring that the investigative site is adhering to the study protocol. Additionally, the monitor ensures that the site is following the legal and ethical requirements as stated in local laws and the principles of GCP.

The interval between monitoring visits will depend on the recruitment rate and the complexity of the study.

Source data verification is an essential part of the monitoring process and the investigator must grant direct access to the subject’s source data.

The extent and nature of monitoring will be described in detail in the monitoring plan.

17.5 Audits and Inspections

Audits will be performed according to the corresponding audit program. The Sponsor’s Quality Assurance Department may visit the investigative site to audit the performance of the study, as well as all study documents. Audits may also be performed by contract auditors who will be instructed about the timing and extent of the audits. In the event of an audit at the investigational site, the monitor will usually accompany the auditor(s).

Inspections by Regulatory Authority representatives and IECs/IRBs are possible at any time, even after the end of study. The investigator is to notify the Sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the IEC/IRB and/or Regulatory Authorities, and will allow direct access to source data and source documents for monitoring, audits, and inspections.

17.6 Archiving

After evaluation and reporting of the study data, all documents relating to the study will be maintained in the Sponsor and study site archives according to applicable regulatory requirements.

18 GENERAL REGULATIONS, AGREEMENTS AND ORGANISATIONAL PROCEDURES

18.1 Study Administrative Structure

Details of the study administrative structure are provided in the TMF.

18.2 Written Agreements

A written agreement will be set up between Biotest and each investigator outlining arrangements about the delegation and distribution of tasks and obligations and, if appropriate, financial matters.

18.3 Insurance/Liability

In accordance with the relevant national regulations, the Sponsor has liability insurance for all subjects who have given their consent to the clinical study. The subjects are insured against injury caused by study drug or study participation. The subjects will be informed about the insurance and their own responsibilities and duties.

For details on the insurance and for the insurance policy number, please refer to the respective country patient information.

18.4 Investigator's Brochure (IB)

The investigator will receive an IB that outlines all current information about the IMP. Investigators will be informed immediately about relevant new information.

18.5 Amendments to the Protocol

Changes to the Clinical Study Protocol must be made in the form of an amendment that has written approval of Biotest and – as applicable – of the appropriate IEC/IRB and Regulatory Authorities. In general, all substantial amendments must be approved by an IEC/IRB prior to enrolling subjects under the amended protocol. Amendments that address the immediate safety of subjects may be implemented before the approval of the IRB/EC and/or Regulatory Authorities, after consultation with Biotest.

Amendments, submission(s), and approvals(s) will be distributed to the concerned study site(s).

If a significant deviation from the protocol is anticipated, or occurs because of an accident or mistake, the investigator or his/her designee must contact [redacted] at the earliest possible time. This will allow an early joint decision to be made as to whether or not the subject should continue in the study. This decision will be documented by both the investigator and [redacted].

18.6 Confidentiality

The objectives and contents of this clinical study as well as its results are to be treated as confidential and may not be made accessible to third parties.

18.7 Final Report and Publication

An integrated final report according to ICH requirements will be produced for this study. At the end of the study the Sponsor will provide the competent authority and IEC/IRB with a summary of the clinical study report within 1 year after the end of the study, when required.

Prior to the publication of articles, lecture manuscripts, or other materials discussing study results, the documents should be reviewed by the coordinating investigator and the Sponsor.

Each investigator is obligated to keep data pertaining to the study confidential. He or she must consult with the Sponsor before any study data are published.

The legitimate interests of the Sponsor, such as acquiring optimum patent protection, coordinating submissions to the health authorities or coordination with other studies in the same field that are underway, protection of confidential data and information, etc. will be given due consideration by all partners involved.

19 LIST OF REFERENCES

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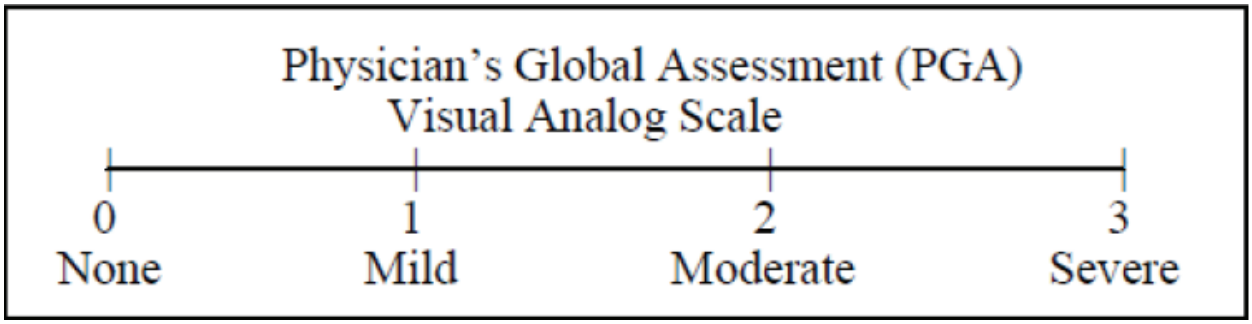
20 APPENDICES

Appendix A Physician's Global Assessment



Appendix B 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *OR* 2. Pericarditis--documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed *OR* 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *OR* 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance

Criterion	Definition
9. Hematologic disorder	1. Hemolytic anemia--with reticulocytosis *OR* 2. Leukopenia--< 4,000/mm3 on ≥ 2 occasions *OR* 3. Lymphopenia--< 1,500/ mm3 on ≥ 2 occasions *OR* 4. Thrombocytopenia--<100,000/ mm3 in the absence of offending drugs
10. Immunologic disorder	1. Anti-DNA: antibody to native DNA in abnormal titer *OR* 2. Anti-Sm: presence of antibody to Sm nuclear antigen *OR* 3. Positive finding of antiphospholipid antibodies on: 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. a positive test result for lupus anticoagulant using a standard method, or 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Appendix C Systemic Lupus Erythematosus Disease Activity Index 2000

SLEDAI-2K: DATA COLLECTION SHEET

Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the **preceding 10 days.**

SLEDAI 2K Weight	SLEDAI 2K SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.

SLEDAI 2K		Descriptor	Definition
Weight	**SCORE**		
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombo-cytopenia	<100,000 platelets / × 10^9/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / × 10^9/L, exclude drug causes.

TOTAL SCORE: _____

Appendix D Cutaneous Lupus Erythematosus Disease Area and Severity Index

Only the activity score will be used in this study.

Cutaneous LE Disease Area and Severity Index (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

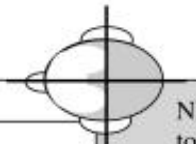
Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)
☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains) ☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

Recent Hair loss (within the last 30 days / as reported by patient)	
1-Yes 0-No	



NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

Appendix E British Isles Lupus Assessment Group Score

BILAG-2004 Index

Only record items due to SLE Disease Activity & assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks).

♦♦ TO BE USED WITH THE GLOSSARY ♦♦

Scoring: **ND Not Done**
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
□ indicate if not due to SLE activity
(default is 0 = not present)

CONSTITUTIONAL

1. Pyrexia - documented > 37.5ºC	(	)
2. Weight loss - unintentional > 5%	(	)
3. Lymphadenopathy/splenomegaly	(	)
4. Anorexia	(	)

MUCOCUTANEOUS

5. Skin eruption - severe	(	)
6. Skin eruption - mild	(	)
7. Angio-oedema - severe	(	)
8. Angio-oedema - mild	(	)
9. Mucosal ulceration - severe	(	)
10. Mucosal ulceration - mild	(	)
11. Panniculitis/Bullous lupus - severe	(	)
12. Panniculitis/Bullous lupus - mild	(	)
13. Cutaneous vasculitis/thrombosis	(	)
14. Digital infarcts/nodular vasculitis	(	)
15. Alopecia - severe	(	)
16. Alopecia - mild	(	)
17. Peri-ungual erythema/chilblains	(	)
18. Splinter haemorrhages	(	)

NEUROPSYCHIATRIC

19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL

39. Definite myositis (Bohan & Peter) ( )
40. Myositis with incomplete criteria ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

CARDIORESPIRATORY

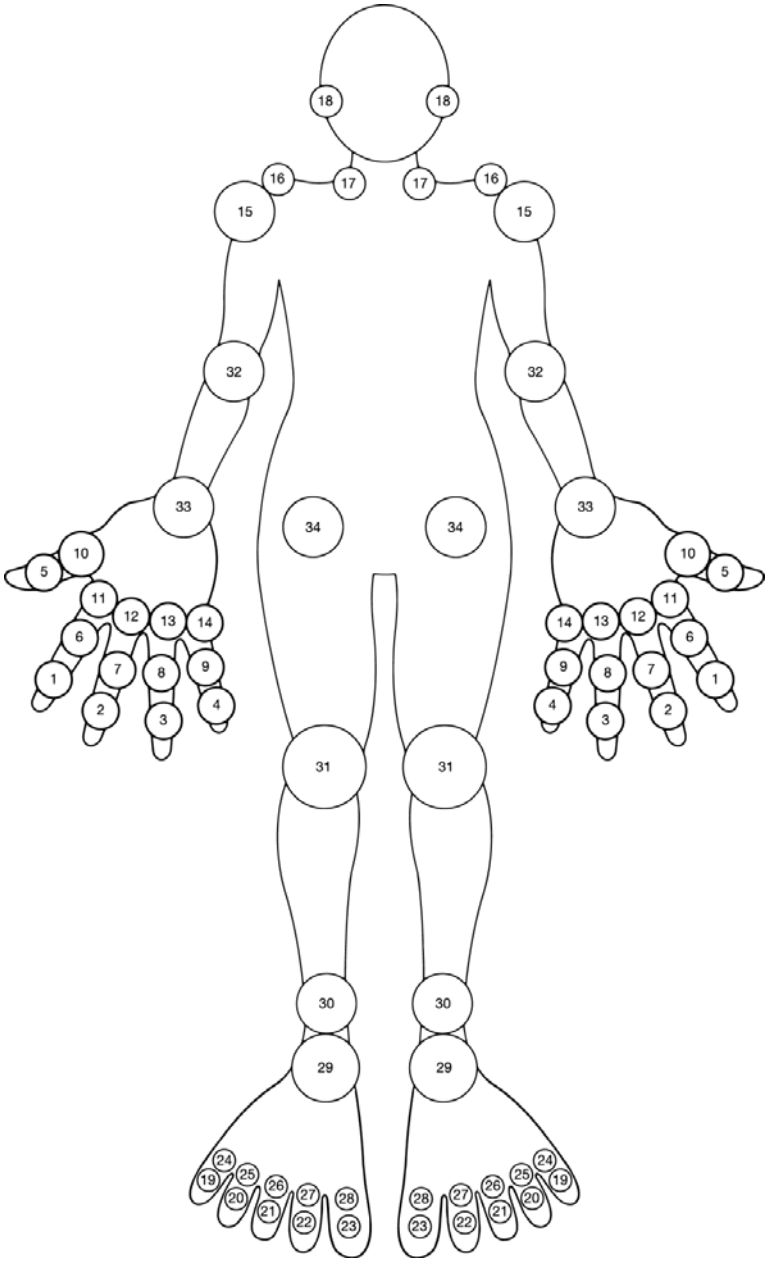
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Serositis (pleuro-pericardial pain) - mild ( )
49. Cardiac tamponade ( )

50. Pleural effusion with dyspnoea		(	)
51. Pulmonary haemorrhage/vasculitis		(	)
52. Interstitial alveolitis/pneumonitis		(	)
53. Shrinking lung syndrome		(	)
54. Aortitis		(	)
55. Coronary vasculitis		(	)
GASTROINTESTINAL			
56. Lupus peritonitis		(	)
57. Abdominal serositis or ascites		(	)
58. Lupus enteritis/colitis		(	)
59. Malabsorption		(	)
60. Protein losing enteropathy		(	)
61. Intestinal pseudo-obstruction		(	)
62. Lupus hepatitis		(	)
63. Acute lupus cholecystitis		(	)
64. Acute lupus pancreatitis		(	)
OPHTHALMIC			
65. Orbital inflammation/myositis/proptosis		(	)
66. Keratitis - severe		(	)
67. Keratitis - mild		(	)
68. Anterior uveitis		(	)
69. Posterior uveitis/retinal vasculitis - severe		(	)
70. Posterior uveitis/retinal vasculitis - mild		(	)
71. Episcleritis		(	)
72. Scleritis - severe		(	)
73. Scleritis - mild		(	)
74. Retinal/choroidal vaso-occlusive disease		(	)
75. Isolated cotton-wool spots (cytoid bodies)		(	)
76. Optic neuritis		(	)
77. Anterior ischaemic optic neuropathy		(	)
RENAL			
78. Systolic blood pressure (mm Hg)	value	(	) □
79. Diastolic blood pressure (mm Hg)	value	(	) □

80. Accelerated hypertension	Yes/No ( )
81. Urine dipstick protein	(+=1, ++=2, +++=3) ( ) □
82. Urine albumin-creatinine ratio	mg/mmol ( ) □
83. Urine protein-creatinine ratio	mg/mmol ( ) □
84. 24 hour urine protein (g)	value ( ) □
85. Nephrotic syndrome	Yes/No ( )
86. Creatinine (plasma/serum)	µmol/l ( ) □
87. GFR (calculated)	ml/min/1.73 m^2 ( ) □
88. Active urinary sediment	Yes/No ( )
89. Active nephritis	Yes/No ( )
HAEMATOLOGICAL	
90. Haemoglobin (g/dl)	value ( ) □
91. Total white cell count (x 10^9/l)	value ( ) □
92. Neutrophils (x 10^9/l)	value ( ) □
93. Lymphocytes (x 10^9/l)	value ( ) □
94. Platelets (x 10^9/l)	value ( ) □
95. TTP	( )
96. Evidence of active haemolysis	Yes/No ( )
97. Coombs' test positive (isolated)	Yes/No ( )

Appendix F Tender/Swollen Joint Count

Documentation of Joint Count on Homunculus



Appendix G SF-36v2 Health Questionnaire

(SF-36v2® Health Survey Standard, United Kingdom (English))

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11.How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix H Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F)

The FACIT and all related works are owned and copyrighted by, and the intellectual property of David Cella, Ph.D. Permission for use of the FACIT-F questionnaire is obtained by contacting Dr. Cella at information@facit.org.

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section. ☐					

GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix I European Consensus Lupus Activity Measurement

European Consensus Lupus Activity Measurement (ECLAM)

Patient No_____ Date_____

1. Generalised manifestations

Any of the following: **0.5**

Fever = Documented basal morning temperature of 37.5°C not due to an infective process.

Fatigue = A subjective feeling of extraordinary tiredness.

2. Articular manifestations

Any of the following: **1**

Arthritis = Non-erosive arthritis involving at least 2 peripheral joints (wrist, metacarpophalangeal or proximal, interphalangeal joints).

Evolving arthralgia = New onset or worsening of specific localised pain without objective symptoms in at least two peripheral joints.

3a. Active muco-cutaneous manifestations

Any of the following: 0.5

Malar rash = Fixed erythema, flat or raised over the malar eminences, and tending to spare the naso-labial folds.

Generalized rash = A maculo-papular rash not induced by drugs, that may be located anywhere on the body, and that is not strictly dependent on sun exposure.

Discoid rash = Erythematosus, raised patches with adherent keratotic scaling and follicular plugging.

Skin vasculitis = Including digital ulcers, purpura, urticaria, bullous lesions. Oral ulcers = Oral or naso-pharyngeal ulcers, usually painless, observed by a physician.

3b. Evolving mucocutaneous

If any of the above muco-cutaneous manifestations are new or have worsened since the last 1 manifestations observation, add **1 point**.

4. Myositis* Confirmed by raised muscle enzymes and/or EMG examination and/or histology. **2**

5. Pericarditis Documented by ECG or rub or evidence of pericardial effusion on ultrasound **1**

6. Intestinal manifestations

Any of the following: 2

Intestinal vasculitis = Evidence of acute intestinal vasculitis.

Sterile peritonitis = Evidence of abdominal effusion in the absence of infective processes.

7. Pulmonary manifestations

Any of the following: **1**

Pleurisy = Clinical or radiological evidence of pleural effusion in the absence of infective processes.

Pneumonitis = Single or multiple lung opacities on chest X-ray thought to reflect active disease not due to an infective process.

Ingravescent dyspnoea = Due to an evolving interstitial involvement.

8. Evolving neuropsychiatric manifest.*

New appearance or worsening of any of the following: **2**

Headache/migraine = Recently developed, persistent or recurrent.

Poorly responsive to the most commonly used drugs, but partially or totally responsive to corticosteroids.

Seizures = Grand mal or petit mal seizures, Jacksonian fits, temporal lobe seizures, or choreic syndrome, in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis or electrolyte imbalance).

Stroke = Cerebral infarction or hemorrhage, instrumentally confirmed

Organic brain disease = Impairment of memory, orientation, perceprion, and ability to calculate.

Psychosis = Dissociative features in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis or electrolyte imbalance.

9a. Renal manifestations* +

Any of the following: **0.5**

Proteinuria = At least 500 mg/day.

Urinary casts = Red cells, hemoglobin, granular, tubular or mixed casts. Haematuria = Microscopic or macroscopic.

Raised serum creatinine or reduced creatinine clearance

9b. Evolving renal manifestations = If any of the above renal manifestations are new or have worsened since the last two observations, add **2 points**.

10. Haematologic features

Any of the following: **1**

Non-haemolytic anemia = Coombs-negative normocytic hypochromic or normochromic anaemia without reticulocytosis.

Haemolytic anemia* = Coombs-positive haemolytic anaemia, with reticulocytosis and elevated LDH, in the absence of offending drugs.

Leukopenia (or lymphopenia) = Less than 3,500/mm3 WBC (or 1,500/mm^3 lymphocytes) in the absence of offending drugs.

Thrombocytopenia = Less than 100,000/mm^3 in the absence of offending drugs.

11. Erythrocyte sedimentation rate 1

Raised ESR > 25 mm/h by Westergren or comparable methods, not due to other concomitant pathological process

12a. Hypocomplementaemia = reduced plasma level of any of the following: **1**

C3 By radial immunodiffusion or laser nephelometer. CH50 By standardized hemolytic methods.

12b. Evolving hypocomplementaemia = significantly reduced level of any of the items mentioned above (plus C4) with respect to the last 1

Final score #

* If this system (or manifestation) is the only involvement present from among items 1 - 10, add 2 more points.

+ Excluding patients with end-stage chronic renal disease.

If the final total score is not an integer number, round off to the lower integer for values < 6 and to the higher integer for values > 6.

If the final total score is > 10, round off to 10.