STATISTICAL ANALYSIS PLAN

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 STUDY PROTOCOL No.: 990

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Statistical Analysis Plan

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Statistical Analysis Plan

Glossary of Abbreviations and Acronyms

AE	adverse event
ADR	adverse drug reaction
ATC	anatomical therapeutic chemical
AUC	area under the curve
BDRM	Blinded Data Review Meeting
BILAG	British Isles Lupus Assessment Group
BMI	body mass index
BP	blood pressure
BSA	body surface area
°C	degrees Celsius
CI	Confidence Interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Sensitivity Index
*C*max	maximum plasma concentration
CMV	Cytomegalovirus
CRF	Case Report Form
CS	clinically significant
CSR	Clinical Study Report
CV	Coefficient of Variation
DNA	Deoxyribose nucleic acid
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus

ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food & Drug Administration
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
ITT	Intent-to-treat
IV	intravenous
LOCF	Last observation carried forward
MedDRA	Medical dictionary for Regulatory Activities
N	Normal or number of sample size
PCS	Physical Component Score
PD	Pharmacodynamics
PGA	Physician's Global Assessment
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred term
QOL	Quality of life
QT	represents the duration of ventricular depolarization and subsequent repolarization; is measured from the beginning of the QRS complex to the end of the T wave
QTc	Corrected QT interval
RBC	Red blood cells

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
SOC	System organ class
TEAE	Treatment emergent adverse event
WBC	White blood cells
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for the analysis of data from Protocol 990 (dated 19 March 2015, version 1.0), "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)".

The structure and content of this SAP provide sufficient detail to meet the requirements identified by FDA and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials. The following documents were reviewed and their guidance was adopted in preparation of this SAP:

- Final Clinical Protocol 990, issued 19 March, 2015 (Version 1.0).
- Case report forms for Protocol 990 (Version 5.0, March 10, 2016)
- ICH Guidance on Statistical Principles for Clinical Trials (E9). [1]
- Guideline on Clinical Investigation of medicinal products for the treatment of systemic lupus erythematosus and the lupus nephritis. [2]

2. STUDY OBJECTIVES AND DESIGN

2.1. Study Objectives

2.1.1. Primary Objective

This study includes 2 parts.

The primary objective of Part I of this study was to evaluate the safety and tolerability of 3 months of treatment with 50 mg BT063 administrated IV versus placebo in subjects with SLE.

The primary objective of Part II of this study is to evaluate the safety and tolerability of 100 mg BT063 versus placebo in subjects with SLE. The dose level for Part II was determined based on an interim analysis conducted after the last subject of Part I has completed week 14 of the study.

2.1.2. Secondary Objectives

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

2.2. 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). In addition, 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 has two consecutive parts: Part I and Part II. Subjects were randomly assigned to receive BT063 or placebo in a 2:1 ratio (BT063 : placebo) for both parts. BT063 dose was 50 mg in Part I and increased to 100 mg in Part II based on Part I outcomes. Part I should enrol 18 subjects:12 subjects to 50 mg BT063 and 6 subjects to matching placebo both 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 completed week 14 of the study, an interim analysis of the available data (including data from follow up visits as available) was performed and the DSMB reviewed the safety and efficacy data. Based on the results of that review, the DSMB recommended to continue the study with Part II and had no objections increasing the dose level to 100 mg. Part II should enrol 18 subjects: 12 subjects to BT063 and 6 subjects to matching placebo, both administered by IV infusion 8 times (week 0 [baseline], and then at weeks 1, 2, 4, 6, 8, 10, and 12). For both study parts, Part I and Part II, subjects were followed for 4 months after their last

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

3. SAMPLE SIZE

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

4. GENERAL ANALYSIS DEFINITION

4.1. General Statistical Considerations

An interim analysis including efficacy and safety variables has been performed for Study Part I and a final analysis will be performed for Study Part I and Study Part II together. Subjects receiving same treatment (Placebo or BT063 with same dose) from both parts will be combined in final analysis. Data on both parts will be combined and presented together in all data listings.

Categorical variables will be summarized by sample size (n), frequency count and percentage of subjects at each level of response. Counts of missing observations will be included in the denominator and presented as a separate category. Continuous variables will be summarized by sample size (n), mean, standard deviation (SD), median, minimum, and maximum values. Time to event data will be analyzed using Kaplan-Meier survival estimates. Summary statistics will include median, 25^{th} and 75^{th} percentile survival times, and corresponding 95% confidence intervals on the median. All summary tables will be presented by treatment group and visit, unless otherwise specified, and up to the including all Follow-up visits.

Baseline measurement will be defined as the last assessment completed prior to initial study drug administration for all analyses.

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

Data from all centers will be combined in the computations of descriptive summaries unless otherwise stated. Individual subject listings of all data represented on CRF will be provided. The data from vendors will be provided as well. In general, listings will be sorted by treatment group and subject number. Additional listings will be provided to support selected summary tables and will be sorted in an appropriate manner.

Computations will be completed using SAS® Version 9.1 or higher.

5. STUDY SUBJECTS

5.1. Analysis Sets

The safety analysis and efficacy analysis subject sets are defined as follows:

Safety Set:

The Safety Set comprises all subjects who have received any study medication at least once. Treatment groups will be assigned as actually administered. The Safety Set is the basis for safety analysis and summaries.

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. According to the ITT principle treatment groups will be assigned as randomized. The ITT Set is the basis for efficacy analysis and summaries.

Per Protocol (PP) 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 Set. Classification of protocol deviations as major or minor will be agreed upon between Sponsor and study statistician prior to the analysis.

Pharmacokinetic (PK) Set:

The Pharmacokinetic (PK) Set (corresponding primarily to BT063 plasma concentrations) 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.

5.2. Disposition of Subjects

Summary statistics for the disposition of subjects will be based on all randomized subjects. The number and percentage of subjects will be tabulated and presented in an overview diagram in

clinical study report. Subjects who discontinued from the study and primary reasons for discontinuation will be summarized. The number of subjects by each site based on all enrolled subjects will also be tabulated.

A data listing sorted by subjects will also be prepared.

5.3. Protocol Deviation

Two blinded Data Review Meetings (BDRM), one is for part I, and another one for part II (or after early termination) of the study, will be held after all case report forms (CRFs) have been entered, with all related queries issued and answered to the possible extent, and prior to locking the database. Classification of deviations from the protocol as minor or major will be defined in blinded Data Review plan and decided on a case-by-case basis at blinded data review meeting (BDRM) and documented prior to database lock. According to the recommendations of the ICH guidelines, the protocol deviations will be classified into, but not necessarily limited to, the following categories:

- Inclusion/exclusion criteria deviation
- Use of non-permitted medication
- Procedure non compliance
- Other treatment non compliance
- IMP compliance issue

All major protocol deviations will be presented in a summary table by protocol deviation category.

A listing of all protocol deviations including major and minor will be also presented and those subjects excluded from analysis sets will be identified in the listing.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summary statistics for demographics and baseline characteristics will be based on the data in the Safety Set as well as ITT and PP Sets. The descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum) will be presented for the subject's age (years), weight

(kg), height (m) and body mass index (BMI) (kg/m^2) at baseline. For the categorical variables gender, race, ethnicity, and family history of Lupus, the number and percentage of subjects falling into each category will be presented.

All data pertaining to demographics and baseline characteristics will be presented in data listing. Data listing will be sorted by treatment group and subject number.

7. BASELINE SLE DISEASE CHARACTERISTICS

SLE disease activity at baseline includes the SLE duration (years), percentage of subjects for each ACR Classification criteria at time of initial diagnosis, values of CLASI activity score, tender/swollen joints counts, SLEDAI-2k score, BILAG score and percentage of subjects with ≥ 2A, ≥ 1A or ≥ 2B, Physician's Global Assessment of disease activity, Subject Report Outcomes (SF-36v2, FACIT-F), ECLAM, complement activity (C3/C4/CH50 concentration and proportion of subjects with low C3, C4 levels), ANA titer, anti-dsDNA antibodies concentration, anti-TPO antibodies concentration, Immunoglobulin (IgG, IgM, IgA and IgE) levels, and previous treatment of SLE (e.g. mean prednisone daily dosage and percentage of subjects taking glucocorticoid, and the percentage of subjects with other immunosuppressive therapy (azathioprine, methotrexate, mycophenolate mofetil) and the percentage of subjects with antimalarial drugs (hydroxychloroquine and chloroquine)) will be summarized via descriptive summary statistics by treatment group.

All data pertaining to SLE history and prior therapies will be presented in data listings.

8. MEDICAL HISTORY

Medical history information will be collected at the Screening visit and coded using MedDRA 18.0. Medical history will be summarized by treatment group and system organ class (SOC). Medical history verbatim terms will be listed.

9. TREATMENT EXPOSURE AND STUDY DRUG COMPLIANCE

Treatment exposure duration (in days) is defined as the number of days from the date of the first dose of study drug to the date of the end of treatment phase. Treatment exposure duration is calculated as follows:

[Date of the last dose - Date of the first dose] + 1

The treatment exposure duration will be summarized using descriptive statistics by treatment group. Compliance (%) with protocol specified dosing instructions will be summarized by treatment group, and will be calculated by dividing the number of actual doses applied by the expected number of doses and multiplying it by 100. A subject will be considered sufficiently compliant with study treatment if he/she has taken at least 75% of his/her prescribed dose over the total duration of study drug dosing. Treatment compliance and exposure will be summarized by means of descriptive statistics (n, mean, SD, median, minimum and maximum) and/or frequency tables, and also presented in data listings.

10. EFFICACY ANALYSES

10.1. Efficacy Endpoints

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 as listed above will be assessed at screening, baseline (day 0), week 2, week 4, week 8, week 12, and week 14 (end of treatment), and follow-up weeks 20 and 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 set, and on PP set if the number of subjects in the PP set differs more than 10% from the ITT set.

10.1.1. 50% improvement of swollen/tender joints or 50% improvement in CLASI score at week 14 and week 28, depending on which endpoint was the more severe manifestation at baseline.

A total of 66/68 joints will be assessed for the tender/swollen joint count. A joint that is normal (no tenderness or swelling), without signs of inflammation will be graded as 0. A joint with tenderness will be graded as 1 for tender joint count and a joint with swelling will be graded as 1 for swollen joint count. Joints suspected or known to have ischemic osteonecrosis are not to be taken into consideration. Higher scores indicate more disease activity. A graphical presentation of the joints to be assessed is provided in Protocol Appendix F.

The 50% improvement of swollen/tender joints is defined as improvement of tender or swollen joint count less than -50% of (post-baseline total 66/68 joints count– baseline total 66/68 joints count) / (baseline total 66/68joints count) ×100(%).

50% improvement means that 50% improvement in either of swollen and tender joint counts is achieved.

In case of missing, if more than 30% of all joints have not been assessed at baseline and post-baseline, it cannot be evaluated; otherwise, the 50% improvement of swollen/tender joints is defined as less than -50% of (post-baseline all non-missing joints count– baseline all non-missing joints count) / (baseline all non-missing joints count) ×100(%).

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be summarized for observed, absolute change and percent change from baseline values at weeks 14 and 28 as well as at each other visit and study end for swollen/tender joints. The number and percentage will be presented for subjects with 50% improvement of swollen/tender joints from baseline.

The CLASI is an assessment over 13 body regions (scalp, ears, nose – including 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 as below.

Anatomical Location	Erythema	Scale/Hyportrophy
Scalp	0 -3	0 -2
Ear	0 -3	0 -2
Nose (incl. malar area)	0 -3	0 -2
Rest of the face	0 -3	0 -2
V-area neck	0 -3	0 -2
Post. Neck &/or Shoulders	0 -3	0 -2
Chest	0 -3	0 -2
Abdomen	0 -3	0 -2
Back, Buttocks	0 -3	0 -2
Arms	0 -3	0 -2
Hands	0 -3	0 -2
Legs	0 -3	0 -2
Feet	0 -3	0 -2
Mucous Membrane		
Mucous Membrane Lesions	0-absent and 1 – lesion or ulceration	
Alopecia		
Recent Hair Loss	1 –Yes and 0 - No	
Alopecia	0 -3	

Note: Score for Erythema: 0 = absent; 1 = pink, faint erythema; 2 = red; 3 = dark red; purple/ violaceous/ crusted /hemorrhagic.

Score for Scale/Hypertrophy: 0 = absent; 1 = scale; 2 = verrucous/hypertrophic.

Alopecia: 0 = absent; 1 = diffuse, non-inflammatory; 2 = focal or patchy in one quadrant; 3= focal or patchy in more than one quadrant.

The total activity score will be added up the scores above. The maximum score possible on this scale is 70 and corresponds with the most degree of disease activity. The grades associated with the CLASI are also as in Section 14.2.2.2 of Protocol and a sample of the CLASI as presented in Protocol Appendix D.

The 50% improvement CLASI score is defined as less than -50% of (post-baseline CLASI score – baseline CLASI score)/baseline CLASI score ×100(%).

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be summarized for observed, absolute change and percent change from baseline values at weeks 14 and 28 as well as at each other visit and study end for CLASI. The number and percentage will be presented for subjects with 50% improvement of CLASI from baseline.

The proportion of subjects who have 50% improvement of swollen/tender joints or 50% improvement in CLASI score at week 14 and at week 28, depending on which of them was the more severe manifestation at baseline, will be analyzed using number and percentage, and 95% CI of percentage for each visit by treatment group.

The more severe manifestation of joints or skin based on CLASI Activity scores and 68/66 tender/swollen joints counts at baseline will be assessed as following:

1. If at baseline CLASI Activity score ≥5 and swollen/tender joint count is less than 5, CLASI Activity score will be assessed.
2. If at baseline swollen/tender joint count ≥5 and CLASI Activity score is less than 5, swollen or tender joint count will be assessed.
3. If at baseline both, CLASI score ≥5 and swollen/tender joint count ≥ 5 , the assessment will be performed as below:
    A. If both swollen joint and tender joint counts are higher than CLASI Activity score, swollen / tender joint count will be assessed.
    B. If both swollen joint and tender joint counts are identical with CLASI Activity score, CLASI or swollen/ tender joint count will be assessed.
    C. Otherwise the CLASI Activity score will be assessed.

The table below summarizes the assessment measurements for the possible baseline conditions:

Bullet point	**CLASI /TJC/SJC Activity Scores**		**Endpoint of 50% Improvement**	
	Baseline		**Week 14**	**Week 28**
1	CLASI ≥5	TJC<5 or SJC<5	CLASI	CLASI
2	CLASI <5	TJC≥5 and SJC≥5	TJC or SJC	TJC or SJC
3	CLASI ≥5	TJC≥5and SJC≥5		
	A. TJC>CLASI and SJC>CLASI		TJC or SJC	TJC or SJC
	B. TJC=SJC=CLASI		TJC or SJC or CLASI	TJC or SJC or CLASI
	C. TJC or SJC <CLASI		CLASI	CLASI

In the case of missing results at week 14 or week 28, the last known non-missing post-baseline score will be carried forward.

10.1.2. Absolute and percent change in SLEDAI-2K scores from baseline to week 14 and at week 28

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 absolute change in SLEDAI-2K score from baseline will be calculated as (post-baseline total SLEDAI-2K score – baseline SLEDAI-2K score).

The percent change in SLEDAI-2K score from baseline will be calculated as (post-baseline total SLEDAI-2K score – baseline SLEDAI-2K score) / baseline SLEDAI-2K score x 100(%).

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be summarized for observed and absolute change and percent change from baseline values at weeks 14 and 28 as well as at each other visit and study end for SLEDAI-2K. In addition, the number and percentage of subjects with more than 3 points reduction in SLEDAI-2K scores from baseline will be calculated at weeks 14 and 28, as well as each other post-baseline visit. In the case of missing results at week 14 or week 28, the last known non-missing post-baseline score will be carried forward.

10.1.3. Flare rate and severity at week 14 and week 28 based on BILAG index A or B

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). 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):

A flare is defined as the presence of 1 or more new BILAG A scores or 2 or more new BILAG B scores and 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 [2].

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. A sample of the BILAG 2004 index is presented in Appendix E of Protocol. The percentage with the response and the partial response will be calculated at each post-baseline visit.

Total flare number will be presented for each post-baseline visit; and flare rate, i.e. the proportion of subjects experiencing at least one flare of BILAG A or B will be calculated per treatment group at each post-baseline visit; and severity (classified as severe and mild to moderate) at week 14 and week 28 as well as at visit based on BILAG index A or B will be summarized using number and percentages by treatment group.

Response and partial response rates at week 14 and week 28 as well as at each visit will be summarized using number and percentages by treatment group.

In the case of missing results at week 14 or week 28, the last known non-missing post-baseline score will be carried forward.

10.1.4. Time to first flare

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 will be performed on observed data and will be calculated as

Time to First Flare (days) = (Date of First Flare – Date of First Dose) + 1 day.

No missing data imputations will be performed. Subjects not having a flare will be censored at their last visit date. Time to first flare will be analyzed using Kaplan-Meier survival estimates. Summary statistics will include median, 25^{th} and 75^{th} percentile survival times, and corresponding 95% confidence intervals on the median by each treatment group.

10.1.5. Number of subjects requiring an increase in oral glucocorticosteroid dose before week 14

Information for subject requiring an increase in oral glucocorticosteroid dose before week 14 will be collected in the concomitant medication CRF page.

Number and percentage of subjects requiring an increase in oral glucocorticosteroid dose before week 14 and between week 14 and 28 will be presented by treatment group. A listing of subjects

who received an increase in oral glucocorticosteroid dose before week 14 and between week 14 and 28 will be provided as well.

10.1.6. Physician's Global Assessment at week 14 and week 28

The Physician's Global Assessment (PGA) of disease activity is based on a 100 mm visual analogue scale (VAS) and classified as None (0), Mild (1), Moderate (2), and Severe (3).

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.

PGA score and absolute change from baseline at weeks 14 and 28 as well as at each other visit will be summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by treatment group.

Data listings will be presented by treatment group. In the case of missing results at week 14 or week 28, the last known non-missing post-baseline score will be carried forward.

10.1.7. Subject Reported Outcomes: Fatigue (FACIT-F) and SF-36v2 Physical Component Score (PCS) at week 14 and week 28

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). A sample of the FACIT-F is presented in Appendix H of Protocol.

The FACIT-Fatigue Scale consists of 40 questions rated on a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much). The responses will be reversed (i.e. 4 becomes 0), to calculate the total score. In case of missing data no imputation methods for the total FACIT- fatigue score applied.

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be summarized for observed and change from baseline values at weeks 14 and 28 as well as at each other visit and study end for total score and subscale of FACIT-F. In the case of missing results at week 14 or week 28, the last known non-missing post-baseline score will be carried forward.

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) and mental component summary (vitality, emotional role functioning, social role functioning, and mental health) will be used. Scores for each concept and overall scores for the physical and mental components are calculated according to the SF-36v2 manual of Quality Metric Scoring Software 8612 v4.5 Higher scores indicate better quality of life. A sample SF-36v2 health questionnaire is presented in Appendix G of Protocol.

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be summarized for observed and change from baseline values at weeks 14 and 28 as well as at each other visit and study end for total score and subscale of SF-36v2. In the case of missing results at week 14 or week 28, the last known non-missing post-baseline score will be carried forward.

Data listings will be presented for single score as well as calculated total score and subscale by treatment group.

10.1.8. ECLAM at week 14 and week 28

The purpose of the ECLAM is to assess SLE disease activity within the past month. The measurement consists of 12 categories and their subcategories, see below.

Category	Subcategory	Score
Generalised manifestations	Fever (≥37.5°C not due to an infective process) or Fatigue (feeling of extraordinary tiredness)	0 or 0.5
Articular manifestations	Arthritis or Evolving arthralgia	0 or 1.0
Active muco-cutaneous manifestations	Malar rash, Generalized rash, Discoid rash, Skin vasculitis, or Oral Ulcers	0 or 0.5
Evolving Muco-cutaneous	New or worsened the above muco-cutaneous manifestations (Malar rash, Generalized rash, Discoid rash, Skin vasculitis, or Oral Ulcers) since the last 1 manifestations observation.	0 or 1.0
Myositis	Myositis (raised muscle enzymes and/or EMG and/or histology)	0 or 2.0
Pericarditis	Pericarditis (ECG or rub or evidence of pericardial effusion)	0 or 1.0
Intestinal manifestations	Intestinal vasculitis or Sterile peritonitis	0 or 2.0
Pulmonary manifestations	Pleurisy, Pneumonitis, Ingravescent dyspnoea	0 or 1.0
Evolving neuropsychiatric manifestations	Headache/migraine, Seizures, Stroke, Organic brain disease, Psychosis	0 or 2.0
Renal manifestations	Proteinuria, Urinary casts, Hematuria, Raised serum creatinine, Reduced creatinine clearance	0 or 0.5
Evolving Renal manifestations	New or worsened the above Renal manifestations (Proteinuria, Urinary casts, Hematuria, Raised serum creatinine, Reduced creatinine clearance)	0 or 2.0
Haematologic features	Non-haemolytic anemia, Haemolytic anemia, Leukopenia (or lymphopenia), Thrombocytopenia	0 or 1.0
Erythrocyte sedimentation rate	Raised ESR >25 mm/h	0 or 1.0
Hypocomplementaemia.	Reduced plasma level of C3 or CH50	0 or 1.0
Evolving Hypocomplementaemia.	Significant reduced level of C3 or CH50 or C4	0 or 1.0

Here, 0 = “Not present”, and scores 0.5, 1.0 and 2.0 = “Present”.

ECLAM total score is obtained by summing together all of the above items. Total score range is from 0 to 10 (if total score is not an integer number, round to lower integer for values < 6 and to the higher integer for values >6; if total scores higher than 10 are rounded off to 10) with lower scores indicating less disease activity. A sample of the ECLAM is presented in Appendix I. of Protocol.

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be summarized for observed and absolute change of ECLAM from baseline at weeks 14 and 28 as well as at each other visit and study end for ECLAM. In the case of missing results at week 14 or week 28, the last known non-missing post-baseline score will be carried forward.

10.2. Pharmacokinetic Parameters

Pharmacokinetic data concentrations will be measured before and after investigational medicinal product BT063 (IMP) infusion on the following days: day 0 (pre-dose and post-dose), day 4 or 5, day 7 (pre-dose and post-dose), day 14 (pre-dose and post-dose), day 28 (pre-dose and post-dose), day 42 (pre-dose and post-dose), day 56 (pre-dose and post-dose), day 70 (pre-dose and post-dose), day 84 (pre-dose and post-dose), as well as during follow-up on day 91, day 98, day 140 and day 196.

For each dosing, pre-dose level and serum concentration at End of Infusion level (EOI) will be determined, and summarized by descriptive statistics for each dose visits (n, mean, SD, median, minimum and maximum) for each treatment group. For the EOI levels, outliers will be identified as observations falling below the Q1 – 2.0 (IQR) value, or above the Q3 + 2.0(IQR) value, Q1 being the 1st quartile (25%), Q3 the 3rd quartile (75%), and IQR being the interquartile range Q3 –Q1, considering all EOI levels measured after any dosing for the same dose level. EOI defined as outlier will be listed, but not included in the summary statistics. Pre-dose level at Baseline prior to any dosing below the lower limit of quantification (LOQ) could be attributed 0 ng/mL, while any pre-dose level after 1st dosing below the LOQ could be attributed half of the LOQ value (please refer to Data Assay Transfer Report for the exact value of LOQ). In addition, Summary Table must include plasma concentration measured a Follow-up visits. Figure displaying mean ± SD of pre-dose and EOI over time for each dose group must be provided, in addition to overlay of individual Time-Concentration profile, for each treatment arm, including all available time points.

Same analysis will be performed (and presented in a Summary Table) while separating subjects with positive detection of anti-Drug Antibodies (ADAs) anytime after 1st dosing, and subjects remaining ADA-negative.

Pharmacokinetic parameters will be determined by a non-compartmental procedure as a first step using individual BT063 serum concentrations. The following pharmacokinetic parameters will be derived after 1st and last dosing:

- Cmax and Dose normalized C_{max} (Cmax/D)
- Tmax (Time to maximal concentration)
- Area under the concentration-time curve from time 0 or from time of last dosing to the last observable concentration at time t (AUC_{0-t}) of the dosing/observation interval
- Dose normalized AUC_{0-t} (AUC_{0-t}/D)
- Area under the concentration-time curve from time 0 or from time of last dosing extrapolated to infinity (AUCinf), and dose normalized AUCinf (AUCinf/D)
- The percentage of AUCinf based on extrapolation (AUCExtrap, %)
- Elimination half-life ($t_{1/2}$) derived after 1st and last dosing
- Apparent terminal-phase disposition rate constant (λ_Z) calculated through at least two data points
- Accumulation Ratio (RA) calculated on Cmax (RA_{Cmax}) and AUCinf (RA_{AUCinf}) calculated by dividing value obtained after last dosing on value obtained after 1st dosing
- Total body clearance from serum (CL)
- Apparent volume of distribution during the terminal phase (V_Z)

All PK parameters will be presented using descriptive statistics for each dose arm for the respective visits (1st and last dosing). These statistics include arithmetic mean, arithmetic standard deviation (SD), geometric mean, geometric standard deviation (SD), coefficient of variation (CV), minimum, median, and maximum. The PK parameters will be analysed and added to the SAS raw data set after BDRM and data base lock for eCRF-collected data.

Further population PK modelling analysis will be investigated. This will be reported separately from this present SAP.

10.3. Pharmacodynamic Variables

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) cell counts and percentage
- Complement activity CH50, C3, and C4
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Cytokine (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-α, IFN-γ) concentrations in plasma
- Immunoglobulins (IgG, IgM, IgA, IgE)
- Free IL-10 (optional) and total IL10

PD variables will be presented using descriptive statistics for the respective visits and protocol scheduled times. The CH50, Cytokine, and IL 10 parameters will be analysed and added to the SAS raw data set after BDRM and data base lock for eCRF-collected data.

A data listing will be presented for all PD raw data and parameters by subject

10.4. Biomarkers

The biomarker analysis is used to explore the systemic or local biological effect of BT063. Blood samples were collected at Week 0, 2, 6, 14 and 28 for a quantitative, multiplex immunoassay for measurement of cytokines, chemokines, metabolic markers, hormones, growth factors, tissue remodeling proteins, angiogenesis markers, and acute phase reactants, cancer markers, kidney damage markers, central nervous system biomarkers and other important circulating proteins, including characterization of the autoantibodies. The analysis will be performed by Biotest or an independent research laboratory (such as Myriad, and/or Protagen), and the raw data and results presented in a separate study report and summarized in the clinical study report using descriptive statistics based on the ITT population. The Biomarker parameters will be analysed and added to the SAS raw data set after BDRM and data base lock for eCRF-collected data. Biomarker parameters will be listed only and not summarized in tables. Results will be described in a separate report and referenced in the CSR.

10.5. Immunological Parameters

Blood samples were collected for immunological parameters analyses at Week 0, 6 and 12 in order to explore the immunological effect of BT063.
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

The analysis will be performed by an independent research laboratory and the raw data and results will be presented in a separate study report.

11. SAFETY ANALYSES

Safety analyses will be carried out using the data of the Safety Set.

11.1. Adverse Events

All AEs recorded during the course of the clinical study will be coded according to the MedDRA (version 18.0) terminology and assigned to a System Organ Class (SOC) and a preferred term (PT).

Treatment-emergent AEs (TEAEs) will be defined as those events which started on or after the date of first drug administration, or whose severity worsened or causality increased on or after the date of first study drug administration.

All other AEs with an onset date prior to the first dose of study medication will be considered non-treatment emergent.

Adverse events will be summarized by SOC and PT and will include the number and percentage of subjects experiencing each event. The number of subjects in the Safety Set will be used as the denominator for calculating the percentage. All summarises will be sorted alphabetically by SOC and PT within SOC.

The following summaries by treatment groups will be presented:

- Summary of overall TEAEs
- Incidence of TEAEs during the study
- Incidence of TEAEs during the study by severity
- Incidence of TEAEs during the study by relationship to study drug
- Incidence of TEAEs leading to discontinuation
- Incidence of serious TEAEs during the study
- Incidence of serious TEAEs during the study by relationship to study drug
- Incidence of TEAEs of special interest during the study
- Incidence of deaths during the study

For summary of relationship to study drug, the eCRF reported categories of "not related" will be considered not related to study drug. All other categories, including not assessable, will be considered related to study drug.

For all TEAE summaries, if a subject has a missing severity or relationship to study drug, the maximum severity or closest relationship to study medication will be used. If a subject has more than one AE within a preferred term, the subject is counted once in that preferred term at the maximum severity and related to study medication. If a subject has more than one AE within a SOC, the subject is similarly counted once within that SOC.

Adverse event data listings will be provided.

11.2. Clinical Laboratory Evaluations

The tests listed in Table 1 as below will be conducted on samples collected and analysed by standard laboratory procedures and laboratory parameter will be assessed at Visit 1 (Screening), Visit 2 (Baseline, Day 0), and Weeks 1, 2, 4, 8, 12, 14, 20, and 28. 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 (Week 14).

Table 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) Reticulocytes
Clinical Chemistry		
Alanine aminotransferase Aspartate aminotransferase Gamma glutamyl transferase Alkaline phosphatase Lactic dehydrogenase Lipase	Bilirubin Total protein Albumin Creatinine Urea Sodium	Chloride Potassium Calcium Creatine phosphokinase
Urinalysis		
pH Specific gravity Erythrocytes Leucocytes Total Protein	Glucose Ketones Bilirubin Urobilinogen Protein-Creatinine Ratio	Microscopy (Erythrocytes sed., Leucocytes sed., Squamous epithelial cells, Renal epithelial cells, Erythrocyte casts, Leucocyte casts, Hemoglobin casts, Bacteria, Uric acid crystals)
Other tests		
Thyroid stimulating hormone Free triiodothyronine Free thyroxine Fasting glucose	Fasting triglycerides Fasting total cholesterol Fasting high-density lipoprotein Fasting low-density lipoprotein	Faecal occult blood test

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.

Each laboratory result will be classified as low (L), normal (N), and high (H) at each visit according to the laboratory-supplied delta limits. The shift summary from baseline based on delta limits for each lab parameter will be presented for each post-baseline visit and end of study. A listing including all subjects with abnormal clinically significant results will be provided as well.

11.3. Immunological Status

For immunological status including infection status of human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Barr virus (EBV), Cytomegalovirus (CMV), tetanus, tuberculosis, diphtheria, as well as EBV and CMV serology, the response results at the relevant visits (V1 and V12, optionally, V2 or/and V14) will be summarized using number and percent for each category (Negative, Positive, or Not done) at each schedule visit by treatment group.

11.4. Auto-antibodies

For auto-antibodies including anti-dsDNA, anti-nucleus (ANA), anti-thyroid gland (TPO), anti-thyroid stimulating hormone receptor (TSHR), anti-islet cells, anti-cyclic citrullinated peptide (CCP) and Coombs test, the response results will be summarized using number and percent for each category (Negative, Positive, and Not done) at each schedule visit by treatment group.

11.5. Anti-drug Antibodies

The results of anti-drug antibodies against BT063 will be summarized in Table for each individual determined as ADA-positive, including onset (first visit/week with ADA-positive, duration (last visit with ADA-positive, and corresponding ADA titers at first and last visit).

In addition, data will be summarized using number and percent for each category (Negative, Positive, and Not done) at each schedule visit by treatment group. The ADA parameters will be analysed and added to the SAS raw data set after BDRM and data base lock for eCRF-collected data

11.6. Vital Signs

Descriptive statistics will be presented for the vital sign measurements captured during the study, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute) and temperature (^{o}C).

For each vital sign, descriptive statistics for the observed and change from baseline values (n, mean, SD, median, minimum and maximum values) will be presented for baseline and each post-baseline time point by treatment group.

A data listing will also be presented.

11.7. 12-lead ECG

During the study, 12-lead ECGs were performed at the time points screening and week 14. The subject should be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment was 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.

Observed and changes from values at screening for the 12-lead ECG parameters including RR interval, PR interval, QRS duration, QT interval and QTc (Fridericia and Bazzet) interval will be summarized for Baseline and Week 14. Baseline will be defined as ECG values collected at Screening. The number and percentage of subjects with normal, abnormal (not clinically significant), and abnormal (clinically significant) ECG overall impression results at Week 14 will be summarized by treatment group as well.

A Listing of ECG findings and values by subject number and time point will be provided respectively.

11.8. Prior and Concomitant Medication

Prior medications and therapies will include all medications used for SLE since diagnosis, but maximal 5 years prior to enrollment. Concomitant medications and therapies will be defined as any medication taken on or after the start time of study drug.

In case the medication start/end date is incomplete, a worst-case allocation will be done according to the available parts of the medication start date.

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary March 2015. In this system, drugs will be classified into groups at 5 different Anatomical Therapeutic Chemical (ATC) levels according to the organ or system, therapeutic, pharmacological and chemical properties. The start/stop dates recorded by the Investigator and his/her research staff in the eCRF will be used to identify when a concomitant medication was taken during the study.

A summary of the number and percentage of subjects with concomitant medications will be displayed. Concomitant medications will be reported by ATC level two (therapeutic) and ingredients of drugs. Previous medications will be summarized in same manner as well.

A data listing will be generated for prior and concomitant medications.

11.9. Physical Examination

The investigator or qualified designee should perform a complete physical examination (genitourinary examination not required) at screening and baseline and then targeted physical examinations at the scheduled time point. 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 page in eCRF.

A full physical examination including body systems such as general appearance, skin, neck (including thyroid), head, eye, ear, nose, and throat (HEENT), lymph nodes, cardiovascular, abdomen, extremities, neurologic and others should be performed at the screening, baseline (day 0), weeks 1, 2, 4, 6, 8, 10, 12, 14, 20, and 28.

Each physical examination result will be classified as normal (N), abnormal (AB), not done (ND) at each visit. The shift summary from baseline (Day 0 Pre-dose) will be presented for each post-baseline visit.

Data listings will be provided as well.

11.10. Pregnancy Test

Serum pregnancy test should be performed at screening, baseline (Day 0), weeks 4, 8, 12, and 14 and test results of female subject's pregnancy should be recorded on eCRF. Data listing for the information of female subject's pregnancy test will be provided.

12. INTERIM ANALYSES

Data Safety Monitoring Board (DSMB)

It was anticipated that DSMB data review meetings will be scheduled for setup and after the 3rd, the 9th and the 18th subject has completed the End-of-Treatment/Early Termination Visit during study Part I, after the 3rd and the 9th subject has completed the End-of-Treatment/Early Termination Visit during study Part II, resulting in a total of six planned data review meetings.

Data included in each DSMB Data Report should be cumulative-to-date at the time of the established data cut-off and should be retrieved from the eCRF. The cut-off date for the data was the defined time point for each DSMB meeting and included in the Data Reports, as well as the current enrollment status, which should be stated in a cover letter. The Data report should be sent one week prior to each DSMB meeting.

More information including the timing and frequency of the DSMB meetings as well as a list of proposed DMC tables and listings can be found in the DSMB charter.

Interim Analysis

After the last subject in Part I has completed week 14 of the study, an interim analysis was performed.

Therefore, after database lock for Study Part I, randomized codes were unblinded for one biostatistician of [redacted] to generate the unblinded interim results.

The unblinded interim results consist of the descriptive safety and efficacy summary tables as well as individual listings, respectively. All tables and listings for interim analysis are included in table shells.

The unblinded interim results were distributed to the DSMB as well as to the biostatistician of Biotest. The biostatistician distributed the unblinded interim results to the unblinded team of Biotest. The complete operative study team was kept blinded until end of study.

Statistical Analysis Plan

The unblinded team of Biotest and [redacted] is listed below:

Name	Function
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The DSMB reviewed the safety and efficacy data. Depending upon the results of that review, the DSMB recommend that Part II be started at a higher dose of BT063 (100 mg). After reviewing the DSMB recommendation, Biotest decided to continue the study with 100 mg BT063 in Part II.

The unblinding of Part I data for the interim analysis did not impact the performance of the study Part II, as the operational study team, all investigators and subjects were kept blinded to therapy and results of Part I. The Part II will be kept blinded to study team until final database lock.

13. FINAL ANALYSIS AND REPORTING

Final database lock will occur when all subjects have completed the study or early discontinuation and all data during the assessment period have been monitored, reviewed and considered as clean.

All analyses outlined in the protocol and in this SAP will be carried out after:

- The SAP has been approved;
- The study database has been authorized by the Biotest clinical team as complete and final;
- All analysis sets are determined;
- Protocol deviations have been identified; and
- The study has been unblinded.

Further exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not identified in this SAP will be clearly identified in the clinical study report (CSR).

14. REFERENCE LIST

1 Guidelines for Industry: Statistical Principles for Clinical Trials (E9), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, September 1998

2 Guideline on Clinical Investigation of medicinal products for the treatment of systemic lupus erythematosus and the lupus nephritis, 26 February 2015, EMA/CHMP/51230/2013, Committee for Medicinal Products for Human use (CHMP)

15. Appendices

15.1. 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,		•	•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**	
diphtheria, tuberculosis)															
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, CD45RA)			•		•			•			•				•
Complement activity CH50, C3, and C4		•	•			•	•		•		•		•	•	•
ESR and CRP			•			•	•		•		•		•	•	•

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**	
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, reticulocytes), 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, creatine phosphokinase), urinalysis: dipstick (pH, qualitative for blood, leucocytes, protein, glucose, ketone bodies, bilirubin, urobilinogen, nitrites, specific gravity, protein-creatinine ratio) 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.

15.2. List of Tables, Listings, and Figures for Interim Analysis for Part 1

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