Clinical Study Protocol

Protocol Title:	**A Randomized, Double-blind, Parallel Group, Multicenter Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy of SAIT101 versus MabThera® versus Rituxan® in Patients with Rheumatoid Arthritis (RA).**
Protocol Number:	**AGB 001**
Date of Protocol:	**26APR2017 (Amendment 04)**
Product:	**SAIT101**
Clinical Trails Identifier:	**NCT02819726**
EudraCT No.:	**2014-005368-13**
Study Phase:	**I/III**
Sponsor:	**Archigen Biotech Limited** **1 Francis Crick Avenue** **Cambridge Biomedical Campus, Cambridge** **CB2 0AA, United Kingdom**
Sponsors Representatives:	[redacted] **16F Kamco Yangjae Tower** **262 Gangnam-daero, Gangnam-gu, Seoul,** **South Korea**

Signatures

PROTOCOL TITLE: **A Randomized, Double-blind, Parallel Group, Multicenter Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy of SAIT101 versus MabThera® versus Rituxan® in Patients with Rheumatoid Arthritis (RA).**

PROTOCOL NO: **AGB 001**

Signature of Sponsor's authorized representative(s):

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Name	**Signature**	**Date**
[redacted]		

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Name	**Signature**	**Date**
[redacted]		

SYNOPSIS

Name of Sponsor/Company:	Archigen Biotech Ltd	
Name of Finished Product:	SAIT101 (proposed rituximab biosimilar)	
Name of Active Ingredient:	Rituximab	
Title of Study:	A Randomized, Double-blind, Parallel Group, Multicenter Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy of SAIT101 versus MabThera® versus Rituxan® in Patients with Rheumatoid Arthritis (RA).	
Protocol No:	AGB001	**Phase:** I/III
Investigators:	Approximately 70 Investigators	
Study centers:	Approximately 70 study centers globally	

Objectives:

Primary Objective:

The primary objective of the study is to compare the pharmacokinetics (PK) of SAIT101 (proposed rituximab biosimilar) versus rituximab licensed in the European Union (hereafter designated MabThera®, brand name in EU) versus rituximab licensed in the United States (hereafter designated Rituxan®, brand name in US) in patients with rheumatoid arthritis (RA).

Secondary Objectives:

The secondary objectives of the study are to compare the safety, additional PK, pharmacodynamics (PD), efficacy, tolerability, and immunogenicity of SAIT101 versus MabThera® versus Rituxan® in patients with rheumatoid arthritis (RA).

Methodology:

This is a multicenter, randomized, double-blind, parallel group study to compare the PK, PD, safety, efficacy, tolerability, and immunogenicity of SAIT101 versus MabThera® versus Rituxan® in patients with RA. This study consists of Part A up to 24 weeks followed by Part B up to Week 52 that also collects transition data in patients eligible for a second course of treatment.

It is planned to randomize approximately 282 patients.

The regular study duration per individual patient will be 52 weeks from the start date of the first course.

Overview of Study Design

Part A - First Course: Patients will be randomized in a 1:1:1 ratio to receive one course of SAIT101 (n=94) versus Rituxan® (n=94) versus MabThera® (n=94).

Part B - Second Course:

Eligible patients in the SAIT101 arm will receive the second course of SAIT101 treatment at Week 24 and Week 26.

Eligible patients in the MabThera® arm will receive the second course of MabThera® treatment at Week 24 and Week 26.

Eligible patients in the Rituxan® arm will be randomized in a 1:1 ratio to receive SAIT101 or Rituxan® treatment at Week 24 and Week 26.

Study Population

Patients with RA who have had an inadequate response to at least 3 months' treatment (according to the approved treatment and dosage) or intolerance (at Investigator's discretion and/or experience of severe adverse event [AE] or toxicity such as infusion related reaction, hypersensitivity, anaphylaxis or severe toxicity) to anti-tumour necrosis factor (TNF) therapy.

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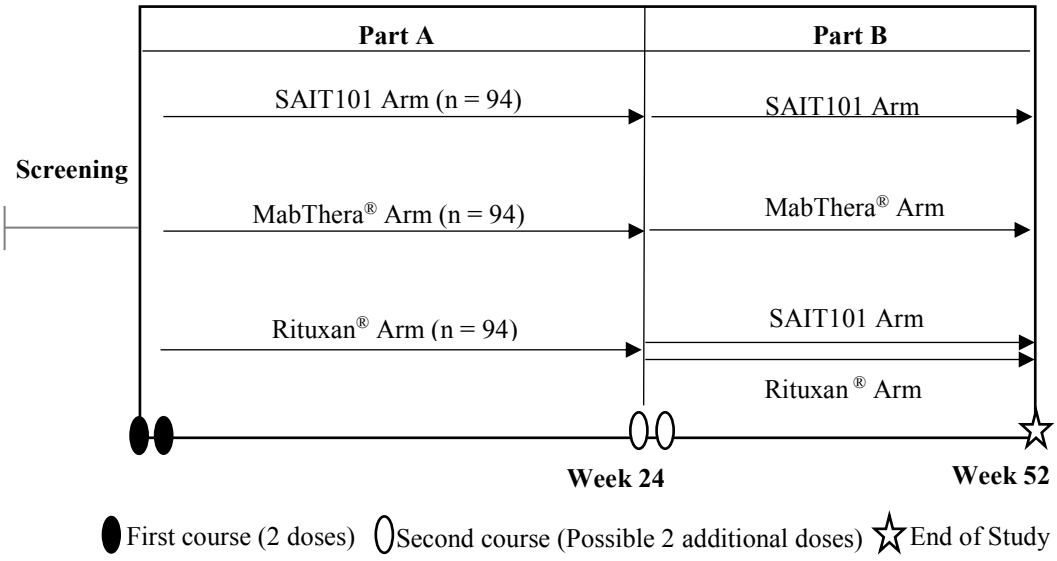
Name of Active Ingredient:	Rituximab	



Screening and Baseline

All the Screening assessments should be performed within 30 days prior to randomization on Day 1 (Visit 2, Baseline), except in patients who require prophylaxis of latent tuberculosis or a washout of current anti-TNF medication or other biologic and non-biologic disease-modifying anti-rheumatic drug (DMARD) treatment (except methotrexate [MTX]). For these patients the Screening Period may be extended to allow for the washout required, but will not exceed 60 days. In these patients all Screening assessments must be performed within 30 days prior to randomization with the exception of the informed consent and chest X-ray.

Treatment Regimen

Each patient will receive first course which includes two intravenous (i.v.) 1,000 mg study drug infusions: one on Day 1 (Visit 2) and the second on Day 15 (Visit 5). Patients will receive an anti-pyretic and an anti-histamine, e.g., paracetamol and diphenhydramine or equivalent, 30 to 60 minutes before each infusion, plus 100 mg i.v. methylprednisone within 30 minutes prior to each infusion.

Patients with an inadequate response (<50% improvement from Baseline in both the swollen and tender joint counts) at Week 24 (Visit 12), will be eligible to receive the second course of two 1,000 mg i.v. infusions (one at Week 24 and the second infusion at Week 26 [14 days later]) of study drug.

On Day 1 and Day 15 (first and second infusions) blood PK samples and PD (CD19+ B-cell) samples will be collected before and 3 hours after the start of infusion and immediately (within 10 minutes) before and 1 hour after the end of infusion, at 48 hours after the start of each infusion (Days 3 and 17).

The PK/PD samples will also be taken at Weeks 4, 8, 12, 16, 20, and 24 to estimate elimination.

Blood PD samples will be additionally collected simultaneously at Weeks 36 and 52.

The main efficacy variable change from baseline in DAS28 (Disease Activity Score) will be evaluated on completion of 24 weeks of study assessments.

- All patients will be followed up for up to 52 weeks from the start date of the first infusion.
- Patients will attend the study center approximately every 12 weeks during Part B, from the start date of the second course of infusions. Patient who are not eligible for the second course of study treatment will also attend all visits until week 52.

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Name of Active Ingredient:	Rituximab	

- To prevent missing data in important supportive efficacy and safety analysis, patients who discontinued study treatment, will also attend all visits until week 52.
- Patients, Investigators, joint assessor and other study personnel (except pharmacist) will remain blinded to the treatments throughout the entire Treatment Period (52 weeks).
- An interim analysis of 10 patients per arm (30 patients in total) of safety data collected up to Week 4 and 20 patients per arm (60 patients in total) of safety data collected upto Week 12 are planned.
- The study will be unblinded at Week 24 and an interim CSR will be prepared based on the 24-week data of all patients. The investigators and patients will remain blinded to treatment assignment during the post Week 24 follow-up period.
- An independent Data Safety Monitoring Board (DSMB) will be assigned for this study. The DSMB will review available study data at pre-specified time points as outlined in the DSMB charter.
- Investigators will be instructed to monitor the patients throughout the study to detect the first symptoms or neurological signs suggestive of progressive multifocal leukoencephalopathy (PML, i.e., cognitive or visual disorders, hemiparesis, confusion or behavior disorders). If the patients develop new neurological signs or symptoms they should be evaluated for PML. Neurological warning signs include: major changes in vision, unusual eye movements; loss of balance or coordination; and disorientation or confusion. Any patient who is suspected of developing PML will be discontinued from the study treatment and the AE will be followed closely, at the discretion of the Investigator.

Number of patients:	Approximately 282 patients will be randomized into the study, at approximately 70 investigative centers.
Diagnosis and main criteria for inclusion:	Male and female patients aged between 18 and 80 with severe RA who have had an inadequate response to at least 3 months' treatment (according to the approved treatment and dosage) or intolerance (at Investigator's discretion and/or experience of intolerable adverse events or toxicity such as infusion related reaction, hypersensitivity, anaphylaxis or severe toxicity) to anti-TNF therapy (experience of severe adverse event or toxicity). Patients have to be on a stable weekly dose of MTX, 7.5 – 25 mg/week at least 12 weeks, including the last 4 weeks prior to Day 1 at a stable dose (lower doses of MTX <10 mg/week are only permitted if patients have documented evidence of intolerance to higher doses of MTX).
Test product, and comparator, dose and mode of administration:	1,000 mg (10 mg/mL) SAIT101 or Rituxan® or MabThera® for i.v. infusion. In Part A, each patient will receive one course of two 1,000 mg study drug infusions: one infusion on Day 1 and the second on Day 15. In Part B, patients with an inadequate response (<50% improvement from Baseline in swollen and tender joint counts at Week 24 [Visit

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Name of Active Ingredient:	Rituximab	
	12]) will be eligible for a further course of two 1,000 mg drug infusions: one infusion at Week 24 and the second one at Week 26: • Eligible patients in the SAIT101 arm will receive additional SAIT101 treatment at Week 24 and Week 26. • Eligible patients in the MabThera® arm will receive additional MabThera® treatment at Week 24 and Week 26. • Eligible patients in the Rituxan® arm will be randomized in a 1:1 ratio to receive SAIT101 or Rituxan® treatment at Week 24 and Week 26.	
Method of administration:	Patients will receive an anti-pyretic and an anti-histamine, e.g., paracetamol and diphenhydramine, or equivalent 30 to 60 minutes before each infusion, plus 100 mg i.v. methylprednisone at least 30 minutes prior to each infusion. The Day 1 infusion rate (both first and second courses) of SAIT101 or MabThera® or Rituxan® will be 50 mg/hour; after the first 30 minutes, it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. If there has been no infusion related reaction on Day 1, the Day 15 infusion (both first and second courses) can be started at 100 mg/hour and increased by 100 mg/hour increments at 30 minute intervals, to a maximum of 400 mg/hour. Drug infusions will take place under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available.	
Duration of study:	Total study duration up to 52 weeks for each patient, including Baseline, Part A and Part B.	

Main criteria for evaluation:

Pharmacokinetics

Primary PK endpoints

- Area under the concentration-time curve from time 0 (immediately predose on Day 1) to last quantifiable concentration (AUC_{0-t})
- AUC from time 0 to infinity ($AUC_{0-\infty}$)
- AUC from time 0 to Day 15 prior to infusion (AUC_{0-d15})
- Maximum concentration (C_{max}) after Day 15 infusion
- Trough concentration (C_{trough}) before the second infusion on Day 15

Secondary PK endpoints

- AUC from Week 2 to Week 24 (AUC_{w2-w24})
- AUC from time 0 (immediately predose on Day 1) to Week 12 (AUC_{0-w12})
- Time of maximum concentration (T_{max}) post infusion on Day 15
- Systemic clearance (CL)
- Volume of distribution (V_D)
- Terminal half-life ($t_{½}$)

Efficacy

Main Efficacy endpoint

- Change from Baseline in DAS28 at Week 24

Other Efficacy endpoints

- Change from Baseline in DAS28 at Weeks 8, 16, 36, and 52
- ACR20 response rates at Weeks 8, 16, 24, 36, and 52
- ACR50 response rate and ACR70 response rate at Weeks 8, 16, 24, 36, and 52
- Individual components of the ACR improvement criteria on Day 1 and at Weeks 8, 16, 24, 36, and 52
  - Swollen and tender joint count (the 66/68 joint count system)
  - Patient's assessment of pain (assessed on 1 to 100 mm Visual Analogue Scale [VAS])
  - Physician's global assessment of disease activity (assessed on 1 to 100 mm VAS)
  - Patient's global assessment of disease activity (assessed on 1 to 100 mm VAS)
  - Patient's assessment of disability (Health Assessment Questionnaire-Disability Index; HAQ-DI)
  - C-reactive protein level.
- Change from Baseline in DAS28-CRP to Weeks 8, 16, 24, 36, and 52
- Major clinical response (continuous ACR70 for at least 24 weeks)
- Clinical remission (defined by SDAI <3.3) at Weeks 8, 16, 24, 36, and 52
- Proportion of patients with European League Against Rheumatism (EULAR) response (good response, moderate response or no response) at Weeks 8 16, 24, 36, and 52

Pharmacodynamics

The CD19+ B cell count at the pre-infusion on Day 1 will be used as Baseline. The following PD variables will be calculated:

- Depletion of CD19+ B cell count at Week 24
- Time needed to B cell depletion
- Duration of CD19+ B cell depletion
- % CD19+ B-cell count vs. baseline at Week 24
- AUC of CD19+ B-cell count change at Week 24
- Change from Baseline in CD19+ B cell count during the study period
- Change from Baseline in immunoglobulin (Ig) IgG, IgM, and IgA levels at Weeks 24 and 52
- Change from Baseline in CRP levels at Weeks 8, 16, 24, 36, and 52

Safety

- Serious adverse events (SAEs), adverse events (AEs), adverse drug reactions (ADRs)
- Vital signs
- Clinical laboratory parameters including hematology, chemistry and urinalysis
- Physical findings
- Concomitant medication, incidence of rescue medication, where rescue medication is defined as the use of non-biologic DMARDs after Week 16 of the study
- B cell recovery measured by a CD+19 B cell count after Week 24

Immunogenicity (HACA and Neutralizing Antibody)

- Incidence of human anti-chimeric antibodies (HACA) and neutralizing antibody at Day 1 predose and at Weeks 1, 2, 4, 12, 16, 24, 36, and 52

Statistical methods:

Pharmacokinetic Analyses

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The PK analysis will be performed on the PK Analysis Set. The PK parameters, AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-d15}, C_{max} after the second infusion on Day 15 and C_{trough} before the second infusion on Day 15 will be considered the co-primary PK endpoints. All other PK endpoints will be regarded as secondary.

The statistical analysis of the log_e-transformed primary endpoints will be based on an analysis of variance model. The difference in least squares means between each of the three pairs (SAIT101 vs. MabThera®, SAIT101 vs. Rituxan®, and MabThera® vs. Rituxan®) and the associated 90% confidence interval (CI) will be determined. Back transformation will provide the ratio of geometric means and 90% CI for this ratio. Equivalence will be concluded if the 90% CI for the ratio of geometric means of each of the three pairs for primary endpoints are completely contained within the acceptance interval of 0.8 to 1.25.

Descriptive statistics (N, mean, standard deviation, coefficient of variation (CV), minimum, median, and maximum) will be used to summarize serum concentration data by treatment at each planned sampling time point. Concentrations that are below the lower limit of quantification will be assigned a value of 0 for the purposes of computing descriptive statistics. Serum PK parameters calculated from the concentration-time data will also be summarized by treatment using descriptive statistics.

Plots of the mean and individual serum rituximab concentrations over time for SAIT101 and MabThera® or Rituxan® will be provided following i.v. infusions.

Pharmacodynamic Analyses

Observed, change from Baseline, and percent change from Baseline in CD19+ B cell counts, depletion incidence for CD19+ B cell counts, time needed to B cell depletion, duration of CD19+ B cell depletion and IgG, IgM, IgA, CRP levels will be summarized using descriptive statistics.

Efficacy Analyses

The change from Baseline in DAS28 at Week 24 will be considered the main efficacy endpoint.

Two-sided 95% CI for the difference between SAIT101 and MabThera® in DAS28 change from Baseline at Week 24 will be computed from an analysis of covariance using Baseline DAS28 as covariate and treatment as model factors. Equivalence will be concluded if the 95% CI for the mean difference for main endpoint is completely contained with the equivalence margin of -0.6 to 0.6. Both of the per protocol (PP) set and full analysis set (FAS) will be considered as the efficacy analysis population and no missing data will be imputed for the efficacy analyses in FAS.

Continuous variables will be summarized using N, mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Safety Analyses

All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). No statistical testing will be performed for AEs. For all AE and SAE tables, patients will be counted at most once for each Preferred Term (PT) and each System Organ Class (SOC). Adverse events will be summarized by the number and percentage of patients experiencing events by SOC, PT and severity.

Changes in vital signs and clinical laboratory measurements will be summarized descriptively by visit. Other safety variables will be summarized and listed.

Immunogenicity Analyses

Incidence of HACA and neutralizing antibody and summary of counts of antibodies per patient at prior first dose on Day 1 and at Week 1, 2, 4, 12, 16, 24, 36 and 52 will be summarized overall and by treatment group.

Interim Analysis

Interim Analyses of 10 patients per group (30 patients in total) of safety data collected up to Week 4 and 20 patients per group (60 patients in total) of safety data collected up to Week 12 are planned.

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The study will be unblinded at Week 24 and an interim CSR will be prepared based on the 24-week data of all patients. The investigators and patients will remain blinded to treatment assignment during the post Week 24 follow-up period.

Sample Size

A percentage co-efficient of variation (CV%) ranging from 26.3 to 37.3% for the five co-primary parameters is assumed for this study based on a recent study in RA patients treated with rituximab.

When the evaluable sample size in each group is 84, a three group design will have 81% power to reject both the null hypothesis that the ratio of test to standard geometrics means is below 0.800, and the null hypothesis that the ratio of test to standard geometrics means is above 1.250 (i.e., that the test and standard are not equivalent), in favor of the alternative hypothesis, that the means of the two groups are equivalent, assuming that the expected ratio of means is 1.000, the CV% for the standard is 0.330, that data will be analyzed in the log scale using analysis of variance (ANOVA) and that each one sided test is made at the 5% level. Each of the 15 hypotheses tests (five co-primary endpoints × three pairwise comparisons) are powered at 98% to 99.0% to yield 81% study-wide power.

Approximately 282 patients (94 patients per group) will be randomized in order to yield a minimum of 84 patients per group to account for a presumed 10% withdrawal.

This 94 patients in SAIT101 group and MabThera® group will provide 96% probability of declaring the equivalence in FAS with each one sided test at the 2.5% level, accounting for a presumed 1.0 standard deviation of DAS28 from the REFLEX study, and the equivalence margin of -0.6 to 0.6 chosen as the half of a clinical meaningful improvement of 1.2 in DAS28. Considering 18% withdraw from the REFLEX study, approximately 77 patients per group will provide approximately 91% probability of declaring the equivalence in the PP set.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% response criteria
ACR50	American College of Rheumatology 50% response criteria
ACR70	American College of Rheumatology 70% response criteria
ADCC	Antibody dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of variance
$AUC_{(0-t)}$	Area under the concentration-time curve from time 0 to the last quantifiable concentration
$AUC_{(0-d15)}$	Area under the concentration-time curve from time 0 to Day 15
$AUC_{(0-\infty)}$	Area under the concentration-time curve from time 0 extrapolated to infinite time
$AUC_{(w2-w24)}$	Area under the concentration-time curve from Week 2 to Week 24
$AUC_{(0-w12)}$	Area under the concentration-time curve from time 0 to Week 12
B cell	B lymphocyte
CCP	Cyclic citrullinated peptide
CD_{20}	Activated-glycosylated phosphoprotein expressed on the surface of all B cells
CDC	Complement-dependent cytotoxicity
CHO	Chinese hamster ovary
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence interval
CL	Systemic clearance
CLL	Chronic lymphoid leukemia
C_{max}	The maximum concentration after the Day 15 infusion
C_{trough}	The lowest (trough) concentration before the Day 15 infusion
COPD	Chronic obstructive pulmonary disease
CRO	Contract research organization
CRP	C-reactive protein

CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical trial management system
CV	Coefficient of variation
DAS	Disease Activity Score
DAS28	Disease Activity Score based on a 28 joint count
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic Acid
EOS	End-of-Study
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyl transpeptidase
GLS	Geometric Least Square
HACA	Human anti-chimeric antibodies
HAQ-DI	Health Assessment Questionnaire-Disability Index
HbcAb	Hepatitis B core antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonization
ID	Identification
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
i.v.	Intravenous

IRB	Institutional Review Board
IUD	Intrauterine device
IXRS	Interactive voice / web response system
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NSAIDs	Non-steroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PE	Polyethylene
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
PP	Per Protocol
PT	Preferred Term
PVC	Polyvinyl chloride
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RNA	Ribonucleic Acid
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SDAI	Simple Disease Activity Index
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
$t_{½}$	Terminal half-life
T_{max}	Time of maximum concentration
TNF	Tumour necrosis factor
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
V_D	Volume of distribution

WBC	White blood cell
WHO-DD	World Health Organization-Drug Dictionary

1 INTRODUCTION

1.1 Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterized by inflammation in the synovium of joints, which is associated with progressive joint destruction, and depending on the severity, may be accompanied by systemic manifestations including lung disease, rheumatoid nodules, and effects on the cardiovascular system. If left untreated, RA may lead to severe functional disabilities, and therefore a considerable reduction in quality of life for the patient.[1,2] The prevalence of RA is relatively constant in many populations, at 0.5 to 1%, but can vary with factors such as gender, race and smoking status.[3]

B lymphocytes (B cells) are thought to contribute considerably to the pathogenesis of RA. B cells contribute to the formation of immune complexes and complement activation in affected joints as they are the primary source of rheumatoid factors (RFs) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. They are highly efficient antigen-presenting cells and therefore contribute to the auto-immune response through downstream activation of T cells via co-stimulatory molecules. B cells respond to, and produce, chemokines and cytokines that promote lymphocyte infiltration into joints, formation of ectopic lymphoid structures, angiogenesis, and synovial hyperplasia that characterize the pathology observed in the rheumatoid joint.[4]

Traditionally, RA has been treated with a combination of anti-inflammatory agents and disease-modifying anti-rheumatic drugs (DMARDs). While therapeutic options have improved with the introduction of biologic DMARDs, neutralizing cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) which have been shown to both control signs and symptoms of joint inflammation and retard progression of joint destruction, targeting other mediators and pathways might improve the overall response rate. Although TNF-α antagonists and other biologic therapies represent an important advance in the management of patients with RA, there remains a significant unmet medical need for effective novel therapies given the significant non-responder rates and well-documented systemic toxicities of the traditional treatments.

1.2 Overview of SAIT101

SAIT101 is a proposed biosimilar product rituximab being developed by Archigen Biotech. Similar to rituximab, SAIT101 has 1,328 amino acids with an approximate molecular weight of 145 kDa with a similar glycan profile to rituximab, and is a genetically engineered chimeric

human/mouse glycosylated monoclonal antibody specific to the human antigen CD20 expressed on lymphocytes. SAIT101 consists of human IgG1 heavy and kappa light chain constant regions, and murine heavy and light chain variable regions, which is similar to rituximab.[4,5,6,7] It is produced by Chinese hamster ovary (CHO) cell suspension culture and purified by various affinity and ion exchange chromatography steps that include specific viral inactivation and removal procedures.

SAIT101 has been demonstrated to be similar to MabThera® (rituximab licensed in the European Union) and Rituxan® (rituximab licensed in the United States) in the extensive similarity studies using state-of-art techniques. Quality and in vitro characterization studies have been performed to date.

An in vitro study confirmed that SAIT101 has similar pharmacological actions to rituximab, resulting from its binding to CD20-positive antigen. In vivo efficacy studies using murine xenograft models confirmed similar profiles of tumor suppression activity for SAIT101, MabThera® and Rituxan®.
Pharmacokinetics (PK) and pharmacodynamics (PD) studies in cynomolgus monkeys have also shown similarity of PK/PD profiles between SAIT101 and rituximab. Furthermore, the single- and repeat-dose toxicity studies confirmed that SAIT101 did not show any toxicity at dose levels up to 10 times higher than the clinical dose (~10 mg/kg). The single-dose toxicity, repeat-dose toxicity, toxicokinetics and immunogenicity profiles of SAIT101 were similar to MabThera® and Rituxan®.

Clinical Data of SAIT101

The first clinical study with SAIT101 began in May 2011. S101-NKR-001 was a first-in-human Phase I study conducted in 14 centers in Korea aimed to compare and assess PK and PD profiles, and preliminary efficacy and safety of SAIT101 compared to MabThera®, after intravenous (i.v.) infusion of MabThera® or SAIT101. As of 26 September 2011, a total of 24 diffuse large B cell lymphoma patients had been randomized to receive either SAIT101 (proposed rituximab biosimilar) or MabThera® (rituximab, Roche) in combination with the chemotherapy regimen, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).

Kim et al reported that the ratio of geometric least square (GLS) mean (90% confidence interval, CI) of SAIT101 versus MabThera® were 0.92 (0.78 to 1.09) for AUC_{last} and 0.93 (0.78 to 1.13) for C_{max}. The LS means change from baseline of B-cell (%) in SATI101 and MabThera® group were -7.7% and -8.0% respectively and the difference between two groups was 0.3% (90%CI, -0.9 to 1.4). The safety and efficacy profile of SAIT101 were not significantly different from MabThera®.[9]

1.3 Comparator drug: Rituximab

Rituximab is a genetically engineered recombinant chimeric human/murine antibody directed against the CD20 antigen. Following binding of CD20, rituximab triggers a cytotoxic immune response against CD20-positive cells.

Rituximab was initially developed by IDEC Pharmaceuticals. Based on its safety and effectiveness in clinical studies, rituximab was approved under the trade name Rituxan® by the US Food and Drug Administration (FDA) in 1997 to treat B cell non-Hodgkin's lymphomas (NHL) resistant to other chemotherapy regimens. Rituximab, in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy, is now a standard therapy in the initial treatment of diffuse large B cell lymphoma and many other B cell lymphomas. It has been approved as a therapeutic agent for patients with NHL, chronic lymphocytic leukemia (CLL) and RA.[10, 11]

Rituxan® was co-developed and marketed in the US (under the brand name Rituxan®) by Biogen Idec and Genentech (now a part of Roche). It is marketed outside the US by Roche under the brand name MabThera®.

Antigen CD20 is a hydrophobic transmembrane protein with a molecular weight of approximately 35 kDa located on pre-B and mature B lymphocytes. The antigen is expressed on more than 90% of B cell NHL, but is not found on hematopoietic system cells, pro-B cells, normal plasma cells, or other normal tissues. CD20 regulates early steps in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. CD20 is not shed from the cell surface and does not internalize upon antibody binding. Free CD20 antigen is not found in the circulation.

B cells are believed to play a role in the pathogenesis of RA and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of RF and other autoantibodies, antigen presentation, T-cell activation and/or pro-inflammatory cytokine production.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC).

1.3.1 Clinical Pharmacokinetics of Rituximab

In one of the Phase IIa double blind studies conducted in RA patients to evaluate the PK of rituximab, it was found that the mean areas under the plasma concentration–time curves for rituximab were similar across treatment groups (rituximab alone, rituximab in combination with cyclophosphamide and rituximab in combination with methotrexate [MTX]). The mean terminal half-life ($t_{1/2}$) of 19 to 22 days was observed in rituximab after the second infusion. Systemic clearance of rituximab was slow at 242, 226, and 221 mL/d in all 3 treatment groups. The volume of distribution (V_D) of rituximab at steady state was low at 4.28 to 4.74 L and similar to normal plasma volume in all treatment groups. These data indicate that the PK characteristics of rituximab are not discernibly altered when it is administered in combination with either cyclophosphamide or MTX. This observation is supportive of the contention that rituximab does not require dose adjustments when administered with either cyclophosphamide or MTX.[12]

1.3.2 Clinical Data of Rituximab

In one of the recent (2006) RA studies conducted in 520 patients to determine the efficacy and safety of rituximab along with MTX in patients with active RA who had an inadequate response to anti-tumor necrosis factor (anti-TNF) therapies, it was found that patients who received two 1,000 mg infusions of rituximab the Disease Activity Score (DAS) improved -1.9 when compared with MTX alone (-0.4%; $p < 0.0001$) and met the American College of Rheumatology (ACR) 20% improvement criteria (achieved an ACR20 response) at Week 24, 51% when compared with placebo (18%; $p < 0.0001$).[13, 14]

In another long-term safety study (2010), it was observed that rituximab was well tolerated over time and multiple courses. Overall, the findings indicated that there was no evidence of an increased safety risk or increased reporting rates of any types of AEs with prolonged exposure to rituximab.[15]

2 STUDY RATIONALE AND OBJECTIVES

2.1 Study Rationale

SAIT101, as a proposed biosimilar of rituximab in pharmaceutical form, strength and administration route, is expected to play an important role in the treatment of RA. The substitution of rituximab by SAIT101 is expected to provide similar efficacy, PK, PD, safety, tolerability, and immunogenicity in patients with RA. The dose selected for this study is based on the clinically effective dose of rituximab.

This study is to evaluate similarity in terms of PK, PD, safety, efficacy, tolerability, and immunogenicity between SAIT101 and rituximab and also to provide a benefit and risk profile of SAIT101.

This study will be conducted in compliance with the protocol, the International Council for Harmonization (ICH) guidelines, Good Clinical Practice (GCP) and with all applicable and current regulatory requirements.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of the study is to compare the PK of SAIT101 versus rituximab licensed in the European Union (hereafter designated MabThera®, brand name in EU) versus rituximab licensed in the United States (hereafter designated Rituxan®, brand name in US) in patients with RA.

2.2.2 Secondary Objectives

The secondary objectives of the study are to compare the safety, additional PK, PD, efficacy, tolerability, and immunogenicity of SAIT101 versus MabThera® versus Rituxan® in patients with RA.

2.3 Study Endpoints

2.3.1 Pharmacokinetics

Primary PK Endpoints

- Area under the concentration-time curve from time 0 (immediately predose on Day 1) to last quantifiable concentration (AUC_{0-t})
- AUC from time 0 (immediately predose on Day 1) to infinity ($AUC_{0-\infty}$)

- AUC from time 0 (immediately predose on Day 1) to Day 15 prior to infusion ($AUC_{0\text{-}d15}$)
- Maximum concentration (C_{max}) after the second infusion on Day 15
- Trough concentration (C_{trough}) before the second infusion on Day 15

Secondary PK Endpoints

- AUC from Week 2 to Week 24 ($AUC_{w2\text{-}w24}$)
- AUC from time 0 (immediately predose on Day 1) to Week 12 ($AUC_{0\text{-}w12}$)
- Time of maximum concentration (T_{max}) post infusion on Day 15
- Systemic clearance (CL)
- Volume of distribution (V_D)
- Terminal half-life ($t_{½}$)

2.3.2 Efficacy

Main Efficacy Endpoints

- Change from Baseline in DAS28 at Week 24

Other Efficacy Endpoints

- Change from Baseline in DAS28 at Weeks 8, 16, 36, and 52
- ACR20 response rates at Weeks 8, 16, 24, 36, and 52
- ACR50 response rates and ACR70 response rates at Weeks 8, 16, 24, 36, and 52
- Individual components of the ACR improvement criteria on Day 1 and at Weeks 8, 16, 24, 36, and 52
  - Swollen and tender joint count (the 66/68 joint count system)
  - Patient's assessment of pain (assessed on 1 to 100 mm Visual Analogue Scale [VAS])
  - Physician's global assessment of disease activity (assessed on 1 to 100 mm VAS)

  - Patient's global assessment of disease activity (assessed on 1 to 100 mm VAS)
  - Patient's assessment of disability (Health Assessment Questionnaire-Disability Index [HAQ-DI])
  - CRP level

- Change from Baseline DAS28-CRP at Weeks 8, 16, 24, 36, and 52
- Major clinical response (continuous ACR70 for at least 24 weeks)
- Clinical remission (defined by SDAI < 3.3) at Weeks 8, 16, 24, 36, and 52
- Proportion of patients with European League Against Rheumatism (EULAR) response (good response, moderate response or no response) at Weeks 8, 16, 24, 36, and 52

2.3.3 Pharmacodynamics

- Depletion of CD19+ B cell count at Week 24
- Time needed to B cell depletion
- Duration of CD19+ B cell depletion
- % CD19+ B-cell count vs. baseline at Week 24
- AUC of CD19+ B-cell count change at Week 24
- Change from Baseline in CD19+ B cell count during the study period
- Change from Baseline in IgG, IgM, and IgA levels at Weeks 24 and 52
- Change from Baseline in CRP levels at Weeks 8, 16, 24, 36, and 52

2.3.4 Immunogenicity

- Incidence of HACA and neutralizing antibody at Day 1 predose and at Week 1, 2, 4, 12, 16, 24, 36, and 52

2.3.5 Safety

- SAEs, AEs, ADRs
- Vital signs

- Clinical laboratory parameters including hematology, chemistry and urinalysis
- Physical findings
- Concomitant medication, incidence of rescue medication, where rescue medication is defined as the use of non biologic DMARDs after Week 16 of the study
- B cell recovery measured by a CD19+ B cell count after Week 24

3 STUDY DESIGN

3.1 Summary of Study Design

This is a multicenter, randomized, double-blind, parallel group study to compare the PK, PD, safety, efficacy, tolerability, and immunogenicity of SAIT101 versus MabThera® versus Rituxan® in patients with RA. This study will take place globally across approximately 70 study centers in order to randomize approximately 282 patients. The study consists of Part A from baseline for PK and efficacy analysis, followed by Part B from Week 24 to 52 for safety follow-up that also collects transition data.

Patients with RA who have had an inadequate response to at least 3 months' treatment (according to the approved treatment and dosage) or intolerance (at Investigator's discretion and/or experience of severe adverse event [AE] or toxicity such as infusion related reaction, hypersensitivity, anaphylaxis or severe toxicity) to anti-TNF therapy. All the Screening assessments should be performed within 30 days prior to randomization on Day 1 (Visit 2, Baseline), except in patients who require prophylaxis of latent tuberculosis or a washout of current anti-TNF medication or other biologic and non-biologic DMARD treatment except MTX. For these patients the Screening period may be extended to allow for the washout required, but will not exceed 60 days. In these patients all Screening assessments must be performed within 30 days prior to randomization with the exception of the informed consent and chest X-ray (see Section 3.2.5).

In Part A, patients will be randomized in a 1:1:1 ratio to receive one course of SAIT101 (n=94) versus Rituxan® (n=94) versus MabThera® (n=94).

At Week 24, patients will be evaluated for a second course of the infusion.

In Part B, eligible patients in the SAIT101 arm will receive the second course of SAIT101 treatment at Weeks 24 and 26. Eligible patients in the MabThera® arm will receive the second course of MabThera® treatment at Week 24 and 26. Eligible patients in the Rituxan® arm will be randomized in a 1:1 ratio to receive SAIT101 or Rituxan® treatment at Weeks 24 and 26. Patients will be followed up for safety till Week 52.

For each course of infusion, patients will receive two infusions of 1,000 mg (10 mg/mL) SAIT101 or Rituxan® or MabThera® for i.v. infusion for the treatment.

Patients will continue to take their usual prescribed concomitant medications as allowed by the protocol. It is mandatory that doses of all RA medications (MTX, steroids and non-steroidal anti-inflammatory drugs [NSAID]) taken during the first 24-week period must

remain stable (see Section 3.2.5). Patients will also receive an anti-pyretic and an anti-histamine, e.g., paracetamol and diphenhydramine or equivalent, 30 to 60 minutes before each infusion, plus 100 mg i.v. methylprednisone (or its equivalent) at least 30 minutes prior to each infusion.

The study design for individual patients is schematically detailed in Figure 1.

At each visit, blood PK and PD samples should be taken at the same time of day as the start of the first infusion, within a window of ± 10 minutes of the determined time points of Days 1, 3, 8, 15, 17 and ± 3 hours at all other time points. All patients will be followed up for safety up to 52 weeks from the start date of the first infusion.

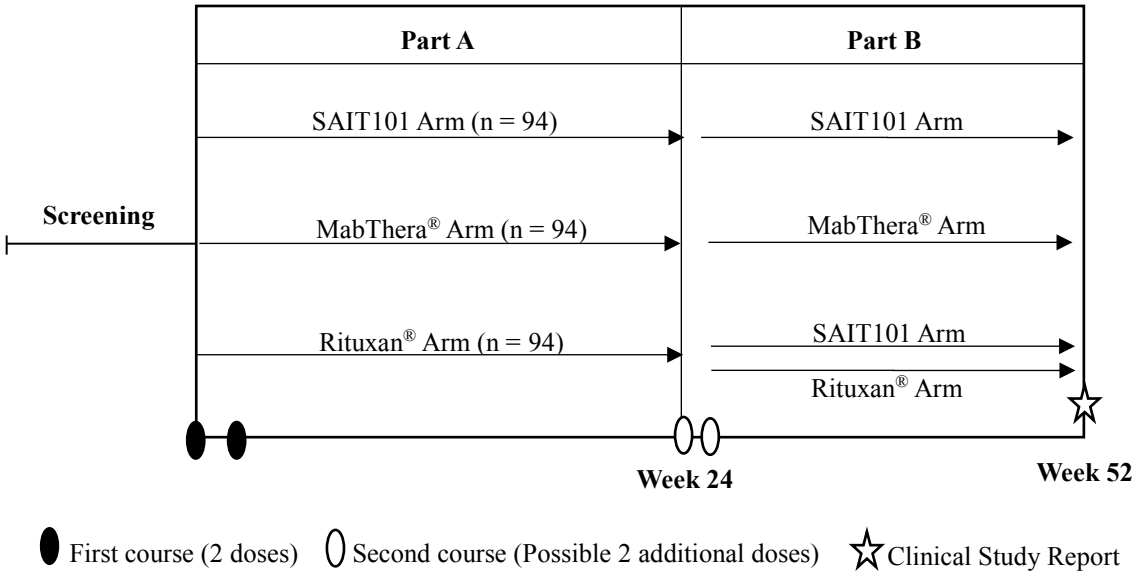

Figure 1 Study Design

Standard arthritis assessments and safety assessments will be performed. A disease activity score based on a 28 joint count (DAS28) will be calculated by the study personnel at regularly scheduled visits. At least one experienced, independent joint assessor, blinded to other study assessments as well as the dosing regimen, will be identified at each study center to perform the swollen and tender joint counts.

A provision is made for patients to initiate "rescue therapy" with the use of one non-biologic DMARD after Week 16 of the study (see Section 3.2.6).

Patients with rheumatoid arthritis (<50% improvement from Baseline in both the swollen and tender joint counts) who have been followed up during Part A will be provided with

additional treatment of study drug with two 1,000 mg i.v. infusions (at Week 24 and Week 26 [14 days later]). Patients will attend the study center approximately every 12 weeks during Part B. Patient who are not eligible for the second course of study treatment will also attend all visits until week 52.

Patients may return for unscheduled visits if their medical condition requires immediate attention.

To prevent missing data in important supportive efficacy and safety analysis, patients who discontinued study treatment, will also attend all visits until week 52.

The primary safety concerns associated with rituximab are progressive multifocal leukoencephalopathy (PML), anaphylactic reactions, hepatitis reactivation, and severe mucocutaneous reactions. Patients will be monitored carefully for these during the study.

Any patient who is suspected of developing PML, anaphylactic reactions, hepatitis reactivation, and severe mucocutaneous reactions will be discontinued from the study treatment and the AE will be followed closely, at the discretion of the Investigator.

3.2 Treatments

3.2.1 Test Product and Comparator, Dose and Mode of Administration

SAIT101 is a sterile, clear to opalescent and colorless or a pale yellow, preservative-free solution for i.v. infusion. The formulation of SAIT101 is similar to MabThera® or Rituxan®.

Each patient will be randomized on Day 1 to receive one of three possible treatments (study drug):

- SAIT101: 1,000 mg (10 mg/mL)-Test product;
- Rituxan®: 1,000 mg (10 mg/mL)-Comparator;
- MabThera®: 1,000 mg (10 mg/mL)-Comparator.

All patients received premedication with 100 mg i.v. methylprednisolone (or its equivalent), an antipyretic and an antihistaminic (e.g. acetaminophen and diphenhydramine) per the accepted infusion protocols for rituximab prior to study drug infusions to decrease incidence rate and severity of acute infusion-related reactions.

Since hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the infusion.

The Day 1 infusion rate (both week 0 and week 24) of SAIT101 or MabThera® or Rituxan® will start at 50 mg/hour; after the first 30 minutes, it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. If there has been no infusion related reaction on Day 1, the Day 15 infusion (both first and second courses) can be infused at 100 mg/hour and increased by 100 mg/hour increments at 30 minute intervals, to a maximum of 400 mg/hour.

The recommended infusion rates are presented in Table 1.

Table 1 Recommended Infusion Rates

Day 1 infusion	Total dose (mg)	Time (minutes)***	Day 15 infusion	Total dose (mg)	Time (minutes)***
50 mg/h	25	0-30	100 mg/h	50	0-30
100 mg/h	50	31-60	200 mg/h	100	31-60
150 mg/h	75	61-90	300 mg/h	150	61-90
200 mg/h	100	91-120	400 mg/h	700	91-196**
250 mg/h	125	121-150	-	-	-
300 mg/h	150	151-180	-	-	-
350 mg/h	175	181-210	-	-	-
400 mg/h	200	211-240	-	-	-
400 mg/h	100	241-255*			

* Approximately at 255 minutes (4 hours 15 minutes) to complete the 1,000 mg total dose.

** Approximately at 196 minutes (3 hours 16 minutes) to complete the 1,000 mg total dose.

***Allowed window for infusion rate time: For each time point: ± 5 minutes (e.g. when start 50 mg/h for first course: 25~35 minutes can be allowed).

In the event that a patient experiences an infusion-related reaction or an adverse drug reaction (ADR), the infusion rate should be reduced to half the rate (e.g., from 100 mg/hour to 50 mg/hour). Once the infusion-related reaction or ADR has resolved, the Investigator should wait an additional 30 minutes while delivering the infusion at the reduced rate. If tolerated, the rate may be increased to the next closest rate on the patient's infusion schedule. Please refer to the following examples:

(Example 1) An infusion-related reaction or an ADR at a rate of 50 mg/h → change rate to 25 mg/h → reaction resolved → additional 30 minutes at a rate of 25 mg/h → change back to 50 mg/h.

(Example 2) An infusion-related reaction or an ADR at a rate of 300 mg/h → change rate to 150 mg/h → reaction resolved → additional 30 minutes at a rate of 150 mg/h → change back to 200 mg/h.

Drug infusions will take place under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available. Although the study drug may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the Investigator, and such instances of planned hospitalization will NOT be recorded as a serious adverse event (SAE).

Any drugs that are used to manage hypersensitivity reactions or ADRs, including but not limited to epinephrine, antihistamine, and corticosteroid, should be immediately available in case of emergency.

Attention should be given to the development of anaphylaxis during infusion of the study drug. When an anaphylactic reaction is suspected during infusion of the study drug:

- Discontinue the study drug.
- Apply a tourniquet close to the infusion site in order to slow systemic absorption of the study drug. Do not block artery flow.
- Perform appropriate airway management.
- If required, administer antihistamine, epinephrine, or other drugs.
- Closely monitor the patient and document the observations.

Patients who experience a moderate to severe infusion-related reaction (fever, chills or hypotension), should have their infusion interrupted immediately and should receive aggressive symptomatic treatment, such as glucocorticoids, epinephrine, bronchodilators or oxygen, as per local practice. Depending on the severity of the infusion reaction and the required interventions, patients should either have their infusion temporarily interrupted or be discontinued from the study treatment. The infusion should not be restarted before all the symptoms have disappeared, and then it should be restarted at half the rate. If the patient tolerates the reduced rate for 30 minutes then the infusion rate may be increased to the next closest rate on the patient's infusion schedule. If the subject does not tolerate the reduced rate for at least 30 minutes or, if the same severe (NCI-CTCAE Grade 3) infusion reaction occurs for a second time, the patient can be discontinued from the study treatment.

At the end of each infusion, the i.v. line is recommended to remain in place for at least 1 hour to allow infusion of i.v. drugs if necessary. If no AE occurs during this time, the i.v. line may be removed.

3.2.2 Study Drug Administration (Part A)

First Infusion (Day 1 of First Course)

The first infusion rate of SAIT101 or MabThera® or Rituxan® will be 50 mg/hour; after the first 30 minutes, it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour (see Table 1).

Second Infusion (Day 15 of First Course)

Patients who experienced infusion-related reactions to the first infusion should receive study drug as per the initial infusion schedule, with the rate of infusion not exceeding half that associated with the prior reactions. If this reduced rate is tolerated for 30 minutes, then the infusion rate may be increased to the next closest rate following the infusion schedule.

Patients who miss the allocated day (Day 15 ± 1 day) for the second infusion (the first infusion will be administered following randomization on Day 1) will be contacted and another visit arranged as soon as practically possible in order to administer study drug. Such cases will be considered protocol deviations (see Section 3.13).

If a patient experiences a new infection or other AE between the Day 1 and Day 15 infusions of any treatment, the Day 15 infusion should be delayed until the infection or AE has completely resolved and the Investigator considers it safe to resume treatment. A maximum delay of 15 days from the scheduled date of the second infusion is permitted. Patients who have a delay of >15 days in receiving the second infusion due to an AE or otherwise will be discontinued from the study treatment.

3.2.3 Study Drug Administration (Part B)

Patients with active rheumatoid arthritis (<50% improvement from Baseline in both the swollen and tender joint counts) who have been followed up during Part A will be provided with continued (or additional) treatment of rituximab.

Before subsequent dose, absolute neutrophil count must be $\geq 1.5 \times 10^9$/L and platelet counts must be $\geq 75 \times 10^9$/L. If the Absolute Neutrophil Count (ANC) value and platelet count are marginally lower, re-testing at an unscheduled visit may be performed at the discretion of the Investigator within the 4-week period between Week 20 and Week 24. In case Visit 11 is missed, all safety evaluations including ANC value and platelet count must be completed as an unscheduled visit for patient to be eligible for second course of infusion.

Eligible patients in the SAIT101 arm will receive additional SAIT101 treatment at Week 24 and Week 26. Eligible patients in the MabThera® arm will receive additional MabThera® treatment at Week 24 and Week 26. Eligible patients in the Rituxan® arm will be randomized in a 1:1 ratio to receive SAIT101 or Rituxan® treatment at Week 24 and Week 26.

Patients who develop an infusion reaction during the second course of treatment should be managed as described in Section 3.2.1.

Patient who are not eligible for the second course of study drug will also attend all visits after Week 24.

3.2.4 Dosage Modification

Dose modification of rituximab is not permitted during this study. In the event of an infusion-related reaction, the rate of infusion may be adjusted (see Section 3.2.1). Patients who experience a life-threatening event, as considered by the Investigator, during an infusion of study drug should have their infusion stopped and no further infusions should be administered.

3.2.5 Allowed Concomitant Medication

It is mandatory that all doses of all RA medications (MTX, steroids and NSAIDs) taken during the first 24-week period (Part A) must remain stable.

Patients will continue to take their usual prescribed concomitant medications as allowed by the protocol, including MTX (7.5 to 25 mg/week) and folic or folinic acid, from their usual source, according to local standards and availability.

All patients should also continue to receive if there is any background oral corticosteroids (≤10 mg/day prednisone or equivalent) or NSAIDs. During the 4 weeks (for oral corticosteroids) or 3 weeks (for NSAIDs) prior to Day 1, the doses must remain stable.

If clinically required for safety reasons, modifications to doses of MTX, corticosteroids and NSAIDs will be allowed. The Investigator must use the procedures outlined below in making modifications to these medications and document all changes and the reason for the changes should be documented in the patient's electronic case report form (eCRF).

Methotrexate: Dose of MTX should remain stable throughout the study. Reductions for MTX dose or a change of route of administration may be performed after visit at Week 24 for safety reasons only.

Lower doses of MTX (<10 mg/week) are only permitted if patients have a documented evidence of intolerance to higher doses of MTX.

If dose reduction is a result of intolerance, such intolerance must be recorded as an AE and the dose modification recorded in the eCRF.

Oral corticosteroids: If receiving current treatment with oral corticosteroids (other than intra-articular or parenteral corticosteroids), the dose must not exceed 10 mg/day prednisone or equivalent. The dose should remain stable from 4 weeks prior to randomization throughout the study. From Visit 12 at Week 24, reductions in these treatments will be allowed only for safety reasons. Increases in corticosteroids for treatment of RA are not allowed over the study period and should be avoided. To treat non-RA conditions, increased doses of oral corticosteroids, up to 40 mg of prednisone daily (or

equivalent), for 2 weeks or less will be permitted. The corticosteroid dose should be tapered down to the previous level as rapidly as medically possible.

NSAIDs: Patients may be treated with NSAIDs, up to the maximum recommended dose, (including cyclooxygenase-2 inhibitors) throughout the study. The choice and doses of NSAIDs used to treat patients are at the discretion of the Investigator. Patients on NSAIDs at Screening should continue at a stable dose from 3 weeks prior to randomization throughout the study. The dose and type of NSAID may be changed after Visit 12 at Week 24 of the study. Aspirin may be taken to reduce cardiovascular risk, but should not exceed 350 mg/day. NSAIDs or other analgesics for treatment of conditions other than RA may be used for short periods not exceeding 7 days.

3.2.6 Rescue Therapy

From Week 16, patients who have less than a 20% improvement in both tender and swollen joint counts compared to Baseline (<ACR20) may receive "rescue" treatment with one non-biologic DMARD. The patient will be discontinued from the study treatment and the choice of DMARD is at the discretion of the Investigator, but could be hydroxychloroquine or sulfasalazine. Patients receiving "rescue" medication attend all visits until week 52.

The following medications are not permitted for use as "rescue" treatment: azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine or any biologic agent. Any patient requiring medication mentioned above, should be discontinued from study treatment but will attend all visits until week 52.

3.2.7 Management of Hepatitis Reactivation and Other Infections During Rituximab Therapy

Patients with HBV DNA >20 IU/ml are ineligible as per exclusion criteria. Patients who show evidence of prior hepatitis B infection may participate in the study following consultation with a hepatitis expert regarding monitoring and use of HBV antiviral therapy, and provided that they agree to undergo monthly PCR HBV DNA testing during treatment and to receive treatment as indicated. During the study, a HBV re-test will be performed monthly including Day 1, Weeks 4, 8, 12, 16, 20, 24, 36, 52, or unscheduled visit if required.

Patients will receive HBV antiviral prophylaxis therapy and be monitored as recommended by hepatitis experts. HBV reactivation has been reported up to 24 months following completion of rituximab therapy. If a patient develops reactivation of HBV or any other significant infections while on rituximab, the Investigator should immediately discontinue study drug, consult with hepatitis experts, and institute appropriate treatment. For details and management of other infections, refer to the current marketed rituximab prescribing information.[6, 7]

3.3 Study Population

Patients with RA who have had an inadequate response (at least 3 months' treatment according to the approved treatment and dosage of each TNF inhibitor) or intolerance (at Investigator's discretion and/or experience of intolerable AE such as infusion related reaction, hypersensitivity, anaphylaxis or severe toxicity) to one or more anti-TNF therapies.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Patients must have the ability and willingness to provide written informed consent, prior to any study-specific procedures, and to comply with the requirements of the protocol.

3.4.2 Inclusion Criteria

Patients are required to meet the following inclusion criteria:

1 Male or female outpatient, between 18 and 80 years of age at Screening.

2. Severe RA defined as:
   - Diagnosis of RA according to the revised (1987) ACR criteria for the classification of RA for at least 3 months prior to screening visit (see Appendix 3).
   - And ≥6 swollen joints and ≥6 tender/painful joints (from the 66/68 joint count system).
   - And C-reactive protein (CRP) ≥1.0 mg/dL or an ESR ≥28 mm/hour at Screening.
   - And positive RF (≥20 units/mL) or anti-CCP antibodies (≥10 units/mL) at Screening.

3. Patients with severe RA who have had an inadequate response to at least 3 months' treatment (according to the approved treatment and dosage) or intolerance (at Investigator's discretion and/or experience of intolerable AE or toxicity such as infusion related reaction, hypersensitivity, anaphylaxis or severe toxicity) to anti-TNF therapy (experience of severe AE or toxicity).

4. Current treatment for RA on an outpatient basis:
   - Receiving MTX 7.5 - 25mg/week (oral or parenteral) for at least 12 weeks, including the last 4 weeks prior to Day 1 at a stable dose, via the same route of administration, dose, and formulation. Patients receiving a lower dose of MTX (<10 mg/week), stable for 4 weeks prior to Day 1, should be doing so as a result of a documented evidence of intolerance to higher doses of MTX.
   - Leflunomide must be withdrawn at least 12 weeks prior to Day 1 or a minimum of 4 weeks prior to Day 1 if after 11 days of standard cholestyramine washout.
   - All DMARDs different from MTX and leflunomide must be withdrawn at least 4 ~ 8 weeks as described in Table 4 prior to Day 1.
   - If receiving current treatment with oral corticosteroids, the dose must not exceed 10 mg/day prednisone or equivalent. During the 4 weeks prior to Day 1 the dose must be stable.
   - The most recent IM/intra-articular steroid injection should be ≥6 weeks prior to Day 1.
   - If receiving current treatment with NSAIDs at the time of Screening, the patient must remain on a stable dose for at least 3 weeks prior to Day 1.
   - Patients are willing to receive oral folic or folinic acid or equivalent during the entire study (mandatory co-medication for MTX treatment), according to local standards and availability.

5 Men and women of childbearing potential must use highly effective methods of contraception during the course of the treatment period and for at least 12 months after the last infusion of study drug. A man or women is of childbearing potential if, in the opinion of the investigator, he or she is biologically capable of having children and is sexually active. Examples of highly effective contraception include:
   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
     - oral
     - intravaginal
     - transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation 1:
     - oral
     - injectable
     - implantable [2]
   - intrauterine device (IUD) [2]
   - intrauterine hormone-releasing system (IUS) [2]
   - bilateral tubal occlusion [2]
   - vasectomised partner [2,3]
   - sexual abstinence [4]

   [1] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraception method.

   [2] Contraception methods that in the context of this guidance are considered to have low user dependency.

   [3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the study participant and that the vasectomised partner has received medical assessment of the surgical success.

   [4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the

	study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
6	Female patients of childbearing potential must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at each applicable visit thereafter. Females will be considered to be of non-childbearing potential if they fulfill one of the following criteria at Screening: • Postmenopausal defined as amenorrheic for at least 12 months following cessation of all exogenous treatments • Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

3.4.3 Exclusion Criteria

Patients will be excluded if they meet any of the following exclusion criteria:

1	Females who are pregnant, breastfeeding, or planning a pregnancy during the Treatment Period of and 12 months after the last infusion of study drug.
2	Class IV as per the Classification of Global Functional Status in Rheumatoid Arthritis (as per ACR 1991 Revised Criteria) (see Appendix 4) or wheelchair/bed-bound.
3	History of or current inflammatory joint disease other than RA (including but not limited to gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy or Lyme disease).
4	History of or current systemic autoimmune disorder (including but not limited to systemic lupus erythematosus, inflammatory bowel disease, pulmonary fibrosis, Felty syndrome, scleroderma, inflammatory myopathy, fibromyalgia, juvenile idiopathic arthritis, mixed connective tissue disease, vasculitis or other overlap syndrome), with the exception of the secondary Sjögren's syndrome.
5	Primary or secondary immunodeficiency (history of, or currently active), including known history of human immunodeficiency virus (HIV) infection or positive test at screening.
6	History of opportunistic infection.
7	History of deep space/tissue infection (e.g., fasciitis, abscess, osteomyelitis) and infected prosthetic joint.
8	Active infection of any kind (excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with i.v. anti-infective agents within 4 weeks prior to Screening or oral anti-infective agents within 2 weeks prior to Screening or use of antibiotic therapy three or more times in the last six months prior to Screening
9	Positive serological test for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C serology. • Patients with a negative HBsAg and positive HBcAb must have a hepatitis B virus (HBV) deoxyribonucleic acid (DNA) level <20 IU/mL (or 112 copies/mL) by polymerase chain reaction (PCR). These HBV patients must be willing to undergo monthly PCR HBV DNA testing during treatment and may participate following consultation with a hepatitis expert regarding monitoring and use of HBV antiviral therapy, and provided they agree to receive treatment as indicated. An HBV re-test will be performed monthly including Day 1, Weeks 4, 8, 12, 16, 20, 24, 36, 52, and unscheduled visit if required. • Patients with a positive test because of HBV vaccine may be included (i.e., anti-HBs+ and anti HBc–). • Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV ribonucleic acid (RNA).
10	Confirmed current active tuberculosis (TB). • Patients with latent TB as determined by positive QuantiFERON-TB test may be enrolled if such patients have written confirmation from health care provider (e.g., Pulmonologist or Infection

Specialist) of adequate prophylaxis before or within the screening period and no evidence of tuberculosis on a chest X-ray performed within 3 months from Day 1.

- Screening period can be extended to 60 days for prophylaxis of latent TB.
- QuantiFERON-TB test can be re-tested, if inconclusive.

11 Any significant cardiac disease (e.g., coronary artery disease with unstable angina, coronary heart failure New York Heart Association Class III and IV, familial long QT syndrome, uncontrolled cardiac disease).

12 History of moderate to severe chronic obstructive pulmonary disease (COPD) and/or history of severe COPD exacerbation(s) within the last 12 months of Screening.

13 Vaccination with live or attenuated vaccines within 6 weeks prior to first dose of study drug or planned administration during study participation or within 4 weeks following last dose of study drug. Treatment with IV Gamma Globulin or the Prosorba® Column within 6 months prior to Day 1.

14 History of a severe allergic reaction or anaphylactic reaction to a biological agent or history of hypersensitivity to any component of the study drug including known hypersensitivity or allergy to a murine product.

15 Hypogammaglobulinemia at screening (IgG <600 mg/dL).

16 Patients with hemoglobin <8.5 g/dL, ANC <1,500 cells/µL or platelet count <75,000 cells/µL at Screening. If a patient has findings marginally below this limit, re-testing is allowed, at the Investigator's discretion, within the 30 day period between Visit 1 and Visit 2.

17
- Creatinine clearance < 50 mL/min (Cockroft-Gault formula)
- Liver function: Total bilirubin >2.0 mg/dL (>34 µmol/L) except for patients with Gilbert's Syndrome or hemolysis. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >3 × upper limit of normal (ULN). Patients with total bilirubin >2.0 mg/dL possibly due to Gilbert's Syndrome should have a direct bilirubin checked. If the direct bilirubin is normal and medical history is suggestive/positive for Gilbert's Syndrome, the patient successfully meets the criteria.

The AST and ALT may be repeated once within the Screening period if the initial result exceeds this limit, and the lesser value accepted if it meets this criterion.

18 History of cancer within the last 5 years prior to Screening, treated with anti-cancer chemotherapy, including solid tumors and hematologic malignancies and carcinoma in situ (except basal cell and squamous cell carcinomas of the skin or carcinoma in situ of the cervix uteri that have been excised and cured).

19 Major surgical procedure within 4 weeks prior to or planned within 24 weeks of Day 1, with the exception of surgical procedures for dental prosthesis.

20 Previous treatment with a B cell modulating or B cell depletion therapy, such as, but not limited to rituximab, belimumab, atacicept, tabalumab, ocrelizumab, ofatumumab, obinutuzumab, epratuzumab and other experimental treatments.

21 Injectable corticosteroids within 6 weeks prior to Day 1.

22 Participation in a previous clinical study within 4 weeks of Screening or having received treatment with a drug that has not received regulatory approval for any indication within a minimum of 5 half-lives prior to Day 1.

23 Patients who, based on the Investigator's judgment, have a clinically significant or unstable medical or surgical condition that may preclude safe and complete study participation. Conditions may also include cardiovascular, vascular, pulmonary, hepatic, renal, endocrine or neurological conditions as determined by medical history, physical examination, laboratory tests or electrocardiogram (ECG).

24 Patients who, in the judgment of the Investigator, are likely to be non-compliant or uncooperative during the study.

25 History of substance abuse (alcohol or drug).

26	History of demyelinating disorders (such as multiple sclerosis or Guillain-Barré syndrome).
27	Patients at risk of PML: • Patients with immune deficiency such as transplant patients on immunosuppressive medications • Patients receiving certain kinds of chemotherapy • Patients receiving natalizumab (Tysabri®) for multiple sclerosis • Patients with psoriasis on longer term efalizumab (Raptiva®) or patients with acquired immunodeficiency syndrome (AIDS)

3.4.4 Patient Withdrawal

All patients are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. If the withdrawn patients meet the PK data set, then those patients can be included in the PK analysis.

Patients will be withdrawn from the study in the following circumstances:

- The patient withdraws consent to contribute additional outcome information or is lost to follow-up despite reasonable efforts to make contact with the patient

Adverse events will be followed up as detailed in Section 5.10. Investigators are encouraged to discuss the patient's case with the Sponsor physician or representative to agree upon appropriate action.

3.5 Measures to Minimize/Avoid Bias

The treatment groups will be blinded to minimize any bias that could be introduced by knowledge of the treatment by either Investigator or patient, which is especially important given that many of the efficacy and safety measures are subjective. Potential bias will be further minimized by identifying at least one experienced, blinded, joint assessor at each study center who will be independent of the rest of the study team. This person will perform the swollen and tender joint counts without access to any other study-related outcomes. The parallel group design takes into account the progressive nature of RA.

3.5.1 Blinding

This will be a double-blind study. Patients, Investigators, the joint assessor and other site personnel will remain blinded throughout the entire Study Period except for the study pharmacist or designee. The study will be unblinded at week 24 to facilitate the primary analysis although investigators and patients remain blinded to treatment assignment during the post week 24 follow-up period.

The interactive voice / web response system (IXRS) will be used to manage randomization to treatment groups in a blinded manner. This includes maintaining the blind for those patients who are eligible to receive a further course of study drug.

To ensure blinding of the treatments, the SAIT101, Rituxan® and MabThera® should only be managed by the pharmacist or designee from the time of reception till the time the prepared infusion is dispensed to the blind study team.

The SAIT101, Rituxan® and MabThera® solutions will be provided in a blinded manner to the blinded Investigator's team. Patients will receive the i.v. drug infusions in the same manner regardless of the treatment group they are randomized to. All details will be provided in the Pharmacy Manual.

3.5.2 Randomization

Patients will be assigned a unique patient number at Screening. The patient number will be used to register the patient using the IXRS and the patient will then be randomized (in a 1:1:1 ratio) to either SAIT101, Rituxan® or MabThera®.

Eligible patients in the SAIT101 arm will receive the second course of SAIT101 treatment at Weeks 24 and 26. Eligible patients in the MabThera® arm will receive the second course of MabThera® treatment at Weeks 24 and 26. Eligible patients in the Rituxan® arm will be randomized in a 1:1 ratio to receive SAIT101 or Rituxan® treatment at Weeks 24 and 26.

This randomization will occur according to a computer-generated randomization scheme. This will randomize patients at study level. If patients are withdrawn the patient number will not be re-used.

At the time of study drug infusion the Investigator or designee will contact the IXRS and a Medication ID will be provided. These codes will indicate which vials should be allocated to the patient. Further details on using the IXRS system are presented in the IXRS manual.

3.5.3 Unblinding Procedure

The IXRS will be used to break the blind and details on how to do this are provided in the IXRS manual. Investigators are strongly discouraged from requesting that the blind be broken for an individual patient, unless there is a patient safety issue that requires unblinding and would change patient management. If the blind is broken, it may be broken only for the patient in question and the patient must be discontinued from the study treatment. If time permits, before requesting that the blind be broken for an individual patient, the Investigator should discuss the situation with the Sponsor or designee via phone or e-mail. The Sponsor or designee must be notified immediately if a patient and/or Investigator is unblinded during the course of the study along with the reason for breaking

the blind. Pertinent information regarding the circumstances of unblinding of a patient's treatment code must be documented in the patient's source documents and IXRS. This includes who performed the unblinding, the patient(s) affected, the reason for the unblinding, the date of the unblinding and the relevant study drug information. The Investigator should ensure that the appropriate measurements are taken at the study center to maintain the blinding of the study.

3.5.4 Unblinding for Interim Analysis

An interim analysis of 10 patients per arm (30 patients in total) of safety data collected up to Week 4 and 20 patients per arm (60 patients in total) of safety data collected up to Week 12 are planned. Safety data will be handled by unblinded study team in CRO for interim analysis (see Section 6.9). The study will be unblinded at Week 24 and an interim CSR will be prepared based on the 24-week data of all patients. The investigators and patients will remain blinded to treatment assignment during the post Week 24 follow-up period.

For review purposes, the DSMB members will be unblinded to treatment assignment (see Section 3.6.7).

3.6 Study Procedures

A schedule of assessments is provided in Table 2.

Table 2 Schedule of Assessments

	Screening[a]	Part A										Part B			EOS[k]	Un-Scheduled[k]
Week		**Baseline[b]**	**0**	**1**	**2**	**2**	**4**	**8**	**12**	**16**	**20**	**24[j]**	**26**	**36**	**52**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Day (± window in days)	**-30 (within -60)[a]**	**1**	**3**	**8**	**15 ±1**	**17 ±1**	**29 ±3**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**183 ±3**	**253 ±7**	**365 ±7**	
Assessments																
Informed consent	**X**															
Inclusion/exclusion criteria	**X**	**X[c]**														
Demography	**X**															
Medical/surgical history	**X**															
Physical examination[d]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Neurological examination[e]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vital signs[f]	**X**	**X**			**X**							**X**	**X**		**X**	**X**
Chest X-ray[g]	**X**															**X[s]**
Resting 12-ECG[h]	**X**														**X**	**X**
AEs/Serious AEs/ADRs		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Prior/concomitant medication	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Urine or serum pregnancy test[i]	**X**	**X**			**X**							**X**	**X**		**X**	**X**
Study drug																
Contact IXRS	**X**	**X**			**X**							**X[l]**	**X[l]**		**X**	
Randomization		**X**										**X**				
Drug infusion[m]		**X**			**X**							**X**	**X**			

	Screening[a]	Part A										Part B			EOS[k]	Un-Scheduled[k]
Week		**Baseline[b]**	**0**	**1**	**2**	**2**	**4**	**8**	**12**	**16**	**20**	**24[j]**	**26**	**36**	**52**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Day (± window in days)	**-30 (within -60)[a]**	**1**	**3**	**8**	**15 ±1**	**17 ±1**	**29 ±3**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**183 ±3**	**253 ±7**	**365 ±7**	
Efficacy assessments																
HAQ-DI, including Patient's pain VAS[n]		**X**						**X**		**X**		**X**		**X**	**X**	
Patient Global Assessment VAS[n]		**X**						**X**		**X**		**X**		**X**	**X**	
Physician Global Assessment VAS		**X**						**X**		**X**		**X**		**X**	**X**	
Swollen and tender joint counts[o]		**X**						**X**		**X**		**X**		**X**	**X**	
Laboratory assessments																
Virology screening[p]	**X**	**X**					**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**
QuantiFERON®-TB Gold[q]	**X**															**X**
IgG, IgM, IgA	**X**[r]							**X**		**X**		**X**		**X**	**X**	
CRP / ESR	**X**	**X**						**X**		**X**		**X**		**X**	**X**	
RF	**X**															**X**
Clinical chemistry, hematology and urinalysis	**X**	**X**			**X**		**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**
PK sampling[s]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**				**X**
PD (CD19+ B-cell) sampling[s]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**
Immunogenicity sampling[t]		**X**		**X**	**X**		**X**		**X**	**X**		**X**		**X**	**X**	

ADR: Adverse drug reaction; AE: Adverse event; CRP: C-reactive protein; DNA: Deoxyribonucleic acid; ECG: Electrocardiogram; EOS: End-of-Study; ESR: Erythrocyte sedimentation rate; HACA: Human anti-chimeric antibody; HAQ-DI: Health Assessment Questionnaire-Disability Index; HBV: Hepatitis B virus; HbcAb: Hepatitis B core antibody; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; Ig: Immunoglobulin; IXRS: Interactive voice/web response system; PCR: Polymerase chain reaction; PK: Pharmacokinetic; PD: Pharmacodynamic; PML: Progressive multifocal leukoencephalopathy; RF: Rheumatoid factor; SAE: Serious adverse event; TB: Tuberculosis; TNF: Tumor necrosis factor; VAS: Visual analogue scale.

a The total time period for Screening is not to exceed 30 days. However, in case a washout of currently used anti-TNF medication or DMARDs is required or prophylaxis of latent TB is required, the Screening may be extended to allow for this washout, but is not to exceed 60 days. (Refer to Table 6 for examples of washout periods.)

b Prior to Visit 2, Baseline, patients will be discontinued from their current anti-TNF medication or other biologic and non-biologic DMARDs, except MTX.

c Exclusion criteria to be re-checked at admission to the study center.

d The physical examination should include assessment of general appearance, skin, head, neck, throat, lymph nodes, thyroid, abdomen, and cardiovascular, neurological, musculoskeletal/extremities, and respiratory systems. Body weight will be measured. Height will be measured at Screening only.

e Neurological examination for signs and symptoms of PML.

f Blood pressure measurement can be performed prior to drug infusion. To be measured after the patient has been in a sitting/lying down position for at least 5 minutes. During all infusions of study drug, vital signs will be assessed at the following time points: pre-infusion (within 10 minutes prior to the start of the infusion); at the start of infusion (within 30 minutes after the start of the infusion); and at the end of infusion (within 10 minutes from the end of the infusion). Additional readings may be taken at the discretion of the Investigator in the event of an infusion-related reaction.

g Posterior-anterior and lateral chest X-rays (or chest radiographs in accordance with local requirements) should be obtained and reviewed by the Investigator or designee. If chest radiographs taken within the past 3 months show no clinically significant abnormality, and there are no signs or symptoms suggestive of pulmonary disease that would exclude the patient from the study, then a chest radiograph does not need to be repeated. Chest X-rays may be repeated at any time during the study for suspected TB or chest infection.

h Patients should rest for at least 5 minutes in a supine position before ECG evaluation.

i In women of childbearing potential; serum pregnancy test (central laboratory) at Screening and EOS. Urine pregnancy test prior to each dose (first and second courses of treatment).

j All patients except withdrawn patients will continue to attend visits until Week 52 regardless of the second course infusion to obtain PK / PD, safety, efficacy, and immunogenicity data.

k Unscheduled visits should be scheduled as per Investigator discretion. Tests will be performed as per Investigator's discretion.

l Study drug is required to be dispensed at Week 24 and Week 26, based on ANC value and platelet count at Week 20 and both the swollen and tender joint counts assessed at Week 24. If the ANC value and platelet count are marginally lower, re-testing at an unscheduled visit may be performed at the discretion of the Investigator within the 4-week period between Week 20 and Week 24. In case Visit 11 is missed, all safety evaluations including ANC value and platelet count must be completed as an unscheduled visit for patient to be eligible for second course of infusion.

m SAIT101 or Rituxan® or MabThera® for intravenous infusion. On Days 1 and 15, each patient will receive one course of two 1,000 mg (10 mg/mL) drug infusions. Patients who, at Week 24, have a <50% improvement from Baseline in both the swollen and tender joint counts will be eligible for a further course of two 1,000 mg drug infusions. Eligible patients in the SAIT101 arm will receive the second course of SAIT101 treatment at Week 24 and Week 26. Eligible patients in the MabThera® arm will receive the second course MabThera® treatment at Week 24 and Week 26. Eligible patients in the Rituxan® arm will be randomized in a 1:1 ratio to receive SAIT101 or Rituxan® treatment at Week 24 and Week 26.

n Questionnaires must be completed in the study center by the patient or patient's representative (in case patient is unable to read and/or write) based on the patient's verbal answers.

o Joint assessor(s) will be independent to the rest of the study team.

p To be performed by the central laboratory. Screening performed to confirm negative serology for HIV, HBV and HCV. Patients with negative HBsAg and positive HBcAb must have a HBV DNA level <20 IU/mL (or 112 copies/mL) by PCR test. These HBV patients must be willing to undergo PCR HBV DNA testing during treatment and may participate following consultation with a hepatitis expert regarding monitoring and use of HBV antiviral therapy, and provided they agree to receive treatment as indicated. An HBV re-test will be performed monthly including Day 1, Weeks 4, 8, 12, 16, 20, 24, 36,52, early EOS or unscheduled visit, if required. Patients who are confirmed positive and those who have active infections will be excluded from the participation in the study.

q QuantiFERON Gold test is conducted at Screening. If TB is suspected at any time during the study, chest X-ray and/or QuantiFERON Gold test should be performed (Central Laboratory)

r To determine presence of hypogammaglobulinemia (IgG <600mg/dL), which is an exclusion criterion.

s On Day 1 and Day 15 (first and second infusions) blood PK and PD (CD19+ B-cell) samples will be collected before and 3 hours after the start of infusion and immediately (within 10 minutes) before and 1 hour after the end of infusion, **at 48 hours after the start of infusion (Days 3 and 17, in case of 2nd infusion at Day 16, the following PK sampling should be on Day 18).** The PK and PD samples will also be taken (at the same time of the day first infusion started) at Day 8 (Week 1), Days 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20), 169 (Week 24). PD sampling will be additionally collected at D 253 (Week 36), and 365 (Week 52, EOS). Window of each sampling is ± 10 minutes of the determined time points of Days 1, 3, 8, 15 and 17 and ± 3 hours at all other time points.

t On Day 1, Day 15 (Week 2), and Week 24: immunogenicity sample will be collected before start of infusion. Wherever possible immunogenicity blood samples will be taken at the same time as blood is drawn for other analyses to limit repeated venipuncture. Immunogenicity sampling is also taken when patients show signs or symptoms of immune-response-related adverse events.

3.6.1 Schedule of Assessments

The sequence of assessments at each visit will be standardized as follows (at visits as required by the schedule of assessments):

1. At Visit 1 (Screening): Obtaining of informed consent
2. General assessments: Physical examination, Neurological examination, and Vital signs
3. Efficacy assessments: Patient-reported assessments (patient pain VAS, global VAS, and HAQ-DI)
4. Efficacy assessments: Investigator assessments (swollen and tender joint counts, physician's global assessment of disease activity VAS, EULAR, DAS28)
5. Laboratory/Safety assessments
6. PK/PD/immunogenicity assessments, where applicable
7. If applicable, pre-medication and study drug

All assessments will be performed prior to administration of pre-medication, unless otherwise specified.

Patient-reported data (pain VAS, global VAS, HAQ-DI) should be recorded by the patient on the relevant source documents. In special circumstances when the patient has difficulty writing or is unable to read, the study personnel or patient representative can record this data on behalf of the patient and based on responses provided by the patient verbally. The procedure followed must be documented clearly in the patient notes.

3.6.1.1 Screening Period

Visit 1 (-30 days and not to exceed 60 days before Day 1)

Patients must have the ability and willingness to provide written informed consent (prior to any study-specific procedures being performed) and to comply with the requirements of the protocol. All the Screening assessments should be performed within 30 days prior to randomization on Day 1 (Visit 2, Baseline).

However, in patients who require a washout of current anti-TNF medication or other biologic and non-biologic DMARD treatment (except MTX) the Screening period may be extended to allow for the washout required, but will not exceed 60 days. In these patients all Screening assessments must be performed within 30 days prior to randomization with the exception of the informed consent and chest X-ray.

Once the patient has provided written informed consent and meets the inclusion and exclusion criteria (see Section 3.4), the study center will register the patient in the IXRS.

The following must also be performed:

- Document patient's demographic information (including gender, date of birth and, when possible per local regulations, race), and medical and surgical history (including RA history;
- Physical examination, including height (cm) and weight (kg);
- Neurological examination (for signs and symptoms of PML);
- Chest X-ray, unless taken within the previous 3 months;
- Serum pregnancy test;
- Vital signs;
- Document previous and concomitant medications (including vaccination history);
- Resting 12-lead ECG.

The following safety/laboratory assessments will be performed:

- QuantiFERON® TB- Gold test;
- Serology (HBsAg and HBcAb, HBV DNA by PCR [<20 IU/mL or 112 copies/mL], anti-HCV, and HIV test), IgG, IgM, IgA, clinical chemistry, hematology, and urinalysis;
- CRP, ESR;
- RF.

3.6.1.2 Study Drug Administration Part A

Prior to Day 1, patients will be discontinued from their current anti-TNF medication, other biologic DMARDs or non-biologic DMARDs, except MTX.

The following must be performed on **Baseline (Day 1, Week 0):**

Review inclusion and exclusion criteria and confirm patient eligibility. If eligible, the following procedures should be performed:

- Physical examination and vital signs;
- Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs;
- Urine pregnancy test for applicable female;
- Randomization to one of the study drugs;
- Contact IXRS.

The following efficacy assessments will be performed:

- Patient's assessment: global VAS and HAQ-DI, including patient's pain VAS;
- Physician's assessment: global VAS;
- Joint assessment. Each of the 66/68 joints will be evaluated for tenderness and swelling.

The following laboratory assessments will be performed:

- Clinical chemistry, hematology, urinalysis and HBV DNA only when negative HBsAg and positive HbcAb at screening;
- CRP, ESR;
- PK and PD sample collection;
- Immunogenicity.

The following must be also performed:

- The first of the two infusions of the study drug, as per IXRS.

The following must be performed on **Day 3 (Week 0)**:

- Physical / Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs;
- PK and PD sample collection.

The following must be performed on **Day 8 (Week 1)**:

- Physical / Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs;
- PK and PD sample collection;
- Immunogenicity.

The following must be performed on **Day 15 ± 1 day (Week 2):**

- Physical examination and vital signs;
- Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs;
- Urine pregnancy test for applicable female;
- Contact IXRS;
- The second of the two infusions of study drug, as per IXRS;
- Clinical chemistry, hematology, urinalysis
- PK and PD sample collection;

- Immunogenicity.

The following must be performed on **Day 17 ± 1 day (Week 2)**:

- Physical / Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs;
- PK and PD sample collection.

The following must be performed on **Day 29 ± 3 days (Week 4):**

- Physical / Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs.

The following laboratory assessments will be performed:

- Clinical chemistry, hematology, urinalysis and HBV DNA only when negative HBsAg and positive HbcAb at screening;
- PK and PD sample collection;
- Immunogenicity.

The following must be performed on **Day 57 ± 3 days (Week 8):**

- Physical / Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs.

The following efficacy assessments will be performed:

- Patient's assessment: global VAS and HAQ-DI, including patient's pain VAS;
- Physician's assessment: global VAS;

- Joint assessment. Each of the 66/68 joints will be evaluated for tenderness and swelling.

The following laboratory assessments will be performed:

- Clinical chemistry, hematology, urinalysis and HBV DNA only when negative HBsAg and positive HbcAb at screening;
- IgG, IgM, IgA;
- CRP, ESR;
- PK and PD sample collection.

The following must be performed on **Day 85 ± 3 days (Week 12):**

- Physical / Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs.

The following laboratory assessments will be performed:

- Clinical chemistry, hematology, urinalysis and HBV DNA only when negative HBsAg and positive HbcAb at screening;
- PK and PD sampling;
- Immunogenicity.

The following must be performed on **Day 113 ± 3 days (Week 16):**

- Physical / Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs.

The following efficacy assessments will be performed:

- Patient's assessment: global VAS and HAQ-DI, including patient's pain VAS;
- Physician's assessment: global VAS;

- Joint assessment. Each of the 66/68 joints will be evaluated for tenderness and swelling.

The following laboratory assessments will be performed:

- Clinical chemistry, hematology, urinalysis and HBV DNA only when negative HBsAg and positive HbcAb at screening;
- IgG, IgM, IgA;
- CRP, ESR;
- PK and PD sample collection;
- Immunogenicity.

The following must be performed on **Day 141 ± 3 days (Week 20):**

- Physical / Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs.

The following laboratory assessments will be performed:

- Clinical chemistry, hematology, urinalysis and HBV DNA only when negative HBsAg and positive HbcAb at screening;
- PK and PD sampling.

To be eligible for the second course of treatment, patients must have an absolute neutrophil count (ANC) $\geq 1.5 \times 10^3/\mu L$ and platelet counts $\geq 75 \times 10^9/L$ observed at Week 20 (V11). If the ANC value and platelet count are marginally lower, re-testing at an unscheduled visit may be performed at the discretion of the Investigator within the 4-week period between Week 20 and Week 24. In case Visit 11 is missed, all safety evaluations including ANC value and platelet count must be completed as an unscheduled visit for patient to be eligible for second course of infusion.

Following must be performed in the unscheduled visit in this case:

- Neurological examination;
- Physical examination and vital signs;

- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs;
- Clinical chemistry, hematology, and urinalysis;

3.6.1.3 Study Drug Administration Part B

Patients with an inadequate response (<50% improvement from Baseline in both the swollen and tender joint counts) at Week 24 (Visit 12), will be eligible to receive a further course of two 1,000 mg i.v. infusions, one infusion at Week 24 (Day 1 of second course) and the second infusion at Week 26 (14 days after first dose of second course).

The following must be performed on **Day 169 ± 3 days (Week 24, Day 1 of the Second course of infusion):**

Following must be performed:

- Physical examination and vital signs;
- Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs;
- Urine pregnancy test for applicable females administered the second course of the study drug;

The following efficacy assessments will be performed:

- Patient's assessment: global VAS and HAQ-DI, including patient's pain VAS;
- Physician's assessment: global VAS;
- Joint assessment. Each of the 66/68 joints will be evaluated for tenderness and swelling.

The following laboratory assessments will be performed:

- IgG, IgM, and IgA;

- Clinical chemistry, hematology, urinalysis and HBV DNA only when negative HBsAg and positive HbcAb at screening;
- CRP, ESR;
- PK and PD sampling;
- Immunogenicity.

The following must be also performed:

- Contact IXRS;
- Randomization;
- The first of the two infusions of the study drug (see Section 3.2.1), as per IXRS for eligible patients only.

The following must be performed on **Day 183 ± 3 days (Week 26, Day 15 of the Second course of infusion):**

- Physical examination and vital signs
- Neurological examination;
- Documentation of concomitant medications;
- Assessment of AEs/SAEs/ADRs;
- Urine pregnancy test for applicable females administered the second course of the study drug;
- Contact IXRS;
- The second of the two infusions of study drug (see Section 3.2.1), as per IXRS, for eligible patients only.

The following assessments will be performed on **Day 253 ± 7 days (Week 36):**

- Physical / Neurological examination;
- Document concomitant medications;

- Assessment of AEs/SAEs/ADRs.

The following efficacy assessments will be performed:

- Patient's assessment: global VAS and HAQ-DI, including patient's pain VAS;
- Physician's assessment: global VAS;
- Joint assessment. Each of the 66/68 joints will be evaluated for tenderness and swelling.

Laboratory assessments

- Clinical chemistry, hematology, urinalysis and HBV DNA only when negative HBsAg and positive HbcAb at screening;
- IgG, IgM, IgA;
- CRP, ESR;
- PD sampling;
- Immunogenicity.

End of Study Visit

The following assessments will be performed on **Day 365 ± 7 days (Week 52):**

- Physical examination and vital signs;
- Neurological examination;
- Document concomitant medications;
- Resting 12-ECG;
- Assessment of AEs/SAEs/ADRs;
- Serum pregnancy test for applicable female;
- Contact IXRS.

The following efficacy assessments will be performed:

- Patient's assessment: global VAS and HAQ-DI, including patient's pain VAS;
- Physician's assessment: global VAS;
- Joint assessment. Each of the 66/68 joints will be evaluated for tenderness and swelling.

The following laboratory assessments will be performed:

- Clinical chemistry, hematology, urinalysis and HBV DNA only when negative HBsAg and positive HbcAb at screening;
- IgG, IgM, and IgA;
- CRP, ESR;
- PD sampling;
- Immunogenicity.

Unscheduled Visit Assessments

Patients may attend the clinic for unscheduled visits at any time for additional safety monitoring at the discretion of the Investigator.

3.6.2 Efficacy Assessments

3.6.2.1 ACR and DAS28 Score

The following assessments will be performed at the time points indicated in Table 2 for the purposes of calculating the ACR and DAS28 response scores.

3.6.2.1.1 Joint Assessments

Wherever possible, the same person should perform the joint assessment throughout the study (i.e., for all patients at each study center). Independent joint assessors (require at least one or more if necessary) will be assigned at each study center. This person will be independent to the rest of the study team in order to minimize any bias that could be introduced as a result of the assessment. Standardized training will be provided and the training records filed.

Each of the 66/68 joints will be evaluated for tenderness and swelling (prior to taking any required analgesic that day if possible). Immobilized or injected joints and prosthetic joints and joints which have undergone surgery within 1 year of the Screening visit will be excluded from the assessments.

The 66/68 Joint Count evaluates 66 joints for swelling and 68 joints for tenderness and pain with movement. Hip joints can be evaluated for tenderness only - but not for swelling.

The 66/68 joint count includes the following joints: the temporomandibular; sternoclavicular; acromioclavicular; shoulder; elbow; wrist; metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of the hands; hip; knee; ankle; tarsus; and the metatarsal phalangeal and proximal joints of the feet.

3.6.2.1.2 Patient's Global Assessment of Disease Activity

Patients will mark on a VAS their overall assessment of how their RA has affected them, rating how they are managing from 0 (very well) to 100 (very poor). This is equivalent to the General Health component of the DAS (see Appendix 5).

Patients will sign and date the completed VAS.

Patient-reported outcomes and physician-reported outcomes should be completed independently of each other (to avoid bias of the Investigator or the patient).

3.6.2.1.3 Physician's Global Assessment of Disease Activity

The physician's assessment of the patient's current disease activity will be documented on a VAS, ranging from 'no disease activity' (0) to 'maximum disease activity' (100) (see Appendix 5). Wherever possible, the same physician should perform the assessment for a given patient at every visit.

The physician will sign and date the completed VAS.

Physician-reported outcomes and patient-reported outcomes should be completed independently from each other (to avoid bias of the Investigator or the patient).

3.6.2.1.4 Patient's Assessment of Disability

If the patient is unable to read and/or write, the HAQ-DI can be completed by the patient's representative based on the patient's verbal responses.

The patient's ability to function in daily life will be assessed using the HAQ-DI questionnaire. This is a widely used patient self-report tool which assesses the degree of difficulty the patient has in accomplishing tasks in eight functional areas, over the previous week, taking into account any aids or help required. It consists of eight component sets: (1) dressing and grooming, (2) rising, (3) eating, (4) walking, (5) hygiene, (6) reach, (7) grip and (8) common daily activities (see Appendix 5).

The HAQ-DI questionnaire includes a pain VAS. Patients will mark on a VAS the current level of pain due to their RA, ranging from 0 (no pain) to 100 (severe pain) (see Appendix 5).

Patients will sign and date the completed questionnaire.

3.6.2.2 Systemic Inflammation: CRP Level and ESR

A blood sample for CRP assessment will be collected and analysis will be conducted by a suitably qualified central laboratory using validated methods.

A whole blood sample (2 mL) will be collected for the erythrocyte sedimentation rate (ESR) value to be measured locally by Westergren method.

3.6.3 Pharmacokinetic and Pharmacodynamic Assessments

3.6.3.1 Pharmacokinetic Assessments

Blood samples for the determination of concentrations of rituximab will be taken for each treatment at the times presented in the schedules of assessments (see Table 2).

Individual venipunctures for each time point may be performed or an indwelling catheter may be used. The exact date/time of the blood sample collection will be recorded in the patient's eCRF.

The blood samples (approximately 5 mL) will be drawn in K_2EDTA tubes and processed using instructions provided by designated central laboratory. Serum will be harvested in duplicate samples approximately 2.5 mL respectively including back-up sample.

Determination of serum concentrations of rituximab will be performed by central laboratory using validated analytical methods. Detailed sample collection, labeling, storage, and shipment information will be described in the Laboratory Manual.

3.6.3.2 Pharmacodynamic Assessments

Blood samples for the determination of CD19+ count will be taken for each treatment at the times presented in the schedules of assessments (see Table 2). The exact date/time of the blood sample collection will be recorded in the patient's eCRF.

The blood samples (approximately 5 mL) will be drawn and processed using instructions provided by the designated laboratory retained by the Sponsor.

The samples will be analyzed for CD19+ count by designated central laboratory using validated analytical methods. Detailed sample collection, labelling, storage, and shipment information will be described in the Laboratory Manual.

3.6.4 Immunogenicity Assessments

Blood samples (approximately 5 to 8 mL) will be taken at the visits shown in (Table 2) to determine the incidence of HACA and neutralizing antibody (using validated analytical methods).

Blood immunogenicity samples will be collected on Day 1 of First course (prior to the start of the first infusion), and on Weeks 1, 2, 4, 12, 16, 24, 36, and 52 with date and time of sampling accurately recorded. Wherever possible immunogenicity blood samples will be taken at the same time as blood is drawn for other analyses to limit repeated venipuncture. Additionally, immunogenicity should be assessed when patients show signs or symptoms of immune-response-related adverse events.

Human anti-chimeric antibody will be detected in serum samples using validated analytical methods. Serum samples in which HACA are detected will be reflexed to a Neutralizing Antibody Assay to evaluate the effect of the HACA on the biological activity of rituximab. Full instructions for collection, labeling, storage, and shipment of samples are provided in the Laboratory Manual.

3.6.5 Safety Assessments

All the safety assessments must be performed as provided in Table 2.

3.6.5.1 Adverse Events

The details of the assessment of AEs are presented in Section 5.

3.6.5.2 Clinical Laboratory Assessments

The list of clinical laboratory assessments is provided in Table 3.

Table 3 Clinical Laboratory Assessments

Hematology	White blood cell count, red blood cell count, hemoglobin, platelets, absolute neutrophil count
Clinical chemistry (serum)	Creatinine, aspartate transaminase, alanine transaminase (ALT), lactate dehydrogenase, alkaline phosphatase (ALP), total bilirubin, cholesterol, calcium, glucose, gamma glutamyl transferase (GGT), phosphate, hCG
Urinalysis	Glucose, blood, protein, hCG
Virology	Hepatitis C virus antibodies, human immunodeficiency virus, hepatitis B surface antigen, and hepatitis B core antibody (total and immunoglobulin M), HBV DNA
Other	C-reactive protein, rheumatoid factor, erythrocyte sedimentation rate*, QuantiFERON-TB Gold

* ESR estimation (Westergren method) and urine pregnancy test would be performed locally

3.6.5.3 Physical Examination

A physical examination will be performed by the Investigator and recorded as 'normal' or 'abnormal' with specified abnormalities at the visits indicated in Table 2. Any persisting abnormalities should be stated each time the examination is performed. Diagnosis of new abnormalities, or worsening of abnormalities, should be recorded as AEs if appropriate.

Wherever possible, the same person should perform the physical examination throughout the study (i.e., for all patients at each study center). The physical examination should include assessment of general appearance, skin, head, neck, throat, lymph nodes, thyroid, abdomen, and cardiovascular, neurological, musculoskeletal/extremities, and respiratory systems.

Body weight will also be measured. Height will be measured at Screening (Visit 1) only.

3.6.5.4 Vital Signs

Vital signs (blood pressure, pulse rate, respiratory rate, and oral or tympanic body temperature) will be assessed at the visits indicated in Table 2. BP measurements should be performed after the patient has been in a sitting/lying down position for at least 5 minutes

During all infusions of the study drug, vital signs will be assessed at the following time points:

1. Pre-infusion (within 10 minutes prior to the start of the infusion);
2. Start of infusion (within 30 minutes after the start of the infusion);
3. End of infusion (within 10 minutes after the end of the infusion).

Additional readings may be assessed at the discretion of the Investigator in the event of an infusion-related reaction.

The Investigator must assess all vital signs findings at each visit. If the Investigator finds any clinically relevant abnormalities, these should be reported as AEs/SAEs as appropriate.

3.6.5.5 Resting 12-lead ECG

Resting 12-lead ECG data will be collected at Screening (Visit 1) and EOS (see Table 2).

Patients should rest for at least 5 minutes in a supine position before ECG evaluations.

The original ECG traces and variables must be stored in the patients' medical record as source data. The Investigator should evaluate the ECG from a clinical perspective and the result (whether the ECG result is normal or abnormal) should be recorded on the ECG tracing and on the appropriate section of the eCRF.

3.6.5.6 Pregnancy Test

A serum pregnancy test will be performed at Screening and EOS. Urine pregnancy tests will be performed at the different time points indicated in Table 2 to rule out pregnancy in patients of childbearing potential. If a pregnancy test was performed within 4 weeks prior to the relevant time point, it need not be repeated.

3.6.5.7 Chest X-ray

Posterior-anterior and lateral chest X-rays (or chest radiographs in accordance with local requirements) should be obtained at Screening and reviewed by the Investigator or designee. At Screening, if chest radiographs taken within the past 3 months show no clinically significant abnormality, and there are no signs or symptoms suggestive of pulmonary disease that would exclude the patient from the study, then a chest radiograph does not need to be repeated.

3.6.6 End of Study

All patients will be followed up for up to 52 weeks from the start date of the first course of study drug. The patients who discontinue the study treatment attend all visits until Week 52 in order to address any safety concerns, to record the concomitant medications, and to measure drug level, CD19+ B cell count immunogenicity and efficacy (if applicable).

3.6.7 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be assigned for this study. The DSMB will review available study data at pre-specified time points as outlined in the DSMB charter. The details of the DSMB roles and responsibilities and details of the review process will be outlined in the DSMB Charter.

3.7 Stopping Rules, Discontinuation Criteria, and Procedures

3.7.1 Entire Study or Treatment Arms

If the Sponsor decides to terminate or suspend the study for safety or unanticipated other reasons, the Sponsor will promptly notify the Investigators, Sub-investigators, Institutional Review Boards/Independent Ethics Committees (IRBs/IECs), and Regulatory Authorities as required by the applicable regulatory requirements.

3.7.2 Individual Study Center

The Sponsor, IRB/IEC and/or Regulatory Authorities have the right to close an individual study center at any time. In case of premature termination of an individual study center, the Sponsor, Investigator, participating study patients, IRB/EC and Regulatory Authorities should be informed as described in ICH-GCP and according to other applicable regulatory requirements.

Prior to closure of the study center, the Investigator or institution must assure appropriate therapy and follow-up for the patients.

The Sponsor may decide to close an individual study center prematurely for the following reasons:

- Lack of enrollment;
- Non-compliance with the requirements of the study protocol;
- Non-compliance with ICH-GCP and/or other applicable regulatory requirements.

3.7.3 Individual Patient

If a patient discontinues the study treatment prematurely, the reason given must be fully evaluated and recorded appropriately in the source documents and the patient's eCRF. If the patient is discontinued from study treatment because of an AE, that AE should be indicated as the reason for discontinuation.

The Investigator can discontinue treatment of a patient at any time if medically necessary. In addition, patients meeting the patient discontinuation criteria must be discontinued from the study treatment.

Patients will be discontinued from the study treatment in the following circumstances:

- A patient who does not meet the enrolment criteria is inadvertently randomized, that patient must be discontinued from study treatment and the Sponsor or Clinical Research Organization (CRO) must be contacted.
- The Investigator decides that the patient should be discontinued from study treatment. If this decision is made because of an intolerable AE or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. The Sponsor or designee is to be notified immediately.
- Patient non-compliance, defined as refusal or inability to adhere to the study schedule or procedures (see Section 3.12).

- Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under the direction of the Sponsor and/or Investigator or Sub-investigator

- Lack of efficacy. Subjects who lack efficacy can be included in the PK and efficacy analysis. Patients receiving rescue therapy prior to Week 24 would not be eligible for second course of infusion.
- Patients who meet any of the following specific safety discontinuation criteria, however can be included for the PK analysis:

  – Patients who develop severe infusion-related reactions, especially severe dyspnea, bronchospasm or hypoxia, should have the infusion interrupted immediately to receive aggressive symptomatic treatment. In all patients, the infusion should not be restarted on the same day until complete resolution of all symptoms. At this time, the infusion may be initially resumed at the discretion of the Investigator at not more than one-half the previous rate. If the same ADRs occur for a second time, the infusion should be permanently discontinued.

  – Active TB

  – Invasive fungal infection or opportunistic infection including, but not limited to, listeriosis, legionellosis or pneumocystis.

  – Hepatitis B virus reactivation, in some cases resulting in fulminant hepatitis, or hepatic failure

- Any other AEs which, in the opinion of the Investigator or the Sponsor, could compromise the patient's safety or well-being if they continue to participate in the study.

- PML. Neurological warning signs include: major changes in vision, unusual eye movements; loss of balance or coordination; and disorientation or confusion

- Cancer: any malignant lesion. Patients with basal cell and squamous cell carcinomas of the skin or carcinoma in situ of the cervix uteri that has been excised and cured, may be continued on the study at the discretion of the Investigator.

- Pregnancy in a female participant

- Patient lost to follow-up despite reasonable efforts to make contact with the patient

- Patients who have a delay of >15 days in receiving the second infusion due to an AE or otherwise

- Judgment by the Investigator or Sub-investigator that study treatment discontinuation is necessary for reasons other than those described above.

To prevent missing data in important supportive efficacy and safety analysis, patients who discontinued study drug, will also attend all visits until week 52.

3.8 Screen Failures

A screen failure patient is a patient who provided written informed consent (i.e., the patient signs an informed consent form [ICF]), but failed to meet all the inclusion criteria or who meets any of the exclusion criteria or withdraws consent prior to randomization. The reason for screen failure will be documented in the source documents.

Patients are only allowed to be re-screened once and it should be performed in consultation with the Sponsor or representative.

Laboratory tests if marginally abnormal may be repeated once at the discretion of the Investigator during the Screening period if the patient does not meet the criteria the first time. If the patient fails the laboratory criteria a second time, they will be considered a screen failure. Re-testing may only be done at the central laboratory except for ESR.

3.9 Re-screening

Re-screening may be required if a patient has not met all the eligibility criteria. Patients are only allowed to be re-screened once and it should be performed in consultation with the

Sponsor or representative. Each patient must give written informed consent before re-screening occurs.

3.10 Definition of Completed Patients

In this study, patients who complete at least the first course of study drug in Part A and undergo the tests and assessments at Week 52 will be defined as study completers.

3.11 Definition of Patients Lost to Follow-up

Lost to follow-up is defined as a patient who stops attending study visits and study personnel are unable to contact the patient.

To prevent lost to follow-up, several approaches should be implemented to retain patients who fail to actively maintain contact with the investigator (e.g., telephone calls to friends or family members, emails, offers for transportation to the clinic, etc.).

If a patient is lost to follow-up, every possible effort must be made by the study center personnel to contact the patient and determine the reason for withdrawal. The measures taken to follow up must be documented.

3.12 Treatment Compliance

The administration (dose, frequency and dates) of all concomitant medications (including new medications taken during the study and investigational product) should be recorded in the appropriate sections of the eCRF from Visit 1.

The infusion schedule consists of two 1,000 mg i.v. drug infusions of either SAIT101 or MabThera® or Rituxan® (the first on Day 1 and the second on Day 15) with the possibility of a further course of two 1,000 mg infusions (see Section 3.2.1). The study drugs will be administered at the study center. This should guarantee that full compliance was achieved, provided the patient attended the appropriate visits. Patients who miss the allocated day for the second of their two infusions will be contacted and another visit arranged as soon as practically possible in order to administer the missed dose of the study drug.

The prescribed dosage, timing, and mode of administration of the study drug may not be changed. Any departures from the intended regimen must be recorded in the eCRF.

Patients exhibiting poor compliance as assessed by attendance to appointments for their drug infusions should be counseled on the importance of good compliance to the study dosing regimen.

3.13 Protocol Deviations

This study is intended to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (e.g., violation of the informed consent process, study drug dispensing or patient dosing error, treatment assignment error, patient enrolled in violation of eligibility criteria or concomitant medication criteria), the Investigator or Sub-investigator must contact the Sponsor at the earliest possible time. This will allow an early joint decision regarding the patient's continuation of study treatment. This decision will be documented by the Investigator and confirmed by the Sponsor.

4 RESTRICTIONS

4.1 Measures Regarding Patients Being Treated or Scheduled for Treatment at another Department or Hospital

When obtaining informed consent, the Investigator or Sub-investigator will confirm with the patient whether they are being treated or are scheduled for treatment at another department or hospital and note any drugs that they are using. If the patient is being treated by another physician (receiving treatment at another department or medical institution), the Investigator or Sub-investigator will contact the treating physician and inform them of the patient's participation in the study and provide information on the study drug. In addition to obtaining and recording the information on the medications prescribed at the other department or hospital, the appropriateness of the patient's study participation or continuation in the study will be decided.

4.2 Prohibited Medications/Therapies

Prior treatments required to be discontinued prior to Baseline is summarized in Table 4.

Table 4 Prior Treatments Required to be Discontinued Prior to Baseline

Treatment	Restriction
Leflunomide	Not permitted. Must be withdrawn at least 12 weeks prior to the beginning of the Treatment Period or a minimum of 4 weeks prior Day 1 if after 11 days of standard cholestyramine washout
Sulfasalazine	Not permitted within 4 weeks prior to Day 1
Hydroxychloroquine	Not permitted within 8 weeks prior to Day 1
Other non-biologic (conventional) DMARDs	Not permitted within 4 weeks prior to Day 1
Biologic DMARDs	Not permitted within defined washout period prior to Day 1 (see Table 6)

Treatment	Restriction
Intravenous or intramuscular corticosteroids	Not permitted within 6 weeks prior to Day 1
Intra-articular corticosteroids	Not permitted within 6 weeks prior to Day 1
Anti-infective agents	Intravenous anti-infective agents within 4 weeks prior to Screening or oral anti-infective agents within 2 weeks prior to Screening are not permitted
Live/attenuated vaccine	Not permitted within 6 weeks prior to Day 1 or during the study
Any drug that has not received regulatory approval for any indication	Not permitted within 4 weeks or a minimum of 5 half-lives, whichever is longer, prior to Day 1
Traditional herbal medicines (e.g., preparations containing derivatives of *Tripterygium wilfordii Hook*, *Sinomenium acutum* and *Paeonia lactiflora*)	Any traditional herbal medicine which has RA as an indication in its label is not permitted
Anti-cancer chemotherapy	Not permitted within 5 years prior to Screening
Surgical procedure	Not permitted within 4 weeks prior to Day 1
B cell modulating or B cell depletion therapies	Treatment with such therapies, such as, but not limited to rituximab, belimumab, atacicept, tabalumab, ocrelizumab, ofatumumab, obinutuzumab, epratuzumab and other experimental treatments is not permitted prior to or during the study

4.3 Concomitant Medications with Restrictions

Other medication that is considered necessary for the patient's safety and well-being (e.g., as a result of an AE) may be given at the discretion of the Investigator. Investigators are encouraged to discuss the introduction of any restricted medications with the Sponsor physician or representative. Any concomitant medications should be recorded in the appropriate sections of the eCRF.

The list of medications permitted during the study is presented in Table 5.

Table 5 List of Medications Permitted During the Study

Treatment	Restriction
Methotrexate	Patients must be taking MTX at a dose of 7.5-25 mg/week (oral or parenteral) throughout the study and for at least 12 weeks prior to study entry. Patients receiving a lower dose of MTX (<10 mg/week) should be doing so as a result of a documented evidence of intolerance to higher doses of MTX. The dose and route of administration should remain stable from 4 weeks prior to randomization and where possible, throughout the entire study period.
Folic or folinic acid	Patients must be taking oral folic or folinic acid or equivalent during the entire study (mandatory co-medication for MTX treatment), according to local standards and availability. The dosing regimen is at the Investigator's discretion.
Antipyretics	Patients will receive an antipyretic, e.g., paracetamol or equivalent, 30 to 60 minutes before each drug infusion.
Antihistamines	Patients will receive an antihistamine, e.g., diphenhydramine or equivalent, 30 to 60 minutes before each drug infusion.
Oral corticosteroids	If receiving current treatment with oral corticosteroids at the time of Screening (≤10 mg/day prednisone or equivalent), the dose must remain stable during the 4 weeks prior to Day 1. Increases in corticosteroids for treatment of RA are not allowed over the study period and should be avoided (see Section 3.2.5). Reductions in the dose of corticosteroids will be allowed as clinically required only for safety reasons.
Intravenous or intramuscular corticosteroids	Use of i.v. or intramuscular corticosteroids for RA will be considered worsening of a patient's condition from Baseline and should be recorded as an AE in the eCRF. The only exception will be the administration of 100 mg i.v. methylprednisone or equivalent within 30 minutes before each infusion as part of the study procedures.
Intra-articular corticosteroids	Injection of intra-articular steroids during the study period is discouraged, but may be used in a limited fashion. Joints injected within 8 weeks prior to Week 24 and Week 52 will cause the exclusion of the joint from the subsequent efficacy analysis and therefore should be avoided. No more than 1 joint per 24-week period may be injected during the study period. No single injection should exceed 40 mg of triamcinolone (or equivalent) and the total dose of intra-articular corticosteroid may not exceed 80 mg of triamcinolone (or equivalent) during any 52-week period.
Inhaled/topical/ophthalmic steroids	Limited uses of these preparations are allowed during the study.
NSAIDs	Patients may be treated with NSAIDs, up to the maximum recommended dose, (including cyclooxygenase-2 inhibitors) throughout the study. The choice and doses of NSAIDs used to treat patients is at the discretion of the Investigator. Increases in the NSAID dose are not allowed over the study period and should be avoided. After Week 24, dose adjustments may be made only for safety reasons, and if absolutely required to treat disease flares, according to the Investigators' normal practices. Dose adjustments in NSAIDs cannot be made within 24 hours of a study visit. Aspirin may be taken to reduce cardiovascular risk, not to exceed 350 mg/day.

Treatment	Restriction
Analgesics (other than NSAIDs)	Analgesics up to the maximum recommended doses may be used for pain as required. However, patients should not take analgesics within 24 hours prior to a visit where clinical efficacy assessments are performed and recorded.
Non-pharmacological treatments (e.g., physical therapy)	Permitted freely.

Example washout periods for prior medications are presented in Table 6.

Table 6 Example of Washout Periods

Treatment	Washout period
Leflunomide	12 weeks*
Abatacept	8 weeks
Adalimumab	8 weeks
Certolizumab	8 weeks
Infliximab	8 weeks
Golimumab	8 weeks
Tocilizumab	8 weeks
Hydroxychloroquine	8 weeks
Tofacitinib	8 weeks
Etanercept	4 weeks
Anakinra	4 weeks
Sulfasalazine	4 weeks
Azathioprine	4 weeks

* At least 12 weeks or a minimum of 4 weeks prior to the beginning of Part A if after 11 days of standard cholestyramine washout.

5 REPORTING OF ADVERSE EVENTS

5.1 Adverse Event (AE)

An AE is defined as "any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment."

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

5.2 Serious Adverse Events (SAE)

A SAE is any untoward medical occurrence that:

- results in death;
- is life-threatening. The term "life-threatening event" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe;
- requires inpatient hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study. Hospitalizations required purely for the purposes of performing study procedures are not SAEs;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect, which includes ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, or neonatal death. In addition, infant death after 1 month should be reported as a SAE when the investigator assesses the infant death as related or possibly related to exposure to investigational product;
- any other medically or scientifically significant event that, although it may not be immediately life-threatening or result in death or hospitalization, endangers the patient or requires that appropriate measures be taken to avoid any of the events listed above (e.g., bronchospasm requiring intensive treatment, blood dyscrasia or convulsion not requiring hospitalization, drug dependency or abuse).

5.3 Adverse Drug Reactions

An adverse drug reaction (ADR) is defined as a noxious and unintended response to a medicinal product related to any dose.

AEs which meet all of the following criteria:

- Serious
- Unexpected (i.e. is not consistent with the currently applicable Investigator Brochure list of AEs)
- There is at least a reasonable possibility that there is a causal relationship between the event and the medicinal product

will be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs) and should be reported to the relevant ethics committee and to the relevant Health Authorities for expedited reporting in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

5.4 Adverse Event of Special Interest (AESI)

An AE of special interest (AESI) is one of scientific and medical interest specific to understanding of the study drug and may require close monitoring and rapid communication by the Investigator to the Sponsor and/or QuintilesIMS. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this study drug. All AESIs must be reported in an expedited manner similar to SAEs (i.e., non-serious AESIs also must follow serious timelines).

The following will be considered AESIs in this study: PML, hepatitis reactivation, mucocutaneous reactions, infusion reactions, anaphylactic reactions, and serious infections.

5.4.1 Progressive Multifocal Leukoencephalopathy

The Investigator is required to monitor the patients throughout the study for any new or worsening neurological symptoms or signs that may be suggestive of PML. Typical symptoms are diverse, and include cognitive or visual disorders, hemiparesis, confusion, and behavioral disorders. If a patient develops new or worsening neurological signs or symptoms, he/she will be evaluated for PML. Neurological warning signs include:

- Major changes in vision, unusual eye movements.
- Loss of balance or coordination.

- Disorientation or confusion.

If PML is suspected, further dosing must be suspended until PML has been excluded.

Consultation with a neurologist should be considered as clinically indicated. If any doubt exists, further evaluation, including an MRI scan (preferably with contrast), cerebrospinal fluid testing for John Cunningham viral deoxyribonucleic acid (DNA), and repeat neurological assessments, should be considered.

The Sponsor must be notified of any suspected PML cases within 24 hours of awareness according to the procedure outlined in the Site Manual. If any patient reports PML during the study, the patient must be discontinued from study treatment and followed up until resolution at the discretion of the Investigator.

5.4.2 Hepatitis Reactivation

If a patient develops reactivation of HBV while on rituximab, the patient should be managed as outlined in Section 3.2.7.

5.4.3 Serious Infections

Serious infections are defined as infections requiring i.v. antibiotics or meeting the definition of an SAE.

5.4.4 Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure. Rituximab should be discontinued in patients who experience a severe mucocutaneous reaction. The safety of re-administration of rituximab to patients with severe mucocutaneous reactions has not been determined.

5.4.5 Infusion Reactions

An acute onset infusion reaction generally occurs within 24 hours of infusion of the study drug. Rituximab can cause severe, including fatal, infusion reactions. Severe reactions typically occur during the first infusion with time to onset of 30 to 120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome,

myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Medical management (e.g., glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions must be instituted as needed. Depending on the severity of the infusion reaction and the required interventions, rituximab may be temporarily or permanently discontinued. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor patients with pre-existing cardiac or pulmonary conditions.

Infusion reactions should be reported in the eCRF as AEs, or SAEs if it meets the seriousness criteria, with the event term "infusion-related reaction". The signs and symptoms of the infusion reaction should be described in the appropriate part of the eCRF. Please refer also to Section 5.4.6 (Anaphylaxis).

5.4.6 Anaphylaxis

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Diagnostic criteria are outlined in Table 7.

Table 7 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips/tongue/uvula) AND AT LEAST ONE OF THE FOLLOWING a. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia) b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin/mucosal tissue (e.g., generalized hives, itch/flush, swollen lips/tongue/uvula) b. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure b. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

As with the treatment of any critically ill patient, the treatment of anaphylaxis begins with a rapid assessment and maintenance of airway, breathing, and circulation. When a patient fulfills any of the 3 criteria of anaphylaxis outlined above, the patient should receive

epinephrine immediately because epinephrine is the treatment of choice in anaphylaxis. There undoubtedly will be patients who present with symptoms not yet fulfilling the criteria of anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine, such as a patient with a history of near-fatal anaphylaxis to peanut who ingested peanut and within minutes is experiencing urticaria and generalized flushing. Subsequent interventions are determined on the basis of the clinical course and response to epinephrine.

Anaphylaxis should be reported in the eCRF as AE or SAE if it meets the seriousness criteria, with the event term "anaphylaxis". The signs and symptoms of the anaphylaxis should be described in the appropriate part of the eCRF.

5.5 Pregnancy

Any pregnancy in a female patient should be reported to the Sponsor from the time the patient signed the ICF until 12 months after the last infusion of study drug. Pregnancy reports should be submitted to the Sponsor within 24 hours of awareness of the pregnancy by the Investigator as per the reporting procedure outlined in the Site Manual.

Pregnancy occurring in the partner of a male patient participating in the study should be reported to the Investigator and the Sponsor following the same procedure for pregnancy in the female patient. The partner should be counseled, the risks of continuing the pregnancy discussed, as well as the possible effects on the fetus. Monitoring of the pregnant female should continue until conclusion of the pregnancy. The pregnant partner will need to sign an Authorization for "Use and Disclosure of Pregnancy Health Information" (a sort of specific consent form) to allow for follow-up of her pregnancy.

Although pregnancy is not an AE, all pregnancies must be followed until 6 to 8 weeks after the estimated date of delivery to determine their outcome. The pregnancy outcome will be notified to the Sponsor by submitting a follow-up pregnancy report form. If the outcome of the pregnancy meets the SAE criteria then the Investigator should report this case according to the SAE reporting process (Section 5.9).

5.6 Overdose

An overdose of SAIT101 or MabThera® or Rituxan® is defined as an infusion of >1,000 mg during a single infusion in this study.

In case of overdose, the patient must be managed for any AE caused by overdose as per standard of care at the site or symptomatically and the case discussed with the Clinical Research Organization and Sponsor medical advisor for decision on treatment discontinuation of the patient.

When an overdose is reported during the course of the study, the patient should be monitored closely and evaluated by the Investigator to determine whether the patient experiences any AE or SAE as a result of the overdose.

Overdoses will be reported as protocol deviations. If the overdose is associated with an AE/SAE, the site should follow the AE/SAE reporting procedures described in Section 5 of this protocol and as per the eCRF completion guidelines.

5.7 Changes in Clinical Laboratory Assessment Results

It is the responsibility of the Investigator or Sub-investigator to review the results of all laboratory tests as they become available. For each abnormal laboratory test result, the Investigator or Sub-investigator needs to ascertain if this is an abnormal (i.e., clinically significant) change from Baseline for that individual patient. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The Investigator or Sub-investigator may repeat the laboratory test or conduct additional tests to verify the results of the original clinical laboratory tests. If this laboratory value is determined by the Investigator or Sub-investigator to be a clinically significant change from Baseline for that patient, it is considered to be an AE.

5.8 Recording of Adverse Events

Relationship

The causal relationship of the study drug to all AEs occurring after the start of study drug infusion will be assessed as one of the following two categories.

1. Unrelated (AE for which relationship to the study drug can be ruled out). A reasonable possibility of the AE occurring is considered highly unlikely for one of the following reasons:

    - Occurrence of the event can be expected based on the patient's underlying disease, concurrent illness, or medical history.

    - Occurrence of the event can be expected based on the patient's age, gender, or other characteristics.

    - There is no apparent temporal relationship between study drug infusion and occurrence of the event. Example: Occurrence of an AE after a considerable length of time has elapsed since completion or discontinuation of study drug infusion.

- A causal relationship is considered highly unlikely from the status of study drug infusion and the course of the event. Example: An AE that recovers without treatment while continuing study drug infusion (excluding cases in which the patient becomes accustomed to the condition through continued study drug infusion).

- The event is considered to be the effect of a concomitant drug.

- The event is considered to be incidental (accident, incidental symptom, etc). Example: Occurrence of a femoral fracture resulting from a traffic accident.

- A causal relationship of study drug infusion can be medically ruled out for some other reason.

2. Related (AE for which relationship to the study drug cannot be ruled out). A reasonable possibility of the AE occurring is considered likely for one of the following reasons:

   - Occurrence of the event can be expected from the pharmacological or toxicological action of the study drug. Examples: Occurrence of pancytopenia when an effect on the hematopoietic system has been observed in non-clinical studies, or occurrence of dehydration with a study drug that has a diuretic action.

   - The same event was previously observed in non-clinical studies or clinical studies. Example: Occurrence of an event that was observed at a high incidence in Phase I studies.

   - A temporal relationship between study drug infusion and occurrence of the event is suspected. Example: Occurrence of allergic dermatitis several days after the start of study drug infusion.

   - A causal relationship is suspected from the outcome of the event following discontinuation or dose reduction of the study drug. Example: Rapid recovery of nausea following discontinuation of study drug infusion.

   - A causal relationship of study drug infusion cannot be medically ruled out for some other reason.

Severity

AEs will be graded on a 3-point scale. The intensity of an adverse experience is defined as follows.

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

5.9 Eliciting and Reporting Adverse Events

After the patient has signed the ICF, but prior to initiation of study drug, only SAEs caused by a protocol-mandated procedure should be reported (e.g., SAEs related to invasive procedures such as biopsies). The Investigator or Sub-investigator will periodically assess patients for the occurrence of AEs and record AE information offered spontaneously by patients. To avoid bias in eliciting AEs, patients should be asked the following non-leading question: "How have you felt since your last visit?"

The QuintilesIMS must be notified of any SAEs within 24 hours of awareness according to the procedure outlined in the Site Manual.

5.10 Follow-up of Adverse Events

Any AEs will be followed up to resolution. Resolution means that the patient has returned to a Baseline state of health or the Investigator does not expect any further improvement or worsening of the AE.

5.11 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

Investigators will be notified by the Sponsor or QuintilesIMS of all SAEs that require prompt submission to their IRB or IEC. Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor or QuintilesIMS. The Sponsor or QuintilesIMS will ensure that SAEs are reported to the appropriate regulatory authorities in accordance with the local regulations.

All contact details and detail instructions for SAE reporting will be provided in the site manual, and SAE form completion instruction.

6 STATISTICS

6.1 Sample Size

The PK parameters reported from a recent study with rituximab in patients with RA revealed a percentage coefficient of variation (CV%) ranging from 26.3% for C_{max} to 37.3% for $AUC_{0-\infty}$.[12]

When the evaluable sample size in each group is 84, a three group design will have 81% power to reject both the null hypothesis that the ratio of test to standard geometrics means is below 0.800, and the null hypothesis that the ratio of test to standard geometrics means is above 1.250 (i.e., that the test and standard are not equivalent), in favor of the alternative hypothesis, that the means of the two groups are equivalent, assuming that the expected ratio of means is 1.000, that data will be analyzed in the log scale using analysis of variance (ANOVA) and that each one sided test is made at the 5% level. Each of the 15 hypotheses tests (five co-primary endpoints × three pairwise comparisons (i.e., SAIT101 vs. MabThera®, SAIT101 vs. Rituxan®, MabThera® vs. Rituxan®)) are powered at 98% to 99.0% to yield 81% study-wide power.

Approximately 282 patients (94 patients per group) will be randomized in order to yield a minimum of 84 patients per group to account for a presumed 10% withdrawal.

This 94 patients in SAIT101 group and MabThera® group will provide 96% probability of declaring the equivalence in FAS with each one sided test at the 2.5% level, accounting for a presumed 1.0 standard deviation of DAS28 from the REFLEX study[13, 14], and the equivalence margin of -0.6 to 0.6 chosen as the half of a clinical meaningful improvement of 1.2 in DAS28.[16] Considering 18% withdraw from the REFLEX study, approximately 77 patients per group will provide approximately 91% probability of declaring the equivalence in the PP set with the same above assumption.

6.2 Statistical Methods

Categorical variables will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized using N, mean, standard deviation (SD), median, minimum, and maximum values.

For all efficacy analyses, patients will be analyzed under the treatment they were randomized to, even if the treatment actually received differs from the treatment the patient was randomized to receive. For all safety analyses, patients will be analyzed under the treatment they actually received.

Generally, the Baseline value to be used in any change from Baseline listings/summaries/graphical presentations or as a covariate in a statistical analysis is defined as the latest available pre-randomization value. If necessary, detailed Baseline definitions of specific parameters or assessments will be defined in the statistical analysis plan (SAP).

6.2.1 Analysis Sets

6.2.1.1 Pharmacokinetic Analysis Set

The PK analysis set will include all patients who receive both planned doses of SAIT101 or MabThera® or Rituxan®, have a measured drug serum concentration and have no major protocol deviations or violations thought to significantly affect the PK of the drug. Reasons for excluding patients from the PK Analysis set will be specified in the statistical analysis plan.

Major protocol deviations or violations thought to significantly affect the PK of the drug include (but not limited to) missing dose or incorrect dose, sampling date and time not available, sample processing errors that might render a subject's bioanalytical data to be inaccurate etc. Subjects with these issues will be reported in the study report.

6.2.1.2 Safety Analysis Set

The Safety Analysis Set (SAF) will consist of all randomized patients who received at least one dose of study drug.

Safety Analysis Set will be used as the basis for all safety analyses.

6.2.1.3 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized patients in accordance with the intended treatment arm, regardless of the treatment actually received.

6.2.1.4 Per Protocol Set

In this study, patients who complete at least the first course of study drug in Part A and continue study treatment up to Week 24 will be included in the PP set. A patient may be excluded from the PP set for, but not limited to, any of the following conditions:

- Patient does not meet inclusion/exclusion criteria.
- Infusion of wrong study drug occurred.

- Patient did not receive both infusions of study drug (Day 1 and Day 15).

- Intake of disallowed concomitant medication, patient to evaluation of clinical relevance of the intake.

6.2.1.5 Pharmacodynamic Analysis Set

The PD analysis set will include all patients who receive both planned doses of SAIT101 or MabThera® or Rituxan®, have at least one measured CD19+ count at scheduled time point postdose and have no major protocol deviations or violations thought to significantly affect the PD of the drug.

6.2.2 Patient Disposition

The number and percentage of patients who were screened, and were randomized will be presented. For the patients who left the study prior to randomization, a summary will be presented for the reasons of screen failure. For the patients who were randomized or re-randomized at Week 24, summaries will be presented for the number and percentage of patients who completed the study, discontinued study drug (by reason for treatment discontinuation), and withdrew early from the study (by reason for study withdrawal).

6.2.3 Demographic and Baseline Characteristics Analysis

Patient demographics and Baseline characteristics will be summarized by treatment group for all randomized patients. Continuous variables (e.g., age, weight, height, disease duration, duration of MTX use, swollen and tender joint count, patient and physician global assessments VAS, patient pain assessment VAS) will be summarized with descriptive statistics (N, mean, SD, median, minimum, maximum). Qualitative variables (e.g., gender, race, ethnicity, number of previous DMARDs) will be summarized with counts and percentages.

Relevant medical history and continuing medical conditions will be summarized by treatment group for all randomized patients.

6.3 Pharmacokinetic Analysis

The PK analysis will be performed on the PK Analysis Set. The PK parameters, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}d15}$, C_{max} after the second infusion on Day 15 and C_{trough} before the second infusion on Day 15 will be considered the primary PK endpoints. All other PK endpoints will be regarded as secondary.

The statistical analysis of the $\log_e$-transformed primary endpoints will be based on an analysis of variance model. Covariates may be added to the planned analysis. The difference in least squares means between each of the three pairs (i.e., SAIT101 vs. MabThera®, SAIT101 vs. Rituxan®, MabThera® vs. Rituxan®) and the associated 90% CI will be determined. Back transformation will provide the ratio of geometric means and 90% CI for this ratio. Equivalence will be concluded if the 90% CI for the ratio of geometric means of each of the three pairs for each primary endpoint are completely contained within the acceptance interval of 0.8 to 1.25.

Descriptive statistics (N, mean, SD, %CV, minimum, median, and maximum) will be used to summarize serum concentration data by treatment at each planned sampling time point. Concentrations that are below the lower limit of quantitation will be assigned a value of 0 for the purposes of computing descriptive statistics. Serum PK parameters calculated from the concentration-time data will also be summarized by treatment using descriptive statistics (N, mean, SD, %CV, geometric mean, geometric %CV, minimum, median, maximum).

Plots of the mean and individual serum rituximab concentrations over time for SAIT101 and MabThera® and Rituxan® will be provided following i.v. infusions.

6.4 Efficacy Analysis

The continuous efficacy endpoint will be analyzed using Analysis of Covariance (ANCOVA) using treatment (SAIT101 and MabThera®) as model factor and Baseline DAS28 as covariate. The Difference between SAIT101 and MabThera® in DAS28 change from Baseline at Week 24 and the associated two-sided 95% CI will be determined.

Equivalence will be concluded if the 95% CI for the mean difference for main efficacy endpoint is completely contained with the equivalence margin of -0.6 to 0.6. Both of the per protocol (PP) set and full analysis set (FAS) will be considered as the efficacy analysis population and the equivalence will be concluded only if the analyses of both PP set and FAS meet the equivalence criteria defined above. No missing data will be imputed for the efficacy analyses in FAS. The possibility of a treatment-by-baseline interaction may be explored as exploratory analyses. In addition, sensitivity analyses will be performed to assess the effect of missing Week 24 data and detailed in the SAP.

Binary endpoints will be analyzed as for the proportion of patients achieving an ACR20 response at Week 24. Two-sided 95% CI for the difference between SAIT101 and

MabThera® in the proportion of patients achieving an ACR20 response at Week 24 will be computed using the Wilson score method.

All statistical comparisons for the secondary efficacy variables will be made using two sided tests at the 0.05 significance level. The 95% CIs of the difference between SAIT101 and MabThera® will be computed.

All efficacy endpoints will be analyzed on the both PP set and FAS.

6.5 Pharmacodynamic Analysis

A listing of PD blood sample collection times by individual, as well as derived sampling time deviations, will be provided.

Area under the depletion-time curve of CD19+ B cells depletion from time 0 across 24 weeks ($AUC_{0\text{-}w24}$), depletion in CD19+ B cell count (defined as a CD19+ B cell count below 14/µL) will be descriptively compared between the test and comparator groups.

Observed, change from Baseline, and percent change from Baseline in CD19+ B cell counts, and depletion of CD19+ B cell counts will be summarized using descriptive statistics. Baseline is defined as the CD19+ B cell count on Day 1 (immediately before the start of the first infusion).

Observed change from Baseline in IgG, IgM, and IgA levels at Weeks 8, 16, 24, 36 and 52 and observed change from Baseline in CRP levels at Weeks 8, 16, 24, 36, and 52 will be summarized using descriptive statistics.

6.6 Safety Analysis

6.6.1 Adverse Events

All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). No statistical testing will be performed for AEs. Adverse events will be summarized by the number and percentage of patients experiencing events by System Organ Class (SOC), Preferred Term (PT) and severity.

A listing of all ADRs will be presented. The listing will present SOC and PT of the ADR, severity, action taken, outcome, start and stop date of the ADR, study day of onset of the ADR, age, race, and gender.

The incidence of AESI in the study will be summarized in the similar way as ADRs.

A listing will be presented for all AEs with an outcome of death. Narratives will be prepared for all patients who died.

The incidence of all SAEs will be summarized by SOC and PT, if there are a sufficient number of SAEs to warrant such a presentation. A listing of all SAEs with an onset date prior to receiving study drug will also be presented. These listings will present SOC and PT of the SAE, severity, action taken, outcome, and relationship of the SAE to study drug, start and stop date of the SAE, study day of onset of the SAE, age, race, and gender.

Narratives will be prepared for all patients with a SAE, including deaths.

Narratives will be prepared for patients who permanently discontinued from study drug due to an AE.

6.6.2 Clinical Laboratory Tests

Summary statistics will be presented for observed values of all hematology, chemistry, and urinalysis parameters at each visit with laboratory assessment and at End-of-Study, and also for changes from Baseline to each post-baseline visit with laboratory assessment and End-of-Study.

Shifts (abnormal low, normal, and abnormal high) for changes from Baseline to each post-baseline visit with laboratory assessment and End-of-Study, based on normal ranges, will be presented for hematology, chemistry and urinalysis parameters.

The incidence of laboratory abnormalities overall will also be presented. Where applicable, the incidence of abnormal values will be presented separately by whether the value is abnormally high or low. Patients will be counted at most once for a high or low abnormality for each laboratory parameter.

Listings of all laboratory abnormalities will be presented (separately for hematology and blood chemistry parameters). Laboratory ranges used to identify abnormal results will be provided by the central laboratory.

Listings of observed values of all hematology, chemistry, and urinalysis parameters, as well as pregnancy test results will be presented for all randomized patients.

6.6.3 Concomitant Medication

The incidence of concomitant medications will be summarized for the Safety Analysis Set by generic term coded with the World Health Organization-Drug Dictionary (WHO-DD) Enhanced, overall and by treatment group.

To allow assessment of concomitant medication that might affect the efficacy outcomes, counts will be presented for each treatment group at each visit of patients receiving any rescue medication at that visit; counts of patients receiving any rescue medication will also be presented during the study. Rescue medication is defined as the use of non-biologic DMARDs, after Week 16 of the study. Time to first incidence of rescue medication after Week 16 of the study will be estimated for each treatment group and presented using Kaplan-Meier methods. Kaplan-Meier plots will also be presented. In addition, percentiles of time without rescue medication will be presented.

6.6.4 Vital Signs, ECG Findings, and Physical Examination

Summary statistics will be presented for results at each visit with vital sign assessments and at End-of-Study, as well as for change from Baseline results to each visit with vital sign assessments and End-of-Study for systolic and diastolic blood pressure, and pulse rate.

The overall incidence of vital sign abnormalities will also be presented. Patients will be counted at most once for an abnormality for each vital sign parameter.

A listing of all vital sign abnormalities will be presented for the safety set. Criteria used to define abnormal vital sign results will be defined in the SAP. Shifts (abnormal low, normal, and abnormal high) for changes from Baseline to each post-baseline visit with vital sign assessments and End-of-Study, based on normal ranges, will be presented for vital sign parameters.

A table and listing of any ECG abnormalities at Screening will be presented for the Safety Analysis Set.

A listing of physical examination abnormalities will be presented for the Safety Analysis Set.

6.6.5 B Cell Recovery

B cell recovery is defined as “peripheral B cell counts that have returned to Baseline values or the lower limit of normal, whichever is lower”. The incidence of B cell recovery and CD19+ B cell count per patient will be summarized at each visit after Week 24, overall and

by treatment group. The follow-up of patients will be up to Week 52 from the start date of the first course of treatment in order to monitor B cell recovery.

6.7 Immunogenicity Analysis

Incidence of HACA and neutralizing antibody and summary of counts of antibodies per patient at prior first dose on Day 1 and at Week 1, 2, 4, 12, 16, 24, 36, and 52 will be summarized overall and by treatment group.

6.8 Other Analysis

The exploratory subgroup analysis will be performed. The subgroups to be used for this analysis will be based on the results of analysis of PK, PD, efficacy, safety, immunogenicity and concomitant medication.

6.9 Interim Analysis

Interim analysis of 10 patients per group (30 patients in total) of safety data collected up to Week 4 and 20 patients per group (60 patients in total) of safety data collected up to Week 12 are planned. Safety data will be handled by unblinded study team in CRO for interim analysis, and the safety report will be submitted to regulatory. The study will be unblinded at Week 24 and an interim CSR will be prepared based on the 24-week data of all patients. The investigators and patients will remain blinded to treatment assignment during the post Week 24 follow-up period.

After review by DSMB, this analysis will be reported to health authorities upon request.

6.10 Safety Review

An independent DSMB will be established to act in an advisory capacity to monitor patient data. The DSMB will review available study data at pre-specified time-points, as outlined in the DSMB charter.

The details of the DSMB roles and responsibilities, the stopping rules for safety reasons and the logistics of the DSMB activities will be outlined in a DSMB charter.

6.11 Handling of Missing Values and Outliers

No missing data will be imputed for the efficacy analyses in FAS. Treatment of missing values, and outliers, and methodology will be detailed in a separate SAP.

6.12 Procedure for Reporting Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedure that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IRB/IEC approval or favorable opinion of an appropriate amendment, and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data.

All deviations from the approved protocol must be documented and notified to the Sponsor or CRO at the earliest. The Investigator should not deviate from the protocol, except for patient safety reasons, in which case the deviation must be reported to the Sponsor or CRO immediately. The Sponsor will not assume any resulting responsibility or liability from unapproved deviations. The Investigator, according to applicable regulations and the IEC established procedures, will inform the IEC of protocol deviations.

All instances where the requirements of the study protocol are not complied with will be captured in the clinical trial management system (CTMS) and the study monitor will prepare a Protocol Deviation/Violation Log. Corresponding patients may be discontinued from the study treatment at the discretion of the Sponsor/designee. Deviations from the study protocol should not be made other than as part of a protocol amendment. An amendment must be agreed upon by the Sponsor, but not implemented until written IRB/IEC approval is obtained, except where necessary to eliminate an immediate hazard to study patients or when the change(s) involves only logistical or administrative aspects. Protocol deviations/violations and the reason why they occurred will be documented in the clinical study report (CSR).

7 MANAGEMENT OF THE INVESTIGATIONAL MEDICINAL PRODUCT

7.1 Investigational Medicinal Product Identification

SAIT101, Rituxan® and MabThera® will be provided in sterile, preservative-free, non-pyrogenic, single-use vials containing 500 mg of rituximab per 50 mL. Two vials will be used per infusion (1,000 mg per 100 mL) with each carton of study drug containing two 50 mL vials of either SAIT101, Rituxan® or MabThera®.

The SAIT101, Rituxan® and MabThera® vials will be different in size. Therefore, site staff managing medication preparation will be unblinded.

7.2 Packaging and Labeling

Each carton and medication vial will be labelled with all the required information according to local regulations, including the Protocol Number (AGB001) and a unique identifier (Med ID) in a blinded manner. This will be programmed into the IXRS. At each infusion visit, the IXRS will assign the correct vial for the allocated treatment group and visit and the Med ID will be linked to an individual patient. The Med ID is assigned by the IXRS.

Any used and unused product or waste material should be disposed of in accordance with local requirements, when certificates of destruction are available, or in case not possible, centrally as per Sponsor guidance.

7.3 Storage

Study drugs will be stored in a secure area according to local regulations. Access should be strictly limited to unblinded study personnel (e.g., pharmacist). It is the responsibility of the Investigator, Sub-investigator, or authorized person to ensure that study drugs are only administered to study patients.

All study drugs must be kept in a secure place under appropriate storage conditions. The medication vials must be stored in a refrigerator at a controlled temperature (2 to 8°C) and handled according to GCP. Vials should be kept in the outer carton in order to protect it from light. A temperature log must be kept, on which the storage temperature of the study drug is recorded at least once a day. The study drug, SAIT101, Rituxan® and MabThera®, must be kept strictly separate and in a different location than commercially available product at all times. Additional details regarding the storage and handling of the study drugs will be provided to the study centers.

7.4 Preparation, Storage after Preparation and Administration

Study drug preparation should be done using aseptic techniques. Sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks, and transfer tubing, etc., should be used during dosage preparation and infusion.

An unblinded study team member should dilute the 2 vials of study drug (1,000 mg) assigned via IXRS to a calculated concentration of 1 to 4 mg/mL rituximab in a 250 mL, 500 mL or 1,000 mL polyvinyl chloride (PVC) or polyethylene (PE) infusion bag containing either 0.9% sodium chloride or 5% glucose for injection. The unblinded study team member should clearly label the bag in a blinded manner with the study code and patient number and total dose of rituximab contained in the bag.

The prepared infusion solutions of study drug are physically and chemically stable for 24 hours at 2 to 8°C and subsequently 12 hours at room temperature. From a microbiological point of view, the prepared infusion solutions should be used immediately. If not used immediately, the prepared infusion solutions must be stored at 2 to 8°C for no longer than 24 hours. The prepared infusion solutions must be at room temperature prior to infusion.

Infusion of the study drug should be performed according to the recommended infusion rates provided in Table 1.

An infusion device capable of administering the study drug with rates varying from as low as 0.2 mL/minute up to 3.3 mL/minute would be suitable. This would be best achieved by a volumetric infusion pump. An in-line filter is not mandatory.

More detailed instructions for study drug preparation, storage, and infusion will be provided in the Pharmacy Manual.

7.5 Accountability

The unblinded study personnel (e.g., pharmacist) must maintain an inventory record of the study drug (including test or comparator drug) received, dispensed to blinded team and returned. The Investigator or delegate should maintain an inventory record of the study drug (including collection from pharmacy, infusion to the patient). Accountability assures the Regulatory Authorities and the Sponsor that the study drug will not be dispensed to any person who is not a patient under the terms and conditions set forth in this protocol. Records or logs must comply with applicable regulations and guidelines.

7.6 Returns and Destruction

Upon completion or termination of the study, all unused IMP may return to sponsor or may managed in accordance with the local regulation..

All study drug returned to the Sponsor must be accompanied by the appropriate documentation and be clearly identified by protocol number and study center number on the outermost shipping container. Returned supplies should be in the original containers (e.g., patient kits). The assigned study monitor should facilitate the return of unused and/or partially used study drug.

If the study drug is authorized to be destroyed at the study center by the Sponsor, it is the Investigator's responsibility to ensure that arrangements have been made for its disposal. Written authorization should be issued by the Sponsor, procedures for proper disposal should be established according to applicable regulations, guidelines and procedures, and appropriate records of the disposal should be documented and forwarded to the Sponsor.

8 DATA HANDLING AND RECORD KEEPING

8.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, medical records, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the study center or Investigators and, as defined in the ICF, made available for study-related monitoring, audits, IRB/IEC review and regulatory inspection by authorized persons.

8.2 Data Collection

An eCRF will be created for all patients who provide consent to participate in the study. However, no data will be collected in case of screen failure.

During each patient's visit to the study center, the Investigator or Sub-investigator participating in the study will record source documents to document all significant observations. At a minimum, these records will contain:

- Documentation of the informed consent process, including any revised consents;
- The date of the visit and the corresponding Visit or Day in the study schedule;
- General patient status remarks, including any *significant* medical *findings* i.e., the severity, frequency, duration, action taken, and outcome of any AEs and the Investigator's assessment of relationship to study drug must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of each Investigator (or Sub-investigator) who made an entry in the source document.

In addition, any contact with the patient via telephone or other means that provides significant clinical information will also be documented in the source documents as described above.

Information from the source documents will be LEGIBLY and promptly transcribed to eCRFs for transmission to the Sponsor.

1. Patient data entered directly into the database from the study center via a web browser will constitute the patient's eCRF.

2. An eCRF will be created for all patients who provide consent to participate in the study. However, no data will be collected in case of screen failure.

3. Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor (or an appropriate company designated by the Sponsor to perform these activities). Patient data will be captured in an eCRF and reviewed by the monitor to check adherence to the protocol and to detect any data inconsistency or discrepancy.

4. The Investigator or Sub-investigator will ensure that the clinical data are reported in the eCRF in accordance to the study protocol and eCRF completion guidelines created by Clinical and/or Data Management.

5. Forms should be available during periodic visits by study monitors to enable review for completeness and acceptability. Any correction to the data entered into the eCRF must be carried out by the Investigator or study personnel.

6. When data is entered into eCRFs from study centers, an automatic preliminary logical check will be applied. Additionally monitors and clinical data managers will review the eCRF for accuracy and can generate queries to the study personnel for resolution. The Investigator or Sub-investigator will make corrections as necessary. These changes may be made either on the initiative of the site personnel or in response to monitoring or data queries. Any changes to written data must be made using GCP corrections and any change to electronic data should be made in a system which can provide an audit trail.

7. An audit trail history can be provided. All revisions made after the initial data entry is saved on the server, will be recorded within the system (date and time of revision, date and time of query, name of person making revision, name of person issuing query, pre- and post-revision data, reason for revision, etc.).

8. After completion of all eCRF data revisions, and confirmation that the revision history and corrections of revision are correct and complete, the Investigator must provide his/her electronic signature in the relevant signature forms. Thereafter, eCRF in PDF files (CRF and audit trail) will be stored on CD-ROM or DVD-ROM and kept at the study center.

9. Coding: Medical/surgical history and underlying diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities. Concomitant medications will be coded using the World Health Organization-Drug Dictionary Enhanced. The versions of coding dictionaries used will be stated in the study report.

8.3 File Management at the Study Center

It is the responsibility of the Investigator to ensure that the study center file is maintained in accordance with Section 8 of the ICH-GCP Guideline and as required by applicable local regulations. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

8.4 Records Retention at the Study Center

Regulatory requirements for the archiving of records for this study necessitate that participating Investigators maintain detailed clinical data for the longest of the following periods:

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

The Investigator must not dispose of any records relevant to this study without either written permission from the Sponsor or providing an opportunity for the Sponsor to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is patient to inspection by the Sponsor and relevant regulatory authorities. If the Investigator withdraws from the study (e.g., relocation, retirement), all study-related records should be transferred to a mutually agreed-upon

designee within a Sponsor-specified timeframe. Notice of such transfer will be given to the Sponsor in writing.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Monitoring

The Sponsor has ethical, legal, and scientific obligations to follow this study carefully in a detailed and orderly manner in accordance with established research principles, the ICH-GCP Guidelines, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the study), the Sponsor's monitors will visit the study center during the study in addition to maintaining frequent telephone and written communication.

9.2 Auditing

The Sponsor's Quality Management Unit (or representative) may conduct audits at the study centers. Audits will include, but are not limited to, study drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The Investigator agrees to participate in audits conducted at a reasonable time in a reasonable manner.

9.3 Inspection

Regulatory authorities worldwide may inspect the study center during or after the study. The Investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with the inspections conducted at a reasonable time in a reasonable manner.

10 ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the ethical principles outlined in the Declaration of Helsinki, the ICH-GCP Guidelines, all applicable regulatory requirements, and the protocol. Each study center will seek approval by an IRB/IEC according to regional regulations. The IRB/IEC will investigate the ethical, scientific, and medical appropriateness of the study. Further, in preparing and handling eCRFs, the Investigator, Sub-investigator, and their study personnel must take measures to ensure adequate care in protecting patient privacy. To this end, patient numbers will be used to identify each patient.

11 CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. Patient confidentiality requirements of the region(s) where the study is conducted must be met. However, authorized regulatory officials and Sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All study drugs, patient bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Patients will be identified only unique patient numbers in the eCRFs.

12 PUBLICATION POLICY

The Sponsor supports the efforts of health authorities to increase the transparency of medical research conducted in human patients and will register and maintain the information of clinical studies on a public registry program such as www.clinicaltrials.gov. The Sponsor is committed to the public disclosure of the results from clinical studies through posting on public clinical study data banks such as www.clinicalstudyresults.org. The results summary will be posted to the public clinical study data bank within one year after study completion, defined as the last patient's last visit, whether or not the results are favorable to the study drug. For studies involving products whose development program is discontinued before approval, the Sponsor will post the results within one year after such discontinuation. The Sponsor will comply with the guidelines of regulatory authorities with regards to public registration and disclosure of clinical study data.

The Sponsor has no objection to publication by the Investigator of any information collected or generated by the Investigator, whether or not the results are favorable to the study drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the Investigator will provide the Sponsor an opportunity to review any proposed publication or other type of disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) before it is submitted or otherwise disclosed.

If the study is part of a multi-center study, the Investigator agrees that the first publication is to be a joint publication covering all centers. Results from subsets should not be published in advance or without clear reference to the entire primary data. Authors will be the Sponsor, Coordinating Investigator and those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of number of patients enrolled and will be reviewed at the end of the study by the Sponsor. In the event of any disagreement in the content of any publication, both the Investigator's and the Sponsor's opinion will be fairly and sufficiently represented in the publication.

An external CRO or laboratory involved in the conduct of the study has no publication rights regarding the study.

If the Investigator wishes to independently publish/present any results from the study, the draft manuscript, abstract or presentation must be submitted in writing to the Sponsor for comment at least 60 days prior to submission. Comments will be given within 60 days from receipt of the draft manuscript. The Investigator will comply with requests from the Sponsor to delete references to its confidential information (other than the study results) in

any paper, abstract or presentation. If any patent action is required to protect intellectual property rights, the Investigator agrees to withhold publication or presentation to allow sufficient time for the Sponsor.

Publication of study results is also provided for in the Clinical Study Agreement between the Sponsor and the institution.

13 AMENDMENT POLICY

The Investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it is an overall change or a change for specific study centers, must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed by the Investigator(s) and the Sponsor. If agreement is reached regarding the need for an amendment, it will be written by the Sponsor. The written amendment must be submitted to the chairman of the IRB/IEC identified with this responsibility. Except for "administrative" or "non-substantial" amendments, Investigators must await IRB/IEC approval of protocol amendments before implementing the change(s). Administrative amendments are defined as amendments that have no effect on the safety of the research patients, scope of the investigation, conduct or management of the study, quality, the scientific value of the study, or the quality or safety of the study drug used in the study. A protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately, and the IRB/IEC should be notified according to the provisions specified by each IRB/IEC. The Sponsor will ensure protocol amendments are submitted to the applicable regulatory agencies.

When, in the judgment of the chairman of the IRB/IEC, the Investigators and/or the Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the patient, the currently approved written ICF will require similar modification. In such cases, repeat informed consent will be obtained from patients enrolled in the study before expecting continued participation.

14 REFERENCES

1. Ku IA, Imboden JB, Hsue PY, Ganz P. Rheumatoid arthritis: model of systemic inflammation driving atherosclerosis. Circ J, 2009; 73(6): 977-85.

2. Scott DL. Early rheumatoid arthritis. Br Med Bull, 2007. 81-82: 97-114.

3. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res, 2002; 4: 265-72.

4. MabThera®: European Public Assessment Report – EMEA/H/C/259/II/0039, Variation, 29/09/2006. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000165/WC500025822.pdf.

5. MabThera®: European Public Assessment Report – EMEA/H/C/000165/II/0065, Variation, 25/10/2010. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000165/WC500099488.pdf.

6. MabThera®: European Public Assessment Report – Summary of Product Characteristics, 18/01/2011. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf.

7. FDA label for Rituxan® (rituximab), revised 08/2014. Retrieved Jan 30, 2015, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103705s5432lbl.pdf

8. Investigator's Brochure. SAIT101 (Rituximab). Archigen Biotech Ltd. Edition Number: 1.0 (draft). Release date: Feb 2015.

9. Kim WS, Kim SJ, Kang HJ, Kim JS, Choi CW, Lee SI, et al. Safety, Pharmacokinetic, Pharmacodynamic Profile and Efficacy of SAIT101, a Biosimilar Product of Rituximab in Patients with Diffuse Large B-Cell Lymphoma. European Hematology Association 2012. Abstract 780-P

10. Summary of product characteristics. EMA. (n.d.). Retrieved Jan 30, 2015 from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf.

11. Rituxan® highlights of prescribing information. FDA. (2011, April 19). Retrieved Oct 17, 2011 from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf.

12. Ferdinand Breedveld, Sunil Agarwal, Ming Yin, Song Ren et al., Rituximab Pharmacokinetics in Patients With Rheumatoid Arthritis: B-Cell Levels Do Not Correlate With Clinical Response, The Journal of Clinical Pharmacology. 2007; 47:1119-1128.

13. Cohen SB1, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al., Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006; 54: 2793-806

14. Lopez-Olivo MA1, Amezaga Urruela M, McGahan L, Pollono EN, Suarez-Almazor ME. Rituximab for rheumatoid arthritis. Cochrane Database Syst Rev. 2015 Jan 20; 1: CD007356.

15. Vollenhoven RF, Emery P, Bingham CO. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients; Ann Rheum Dis. 2013; 72: 1496-502.

16. Pope JE, Haraoui B, Thorne JC, Vieira A, Poulin-Costello M, Keystone EC. The Canadian methotrexate and etanercept outcome study: a randomised trial of discontinuing versus continuing methotrexate after 6 months of etanercept and methotrexate therapy in rheumatoid arthritis. Ann Rheum Dis. 2014; 73: 2144-51.

15 APPENDICES

Appendix 1 Signature of Investigator

PROTOCOL TITLE: A Randomized, Double-blind, Parallel Group, Multicenter Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy of SAIT101 versus MabThera® versus Rituxan® in Patients with Rheumatoid Arthritis (RA).

PROTOCOL NO: AGB001

This protocol is a confidential communication of Archigen Biotech Ltd, I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Archigen Biotech Ltd.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed page to Archigen Biotech Ltd.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature Principal Investigator: _____

Printed Name: _____

Date: _____

Investigator Title: _____

Name/Address

and Contact Details: _____

_____

_____

Appendix 2 Investigator Responsibilities

Per Good Clinical Practices 21CFR312.53

The Investigator:

- Will conduct the study in accordance with the relevant, current protocol and will only make changes in the protocol after notifying the Sponsor, except when necessary to protect the safety, the rights, or welfare of patients;
- Will comply with all requirements regarding the obligations of clinical Investigators and all other pertinent requirements;
- Will personally conduct or supervise the described investigation;
- Will inform any potential patients that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval are met;
- Will report to the Sponsor adverse experiences that occur in the course of the investigation in accordance with 21CFR312.64;
- Has read and understands the information in the Investigator's Brochure, including the potential risks and side effects of the drug; and
- Will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

Per Good Clinical Practices 21CFR312.60

General Responsibilities of Investigators:

An Investigator is responsible for ensuring that an investigation is conducted according to the signed Investigator's statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of drugs under investigation. An Investigator shall, in accordance with the provisions of part 50, obtain the informed consent of each human patient to whom the drug is administered.

Obligations of the Investigator

The Investigator shall:

- Obtain IEC/IRB approval to conduct the clinical study and report to the IEC/IRB as required. The IEC/IRB must assume continued responsibility for the study and review the research on at least an annual basis.
- Maintain a file of all communications with the IEC/IRB.
- If in the US, complete, sign, and return to CRO a Form FDA 1572 including a current CV for the Principal Investigator and Sub-investigator(s), if listed.
- Conduct the study in strict adherence to the protocol.
- Supervise the use of the investigational product as outlined in the protocol. The investigational product may only be provided by study personnel under the supervision of the Investigator.
- Store the investigational product in a secure and locked area with limited access. The storage and custody of the investigational product are the responsibilities of the Investigator.
- Maintain adequate records of the receipt and disposition of all investigational products (including dates, quantities and use by study patients).
- Inform each patient of the risks and benefits of participating in the study and obtain a properly signed, dated and witnessed (if applicable) ICF for each patient before he or she begins any study-related procedures.
- Document all adverse events on the medical records and the eCRFs; document all SAEs on the SAE form and immediately notify Sponsor or CRO within 24 hours of awareness.
- Report all SAEs to the IEC/IRB, as per IEC/IRB requirements.
- Maintain a master log of all patients screened for the study and establish a system to alert study personnel of scheduled Follow-up visits; provide study personnel with a system for contacting study patients who do not return for scheduled follow-up.

- Document and maintain accurate eCRFs for all patients. As required, sign forms ascertaining the accuracy of data recorded. Storage and custody of all study-related records are the responsibility of the Investigator.

- Retain the copies of the eCRFs, the original ICFs and all study-related documentation at the study center for a period of fifteen (15) years after termination of the study unless CRO authorizes, in writing, earlier destruction. Notify CRO before destroying any study records after the required retention period. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

- Make available all study patients' records to study personnel and representatives from CRO, Sponsor, the IEC/IRB and FDA, or other Regulatory Agency personnel.

- Return to Sponsor or their agent, study materials (which may include unused study supplies) following completion, discontinuation or suspension of the study.

- Be thoroughly familiar with the properties of the investigational product as described in the Clinical Investigator's Brochure.

- Ensure that sufficient time is allotted to conduct and complete the study; ensure adequate study personnel and facilities are available for the duration of the study; and ensure that other studies do not divert essential patients or facilities from the study at hand.

- Provide information to all study personnel involved with the study or with other elements of the patient's management.

- Notify CRO and Sponsor immediately in the event the blind is broken.

- Ensure that the confidentiality of all information about patients and the information supplied by CRO and Sponsor is respected by all persons.

- There is no obligation to complete financial disclosure forms and also no obligation to notify CRO or Sponsor of Regulatory inspections.

Appendix 3 American College of Rheumatology 1987 Revised Criteria for the Classification of Acute Arthritis of Rheumatoid Arthritis

Criterion	Definition
Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling of fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left Proximal Interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, and metatarsophalangeal (MTP) joints.
Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint.
Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result had been positive in <5% of normal control patients.
Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

*For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is *not* to be made.

Reference:

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS *et al*.

The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315-24.

Appendix 4 Functional Class

Classification of Global Functional Status in Rheumatoid Arthritis (as per ACR 1991 Revised Criteria)

Class I	Able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

* Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age-and-sex specific.

Appendix 5 DAS28 and EULAR Response Criteria

DAS28 is a formula combining:

- Tender Joint Count (28 joints)
- Swollen Joint Count (28 joints)
- ESR (mm/hour) or CRP (mg/L)
- General Health - Patient's Global Assessment of Disease Activity (VAS)

$$DAS28\text{-}CRP = [0.56 \times \sqrt{(TJC28)} + 0.28 * \sqrt{(SJC28)} + 0.36 * \log_{nat}(CRP+1)] \times 1.10 + 1.15$$

A calculator is available online at the following website:
http://www.das-score.nl/das28/DAScalculators/dasculators.html

A representation and example is given below:

Based on the DAS28 score, disease activity is classified as:

≤ 2.6	Remission
>2.6 ≤ 3.2	Low disease activity
>3.2 ≤ 5.1	Moderate disease activity
>5.1	High disease activity

EULAR response Criteria:

Based on the DAS, response criteria have been developed, the EULAR response criteria. The EULAR response criteria include not only change in disease activity but also current disease activity. To be classified as responders, patients should have a significant change in DAS (at least >0.6 from Baseline) and also low current disease activity. Three categories are defined: good, moderate, and non-responders.

The EULAR response criteria using the DAS28			
	Improvement in DAS28 from Baseline		
DAS28 at endpoint	> 1.2	>0.6 and ≤1.2	≤0.6
≤3.2	Good	Moderate	None
> 3.2 and ≤5.1	Moderate	None	None
> 5.1	Moderate	None	None