Clinical Study Protocol

Protocol Title:	**A Randomized, Double-blind, Multi-center, Multi-national Trial to Evaluate the Efficacy, Safety, and Immunogenicity of SAIT101 Versus Rituximab as a First-line Immunotherapy Treatment in Patients with Low Tumor Burden Follicular Lymphoma**
Protocol Number:	**AGB 002**
Date of Protocol:	**3NOV2017 (Amendment 03)**
Product:	**SAIT101**
Pre-IND No.:	**PIND 111436**
EudraCT Number:	**2016-001966-27**
NTC Number:	**02809053**
Study Phase:	**III**
Sponsor:	**Archigen Biotech Limited** **1 Francis Crick Avenue** **Cambridge Biomedical Campus, Cambridge** **CB2 0AA, United Kingdom**

SYNOPSIS

Name of Sponsor/Company:	Archigen Biotech Limited	
Name of Finished Product:	SAIT101 (proposed rituximab biosimilar)	
Name of Active Ingredient:	Rituximab	
Title of Study:	A Randomized, Double-blind, Multi-center, Multi-national Trial to Evaluate the Efficacy, Safety, and Immunogenicity of SAIT101 Versus Rituximab as a First-line Immunotherapy Treatment in Patients with Low Tumor Burden Follicular Lymphoma	
Protocol No:	AGB 002	
Investigators:	Approximately 165 investigators	
Study sites:	Approximately 165 study sites globally	
Study duration: 52 week study period, plus up to a 30-day screening period.		**Phase:** III

Objectives:

Primary:

To compare the efficacy of SAIT101 with rituximab licensed in the European Union (hereafter designated MabThera®, brand name in EU) when administered as a first-line immunotherapy in patients with low tumor burden follicular lymphoma (LTBFL).

Secondary:

To evaluate SAIT101 versus MabThera® with respect to:

- Safety and tolerability;
- Immunogenicity;
- Pharmacokinetics (PK) and pharmacodynamics (PD) in a sub-population of patients.

Methodology:

This is a multi-center, randomized, double-blind, parallel-group study to evaluate the statistical equivalence of efficacy, and to assess the safety of SAIT101 versus MabThera® in asymptomatic patients with LTBFL. Patients will be randomized in a 1:1 ratio to receive study drug once a week for 4 weeks, and will then be followed up for up to 52 weeks after the first dose. Randomization will be stratified by inclusion in the PK/PD sub-population and Follicular lymphoma international prognostic index 2 (FLIPI-2) score. Patients will also be administered pre-medication with steroids (according to institutional standards), an analgesic/antipyretic, and an anti-histamine before the start of each study drug infusion. Visits are scheduled at Weeks 1, 2, 3, and 4 (study drug infusion visits), and then at Weeks 5, 12, 20, 28, 36, and 52 (i.e., End of Study [EOS]). Efficacy response assessments will be performed at Weeks 12 and 28, while safety assessments will continue until EOS. Centralized facilities will be used for imaging assessments.

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 statistical analysis of the primary endpoint for this study will be performed after the last patient has completed the Week 28 response assessment. All efficacy data will be analyzed at this time, plus all PK, PD, immunogenicity, and safety data available at the time of data cut-off, and these data will be reported in a CSR (Week 28 CSR). After the last patient has completed Week 52 of the study, a CSR addendum (Week 52 CSR) will be prepared to report the additional safety, PK, and PD data. An interim analysis of data collected upto Week 12 such as PK, PD, efficacy, safety and immunogenicity inclusive of the data from the PK/PD sub-population (134 patients in total) is planned.

Progressive multifocal leukoencephalopathy (PML), hepatitis reactivation, infusion reactions, anaphylactic reactions, mucocutaneous reactions, and serious infection (infections requiring i.v. antibiotics or meeting the definition of a serious adverse event [SAE]) are adverse events of special interest (AESIs) in this study.

These events will be monitored and captured throughout the study.

A sub-population of approximately 134 consenting patients (67 patients per group) will be randomized for PK and PD assessments (PK/PD sub-population)

Planned number of patients:	Sufficient patients will be screened so that approximately 308 patients are enrolled in the study
Diagnosis and main criteria for inclusion:	Patients with histologically-confirmed, Ann Arbor stage II – IVA CD20+ Follicular Lymphoma (FL) (Grades 1, 2, or 3a), aged at least 18 years, not previously treated for their FL, low tumor burden according to Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, at least one measurable lesion per the International Working Group (IWG) criteria 2007 at screening, no evidence of transformation to a large cell histology, and adequate hematological, renal, and liver function.
Test product, dose, and mode of administration:	SAIT101, intravenous (i.v.) infusion, 375 mg/m^2, once a week for 4 weeks
Comparator, dose, and mode of administration:	MabThera®, i.v. infusion, 375 mg/m^2, once a week for 4 weeks
Duration of study:	Total study duration up to 52 weeks for each patient. Efficacy will be followed up to Week 28, and safety will be followed up to Week 52.

Criteria for evaluation:

Primary Efficacy Endpoint:

Overall Response Rate (ORR) (Complete Response [CR] + Partial Response [PR]) at Week 28 as defined by IWG criteria 2007

Secondary Efficacy Endpoints:

Tumor response evaluations as defined by the revised IWG Criteria 2007, for malignant lymphoma:

- ORR at Week 12
- Complete Response (CR) at Weeks 12 and 28
- Partial Response (PR) at Weeks 12 and 28
- Stable Disease (SD) at Weeks 12 and 28
- Progressive disease (PD) at Weeks 12 and 28
- Time to event (TTE), defined as the time from the date of randomization to the date when an event occurs; an event is disease progression, death due to any cause, or the start of new treatment for FL, whichever comes first

Exploratory Efficacy Endpoints:

For patients who have their tumors additionally measured by positron emission tomography computerized tomography (PET-CT) scan, tumor response (CR, PR, SD, and PD), as defined by the IWG Criteria 2014, Lugano Classification, and TTE will also be evaluated.

Pharmacokinetic Endpoints:

The following PK parameters will be determined in the PK/PD sub-population of patients, for each study drug:

- Truncated area under the concentration-time curve (AUC) over the 1st and 4th dosing intervals (AUC_{0-168})
- Maximum concentration (C_{max}) after the 1st dose and the 4th dose
- Accumulation ratio for AUC_{0-168} obtained from the 4th dose versus the 1st dose ($RAUC_{0-168}$)
- Accumulation ratio for C_{max} (RC_{max})
- Trough concentrations on Days 1, 8, 15, 22 and 29 (C_{trough})

$AUC_{0\text{-}168}$ will be considered primary; C_{max} and C_{trough} (Day 29) will be considered secondary.

Pharmacodynamic Endpoints:

The following parameters will be determined for CD19+ B-cell counts in the PK/PD sub-population of patients:

- Observed change from baseline and percent change from baseline CD19+ B-cell counts up to Week 52
- Area under the curve from time 0 to Week 1 ($AUC_{0\text{-}W1}$), AUC from Week 1 to Week 2 ($AUC_{W1\text{-}W2}$), AUC from Week 2 to Week 3 ($AUC_{W2\text{-}W3}$), AUC from Week 3 to Week 4 ($AUC_{W3\text{-}W4}$), $AUC_{0\text{-}W12}$, $AUC_{0\text{-}W28}$, and $AUC_{0\text{-}W52}$ for the observed change from baseline and percent change from baseline CD19+ B-cell count data.

Immunogenicity Data:

- Incidence of human antichimeric antibody (HACA)
- Incidence of neutralizing antibody (if HACA is positive)

Immunogenicity sampling is to be done at Weeks 1, 2, 3, 4, 5, 12, 20, 28, 36, and 52 (EOS). Additionally immunogenicity assessment is also planned when patients show signs or symptoms of immune-response-related adverse events including anaphylaxis (Section 6.4.3) and mucocutaneous reaction (Section 6.4.5)

Safety:

Adverse events (AEs), AESI, physical examination, vital signs, ECG, and standard laboratory tests (including hematology, clinical chemistry, urinalysis, serum β2 microglobulin, and virology), the proportion of patients achieving B-cell recovery (i.e. ≥lower limit of normal (LLN) or at least 50% of the baseline value) at Week 12, 20, 28, 36 and 52.

Statistical methods:

Efficacy analyses:

The main endpoint will be ORR, the proportion of patients with an overall response of CR or PR (ORR, CR+PR, defined by IWG, 2007) assessed at Week 28.

Two-sided 95% CIs for the differences between SAIT101 and rituximab (MabThera®) in the percentage of patients achieving an overall response (CR+PR) at Week 28 will be computed using the Cochran-Mantel-Haenszel (CMH) method. The adjusted proportion difference in ORR and its 95% Newcombe-Wilson CI will be calculated using CMH weight. The efficacy analyses will be applied for both the per-protocol set (PP set) and the full analysis set (FAS). Primary efficacy analysis will be performed based on FAS. Appropriate sensitivity analyses will be applied to explore the robustness of results.

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

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. Treatment-emergent AEs (TEAEs) and SAEs will be summarized by the number and percentage of patients experiencing events by System Organ Class (SOC), Preferred Term (PT), and treatment group; TEAEs by severity and causality will be summarized similarly.

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 at the planned sampling time will be summarized overall and by treatment group.

Pharmacokinetic analyses:

The PK analysis will be performed on the PK/PD sub-population.

Descriptive statistics (number, mean, standard deviation, coefficient of variation [%CV], minimum, median, and maximum) will be used to summarize serum rituximab concentration data by treatment and study day at

each planned sampling time point. The PK parameters calculated from the serum rituximab concentrations will also be summarized by treatment and study day using descriptive statistics.

Plots of the mean and individual serial serum rituximab concentrations over time by treatment and study day, as well as trough concentrations, will be provided following i.v. infusions.

The geometric means of the primary PK parameters ($AUC_{0\text{-}168,1}$ and $AUC_{0\text{-}168,4}$) will be compared between SAIT101 and rituximab (MabThera®) using analysis of variance. The statistical analysis of the loge-transformed primary endpoints will be based on an analysis of variance model. Covariates (e.g., age, sex, body weight, etc.) may be added to the planned analysis. Least-squares geometric means will be presented for each treatment with corresponding 95% CIs. The ratio of least-squares geometric means (SAIT101/ rituximab) will presented with corresponding 90% CIs. Pharmacokinetic similarity will be concluded in the ratio of least-squares geometric means fall between 80.00% and 125.00% for both primary parameters. Estimates and CI will also be provided for secondary C_{max} and C_{trough} (Day 29) parameters.

Pharmacodynamic analyses:

The PD analysis will be performed on the PK/PD sub-population.

Descriptive statistics (n, mean, standard deviation, %CV, minimum, median, maximum, and 95% confidence intervals [CIs]) will be used to summarize CD19+ B cell count, IgG and IgM data (observed change from baseline and percent change from baseline) by treatment and study day at each planned sampling time point. The PD parameters calculated from observed change from baseline and percent change from baseline will also be summarized by treatment and study day using descriptive statistics.

Plots of the mean and individual observed change from baseline and percent change from baseline CD19+ B cell count over time by treatment and study day will be provided following i.v. infusions.

The means of PD parameters will be compared between SAIT101 and MabThera® using analysis of covariance.

Sample size:

The expected treatment effect of rituximab was an ORR of 77% with 95%CI (66%-85%) based on Ardeshna et al. 2014.[2]; an ORR of 6% was the treatment effect of patients in the 'watch & wait' group from the study.

The difference in ORR was estimated to be 71% with 95%CI (59%-79%), and the equivalence margin of ±16.0% (0.59 × [1-73/100] = 0.1593) was calculated to preserve at least 73% of the treatment benefit based on the lower bound 95%CI in the difference in ORR.

To achieve 83% power with a 16.0% margin and a 77% expected ORR for the difference-based approach with 2 one-sided tests at the significance level of 0.025, 154 patients in each group are able to satisfy the primary analysis of ORR, given an 83% probability of declaring the equivalence in the FAS.

Patients who discontinue the study drug early for any reason will be required to have efficacy assessments at Week 28. 154 patients per arm (308 patients overall) should be randomized into the study.

For PK, assuming a CV of 38% in $AUC_{0\text{-}168}$, based on Regazzi et al. 2005 and no true difference between SAIT101 and rituximab in these parameters, 60 evaluable patients per arm are required to yield 81% overall power for comparison of $AUC_{0\text{-}168,1}$ and $AUC_{0\text{-}168,4}$ between the test and comparator treatments, using the standard two one-sided testing procedure, and a 5% significance level for each one-sided test (90% CI). To ensure 120 evaluable patients are available, a total of 134 patients will be randomized for the PK/PD sub-population.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADCC	Antibody-Dependent Cell mediated Cytotoxicity
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase (alanine transaminase)
AST	aspartate aminotransferase (aspartate transaminase)
AUC	area under the concentration-time curve
$AUC_{0\text{-inf}}$	area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-}168}$	truncated AUC over the dosing interval
$AUC_{0\text{-}W1}$	area under the curve from time 0 to Week 1
$AUC_{WX\text{-}WY}$	area under the curve from Week X to Week Y
BCL-2	B cell lymphoma-2
BMWP	Biosimilar Medicinal Products Working Party
BSA	body surface area
BUN	blood urea nitrogen
CD_{20}	activated-glycosylated phosphoprotein expressed on the surface of all B cells
CDC	Complement-Dependent Cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine and prednisone
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computerized/computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

C_{trough}	trough concentration
CV	Coefficient of Variation
CVP	cyclophosphamide + vincristine + prednisone/prednisolone
DEHP	di-(2-ethylhexyl)phthalate
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
ESMO	European Society for Medical Oncology
Fab	fragment antigen-binding
FACS	Flow cytometry
FAS	Full Analysis Set
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma
FLIPI-2	Follicular lymphoma international prognostic index 2
GCP	Good Clinical Practice
GELF	Groupe D'Etude des Lymphomes Folliculaires
GFR	Glomerular Filtration Rate
GLS	geometric least square
GP	General Practitioner
GPA	granulomatosis with polyangiitis
HACA	human antichimeric antibody
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hCG	human chorionic gonadotropin

HIV	human immunodeficiency virus
HRQOL	health related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IUDR	Imputation Using Drop-out Reason
i.v.	intravenous(ly)
IWG	International Working Group
IXRS	Interactive Voice Telephone and Web Response System
LDH	lactate dehydrogenase
LOCF	Last Observation Carried Forward
LTB	low tumor burden
LTBFL	low tumor burden follicular lymphoma
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
Med ID	unique identifier assigned by IXRS
MI	Multiple Imputation
MPA	microscopic polyangiitis
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin’s lymphoma
NRI	non-responder imputation
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PD	progressive disease
PDS	Pharmacodynamic Analysis Set

PE	polyethylene
PEF	peak expiratory flow
PET	positron emission tomography
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PML	progressive multifocal leukoencephalopathy
PP	Per-protocol
PR	partial response
PT	Preferred Term
PVC	polyvinyl chloride
RAN	Randomized Set
$RAUC_{0-168}$	accumulation ratio for AUC_{0-168}
RC_{max}	accumulation ratio for C_{max}
R-CHOP	rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone
RESORT	Rituximab Extended Schedule or Re-Treatment Trial
RNA	Ribonucleic Acid
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	stable disease
SOC	System Organ Class
SOP	standard operating procedure
SPD	sum of the product of the diameters
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TEAE	treatment-emergent AE
TTE	time to event
TTF	time to treatment failure
ULN	upper limit of normal
US	United States
User ID	user identification
WHO-DD	World Health Organization-Drug Dictionary

1.0 INTRODUCTION

1.1 Background Information

1.1.1 Follicular Lymphoma

Non-Hodgkin's lymphoma (NHL), a group of malignancies arising from lymphoid tissue, is one of the leading causes of cancer death in the United States (US) and Europe. Its etiology is still largely unknown, but risk factors include age, certain infections, and treatments and diseases that cause severe immunosuppression. NHL is classified into 2 types: aggressive (fast growing) and indolent (slow growing). Indolent NHLs are highly responsive to initial therapy, but are characterized by repeated relapses and disease progression. Follicular lymphoma (FL) is one of the most common indolent forms of NHL, accounting for approximately 20% to 25% of all lymphomas. Follicular lymphoma commonly manifests as an enlargement of the lymph nodes in the neck, underarm, stomach, or groin, as well as splenomegaly and bone marrow infiltration, and may progress into diffuse large B cell lymphoma. In the World Health Organization (WHO) classification, the histology is further classified into Grade 1, 2, or 3 FL (Appendix 2), depending on the percentage of large cells seen on high power field microscopy. Grade 3 is further divided into 3a and 3b, where 3b represents a distinct biological entity more similar to diffuse large B cell lymphoma.

Patients with low tumor burden follicular lymphoma (LTBFL) have a 10-year survival rate of 75%,[1] and clinical outcome has improved in recent years with the introduction of rituximab. However, some patients are asymptomatic for many years, while others quickly present with a life-threatening disease. Because of this heterogeneity, it is important to stratify patients for treatment decisions based on tumor burden criteria, such as those of the Groupe D'Etude des Lymphomes Follicularies (GELF), and the Follicular Lymphoma International Prognostic Index-2 (FLIPI-2) (see Appendix 3). Based on these criteria, patients with low tumor burden (LTB) may have local or systemic therapy delayed until disease progression – a "watchful wait" strategy. In patients with high tumor burden, combination treatment with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (R-CHOP) or other regimens has resulted in superior treatment outcomes compared with multi-agent chemotherapy alone. Combined immunochemotherapy with rituximab has thus become the new standard of care for high tumor burden patients. The optimal timing of treatment for advanced, asymptomatic, FL is still to be determined, however. Before rituximab became available, patients with asymptomatic, advanced-stage FL showed no benefit with immediate chemotherapy compared with watchful-waiting, and watchful-waiting became the accepted standard of care. Recent data, however, have shown a benefit of first line rituximab monotherapy in delaying chemotherapy treatment in patients with

LTBFL.[2,3] Furthermore, this benefit could be achieved with just 4 injections of rituximab (once a week for 4 weeks), and no maintenance treatment. However, rituximab is not yet approved for monotherapy use in LTBFL.

1.1.2 SAIT101

SAIT101 is being developed as a potential biosimilar 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 immunoglobulin G1 (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®.

Pharmacokinetic (PK) and pharmacodynamic (PD) studies in cynomolgus monkeys have also shown similarity in the 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®.

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 and was designed to compare and assess PK and PD profiles, and preliminary safety and efficacy of SAIT101 compared to MabThera® after intravenous (i.v.) infusion of MabThera® or SAIT101. 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 cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

Kim et al[8] reported that the ratio of geometric least square (GLS) means (90% confidence interval, CI) of SAIT101 versus MabThera® were 0.92 (0.78-1.09) for AUC_{last} and 0.93

(0.78-1.13) for maximum concentration (C_{max}). The LS means change from baseline of B-cells (%) in the SATI101 and MabThera® groups were -7.7% and -8.0% respectively, and the difference between the 2 groups was 0.3% (90% CI, -0.9-1.4). The safety and efficacy profiles of SAIT101 were not significantly different from MabThera®.

Further information is available in the SAIT101 Investigator Brochure.[9]

1.1.3 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.

MabThera® is the commercially available product in the European Union, and Rituxan® is the commercially available product in the US and Japan.

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 relapsed or refractory follicular CD20+ B cell NHL. Since then, it has also been approved for first line follicular lymphoma in combination with chemotherapy or as maintenance for patients who achieved a response in combination with chemotherapy. Rituximab is also indicated for patients with non-progressing CD20+ B cell NHL (including stable disease) as a single agent after first line treatment with cyclophosphamide + vincristine + prednisone/prednisolone (CVP) chemotherapy. Rituximab, in combination with CHOP chemotherapy, is now a standard therapy in the initial treatment of diffuse large B cell lymphoma and many other B cell lymphomas. Additional indications include chronic lymphocytic leukemia (CLL), rheumatoid arthritis, granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis), and microscopic polyangiitis (MPA).[10,11]

Rituximab was co-developed and marketed in the US (under the brand name Rituxan®) by Biogen Idec and Genentech (now a subsidiary of Roche). It is marketed outside of 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 stem 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 of B-cells into plasma cells, 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.

The fragment antigen-binding (Fab) domain of rituximab binds to the CD20 antigen on B lymphocytes, and the fragment crystallizable (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).

1.2 Rationale

1.2.1 Rationale for the Study

The term 'biosimilar' refers to a biologic drug that is developed to be highly similar to an existing licensed reference biologic. Biosimilars are intended to treat the same disease as the reference biologic using the same dose and treatment regimen. Unlike generic versions of chemically-synthesized small molecule therapies, biosimilars are not structurally identical to their reference biologics. This is due to the purity, characteristics, and activity of the specific biologic being dependent on, and sensitive to, changes in the process by which it was manufactured. Therefore the aim is to create a product with no clinically meaningful difference between the biosimilar and the reference biologics in terms of chemistry, manufacturing, and controls (CMC), purity, potency, pharmacokinetics, safety, immunogenicity, and efficacy. SAIT101 is being developed as a potential biosimilar to rituximab. The substitution of rituximab by SAIT101 is expected to provide similar efficacy, PK, PD, safety, tolerability, and immunogenicity in patients with LTBFL, and this will be evaluated in this study.

1.2.2 Rationale for the Study Design

The majority of people with FL have widespread disease when first diagnosed. Bone marrow involvement is common and is present in more than 50% of patients. The vast majority of patients present with advanced disease (Ann Arbor stage III-IV), but are often asymptomatic. The disease is usually characterized by an indolent course, response to initial therapy with frequent relapses and shorter duration of response to salvage therapy. Follicular lymphoma has been associated with the translocation of chromosomes 14 and 18 [t(14;18)], which results in over-expression of the anti-apoptotic protein, B cell lymphoma 2 (BCL 2) and the subsequent inhibition of apoptosis of lymphoid cancer cells.[12] Immunohistochemical stains of excisional lymph-node or tissue biopsies are needed for definitive histopathological diagnosis. Diagnosis requires immunostaining for B cell markers like CD79a and CD20, the T cell marker CD3 and the proliferative marker Ki67 (with Ki67, a cut-off of less than 30% is consistent with follicular lymphoma). Immunohistochemical detection of CD20 antigen on malignant B-lymphocytes is required where treatment with anti-CD20 monoclonal antibodies is planned.

Several studies have shown considerable inter-individual variability in rituximab exposure among patients with NHL.[13,14] Guidance from the European Medicines Agency (EMA) and the FDA indicates that clinical testing of a biosimilar should be conducted in a patient population that is adequately sensitive to allow for the detection of differences in PK and efficacy profiles. Low tumor burden is defined by criteria developed by the GELF, and these criteria have been used in other FL trials.[3,15,16] Patients with a confirmed diagnosis of previously untreated LTBFL, according to GELF criteria, Ann Arbor Stage II-IVA, and Grade 1-3a will be enrolled into the study. This patient population is generally healthier, with fewer co-morbidities and concomitant medications, and thus reduced inter-individual variability, than patients with other types of follicular lymphoma; this will provide a more effective comparison between rituximab and SAIT101.

Rituximab monotherapy in LTBFL is an acceptable treatment option according to various treatment guidelines including the National Comprehensive Cancer Network (NCCN)[17] and the European Society for Medical Oncology (ESMO).[18] Ardeshna et al. demonstrated that single agent rituximab induction or induction plus maintenance (every other month, 12 doses) could significantly delay the initiation of chemotherapy compared to watchful waiting (78% and 88% versus 46% did not require new therapy at 3 years), and improve health related quality of life (HRQOL).[2] More recently, the RESORT (Rituximab Extended Schedule or Re-Treatment Trial) trial assessed the benefit of rituximab maintenance therapy (one dose every 3 months until progressive disease [PD]) versus retreatment following induction therapy with rituximab in patients with follicular lymphomas with low tumor burden. No significant differences were seen in terms of time to treatment failure (TTF), overall survival (OS), and HRQOL[3]. Rituximab monotherapy is an appropriate regimen for a comparability study because the efficacy, safety and immunogenicity results should not be confounded by a combination regimen.

The dose selected for this study is based on the clinically effective dose of rituximab. The duration of the study will be 52 weeks, as recommended by the EMA.

A sub-population of approximately 134 patients (67 patients per group) will be randomized for PK and PD assessments for the analysis of PK and PD.

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

1.3 Summary of Safety Information

The reference safety document for SAIT101 is the Investigator's Brochure; for MabThera® it is the Summary of Product Charactersitics.[6]

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 events during the study.

Rituximab can also cause severe, including fatal, infusion reactions (e.g., cytokine release syndrome, tumor lysis syndrome, and hypersensitivity reactions). Patients will be administered pre-medication with corticosteroids (where this is a local requirement), an analgesic/antipyretic, and an anti-histamine.

Further details of adverse events of special interest (AESI) requiring close monitoring are provided in Section 6.4.

Other risks include severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome), severe bullous skin reaction, and Stevens-Johnson syndrome (reported very rarely, but some with fatal outcome), local cutaneous reactions, cardiac disorders, hematological toxicities, infections, and issues with immunization (vaccines). Full details are available in the Summary of Product Characteristics for MabThera®.[6]

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To compare the efficacy of SAIT101 with rituximab licensed in the European Union (hereafter designated MabThera®) when administered as a first-line immunotherapy in patients with low tumor burden follicular lymphoma (LTBFL).

2.2 Secondary Objectives

The secondary objectives of the study are to evaluate SAIT101 versus MabThera® with respect to:

- Safety and tolerability;
- Immunogenicity;
- Pharmacokinetics (PK) and pharmacodynamics (PD) in the PK/PD sub-population of patients.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

Overall Response Rate (ORR) (Complete Response [CR] + Partial Response [PR]) at Week 28, as defined by International Working Group (IWG) criteria 2007 (Appendix 4). This will be assessed centrally.

2.3.2 Secondary Efficacy Endpoints

Tumor response evaluations as defined by the revised IWG Criteria 2007, for malignant lymphoma (Appendix 4):

- ORR at Week 12
- Complete Response (CR) at Weeks 12 and 28
- Partial Response (PR) at Weeks 12 and 28
- Stable Disease (SD) at Weeks 12 and 28
- Progressive disease (PD) at Weeks 12 and 28
- Time to event (TTE), defined as the time from the date of randomization to the date when an event occurs; an event is disease progression, death due to any cause, or the start of new treatment for FL, whichever comes first

2.3.3 Exploratory Efficacy Endpoints

For patients who have their tumors additionally measured by positron emission tomography (PET) - computerized tomography (CT) scan, tumor response (CR, PR, SD, PD) as defined by the IWG Criteria 2014, Lugano Classification[19], and TTE will also be evaluated.

2.3.4 Pharmacokinetic Endpoints

The following PK parameters will be determined in the PK/PD sub-population of patients, for each study drug:

- Truncated area under the concentration-time curve (AUC) over the 1st and 4th dosing intervals ($AUC_{0\text{-}168}$)
- Maximum concentration (C_{max}) after the 1st dose and the 4th dose
- Accumulation ratio for $AUC_{0\text{-}168}$ obtained from the 4th dose versus the 1st dose ($RAUC_{0\text{-}168}$)
- Accumulation ratio for C_{max} (RC_{max})
- Trough concentrations on Days 1, 8, 15, 22 and 29 (C_{trough})

2.3.5 Pharmacodynamic Endpoints

The following parameters will be determined for CD19+ B-cell counts in the PK/PD sub-population of patients:

- Observed change from baseline and percent change from baseline CD19+ B-cell counts up to Week 52
- Area under the curve from time 0 to Week 1 ($AUC_{0\text{-}W1}$), AUC from Week 1 to Week 2 ($AUC_{W1\text{-}W2}$), AUC from Week 2 to Week 3 ($AUC_{W2\text{-}W3}$), AUC from Week 3 to Week 4 ($AUC_{W3\text{-}W4}$), $AUC_{0\text{-}W12}$, $AUC_{0\text{-}W28}$, and $AUC_{0\text{-}W52}$ for the observed change from baseline and percent change from baseline CD19+ B-cell count data

2.3.6 Immunogenicity Endpoints

- Incidence of human antichimeric antibody (HACA)
- Incidence of neutralizing antibody (if HACA is positive)

2.3.7 Safety Endpoints

Adverse events (AEs), AESI, physical examination, vital signs, electrocardiogram (ECG), and standard laboratory tests (including hematology, clinical chemistry, urinalysis, serum β2 microglobulin, and virology), the proportion of patients achieving B-cell recovery (i.e. ≥

lower limit of normal (LLN) or at least 50% of the baseline value) at Week 12, 20, 28, 36 and 52

3.0 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a multi-center, randomized, double-blind, parallel-group study to evaluate the efficacy, safety, and immunogenicity of SAIT101 versus MabThera® in asymptomatic patients with low tumor burden follicular lymphoma. This study will take place globally across approximately 165 study sites in order to randomize approximately 308 patients.

The primary objective of the study is to compare the efficacy of SAIT101 with MabThera® in patients with LTBFL. The study will also evaluate SAIT101 versus MabThera® with respect to safety and immunogenicity, PK, and PD.

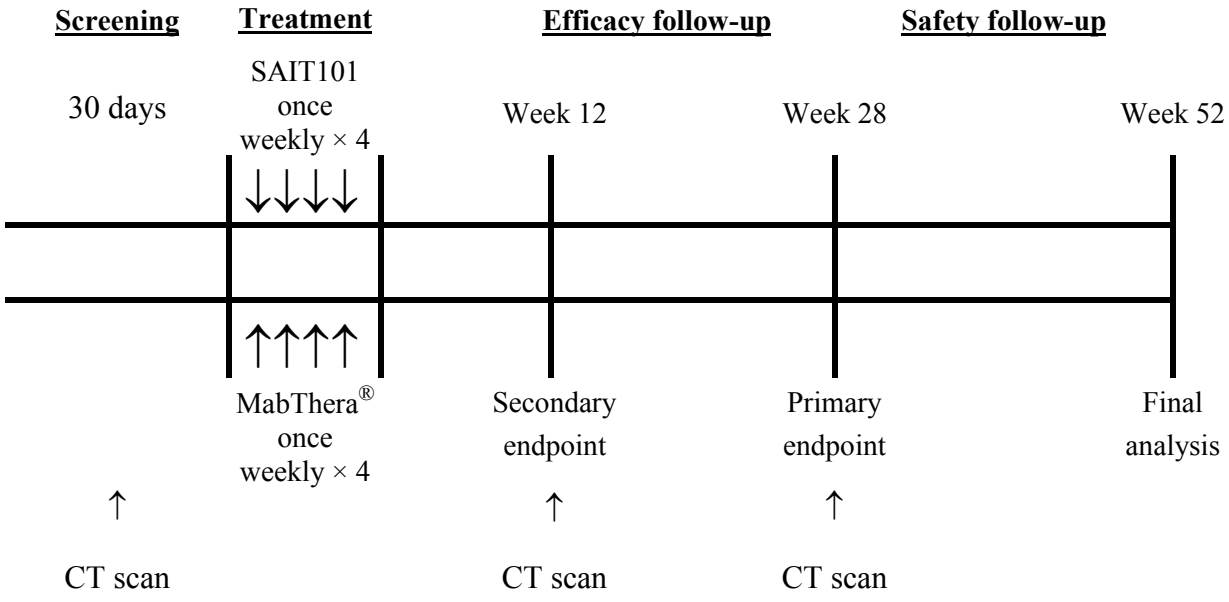
The study will enroll patients with LTBFL who are asymptomatic for lymphoma-specific B-symptoms. Low tumor burden will be assessed according to GELF criteria as used in previous studies.[15] Retrospective histological confirmation of CD20-positive FL will be obtained by a central pathology review.

Eligible patients will be randomized to receive either SAIT101 or MabThera® monotherapy as an i.v. infusion once a week for 4 weeks, at a standard dose of 375 mg/m^2 body surface area. Randomization will be stratified by inclusion in the PK/PD sub-population and FLIPI-2 score. Patients will also be administered corticosteroids (up to 100 mg i.v. methylprednisolone or its equivalent according to institutional standards), an analgesic/antipyretic, and an anti-histamine (e.g., paracetamol and diphenhydramine) before the start of each study drug infusion.

Patients will be followed up for up to 52 weeks from the start of the first infusion. Efficacy will be assessed at Weeks 12 and 28.

A summary of the study design is shown in Figure 1.

Figure 1 Schematic of Study Design for Protocol AGB 002



CT computerized/computed tomography

The primary endpoint is ORR at Week 28. Tumors will be assessed by CT scans of the neck, chest, abdomen, pelvis, and any other areas known or suspected to be involved, at baseline and Week 28. A CT scan will also be performed at Week 12 and at any time when there is clinical suspicion of disease progression or recurrence. Tumor status will be evaluated by central review as defined by the IWG Criteria 2007.

Secondary endpoints include ORR at Week 12 and CR, PR, SD, PD, TTE, drug concentration, CD19 + B-cell count and immunogenicity.

Full details of all the assessments to be performed at each visit are provided in Table 1.

Safety data collected will be reviewed by a Data Safety Monitoring Board (DSMB), as described in Section 8.9.6.

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

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

Patients who discontinue the study drug early for any reason will be required to have efficacy assessments at Week 28, and an early treatment discontinuation visit. If new treatment targeting FL (other than the protocol-defined scheduled treatment with rituximab monotherapy) must be started before the Week 28 assessments, then an early treatment discontinuation visit, including a CT scan (see Table 1), should be performed before the start of the new treatment. Patient who discontinue the study treatment will be followed-up until Week 52 (EOS) for safety and immunogenicity. Patients with progressive disease should be treated with an adequate therapy according to judgment of the treating physician. For patients who need to be withdrawn from the study early, it is highly recommended that efficacy assessments are conducted at Week 28 or an early End of Study (EOS) visit before they are formally withdrawn. Once a patient is withdrawn from the study, no further assessments can be conducted.

The statistical analysis of the primary endpoint for this study will be performed after the last patient has completed the Week 28 response assessment. All efficacy data will be analyzed at this time, plus all PK, PD, immunogenicity and safety data available at the time of data cut-off, and these data will be reported in the Clinical Study Report (CSR) (Week 28 CSR). After the last patient has completed Week 52 of the study, a CSR addendum (Week 52 CSR) will be prepared to report the additional safety, PK, and PD data. An interim analysis of data collected upto Week 12 such as PK, PD, efficacy, safety and immunogenicity inclusive of the data from the PK/PD sub-population (134 patients in total) is planned.

The end of the study is defined as ‘the last visit of the last patient undergoing the study’.

The study has been designed in accordance with the EMA ‘Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues’ (EMA/CHMP/BMWP/403543/2010)[20] and the FDA guidance ‘Scientific Considerations in Demonstrating Biosimilarity to a Reference Product’.[21]

Table 1 Schedule of Assessments

Study Period	**Screening[a]**	**Treatment**				**Follow-up**						**Early treatment discontin-uation visit[c]**	**Unscheduled visit[d]**
Visit	***1***	***2 (Baseline)***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***		
Week		**1**	**2**	**3**	**4**	**5**	**12**	**20**	**28**	**36**	**52/EOS[b]**		
Day (± window in days)	**-30 days[a]**	**1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 3**	**78 ± 3**	**134 ± 7**	**190 ± 7**	**246 ± 7**	**365 ± 7**		
Assessment													
Informed consent	**X**												
Inclusion/exclusion criteria	**X**	**X[e]**											
Demographics	**X**												
Medical/surgical history	**X**												
Study drug													
Contact IXRS	**X**	**X**	**X**	**X**	**X**						**X**	**X**	
Randomization		**X**											
Pre-medication		**X**	**X**	**X**	**X**								
Body weight[f]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study drug infusion[g]		**X**	**X**	**X**	**X**								
Disease assessments													
Histological confirmation of diagnosis[h]	**X**												
Ann Arbor staging	**X**								**X**			**(X[i])**	
FLIPI-2 score	**X**												
Bone marrow biopsy[j]	**X**						**X[j]**					**(X[j])**	
Tumor assessment (CT scan[k])	**X**						**X**		**X**			**(X[k])**	**X**

Study Period	**Screening[a]**	**Treatment**				**Follow-up**						**Early treatment discontin-uation visit[c]**	**Unscheduled visit[d]**
Visit	***1***	***2 (Baseline)***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***		
Week		**1**	**2**	**3**	**4**	**5**	**12**	**20**	**28**	**36**	**52/EOS[b]**		
Day (± window in days)	**-30 days[a]**	**1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 3**	**78 ± 3**	**134 ± 7**	**190 ± 7**	**246 ± 7**	**365 ± 7**		
Laboratory/safety assessments													
Physical examination[l]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[m]	X	X[n]	X[n]	X[n]	X[n]	X	X	X	X	X	X	X	X
12-lead ECG[o]	X								X		X	X	X
ECOG performance status	X					X			X		X	X	X
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[p]	X	X							X		X	X	X
Clinical chemistry, hematology, and urinalysis[q]	X	X	X	X	X	X	X	X	X	X	X	X	X
Virology screen[r]	X												
HBV testing[s]	X	(X)				(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
TB screen[t]	X												X
β2 microglobulin, LDH	X	X				X	X	X	X	X	X	X	X
PK sampling[u]		X	X	X	X	X	X	X	X			X	X
PD sampling[v]		X	X	X	X	X	X	X	X	X	X	X	X
IgG / IgM sampling		X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity sampling[w]		X	X	X	X	X	X	X	X	X	X	X	X

ADR adverse drug reaction; AE adverse event; AESI adverse event of special interest; ALT alanine aminotransferase; AST aspartate aminotransferase; BUN blood urea nitrogen; BSA body surface area; CR complete response; CT computerized tomography; DNA deoxyribonucleic acid; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; EOS End of study; FACS fluorescence-activated cell sorting; FL follicular lymphoma; HACA human antichimeric antibody; HBcAb hepatitis B core antibody; HBsAg hepatitis B surface antigen; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; i.v. intravenous; IWG International Working Group; IXRS Interactive Voice Telephone and Web Response System; LDH lactate dehydrogenase; PCR polymerase chain reaction; PD pharmacodynamics; PE physical examination; PET positron emission tomography; PML progressive multifocal leukoencephalopathy; PK pharmacokinetic; SAE serious adverse event; TB tuberculosis; WHO World Health Organization.

a Most screening assessments should be conducted within 30 days of Day 1. However, the screening CT scan and bone marrow biopsy may be conducted within 60 days before randomization. The total screening period is not to exceed 60 days in this case.

b Patients who withdraw consent from the study will have no further investigations performed after their withdrawal.
Patients who discontinue study drug early will have investigations performed as indicated in footnote c (Early treatment discontinuation visit).
All other patients will continue to attend visits until Week 52 to obtain PK, PD, safety, efficacy, and immunogenicity data.

c Patients who discontinue treatment at any time during the study after Day 1 (but do not withdraw their consent) will be required to have efficacy assessments at Week 28, or before a new anti-lymphoma treatment is started, and an early treatment discontinuation visit. If new treatment must be started before the Week 28 assessments, then the early treatment discontinuation visit, including a CT scan, should be performed before the start of the new treatment.

d Unscheduled visits should be scheduled as per Investigator discretion. Table shows an example of assessments. Tests will be selected as per Investigator's discretion.

e Inclusion and exclusion criteria to be re-checked on admission to the study site.

f Body weight measurement required for BSA calculation; body weight is measured as part of the complete PE at other visits.

g SAIT101 or MabThera® for i.v. infusion, 375 mg/m^2 body surface area.

h Diagnostic biopsies will be reviewed locally and confirmed centrally in a retrospective manner. Patients can be entered based on a diagnosis of CD20+ follicular lymphoma reviewed at the investigational site. If a biopsy has not been performed within the previous 24 months prior to screening visit, a new biopsy is required to confirm that the histology is unchanged.

i For patients who discontinue study drug early for any reason, and need to start a new treatment, Ann Arbor staging should be evaluated at their early treatment discontinuation visit.

j To be reviewed locally and confirmed centrally. Patients with bone marrow biopsies demonstrating lymphoma within the previous year are not required to undergo a repeat bone marrow evaluation prior to study entry. Patients with a prior bone marrow biopsy performed more than 1 year before screening or negative for lymphoma will be required to undergo another bone marrow biopsy within 60 days prior to randomization. From Week 12 until EOS, a second bone marrow biopsy is required **only** if initially positive and to confirm CR based on the investigator's review of CT scan.

k CT scan (neck, chest, abdomen, pelvis, and any other areas known or suspected to be involved) with contrast to be conducted at screening, Week 12 and Week 28 (assessment permitted up to 4 weeks prior to, or 2 weeks after the Weeks 12 and 28 visit). For patients who discontinue study drug early for any reason, and need to start a new treatment before the Week 28 visit, a CT scan should be conducted at their early treatment discontinuation visit. Brain scan (CT or MRI) can be conducted if CNS involvement is suspected.
For Investigators who routinely use PET scans for assessment of their patients, a PET scan may be performed **in addition to** (not instead of) the CT scan at the Investigator's discretion. Combined PET-CT scans may be used only if performed with contrast, and if the resolution is sufficient to allow accurate and consistent comparison of lesion measurements with subsequent CT scans. Where the contrast product is contraindicated, an abdomen-pelvic magnetic resonance imaging scan (MRI) should be performed with a non-contrast chest CT scan. An additional CT scan is recommended during the study if substantial progression is suspected, and mandated if treatment including chemotherapy or radiotherapy is to be started.
Response status will be assessed centrally using the IWG 2007 criteria (Appendix 4).

l The PE should include assessment of general appearance, skin, head, neck, throat, lymph nodes, thyroid, abdomen, cardiovascular, neurological,

musculoskeletal/extremities, and respiratory systems, as appropriate, and consistent with local standard of care. Body weight will be measured. Height will be measured at screening only. Any specific signs or symptoms that are medically significant should be reported. Particular attention should be paid to 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).

m Vital signs include systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature. To be measured after the patient has been in a sitting/lying down position for at least 5 minutes.

n 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.

o Patients should rest for at least 5 minutes in a supine position before ECG evaluation. In the event of an abnormal ECG evaluation, evaluation by a cardiologist may be deemed necessary at the discretion of the Investigator. Patients with a history of cardiac disease should be monitored closely.

p For female patients of childbearing potential, a serum pregnancy test will be performed during screening, Week 28, Week 52 and EOS visit.
Urine pregnancy test will be performed on Day 1 prior to dosing.
Additional test should be performed whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional test may also be undertaken if required by local regulations.

q To be performed by the local laboratory. If screening laboratory tests are performed within 48 hours of the first dose, Cycle 1 Day 1, they do not have to be repeated. Subsequent laboratory tests are to be performed prior to dosing of study drug on dosing days. Results of the laboratory tests should be reviewed before administering each dose.
Clinical chemistry: creatinine, alkaline phosphatase, total bilirubin, AST, ALT, total protein, albumin, calcium, BUN, phosphorus, uric acid, and electrolytes (sodium, potassium, chloride).
Hematology: hemoglobin, hematocrit, platelets, white blood cells with differentiation, and neutrophils (absolute counts).
Urinalysis: glucose, protein, blood and leukocytes.

r To be performed by the local laboratory. Screening performed to confirm negative serology for HIV and HCV. HIV screening test will be performed according to local practice and local regulatory guidance. Patients who are confirmed positive and those who have active infections will be excluded from the participation in the study.

s Screen all patients for HBV infection by measuring HBsAg and anti-HBcAb. Patients who are confirmed positive for chronic hepatitis B infection (defined as positive HBsAg serology) and those who have active infections will be excluded from the participation in the study. Patients with occult or prior hepatitis B infection (defined as positive total HBcAb and negative HBsAg) may be included if HBV DNA is <20 IU/mL (or 112 copies/mL) by PCR test. These HBV patients must be willing to undergo PCR HBV DNA testing (to be performed by the local laboratory) during study and may participate following consultation with a hepatitis expert regarding monitoring and use of HBV antiviral therapy, and provided that they agree to receive treatment as indicated. An HBV re-test will be performed at each study visit from Week 5 onwards, and at the discretion of the Investigator.

t To be performed at screening unless obtained within 3 months prior to Day 1. TB screening test will be performed if required by local regulatory guidance or at the investigator's discretion. A chest X-ray will be required for all patients with a positive TB test to confirm there is no active TB.

u Blood PK samples will be collected **from the PK/PD sub-population of patients only.** Please refer to information about sampling time points as below:
Days 1, 8, 15, and 22: 0 hours (pre-dose), and at the end of infusion (± 10 minutes windows)
For all other time points: Infusion start time on Day 1 (± 6 hours window)

v Blood samples for CD19+ B-cell counts will be collected, **from the PK/PD sub-population of patients only**, at the same time points for PK sampling plus Weeks 36 and 52.

w To be performed by the central laboratory. On infusion visits, the sample should be collected pre-dose. Immunogenicity assessment is also planned when patients show signs or symptoms of immune-response-related adverse events including anaphylaxis (Section 6.4.3) and mucocutaneous reaction (Section 6.4.5)

3.2 Selection of Study Population

3.2.1 Inclusion Criteria

Patients may be entered in the study only if they meet all of the following criteria:

1. Male or female patients aged at least 18 years.
2. Histologically-confirmed, without B symptoms, Ann Arbor stage II to IVA NHL (CD20+ FL of Grades 1, 2, or 3a) (Appendix 5):
   - Patients can be entered based on a diagnosis of CD20+ follicular lymphoma confirmed at the investigational site. Archival tissue or slides must be sent to the central pathology reviewer for retrospective confirmation of diagnosis. Patients must have tissue or slide available for the central pathology review to be enrolled.
   - Patients having both diffuse and follicular architectural elements will be considered eligible if the histology is predominantly follicular (i.e., ≥50% of the cross-sectional area), and there is no evidence of transformation to a large cell histology.
   - If the interval since tissue diagnosis of follicular lymphoma is >24 months prior to screening visit, diagnostic confirmation using either core needle or excisional lymph node biopsy (latter preferred) is required to confirm that the histology remains in one of the eligible categories.
   - Bone marrow biopsy alone is not acceptable.
3. Low tumor burden according to GELF criteria defined as:
   a) Normal serum lactate dehydrogenase (LDH)
   b) No mass ≥7 cm.
   c) Less than 3 nodal sites, each with diameter >3 cm.
   d) No systemic or B symptoms (fever >38°C for 3 consecutive days; recurrent, drenching night sweats; unintentional weight loss exceeding 10% body weight in the last 6 months.
   e) No splenomegaly ≥16 cm by CT scan.
   f) No risk of vital organ compression.
   g) No pleural or peritoneal serous effusion.
   h) No cytopenias (defined as platelets $<100x10^9$/L (100,000/mm^3), hemoglobin <100 g/L (10 g/dL), or absolute neutrophil count $<1.5x10^9$/L (1,500/mm^3)).

4. Patients not previously treated for their FL, including any previous treatment for FL under clinical trials except localized radiation therapy for previous limited stage disease.

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Appendix 6).

6. Have at least one measurable lesion of at least 1.5 cm in longest diameter as per the IWG criteria 2007 (Appendix 4) at screening (lesion clearly measurable in at least 2 perpendicular dimensions).

7. Adequate renal function: Creatinine clearance ≥ 0.835 mL/s (50 mL/min) (Cockroft-Gault formula)

8. Adequate liver function: total bilirubin <34 µmol/L (2.0 mg/dL) except for patients with Gilbert's Syndrome or hemolysis. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <3 × upper limit of normal (ULN) (<5 × ULN is acceptable if abnormalities are thought to be related to hepatic infiltration by FL).

   - Patients with total bilirubin ≥34 µmol/L (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.

9. 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 woman 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.

10. Female patients of childbearing potential must have a negative serum pregnancy test at screening (Visit 1) and a negative urine pregnancy test on Day 1 (randomization, Visit 2). 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.

11. Able to provide written informed consent, which must be obtained prior to any study-related procedures.

3.2.2 Exclusion Criteria

Patients will not be entered in the study for any of the following reasons:

1. Previous treatment with any chemotherapy and/or rituximab or other monoclonal antibody.
2. Prior radiotherapy completed <28 days before study enrollment.
3. Anticipated need for concomitant administration of any other experimental drug, or a concomitant chemotherapy, anticancer hormonal therapy, radiotherapy, or immunotherapy during study participation.
4. Concomitant disease which requires continuous therapy with corticosteroids at doses equivalent to prednisolone >20 mg/day.
5. Leukemia or transformation to diffuse large B cell lymphoma secondary to previously untreated follicular lymphoma.

6. Prior or concomitant malignancies within 5 years prior to screening, with the exceptions of non-melanoma skin cancer, adequately treated carcinoma in situ of the cervix, adequately treated breast cancer in situ, and localized prostate cancer stage T1c, provided that the patient underwent curative treatment and remains relapse free.

7. Patients with a body surface area >3.0 m^2.

8. Major surgery (excluding lymph node biopsy) within 28 days prior to randomization.

9. Primary or secondary immunodeficiency (history of, or currently active), including known history of human immunodeficiency virus (HIV) infection or positive test at screening.

10. Acute, severe infection (e.g., sepsis and opportunistic infections), or active, chronic or persistent infection that might worsen with immunosuppressive treatment (e.g., herpes zoster).

11. 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 PCR HBV DNA testing during study and may participate following consultation with a hepatitis expert regarding monitoring and use of HBV antiviral therapy, and provided that they agree to receive treatment as indicated. An HBV re-test will be performed at each study visit from Week 5 onwards, and at the discretion of the Investigator.
    - Patients with a positive test because of HBV vaccine may be included (i.e., anti-HBs+, anti-HBc–).
    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV ribonucleic acid (RNA).

12. Confirmed current active tuberculosis (TB).

    - Patients with latent TB as determined by tuberculosis skin testing (e.g. Mantoux test) or interferon-gamma release assay (IGRA e.g. QuantiFERON-TB test) may be enrolled if such patients have written confirmation from their 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 of Day 1 or chest CT.

- TB testing is required only if it is required by local regulation or at the investigator's discretion.

13. Central nervous system (CNS) or meningeal involvement, or cord compression by the lymphoma; history of CNS lymphoma. A brain scan (CT or MRI) should be conducted at screening ONLY if lesions are suspected on the brain, to exclude patients with brain localization of FL.

14. History of a severe allergic reaction or anaphylactic reaction to a biological agent or history of hypersensitivity to any component of the trial drug (e.g., hypersensitivity or allergy to murine products).

15. Patients who have significant cardiac disease, including but not limited to history of congestive heart failure (New York Heart Association Class III/IV; see Appendix 7), unstable angina, or uncontrolled cardiac arrhythmia.

16. Uncontrolled or severe hypertension, or cerebrovascular disease.

17. Serious underlying medical conditions that, per the Investigator's discretion, could impair the ability of the patient to participate in the trial (including but not limited to ongoing active infection, severe immunosuppression, uncontrolled diabetes mellitus, gastric ulcers, or active autoimmune disease).

18. Any other co-existing medical or psychological condition(s) that will preclude participation in the study or compromise ability to give informed consent and/or comply with study procedures.

19. Treatment with any investigational medicinal product (IMP) within 4 weeks prior to initiation of 1st infusion of study drug, or treatment with a drug that has not received regulatory approval for any indication within 4 weeks or a minimum of 5 half-lives, whichever is longer, of the 1st infusion of study drug.

20. Receipt of a live/attenuated vaccine within 6 weeks prior to the screening visit.

21. Females who are pregnant, breastfeeding, or planning a pregnancy during the treatment period or within 12 months after the last infusion of study drug.

22. Patients who are investigational site staff members directly involved in the conduct of the trial, and their family members, site staff members otherwise supervised by the investigator, or patients who are Archigen employees directly involved in the conduct of the trial.

3.2.3 Patient Restrictions

For details of medications prohibited before and during the study, please refer to the inclusion and exclusion criteria (Sections 3.2.1 and 3.2.2) and to Section 4.11.

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

There are no other study restrictions.

3.3 Stopping Rules, Withdrawal Criteria, and Procedures

3.3.1 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. The criteria for enrollment are to be followed explicitly.

In addition, patients may be withdrawn from study drug and/or from the study in the circumstances outlined below.

Distinction should be made between discontinuation of study drug treatment and withdrawal from the study, and the reason for treatment discontinuation or study withdrawal should be recorded by the Investigator. The Sponsor should be notified promptly when a patient is withdrawn from either study drug treatment or the study.

3.3.1.1 Withdrawal from Study

Patients may be withdrawn from the study for the following reasons:

a) The patient is unwilling to continue in the study (i.e., withdraws consent). In this case, no more investigations will be performed. The patient does not have to justify their decision.

b) The patient is lost to follow-up despite reasonable efforts to make contact with the patient. In this case, all attempts to contact the patient, request to return for visit and information received during contact attempts must be documented in the patient's medical record. In any circumstances, every effort should be made to document patient outcome, the reason for withdrawal, and any unresolved or new AEs.

c) The Sponsor stops the study (see Section 3.3.2) or closes an individual study site (see Section 3.3.3) due to critical non-compliance with study protocol, ICH-GCP or other applicable regulatory requirements.

Patients who are withdrawn from the study will not be replaced.

Adverse events will be followed up as detailed in Section 6.10. Investigators are encouraged to discuss the patient's case with the Sponsor physician or representative to agree upon appropriate action. For patients who need to be withdrawn from the study early, it is highly

recommended that efficacy assessments are conducted at Week 28. Once a patient is withdrawn from the study, no further assessments can be conducted.

3.3.1.2 Discontinuation of Study Drug

An individual patient may be discontinued from study drug treatment for the following reasons:

- Prohibited treatment such as any other experimental drug or a concomitant chemotherapy, anticancer hormonal therapy, radiotherapy, or immunotherapy.
- Lack of compliance with protocol (e.g., refusal or inability to adhere to the study schedule or procedures).
- Patients who meet any of the following specific safety discontinuation criteria:
  - Patients who develop severe (common terminology criteria for adverse events [CTCAE] Grade 3 or above) 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 reaction was an anaphylactic reaction, or if the same infusion-related reaction occurs for a second time, the infusion should be permanently discontinued (refer to Section 4.5).
  - Active TB.
  - Invasive fungal infection or opportunistic infection including, but not limited to, listeriosis, legionellosis, or pneumocystis.
  - Hepatitis B virus reactivation or hepatic failure.
  - PML: neurological warning signs include major changes in vision, unusual eye movements, loss of balance or coordination, and disorientation or confusion.
  - Cancer: any new 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. If such carcinomas develop during the study, they may be excised and the patient may continue on the study.
  - Any other AEs which, in the opinion of the Investigator or the Sponsor, could compromise the patient's safety or well-being if they continued to participate in the study.

- Pregnancy in a female participant.

Assessments for patients who discontinue the study drug early

Patients who discontinue the study drug early for any reason will be required to have efficacy assessments at Week 28, and an early treatment discontinuation visit. If new treatment must be started before the Week 28 assessments, then an early treatment discontinuation visit, including a CT scan (see Table 1), should be performed before the start of the new treatment. Patient who discontinue the study treatment will be followed-up until Week 52 (EOS) for safety and immunogenicity.

3.3.2 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.

3.3.3 Individual Study Center

The Sponsor, IRB/IEC, and/or regulatory authorities have the right to close an individual study site at any time. In case of premature termination of an individual study site, 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 site, the Investigator or institution must assure appropriate therapy and follow-up for the patients.

The Sponsor may decide to close an individual study site 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.

3.4 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.

Laboratory tests if marginally abnormal may be repeated at the discretion of the Investigator during the screening period.

3.5 Re-screening

Re-screening may be required if a patient has not met all the eligibility criteria. Patients are allowed to be re-screened; this should be performed in consultation with the Sponsor or QuintilesIMS' Medical Advisor. Each patient must give written informed consent before re-screening occurs.

3.6 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.

If a patient is lost to follow-up, every possible effort must be made by the study site personnel to contact the patient and determine the reason for discontinuation. The measures taken to follow up must be documented, and should include at least phone calls to the patient, contact with the patient's family, and contact with the patient's General Practitioner (GP) or care physician.

As a measure to minimize lost to follow-up, a phone visit can be tried to collect data for ECOG performance status, concomitant medications and adverse events (Appendix 8).

3.7 Protocol Deviations

This study is intended to be conducted as described in this protocol. In the event of a major 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 site must contact QuintilesIMS' Clinical Monitor or Medical Monitor at the earliest possible time. This will allow an early joint decision regarding the patient's continuation in the study. This decision will be documented by the Investigator and confirmed by the Sponsor.

4.0 STUDY TREATMENTS

4.1 Treatments Administered

Following randomization, SAIT101 or MabThera® treatment will be administered as an i.v. infusion once a week for 4 weeks, at a standard dose of 375 mg/m^2 body surface area. If the patient's weight changes by more than 10% before the next infusion, then BSA should be recalculated. Cycle 1 Day 1 study drug must be administered within 0 to 4 days after randomization.

Both treatments are anti-CD20+ antibody medications.

For study drug administration details, please see Section 4.5. For pre-medication administration details, please see Section 4.4 and Appendix 8.

4.2 Formulation and Packaging

SAIT101 and MabThera® will be provided in sterile, preservative-free, non-pyrogenic, single-use vials containing 500 mg of rituximab per 50 mL.

Each carton and medication vial will be labelled with all the required information according to local regulations, including the Protocol Number (AGB 002) and a unique identifier (Med ID) in a blinded manner. This will be programmed into the Interactive Voice Telephone and Web Response System (IXRS). At each infusion visit, the IXRS will assign the carton 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 if not possible, centrally as per Sponsor guidance. Further details will be documented in the Pharmacy Manual.

4.3 Storage and Preparation

Study drugs will be stored in a secure area according to local regulations. 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 IMP must be stored in a refrigerator at a controlled temperature (2 to 8°C) and handled according to GCP as well as IB. Vials should be kept in the outer carton in order to protect them from light. A temperature log must be kept, on which the storage temperature of the

study drug is recorded at least once a day. Any deviations below 2°C or above 8°C should be reported to the sponsor or monitor immediately in accordance with ICH GCP and/or local regulations. The study drugs, SAIT101 and MabThera®, must be kept strictly separate and in a different location than commercially available products at all times. Additional details regarding the storage and handling of the study drugs will be provided to the study sites.

For further details on MabThera®, please refer to the product information.[6]

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

Study drug, assigned via IXRS, should be diluted to a calculated concentration of 1 to 4 mg/mL rituximab into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection or 5% D-Glucose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. The bag should be clearly labelled 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.

4.4 Pre-medication

In addition to the study drug treatments, all patients should be administered corticosteroids (up to 100 mg i.v. methylprednisolone or its equivalent according to institutional standards), an analgesic/antipyretic, and an anti-histamine (e.g., paracetamol and diphenhydramine) before the start of each study drug infusion (See Appendix 8).

4.5 Administration

The instructions below provide a summary of the guidance provided in the rituximab product labeling, which should also be followed for SAIT101; rituximab should be administered according to the local product labeling if it differs from these instructions.

- Day 1 infusion will be administered at an initial infusion rate of 50 mg/hour for the first hour. If no toxicity is seen, the rate may be increased gradually in 50 mg/hour increments at 30 minute (±5 minutes) intervals, to a maximum of 400 mg/hour (See Appendix 8).
- If the Day 1 infusion is well tolerated, the initial infusion rate for subsequent doses will be 100 mg/hour, increased gradually in 100 mg/hour increments at 30 minute intervals, to a maximum of 400 mg/hour.
- Patients should be closely monitored for the onset of infusion related reactions. If the patient experiences infusion related reaction or any ADR, the infusion should be discontinued, and the severity of the side effects should be evaluated. Medical management 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. (See Section 6.4.6).

  Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. The Investigator should wait an additional 30 minutes while delivering the infusion at the reduced rate. If tolerated, the rate may then be increased to the next closest rate on the patient's infusion schedule. (See Table 1 in Appendix 8).

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.

4.6 Method of Assigning Patients to Treatment Group

Once the patient meets all the inclusion criteria and none of the exclusion criteria, and has provided written informed consent, the study site will request (register) patient number via the IXRS.

All randomized patients will be managed by IXRS. To randomize a patient, the study site will contact the IXRS. Site will request (register) unique subject identifier via the IXRS. The IXRS will provide the Medication ID of the blinded study drug to be dispensed.

Patients will be randomized to treatment in a 1:1 ratio. Randomization will be stratified by FLIPI-2 score. (For FLIPI-2, see Appendix 3).

Further details on using the IXRS system are presented in the IXRS manual. See also Section 8.3.

Patients will consent separately for the PK and PD sampling. Randomization into the PK/PD part of the study will also be managed using IXRS.

4.7 Selection of Doses in the Study

The primary focus of this study is to evaluate the statistical equivalence of efficacy of SAIT101 with the approved product, MabThera®, in patients with LTBFL. In this patient population, rituximab treatment at a dose of 375 mg/m^2 once a week for 4 weeks has been shown to be beneficial. This is the recommended treatment dose for rituximab given as monotherapy for patients with relapsed or refractory disease, as well as the recommended dose of rituximab in combination with chemotherapy. Therefore, patients will receive SAIT101 and MabThera® at a dose of 375 mg/m^2 of body surface area (BSA) per the proposed dosing.

Calculation of BSA will be based on the height at baseline and weight measured within 7 days of the first infusion. If the patient's weight changes by more than 10% before the next infusion, then BSA should be recalculated. Both height in meters and weight in kilograms will be rounded to 3 significant figures. Body surface area will be rounded to 3 significant figures.

4.8 Timing of Dose for Each Patient

Patients should receive pre-medication consisting of corticosteroids (up to 100 mg i.v. methylprednisolone or its equivalent according to institutional standards), an analgesic/antipyretic, and an anti-histamine (e.g., paracetamol and diphenhydramine) either i.v. or orally, before each infusion of study drug treatment (see Section 4.4).

Patients may be hospitalized for observation at the discretion of the Investigator (such instances of hospitalization will not be recorded as a serious AE [SAE]).

Instructions for the infusion of both study drug treatments are described in Appendix 8.

If a patient experiences a new infection or other AE between one infusion and the next scheduled infusion, the next infusion should be delayed until the infection or AE has completely resolved and the Investigator considers it safe to resume treatment. A delay of >2 days in receiving the next infusion will be considered a protocol deviation, unless it is due to an AE.

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

4.9 Infusion Criteria

If screening laboratory tests are performed within 48 hours of the first dose, Cycle 1 Day 1, they do not have to be repeated. Subsequent laboratory tests are to be performed prior to

dosing of study drug on dosing days. Results of the safety laboratory tests (hematology, clinical chemistry, and urinalysis) should be reviewed before administering each dose.

The Investigator should hold initial or subsequent treatments if National Cancer Institute (NCI) CTCAE (NCI-CTCAE) cytopenia is observed prior to the scheduled infusion. Before each subsequent dose, absolute neutrophil count must be $\geq 1.5 \times 10^9$/L (1,500 /mm^3) and platelet counts must be $\geq 75 \times 10^9$/L (75,000/mm^3).

Patients who miss the allocated day for study drug infusion will be contacted and another visit should be arranged as soon as practically possible.

4.10 Blinding

Two database locks will be performed for the study; the first one will be performed after the last patient completes the Week 28 visit and the second (final database lock) will be performed after the last patient completes the study, or discontinues from the study prior to the Week 52 visit. Patients, Investigators, and all other study personnel will remain blinded until the primary analysis at Week 28. For the primary analysis, the treatment codes will be broken centrally. The patients, study personnel at the study sites and, as far as possible, the Investigators will therefore continue to remain blinded after the primary analysis until the final database lock.

The 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 study drug.

The SAIT101 and MabThera® 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.

4.10.1 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. 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. Any AE or SAE associated with unblinding must be recorded and reported as specified in this protocol. 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 appropriate measurements are taken at the study site to maintain the blinding of the study.

4.10.2 Unblinding for Interim Analysis

An interim analysis of data collected upto Week 12 such as PK, PD, efficacy, safety and immunogenicity inclusive of the data from the PK/PD sub-population (134 patients in total) is planned. An unblinded biostatistician in CRO is to be utilized.

4.11 Allowed and Prohibited Treatments

Medication that is considered necessary for the patient's safety (e.g., as a result of an AE) may be given at the Investigator's discretion.

All concomitant medications, whether allowed or not, must be recorded on the eCRF.

Use of prohibited treatment is a protocol violation.

4.11.1 Allowed Treatments

The use of concomitant therapy, including prescription and non-prescription drugs, non-drug therapy, and dietary supplements and herbal prescriptions, is permitted as appropriate to treat AEs or co-morbid conditions.

4.11.2 Prohibited Treatments

Treatment with any other experimental drug or a concomitant chemotherapy, anticancer hormonal therapy, radiotherapy, or immunotherapy is prohibited during study participation. This includes additional doses of rituximab or SAIT101 after the initial 4-weekly doses.

If a patient requires tumor targeting treatment for FL other than the protocol-defined treatment with rituximab or SAIT101 monotherapy due to disease progression based on tumor assessments done at investigational site, he or she will be considered as a treatment failure and should be discontinued from the study treatment. (See Section 3.3.1.2) Patients with progressive disease should be treated with an adequate therapy according to judgment of the treating physician. In such case, patient will be followed-up until Week 52 (EOS) for safety and immunogenicity.

4.11.3 Management of Hepatitis Reactivation and Other Infections During Rituximab Therapy

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 PCR HBV DNA testing during study and to receive treatment as indicated. During the study, an HBV re-test will be performed at each study visit from Week 5 onwards, and at the discretion of the Investigator.

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.[11]

4.12 Medical Care of Patients after End of Study

The Sponsor will not provide any additional care to patients after they leave the study, because such care should not differ from what is normally expected for patients with FL. Refer to Section 5.2.7 for follow-up in the event of pregnancy, and Section 6.10 for follow-up of AEs.

4.13 Treatment Compliance

All doses of study drug will be administered in the clinic under the supervision of the Investigator or designee and recorded in the eCRFs. This should ensure full compliance.

The prescribed dosage, timing, and mode of administration of the study drugs described in this protocol may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

4.14 Study Drug Accountability

The Investigator must maintain an inventory record of the study drugs (SAIT101 and MabThera®) received, dispensed to blinded team, and returned. The Investigator or delegate should maintain an inventory record of the study drug (including collection from pharmacy and 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.

Upon completion or termination of the study, all unused study drug should be disposed of in accordance with local requirements. Partially used study drug should be destroyed as per local procedures.

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

If the study drug is authorized to be destroyed at the study site 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.

5.0 ASSESSMENTS

When it is not feasible to perform a protocol-required test, the Investigator will take all steps necessary to ensure the safety and well-being of the patient. The Investigator will also document the reason for this, and any corrective and preventive actions taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these circumstances in a timely manner.

5.1 Efficacy Assessments

Disease assessments are to be performed as scheduled according to calendar days, regardless of treatment delays resulting from toxicity. Care must be taken in scheduling disease assessments to prevent introduction of bias on treatment delays.

Assessments are NOT to be scheduled based on the previous visit time-point, but rather Day 1 should be used as baseline when calculating when the on-study tumor assessments are to be performed.

5.1.1 CT Scan

A CT scan (with oral or i.v. contrast unless contraindicated) will be performed on the neck, chest, abdomen, pelvis, and any other areas known or suspected to be involved, at baseline, Week 12 and Week 28. An additional CT scan is recommended during the study if substantial progression is suspected, and mandated if treatment including chemotherapy or radiotherapy is to be started. Where the contrast product is contraindicated, an abdomen-pelvic magnetic resonance imaging (MRI) scan should be performed with a non-contrast chest CT scan. The same modality of examination should be used at all time points.

For Investigators who routinely use positron emission tomography (PET) scans for assessment of their patients, a PET scan may be performed **in addition to** (not instead of) the CT scan at the Investigator's discretion. Combined PET-CT scans may be used only if performed with contrast, and if the resolution is sufficient to allow accurate and consistent comparison of lesion measurements with subsequent CT scans.

The same imaging method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. All imaging performed for the study will be forwarded to the central imaging vendor for confirmation. The Imaging Manual should be followed closely.

The CT scans will be independently assessed centrally. Detailed information will be included in the imaging manual. In an emergency situation, the Investigator may take action based on a local review of the CT scan before confirmation by the central review.

Tumor status will be evaluated as defined by the IWG Criteria 2007 (Appendix 4).

A spiral CT scan of the chest is permitted as an additional assessment if deemed appropriate by the Investigator.

Bone scans may also be performed if clinically indicated (i.e., if disease localization in the bones is suspected).

5.1.2 Bone Marrow Biopsy

A bone marrow biopsy will be performed at screening unless an archived sample is available at the time of screening:

- Patients with bone marrow biopsies demonstrating lymphoma within 12 months are not required to undergo a repeat bone marrow evaluation prior to study entry.
- Patients with a prior bone marrow biopsy negative for lymphoma, or with no bone marrow biopsy, will be required to undergo restaging marrow biopsy within 60 days prior to randomization.
- From Week 12 until EOS, a second bone marrow biopsy is required only if initially positive and to confirm CR based on the investigator's review of CT scan.

5.1.3 Histopathological Review of Diagnostic Tissue

To be eligible for this study, patients must have tumor tissue or slides available for review by a central pathology review committee. If a biopsy has not been performed within the previous 24 months prior to screening visit, a new biopsy is required to confirm that the histology is unchanged. At screening, the diagnosis will be based on histopathological review by the enrolling institution. Tumor tissue blocks or slides will be collected and sent to the central laboratory for retrospective standardized evaluation of the diagnosis of Grade 1-3a, CD20+ follicular lymphoma containing no elements of diffuse large B-cell lymphoma.

5.2 Safety

5.2.1 Adverse Events

Assessment of AEs will include type, incidence, severity (graded by NCI-CTCAE version 4.03), timing, seriousness, and relatedness. (Section 6)

5.2.2 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 1. 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.

Whenever possible, the same person at each study site should perform the physical examination throughout the study. The physical examination should include assessment of general appearance, skin, head, neck, throat, thyroid, abdomen, cardiovascular, neurological, musculoskeletal/extremities, and respiratory systems, as appropriate, and consistent with local standard of care. Lymph nodes, spleen and liver should be included at all times. Any specific signs or symptoms that are medically significant should be reported. Particular attention should be paid to 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).

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

5.2.3 Vital Signs

Vital signs will be assessed at the visits indicated in Table 1. Measurements will include systolic and diastolic blood pressure, pulse, respiratory rate, and oral or tympanic body temperature, and 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 times:

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.

5.2.4 ECOG Performance Status

ECOG performance status will be graded according to the definition in Appendix 6.

5.2.5 Clinical Laboratory Evaluations

A list of clinical laboratory assessments to be measured is provided in Table 2. Additional parameters may be measured in the event of AEs, and as necessary for patient care.

If any laboratory findings meet the definition of hepatic injury (see Appendix 9), patients should be managed according to the instructions in Appendix 9.

Blood and urine samples will be collected at the times indicated in Table 1.

Table 2 Clinical Laboratory Assessments

Hematology	Hemoglobin, hematocrit, platelets, white blood cells with differentiation, and neutrophils (absolute counts)
Clinical chemistry (serum)	Creatinine, alkaline phosphatase, total bilirubin, AST, ALT, total protein, albumin, calcium, BUN, phosphorus, uric acid, and electrolytes (sodium, potassium, chloride)
Urinalysis	Glucose, protein, blood, and leukocytes
Virology	Hepatitis C virus antibodies, human immunodeficiency virus, hepatitis B surface antigen, hepatitis B core antibody (total and immunoglobulin M), and HBV DNA
Pregnancy testing	hCG (serum or urine, as appropriate)
Tumor markers (serum)	β2 microglobulin and LDH

Note: Additional parameters may be measured in the event of AEs, and as necessary for patient care.
ALT alanine aminotransferase; AST aspartate aminotransferase; BUN blood urea nitrogen;
HBV DNA hepatitis B virus deoxyribonucleic acid; hCG human chorionic gonadotropin;
LDH lactate dehydrogenase

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 (Section 6.7).

Blood samples for laboratory safety tests will be analyzed locally according to local practice and local regulatory guidance. Tuberculosis status will be determined using tuberculosis skin test (e.g. Mantoux test) or interferon-gamma release assay (IGRA e.g. the QuantiFERON-TB Gold Assay. TB testing is required only if it is required by local regulation or at the investigator's discretion.

Detailed sample collection, labeling, storage, and shipment information will be described in the Laboratory Manual.

5.2.6 Electrocardiogram

Resting 12-lead ECG data will be collected at the visits indicated in Table 1.

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

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. Any clinically relevant abnormalities will be reported as AEs/SAEs as appropriate. Further ECGs should be performed at the Investigator's discretion.

5.2.7 Pregnancy

A serum pregnancy test will be performed at screening, at Week 28, Week 52 (EOS) and urine pregnancy test will be performed on Day 1 prior to dosing indicated in Table 1 to rule out pregnancy in female patients of childbearing potential. Additional tests may also be undertaken by local regulations.

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 including the information of fetus/ new-born. 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 6.9).

5.2.8 Safety Monitoring

An independent DSMB, consisting of members who are independent from the Sponsor, the contract research organization (CRO) and the study, 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.

5.3 Immunogenicity Assessments

Determination of the incidence of HACA and neutralizing antibody will be performed by central laboratory using validated analytical methods. Blood samples (approximately 5 to 8 mL) will be taken at the visits shown in Table 1. Immunogenicity assessment is also planned when patients show signs or symptoms of immune-response-related adverse events including anaphylaxis (Section 6.4.3) and mucocutaneous reaction (Section 6.4.5). The exact date/time of the blood sample collection will be recorded in the patient's eCRF. Wherever possible, immunogenicity blood samples will be taken at the same time as blood is drawn for other analyses to limit repeated venipuncture.

Approximately 80 mL of whole blood will be obtained from each patient for immunogenicity assessments during the study.

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.

5.4 Pharmacokinetic Assessments

Blood samples for the determination of concentrations of rituximab will be taken at the times specified in the schedule of assessments (Table 1).

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 and processed using instructions provided by the designated central laboratory. Serum (approximately 2.5 mL) will be harvested and evenly divided into 2 samples (duplicates) to allow for a back-up sample.

Approximately 60 mL of whole blood will be obtained from each patient for PK assessments during the study.

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.

5.5 Pharmacodynamic Assessments

Blood samples for the determination of CD19+ count will be taken at the times specified in the schedule of assessments (Table 1). 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 central laboratory.

Approximately 70 mL of whole blood will be obtained from each patient for PD assessments during the study.

Because rituximab depletes B-cells, circulating levels of IgG and IgM may decrease. Blood samples for IgG and IgM will be collected according to the schedule of assessments (Table 1).

The blood 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.

6.0 REPORTING OF ADVERSE EVENTS

6.1 Adverse Events

Definition of AE: An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any 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.

6.2 Serious Adverse Events

A SAE is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death.
- Is life-threatening. The term "life-threatening event" refers to an event in which the subject 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 abnormality/birth defect, which includes ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, or neonatal death. In addition, infant death within 1 month of birth 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 significant event that, although it may not be immediately life-threatening or result in death or hospitalization, endangers the subject 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). Subjects may be hospitalized for observation at the discretion of the Investigator; such instances of hospitalization will not be recorded as SAEs.

6.3 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.

6.4 Adverse Events of Special Interest

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 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: progressive multifocal leukoencephalopathy (PML), hepatitis reactivation, infusion reactions, anaphylactic reactions, mucocutaneous reactions and serious infections.

6.4.1 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.

If any patient is diagnosed of PML during the study, the patient must be discontinued and followed up until resolution at the discretion of the Investigator.

6.4.2 Hepatitis Reactivation

If a patient develops reactivation of HBV while on rituximab, the patient should be managed as outlined in Section 4.11.3.

6.4.3 Anaphylactic Reactions

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Diagnostic criteria are outlined in Table 3.

Table 3 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 (eg, 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 subject (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 subject (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 in Table 3, the patient should receive epinephrine immediately (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 peanuts who ingested peanuts and within minutes is experiencing urticaria and generalized flushing. Subsequent interventions are determined on the basis of the clinical course and response to epinephrine. Additional immunogenicity sampling is required in this case.

6.4.4 Serious Infections

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

6.4.5 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. Additional immunogenicity sampling is required in this case.

6.4.6 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 headache, nausea, fever or chills, dizziness, flush, urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, chest or back pain, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. Distinction between infusion reaction and anaphylaxis is necessary.

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. If the same severe (Grade 3) or above infusion reaction occurs for a second time, the decision to discontinue permanently should be seriously considered. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved (see Appendix 8). Closely monitor patients with pre-existing cardiac or pulmonary conditions.

.Please refer also to Section 6.4.3 (Anaphylactic Reactions) for differential diagnosis with anaphylaxis.

6.5 Adverse Events Due to Malignancy

Progression of FL (underlying disease) and death due to progression of FL are considered as outcome events and are exempted from reporting as SAEs. These outcome events will be collected and monitored by the DSMB.

However, when there is evidence suggesting a causal relationship between study drug and the progression of underlying malignancy, the event must immediately be reported as a SAE. Progression due to the usual disease evolution (or lack of efficacy of study drug) should not

be reported as SAE. Cancers with new histology should always be reported as serious adverse event.

Please refer to definition of progression that warrants initiation of treatment chemotherapy/radiotherapy in Appendix 11.

6.6 Overdose

An overdose of SAIT101 or MabThera® 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 the overdose as per the standard of care at the site, or symptomatically, and the case discussed with QuintilesIMS' and the Sponsor's medical advisors for decision on 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 6.8 of this protocol.

6.7 Changes in Clinical Laboratory Assessment Results

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. (Section 5.2.5)

6.8 Recording of 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).

After initiation of study drug upto 60 days after last dose, all AEs/SAEs, regardless of relationship to study drug, will be reported until the EOS visit. After 60 days from last dose, AEs/SAEs assessed as 'related' will be reported until EOS visit. However, all AESIs should be reported regardless of relationship until EOS regardless of the time elapsed since last dose of study drug.

Adverse events continuing at the EOS visit must be followed until recovery, or if persistent, until sufficient characterization has been achieved or the Investigator and Sponsor (or representative) agree to not follow them further.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken with study drug and the outcome must also be recorded.

Severity

The investigator will grade severity as mild, moderate, severe, life-threatening, or death, according to the US NCI-CTCAE version 4.03. A printable version of the criteria can be found at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a SAE. For example, a pain may be severe (interferes significantly with patient's usual function), but would not be classified as serious unless it met one of the criteria for SAEs.

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.

6.9 Reporting of Adverse Events and Serious 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). After initiation of study drug upto 60 days after last dose, all AEs/SAEs, regardless of relationship to study drug, will be reported. After 60 days from last dose, AEs/SAEs assessed as ‘related’ will be reported until EOS visit. However, all AESIs

should be reported regardless of relationship until EOS regardless of the time elapsed since last dose of study drug.

All AEs are electronically collected and recorded on the appropriate AE pages. Each event should be recorded separately. The Investigator or designee will assess patients at each visit 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 ?"

QuintilesIMS must be notified of any SAEs, whether or not related to the study drug, within 24 hours of awareness according to the procedure outlined in the Site Manual.

In the case of a SAE, the Investigator or designee must complete and sign the SAE pages in the eCRF within 24 hours of awareness, and check that the data are accurate. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, and exposure via breastfeeding.

If the eCRF is not available and is not expected to be available within 24 hours, the Investigator or designee should complete and send a SAE form to QuintilesIMS Lifecycle Safety, using the email address or fax number provided for their country (available in the Site Manual or SAE form instructions).

6.10 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.

6.11 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 local regulations.

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

7.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of GCP (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Site Initiation visit
- Early site visits post-enrollment
- Routine site monitoring
- Ongoing site communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final CSR.

In addition, Sponsor and/or designee may conduct periodic audits of the study processes, including, but not limited to study site, site visits, central laboratories, vendors, clinical database, and final CSR. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

7.1 Monitoring

The Sponsor has engaged the services of a CRO, QuintilesIMS, to perform all monitoring functions within this clinical study. QuintilesIMS' monitors will work in accordance with applicable SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study site, informing the Sponsor about any issues relating to facilities, technical equipment, or medical staff. During the study, monitors

will check that written informed consent has been obtained from all patients correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study site. They might arrange for the supply of study drug and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each site while patients are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification). For the following items, this check will be 100%:

- Patient identification number
- Patient consent obtained
- Patient eligibility criteria (inclusion and exclusion criteria)
- Efficacy variables
- Medical record of AE

7.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs.

Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study site. Data collection will be completed by authorized study site staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study site staff prior to the study being initiated and any data being entered into the system for any study patients.

All data must be entered in English. The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the patient's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not performed, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study site staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the patient's medical history, that verify the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each patient who receives study drug, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

The eCRFs will be automatically appended with the identification of the creator, by means of their unique user identification (UserID). Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events and concomitant diseases/medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Enhanced.

7.3 Audits and Inspections

The Sponsor's Quality Management Unit (or representative) may conduct audits at the study sites. 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.

Regulatory authorities worldwide may inspect the study site 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.

8.0 STATISTICS

8.1 Statistical Design Model

This is a multi-center, randomized, double-blind, parallel-group study. The primary objective of the study is to evaluate the statistical equivalence of efficacy as assessed by the primary endpoint, overall response. The difference in ORR between SAIT101 and MabThera® at Week 28 will be used for analysis of the primary endpoint.

8.2 Null and Alternative Hypotheses

The primary test for statistical equivalence will be performed with respect to SAIT101 versus MabThera®. The primary hypothesis is based on the difference in ORR at Week 28 between the two treatments.

The null hypothesis tested for the primary efficacy analysis is that either (1) SAIT101 is inferior to MabThera® or (2) SAIT101 is superior to MabThera® based on a pre-specified equivalence margin.

The alternative hypothesis is that SAIT101 is equivalent to MabThera®, which can be demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinical acceptable difference. In other words, equivalence will be declared if the 2-sided 95% CI of the difference in the ORR at Week 28 between treatments (SAIT101 versus MabThera®) is entirely contained within the equivalence margin of [-16.0%, 16.0%].

The equivalence margin [-16.0%, 16.0%] for the ORR difference is based on the Ardeshna et al. 2014.[2]

Efficacy will be assessed as CR, PR, SD, and PD, as defined in IWG criteria 2007 (Appendix 4), and TTE, using the Cochran-Mantel-Haenszel (CMH) method as the primary analysis of the difference in response rates between treatments. The adjusted proportion difference in ORR and its 95% Newcombe-Wilson CI will be calculated using CMH weight. The efficacy analyses will be applied for both the per-protocol set (PP) set and full analysis set (FAS) and FAS will be considered primary efficacy analysis population. Appropriate sensitivity analyses will be applied to explore the robustness of results.

8.3 Randomization

Patients who meet the eligibility criteria will be randomized in blocks to double-blind treatment. Patients will be randomly assigned in a blinded fashion to either SAIT101 or MabThera® with a 1:1 allocation ratio.

A patient randomization list will be produced by Clinphone, an IXRS provider, using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. Access to the randomization code will be controlled and documented. Archigen will not have access to the randomization assignments generated by the system. No personnel directly involved in the conduct and analysis of the study will have access to the treatment allocation prior to database lock (refer to Section 4.10). On an individual patient basis, the study drug administered may be revealed during pharmacovigilance activities. The block size(s) of the randomization will be documented in the CSR.

8.4 Determination of Sample Size

Response rate of rituximab 4 weekly dosing in low tumor burden follicular lymphoma was assessed in Ardeshna et al. 2014[2], Kahl et al. 2014[3] and Colombat et al.[15, 22] based on systematic literature search. The Ardeshna study was the only randomized trial which compared the treatment of rituximab alone with the 'watch & wait'. The month 7 response rate in rituximab monotherapy was estimated to be 77% with 95%CI (66%-85%), considering about the lower bound of 95%CI of response rate to be 66%, the highest non-response rate of MabThera® is estimated as 34%. Assuming the rate of non-responders with SAIT101 will not exceed 1.5 times over the expected highest non-response rate with MabThera® at 34%, the equivalence can be declared if the non-response rate in the SAIT101 arm is less than 51%. In other words, with the lower bound of 95% CI of responder rate of MabThera® at 66%, the equivalence can be declared if the response rate in the SAIT101 arm is more than 49%. As above, the estimated margin should set less than ±17.0%.

In the reference, the month 7 response rate in rituximab monotherapy was estimated to be 77% with 95%CI (66%-85%) and response rate of W&W group was estimated to be 6%. The difference in ORR was estimated to be 71% with 95%CI (59%-79%), and the equivalence margin of ±16.0% (0.59 × [1-0.73] = 0.1593) was calculated to preserve at least 73% of the treatment benefit of rituximab based on the lower bound of 95% CI of the difference in ORR.

To achieve 83% power with a 16.0% margin and a 77% expected ORR with 2 one-sided tests at the significance level of 0.025. nQuery Advisor 4.0 calculated the following with the given assumption: With 154 patients in each group, the observed 2-sided 95.0% CI will be expected to lie between -0.160 and 0.160 with 83% power when the Standard proportion, P_s,

is 0.770 and the Test expected proportion, P_t, is 0.770; results are based on 1,000 simulations using the Newcombe-Wilson score method to construct the CI.[22]

Thus, 154 patients in each group are able to satisfy the primary analysis of ORR, given an 83% probability of declaring the equivalence in the FAS. Patients who discontinue the study drug early for any reason will be required to have efficacy assessments at Week 28. Allowing for a 4% drop-out rate and patients with major protocol deviations as seen in the Ardeshna et al[2], 147 patients in each group will give 80% probability of demonstrating the equivalence in the PP set.

At least 154 patients per arm (308 patients overall) should be randomized into the study. With 154 patients, the estimated ORR with 95% CI of SAIT101 is 77% (70%-84%). ORR with 95% CI of rituximab based on a random effect meta-analysis that include Ardeshna et al. 2014, Kahl et al. 2014 and Colombat et al. 2001 was estimated as 72% (68%-76%). Maximum difference in upper and lower 95% CI of ORRs is ±15.0%, which is smaller than the margin ±16.0%, and therefore estimated ORR with 95% CI of SAIT101 is considered to be clinically relevant.

Pharmacokinetic/pharmacodynamic sub-population

Pharmacokinetic variability for both AUC and C_{max} in the LTBFL population is estimated to be approximately 18% based on a randomized, open-label, multi-center study in 24 CD20 positive diffuse large B-cell lymphoma patients.

For PK, assuming a CV of 38% in both $AUC_{0\text{-}168}$, based on Regazzi et al. 2005[23] and no true difference between SAIT101 and rituximab in this parameter, 60 evaluable patients per arm are required to yield 81% overall power for comparison of $AUC_{0\text{-}168,\,1}$ and $AUC_{0\text{-}168,\,4}$ between the test and comparator treatments, using the standard two one-sided testing procedure, a 5% significance level for each one-sided test (90% CI). To ensure 120 evaluable patients are available, a total of 134 patients will be randomized for the PK/PD sub-population.

8.5 Statistical Methods

Categorical variables will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized using number, mean, standard deviation, 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).

8.5.1 Analysis Populations

The following analysis sets are defined for this study:

Randomized Set (RAN)

The Randomized Set (RAN) will consist of all patients who receive a randomization number.

Full Analysis Set (FAS)

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

Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) will consist of all randomized patients who received at least one dose of study drug. The SAF will be used as the basis for all safety analyses.

Per-protocol Set (PP set)

The PP set is defined as FAS patients who have the diagnosis of FL confirmed by central pathology review and have no major protocol deviations that would significantly impact the study outcome, as determined by blinded medical review. A patient may be excluded from the PP set for, but not limited to, any of the following conditions:

- Patient did not meet inclusion/exclusion criteria
- Infusion of wrong study drug occurred
- Patient did not receive all 4 infusions of study drug (Days 1, 8, 15, and 22)
- Intake of prohibited treatment, subject to evaluation of clinical relevance of the intake
- Patient did not have available response assessment at Week 28

All decisions to exclude patients from PP set will be made prior to database release.

The efficacy analyses will be applied for both the PP set and FAS and FAS will be considered as primary efficacy analysis population.

Pharmacokinetic Analysis Set (PKS)

The PKS will include all patients who receive the planned dose of study drug, have at least one measured drug serum concentration at a scheduled time point post-dose, and have no major protocol deviations or violations thought to significantly affect the PK of the drug.

Pharmacodynamic Analysis Set (PDS)

The PDS will include all patients who receive the planned dose of study drug, have at least one measured PD variables (CD19+ B cell count, IgG, and IgM) at a scheduled time point post-dose, and have no major protocol deviations or violations thought to significantly affect the PD of the drug.

8.5.2 Analysis Populations for interim analysis (PK / PD sub-population)

All analysis population in the interim analysis (PK / PD sub-population) are defined in the same way except the PP set, in which patient did not have available response assessment at Week 12 will be excluded.

8.6 Patient Disposition

The number and percentage of patients who were screened and randomized will be presented. For the patients who left the study prior to randomization, a summary will be presented for the reasons of withdrawal. For the patients who were randomized, summaries will be presented for the number and percentage of patients who completed the study, discontinued study drug (with reason for discontinuation), and withdrew early from the study (by reason for withdrawal).

8.7 Patient Characteristics

Patient demographics and baseline characteristics will be summarized by treatment group for the RAN. Continuous variables (e.g., age, weight, height, disease duration, etc.) will be summarized with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum). Qualitative variables (e.g., gender, race, ethnicity, etc.) will be summarized with counts and percentages.

Relevant medical history and continuing medical conditions will be summarized by treatment group for the RAN.

8.8 Efficacy Analyses

The statistical analysis of the primary endpoint for this study will be performed after the last patient has completed the Week 28 response assessment. All efficacy data will be analyzed at this time, plus all PK, PD, immunogenicity, and safety data available at the time of data

cut-off, and these data will be reported in the CSR (Week 28 CSR). After the last patient has completed Week 52 of the study, a CSR addendum (Week 52 CSR) will be prepared to report the additional safety data.

Efficacy will be assessed centrally as CR, PR, SD, and PD, as defined in IWG criteria 2007, and TTE. The main efficacy endpoint will be the difference in ORR (CR+PR) at Week 28, approximately 24 weeks after the completion of study treatment. The efficacy analyses will be applied for both the PP set and FAS. FAS will be considered as primary efficacy analysis population and analysis in PP set will be conducted as a sensitivity analysis.

In FAS, patients without a response assessment at Week 28 will be handled using a conservative approach by imputation using drop-out reason (IUDR), where Non-responder imputation (NRI) method in case of treatment related reasons and otherwise multiple imputation (MI) procedure assuming missing at random (MAR) will be applied. For the PP set, all available data will be used for analysis.

Potential withdrawal reasons are considered as follows based on previous studies; The major reason of missing response assessment at Week 28 is assumed to be either the start of new treatment of FL due to lack of efficacy or toxicity based on Ardeshna et al. In such reasons related to treatment (i.e. treatment failure requiring tumor targeting treatment for FL other than the protocol-defined treatment, death due to progressive disease), patients without a response assessment at Week 28 will be handled as non-responders. Missing responses unrelated to treatment (i.e. withdrawal by subject, pregnancy) as seen in the Colombat et al. would be considered ignorable missing at random (MAR) and multiple imputation procedure using logistic regression method will be used to impute the missing response assessment at Week 28 (responder versus non-responder). No imputation will be applied when the reasons are unknown whether they are related to treatment or not (i.e. lost to follow-up).

The adjusted difference in ORR between SAIT101 and MabThera® and its 95% Newcombe-Wilson CI will be calculated using the CMH weighted method accounting for appropriate stratification factors.

The following sensitivity analyses will be performed to explore the robustness of the primary efficacy result:

- The same adjusted analysis repeated in PPS and FAS with available data (no imputation)
- Unadjusted analysis for ORR (without covariates adjustment) in both the PP set and FAS with IUDR imputation

- A logistic regression model along with Delta method accounting for the same stratification factors will be performed in both the PP set and FAS with IUDR imputation
- Non-responder imputation (NRI) method will be used for patients without a response assessment at Week 28; patients without a response assessment at Week 28 will be handled as non-responders. The same adjusted analysis for NRI imputed ORR including stratification factors will be repeated for FAS
- A multiple imputation (MI) procedure using logistic regression method will be used to impute the missing primary efficacy results (responder versus non-responder) at Week 28, assuming data missing at random (MAR), to assess the impact of missing data and drop-outs. The same adjusted analysis for MI imputed ORR including stratification factors will be repeated for FAS

Further, expanded analysis on subgroup including stratification factors will be applied in an exploratory manner (i.e., region, etc.) and presented in a forest plot.

Efficacy response assessment (CR, PR, SD, and PD) at Week 12 will also be performed. For ORR at Week 12, the adjusted difference in ORR between SAIT101 and MabThera® and its 95% Newcombe-Wilson CI will be calculated using the CMH weighted method accounting for the same stratification factors with those of primary analysis. Previous studies[3, 15] showed that patients without a response assessment at Week 12 are rare and therefore no missing data will be imputed for ORR at Week 12.

For TTE variables of secondary efficacy endpoints, Kaplan-Meier curves will be calculated and displayed. Median survival times and the corresponding 95% CI will be provided using the Kaplan-Meier method. The estimated hazard ratio with 95% CI will be obtained from Cox regression model accounting for the same stratification factors with those of primary analyses.

All efficacy variables will be summarized descriptively by treatment group for the FAS and PP Set.

As an exploratory analysis, tumor response (CR, PR, SD, and PD), as defined by the IWG Criteria 2014, Lugano Classification,[19] and TTE will also be evaluated for any patients who had their tumors measured by PET-CT scan.

8.9 Safety

All safety analyses will be performed using the SAF. The safety variables are defined as follows:

- SAEs, AEs, AESIs, and ADRs
- Clinical laboratory parameters including hematology, chemistry, and urinalysis
- Concomitant medication use
- Vital signs, ECG, and physical examination.
- The proportion of patients achieving B-cell recovery (i.e. ≥lower limit of normal (LLN) or at least 50% of the baseline value) at Week 12, 20, 28, 36 and 52

8.9.1 Adverse Events

All reported terms for AEs will be coded using the MedDRA. No statistical testing will be performed for AEs.

A treatment-emergent AE (TEAE) will be defined as any AE with an onset date on or after the date of first dose of study drug until Week 52, or the EOS visit, if earlier. Adverse events which are already present during the pre-treatment period but increase in severity during the treatment period will be considered as TEAEs. Pre-existing AEs before the treatment period with no increase in severity during the treatment period will not be considered as TEAEs. All AEs will be listed.

For all AE and SAE tables, patients will be counted at most once for each Preferred Term (PT) and each System Organ Class (SOC). The TEAEs and SAEs will be summarized by the number and percentage of patients experiencing events by System Organ Class (SOC), Preferred Term (PT), and treatment group. The TEAEs by severity and causality will be summarized similarly.

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.

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, and for patients who permanently discontinue study drug due to an AE.

8.9.2 Clinical Laboratory Evaluations

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

Shifts (abnormal low, normal, and abnormal high) from baseline to each post-baseline visit with a laboratory assessment and EOS, 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 local laboratory.

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

8.9.3 Concomitant Medication

The incidence of concomitant medications will be summarized for the SAF by PT coded with the WHO-DD Enhanced, overall and by treatment group.

8.9.4 Vital Signs Measurements, Physical Findings and Other Safety Evaluations

Summary statistics will be presented for results at each visit with vital sign assessments and at EOS, as well as for change from baseline results to each visit with vital sign assessments and EOS for systolic and diastolic blood pressure, respiratory rate, body temperature, and pulse.

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 SAF. Criteria used to define abnormal vital sign results will be defined in the SAP. Shifts (abnormal low, normal, and abnormal high) from baseline to each post-baseline visit with vital sign assessments and EOS, based on normal ranges, will be presented for vital sign parameters.

A table and listing of any ECG abnormalities at screening will be presented.

A listing of physical examination abnormalities will be presented.

8.9.5 B-cell recovery

The proportion of patients achieving B-cell recovery (i.e. ≥lower limit of normal (LLN) or at least 50% of the baseline value) at Week 12, 20, 28, 36 and 52

8.9.6 DSMB Review

An independent DSMB, consisting of members who are independent from the Sponsor, the CRO and the study, will be established to act in an advisory capacity to monitor patient data.

Safety data collected at pre-specified time points, as outlined in the DSMB charter, will be reviewed by a DSMB.

The details of the DSMB roles and responsibilities, and details of the review process will be outlined in a DSMB charter.

8.10 Immunogenicity Analyses

Incidence of HACA and neutralizing antibody will be summarized by scheduled visit and treatment group for the SAF.

8.11 Pharmacokinetic Analyses

The PK analysis will be performed on the PK/PD sub-population. A listing of PK blood sample collection times by individual, as well as derived sampling time deviations, will be provided. A patient listing of concentration data by treatment, study day, and nominal time point will be presented.

Concentration data of rituximab will be summarized by treatment, study day, and nominal time point using appropriate descriptive statistics such as number, mean, standard deviation, percentage coefficient of variation (%CV), minimum, median, and maximum. Analyte concentrations which fall below quantifiable concentrations will be set to zero for all concentration summaries.

The following PK endpoints will be determined, where possible. Details of the parameter calculation methods will be included in the SAP. $AUC_{0\text{-}168}$ will be considered primary; C_{max} and C_{trough} (Day 29) will be considered secondary.

- Truncated area under the concentration-time curve (AUC) over the 1st and 4th dosing intervals ($AUC_{0\text{-}168}$) will be calculated with the linear up/log down method
- Maximum concentration after the 1st dose and the 4th dose (C_{max})

- Accumulation ratio for $AUC_{0\text{-}168}$ obtained from the 4th dose versus the 1st dose ($RAUC_{0\text{-}168}$)
- Accumulation ratio for C_{max} obtained from the 4th dose versus 1st dose (RC_{max})
- Trough concentrations on Days 1, 8, 15, 22, and 29 (C_{trough})

The PK parameters will be summarized by treatment and study day using n, mean, standard deviation, %CV, minimum, median, maximum, and geometric mean, except that T_{max} will be reported with n, minimum, median, and maximum only.

Plots of serial mean and individual serum rituximab concentrations over time by treatment and study day will be provided following i.v. infusions. Plots of mean and individual serum rituximab trough concentrations by study day and treatment will also be provided. Additional plots may be generated as appropriate.

The geometric means of the primary PK parameters ($AUC_{0\text{-}168,1}$ and $AUC_{0\text{-}168,4}$) will be compared between SAIT101 and MabThera® using analysis of variance. The statistical analysis of the loge-transformed primary endpoints will be based on an analysis of variance model. Covariates (e.g., age, sex, body weight, and etc.) may be added to the planned analysis. Least-squares geometric means will be presented for each treatment with corresponding 95% CIs. The ratio of least-squares geometric means (SAIT101/MabThera®) will be presented with corresponding 90% CIs. Pharmacokinetic similarity will be concluded in the ratio of least-squares geometric means falls between 80.00% and 125.00% for both primary parameters. Estimates and CI will also be provided for C_{max} and C_{trough} (Day 29) parameters.

8.12 Pharmacodynamic Analyses

The PD analysis will be performed on the PK/PD sub-population. A listing of PD blood sample collection times by individual, as well as derived sampling time deviations, will be provided. A patient listing of CD19+ B cell count, IgG and IgM (observed change from baseline and percent change from baseline) by treatment, study day, and nominal time point will be presented. Change from baseline value will be calculated as (observed [measured] post-dose value minus baseline value). Baseline is defined as the CD19+ B-cell count, IgG and IgM at pre-dose on Day 1.

The observed change from baseline and percent change from baseline data will be summarized by treatment, study day, and nominal time point using appropriate descriptive statistics such as n, mean, standard deviation, %CV, minimum, median, maximum, and 95% CIs. Analyte CD19+ B cell count data which fall below quantifiable concentrations will be set to zero for all CD19+ B-cell count summaries. Plots of mean and individual observed

change from baseline and percent change from baseline over time by treatment and study day will be provided following i.v. infusions.

Where appropriate, the following PD parameters will be calculated from the observed change from baseline and percent change from baseline PD parameter-time data. Details of the parameter calculation methods will be included in the SAP:

- Observed and change from baseline up to Week 52
- Area under the PD parameters versus time curve over the 1st dosing interval ($AUC_{0\text{-}W1}$)
- AUC over the 1st, 2nd, 3rd, and 4th dosing intervals ($AUC_{0\text{-}W1}$, $AUC_{W1\text{-}W2}$, $AUC_{W2\text{-}W3}$, and $AUC_{W3\text{-}W4}$)
- AUC from time 0 to Week 12 ($AUC_{0\text{-}W12}$)
- AUC from time 0 to Week 28 ($AUC_{0\text{-}W28}$)
- AUC from time 0 to Week 52 ($AUC_{0\text{-}W52}$)

The PD parameters will be summarized by treatment and study day using n, mean, standard deviation, %CV, minimum, median, maximum, and 95% CIs.

The means of PD parameters will be compared between SAIT101 and MabThera® using analysis of covariance that includes a covariate for baseline value. Least-squares means for each treatment will be presented for each treatment with corresponding 95% CIs. The difference in least-squares means (SAIT101/MabThera®) will be presented with corresponding 90% CIs.

8.13 Other Analyses

Additional exploratory (post-hoc) subgroup analyses may be performed. The subgroups to be used for these analyses will be based on the results of analysis of PK, PD, efficacy, safety, immunogenicity and concomitant medication, as appropriate.

8.14 Interim Analyses

An interim analysis of data collected upto Week 12 such as PK, PD, efficacy, safety and immunogenicity inclusive of the data from the PK/PD sub-population (134 patients in total) is planned.

9.0 ETHICS

9.1 Institutional Review Board or Independent Ethics Committee

An Ethics Committee should approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will provide the Sponsor or QuintilesIMS with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study site(s). The Investigator should submit the written approval to Archigen Biotech Limited or representative before enrollment of any patient into the study.

Archigen Biotech Limited or representative should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the Sponsor or QuintilesIMS of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of patients or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the Ethics Committee with a brief report of the outcome of the study, if required.

9.2 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (48th General Assembly, Somerset West, Republic of South Africa, October 2008 [or current version]), the applicable guidelines for GCP (CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

9.3 Patient Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient will be entered into the study. The ICF contains a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time. Written consent must be given by the patient and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the infusion of study drug. The Investigator will provide each patient with a copy of the signed and dated consent form.

When patients are enrolled into the study, they will be asked if they will also to consent to participation in the PK and PD part of the study; this will not be mandatory.

10.0 STUDY ADMINISTRATION

10.1 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study site should retain such documents 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 Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact 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 subject to inspection by the Sponsor and relevant regulatory authorities. If the Investigator withdraws from the study (e.g., relocation or retirement), all study-related records should be transferred to a mutually agreed upon designee within a Sponsor-specified time frame. Notice of such transfer will be given to the Sponsor in writing.

It is the responsibility of the Investigator to ensure that the study site 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.

10.2 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each patient randomized to study drug.

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, as defined in the ICF, be made available for study-related monitoring, audits, IRB/IEC review, and regulatory inspection by authorized persons.

10.3 Investigator Information

10.3.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonised Tripartite Guideline for GCP (1997); the US CFR Title 21 parts 50, 56, and 312; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IRB/IEC in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

10.3.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 1). By signing the protocol, the Investigator confirms in writing that he/she has read, understands, and will strictly adhere to the study protocol, and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any site where the Investigator has not signed the protocol.

10.4 Financing and Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study. The terms of the insurance will be kept in the study files.

10.5 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 by unique patient numbers in the eCRFs.

10.6 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study site will be set forth in the Clinical Trial Agreement.

10.7 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 sites, 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 subjects, 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.

10.8 Emergency Contacts

The emergency medical contacts for the study are as follows:

QuintilesIMS Medical Emergency Contact Center:
Telephone number: +1 973 659 6677
Alternative number: +1 570 819 8565

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12.0 APPENDICES

APPENDIX 1: SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Randomized, Double-blind, Multi-center, Multi-national Trial to Evaluate the Efficacy, Safety, and Immunogenicity of SAIT101 Versus Rituximab as a First-line Immunotherapy Treatment in Patients with Low Tumor Burden Follicular Lymphoma

PROTOCOL NO: AGB 002

This protocol is a confidential communication of Archigen Biotech Limited. 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 Limited.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the study will be conducted. Return the signed copy to QuintilesIMS.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

APPENDIX 2: FOLLICULAR LYMPHOMA GRADING

According to the World Health Organization criteria, ICD-10, C82 (http://apps.who.int/classifications/icd10/browse/2010/en#/C81-C96), the disease is morphologically graded into:

- Grade 1 (0-5 centroblasts per high-power field [HPF]).
- Grade 2 (6-15 centroblasts/HPF).
- Grade 3 (>15 centroblasts/HPF).

Grade 3 is further subdivided into:

- Grade 3a (centrocytes still present).
- Grade 3b (centroblasts form solid sheets with no residual centrocytes).

APPENDIX 3: FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX 2: FLIPI-2

Sources:

Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol. 2009;27(27):4555-62.

Dreyling M, Ghielmini M, Marcus R, Salles G, Vitolo U, Ladetto M; ESMO Guidelines Working Group. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014 Sep;25 Suppl 3:iii76-82.

Table 1: FLIPI-2 Scoring Criteria

Parameter	Adverse Factors
Age	>60 years
Hemoglobin level	<120 g/L
β2-microglobulin level	Above upper limit of normal
Longest diameter of largest involved node	>6 cm
Bone marrow involvement	Present

Table 2: Risk Groups According to FLIPI-2 Criteria

Risk Group	Number of adverse factors
Low risk	0-1
Intermediate risk	2
High risk	3-5

APPENDIX 4: MODIFIED RESPONSE AND PROGRESSION CRITERIA – INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR NON-HODGKIN'S LYMPHOMA

Sources:

Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999 Apr;17(4):1244.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al, Revised Response Criteria for Malignant Lymphoma. J Clin Oncol. 2007; 25:579-86.

The response Criteria for Non-Hodgkin's Lymphoma are summarized in Table 1.

CR: The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically fluorodeoxyglucose (FDG)-avid lymphoma: in patients with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and >1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

CRu: The use of the above definition for CR and that below for PR eliminates the category of CRu.

PR: The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6. No new sites of disease should be observed.

7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria

should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by >50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease: Stable disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD):

Lymph nodes should be considered abnormal if the long axis is >1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is >1.0. Lymph nodes ≤1.0 × ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion >1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by >50% and to a size of 1.5 × 1.5 cm or >1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node >1 cm in its short axis.

4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in patients with mucosa associated lymphoid tissue [MALT] lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned unconfirmed (CRu) status, but should be considered partial responses.

Table 1: Response Criteria for Non-Hodgkin's Lymphoma

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

CR complete remission; CT computed tomography; FDG [^{18}F] fluorodeoxyglucose; PET positron emission tomography; PD progressive disease; PR partial remission; SD stable disease; SPD sum of the product of the diameters.

APPENDIX 5: ANN ARBOR STAGING

Sources:

Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease stage classification. Cancer Research. 1971;31:1860-1.

Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. J Clin Oncol. 1989;7(11):1630-6.

Principal Stages

The principal stage is determined by location of the tumor:

- Stage I indicates that the cancer is located in a single region, usually 1 lymph node and the surrounding area. Stage I often will not have outward symptoms.
- Stage II indicates that the cancer is located in 2 separate regions, an affected lymph node or organ and a second affected area, and that both affected areas are confined to 1 side of the diaphragm - that is, both are above the diaphragm, or both are below the diaphragm.
- Stage III indicates that the cancer has spread to both sides of the diaphragm, including 1 organ or area near the lymph nodes or the spleen.
- Stage IV indicates diffuse or disseminated involvement of 1 or more extra lymphatic organs, including any involvement of the liver, bone marrow, or nodular involvement of the lungs

Modifiers

These letters can be appended to some stages:

- A or B: the absence of constitutional (B-type) symptoms is denoted by adding an "A" to the stage; the presence is denoted by adding a "B" to the stage.
- E: is used if the disease is "extranodal" (not in the lymph nodes) or has spread from lymph nodes to adjacent tissue.
- X: is used if the largest deposit is >10 cm large ("bulky disease"), or whether the mediastinum is wider than 1/3 of the chest on a chest X-ray.
- S: is used if the disease has spread to the spleen.

Type of Staging

The nature of the staging is (occasionally) expressed with:

- CS: clinical stage as obtained by doctor's examinations and tests.
- PS: pathological stage as obtained by exploratory laparotomy (surgery performed through an abdominal incision) with splenectomy (surgical removal of the spleen). Note: exploratory laparotomy has fallen out of favor for lymphoma staging.

APPENDIX 6: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Published in:

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

APPENDIX 7: NYHA CLASSIFICATION OF HEART FAILURE

Source:
http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp#.VrDe-LIrLDd

Doctors usually classify patients' heart failure according to the severity of their symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

For Example:

- A patient with minimal or no symptoms but a large pressure gradient across the aortic valve or severe obstruction of the left main coronary artery is classified:
  Function Capacity I, Objective Assessment D

- A patient with severe anginal syndrome but angiographically normal coronary arteries is classified:
  Functional Capacity IV, Objective Assessment A

APPENDIX 8: GUIDELINES FOR PREPARATION AND ADMINISTRATION OF RITUXIMAB

SAIT101 and MabThera® will be provided in sterile, preservative-free, non-pyrogenic, single-use vials containing 500 mg of rituximab per 50 mL.

Stability and Storage

All study drugs must be kept in a secure place under appropriate storage conditions. The IMP must be stored in a refrigerator at a controlled temperature (2 to 8°C) and handled according to GCP as well as IB. Vials should be kept in the outer carton in order to protect them 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 drugs, SAIT101 and MabThera®, must be kept strictly separate and in a different location than commercially available products at all times. Additional details regarding the storage and handling of the study drugs will be provided to the study sites.

No preservative is used in SAIT101/MabThera®; therefore, the vials are intended for single use only. 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.

The products must not be used after the expiry date.

Preparation Materials

In order to guarantee that the product is stable when diluted, it is recommended that the following infusion bags and line materials are used:

Infusion Bag Materials:

- Polyvinyl chloride (PVC)
- PVC free/di-(2-ethylhexyl)phthalate (DEHP) free
- polyethylene (PE)

Infusion Line/Tubing Materials:

- PVC
- PE
- Polyurethane (PUR)

The materials used must be documented on the Subject Drug Dispensing Log. For the PVC free/DEHP free bag, the manufacturer and/or material type used should also be documented.

Preparation of Rituximab for i.v. Administration

1. Calculate the patient's body surface area (BSA). For subsequent doses, if the patient's body weight has changed by more than 10% since the last dose, then BSA should be recalculated.

2. Calculate the dose to be administered, rounding to three significant figures, according to the following formula:

   Dose (mL) = [(Patient BSA in m^2) × (375 mg/m^2)] / 10 mg/mL (volume of rituximab).

3. 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.

4. Dilute the 2 vials of study drug (1000 mg) assigned via IXRS to a calculated concentration of 1 to 4 mg/mL rituximab in a 250, 500, or 1,000 mL infusion bag containing either 0.9% sodium chloride or 5% glucose for injection. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Inspect the vials for particulate matter and discoloration prior to administration.

5. Clearly label the bag with the study code, patient number and total dose of rituximab contained in the bag. Those used materials will be disposed in accordance with site practice.

Instructions for the i.v. Administration of Rituximab (same for both study drugs)

1. Do not administer as an i.v. push or bolus. Do not infuse the study drug concomitantly with another i.v. solution or other i.v. medications.

2. 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 (eg, volumetric infusion pump). An in-line filter is not required.

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

4. The first dose will be administered at an initial infusion rate of 50 mg/hour for the first hour. If no toxicity is seen, the rate may be increased gradually in 50 mg/hour increments at 30-minute intervals, to a maximum of 400 mg/hour.

5. If the first dose is well tolerated, the initial infusion rate for subsequent doses will be 100 mg/hour, increased gradually in 100 mg/hour increments at 30-minute intervals,

to a maximum of 400 mg/hour. 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

6. In patients with detectable circulating malignant cells, it is strongly advised that the initial infusion rate be reduced to 25 mg/hour; these patients may experience more frequent and severe transient fever and rigors, shortness of breath, and hypotension.

7. The exact date and time of start of infusion, end of infusion, any interruptions (stop time, restart time etc.), and total dose administered must be recorded in the patient's eCRF.

Table 1 Recommended Infusion Rates

Day 1 infusion	Dose (mg)	Time (minutes)[a]	Cumulative dose (mg)	Day 8, 15, and 22 infusions	Dose (mg)	Time (minutes)[a]	Cumulative dose (mg)
50 mg/h	50	0-60	50	100 mg/h	50	0-30	50
100 mg/h	50	61-90	100	200 mg/h	100	31-60	150
150 mg/h	75	91-120	175	300 mg/h	150	61-90	300
200 mg/h	100	121-150	275	400 mg/h	(375*BSA)-300	[d]	[d]
250 mg/h	125	151-180	400				
300 mg/h	150	181-210	550				
350 mg/h	175	211-240[b]	725				
400 mg/h	(375*BSA)-725	[c]	[c]				

BSA body surface area in m^2

a Allowed window for infusion rate time at each time point is ± 5 minutes.

b Approximately 240 minutes (4 hours) to complete a dose of 725 mg.

c Total dose and time of infusion will depend on patient's BSA. Total dose is 375 mg/m^2; every additional 50 mg above a 725 mg dose will require 7.5 minutes infusion of the 400 mg/mL dose.

d Total dose and time of infusion will depend on patient's BSA. Total dose is 375 mg/m^2; every additional 50 mg above a 300 mg dose will require 7.5 minutes infusion of the 400 mg/mL dose.

If the patient experiences fever and rigors, or any ADR, the antibody infusion should be discontinued, and the severity of the side effects evaluated. If the symptoms improve, the infusion may be continued, initially at one-half the previous rate. The Investigator should wait an additional 30 minutes while delivering the infusion at the reduced rate. If tolerated, the rate may then be increased to the next closest rate on the patient's infusion schedule. For example:

(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.

If the patient does not tolerate the reduced rate for at least 30 minutes then the infusion should be stopped and the patient discontinued from the study.

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 will be administered on an outpatient basis, and patients discharged after the infusion in accordance with the normal standard of care for rituximab-containing regimens, 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.

Similarly, in the event of any other life-threatening reaction, including hypersensitivity reaction, renal failure, severe cardiopulmonary event and severe mucocutaneous reaction, the study drug will be discontinued and no additional study drug will be administered.

If extravasation occurs during infusion of the study drug, the infusion must be stopped. Restart the remainder of the infusion either in the area of the same arm that is proximal to the body, or in the other arm. The PK, PD and immunogenicity samples will always be drawn from the opposite arm of the infusion arm.

Following the infusion, the i.v. line should be maintained for medications as needed. If there are no complications after 1 hour of observation, the i.v. line may be discontinued. The i.v. line may not be used for sampling for PK, PD, or immunogenicity.

Institutional guidelines for the administration of rituximab, and the kind of premedication, can be followed. Dose modification is not permitted during this study. Any deviation to the dose will be recorded in the eCRF.

APPENDIX 9: CLINICAL EVALUATION OF HEPATIC INJURY

Hepatic injury is defined by the following alterations of liver parameters:

- For patients with normal liver function at baseline: an elevation of AST and/or ALT ≥3 × ULN combined with an elevation of bilirubin ≥2 × ULN measured in the same blood draw sample
- For patients with impaired liver function at baseline: an elevation of AST and/or ALT >5 × ULN combined with an elevation of total bilirubin >2 times ULN measured in the same blood draw sample
- For all patients, marked peak aminotransferase (ALT and/or AST) elevations ≥10 × ULN with or without concurrent elevation of bilirubin.

These laboratory findings constitute a hepatic injury alert, and patients showing these laboratory abnormalities need to be followed up according to the procedures below. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, and total bilirubin) available, the Investigator should make sure these parameters are analyzed, if necessary in an unscheduled blood test. If the results meet the criteria of a hepatic injury alert, the procedures described below and the drug-induced liver injury (DILI) checklist should be followed.

Repeat the following laboratory tests according to the following criteria:

Patients with liver function test (LFT) value(s) within normal limits at baseline:
Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin (total and direct) within 48 to 72 hours. If ALT and/or AST ≥3 times upper limit of normal (ULN) combined with an elevation of total bilirubin ≥2 times ULN are confirmed, results of the laboratory parameters described below must be made available to the Investigator and to Archigen as soon as possible.

Patients with elevated LFT value(s) at baseline:
Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) within 48 to 72 hours. If ALT and/or AST ≥5 times ULN combined with an elevation of total bilirubin ≥2 times ULN are confirmed, results of the laboratory parameters described below must be made available to the Investigator and to Archigen as soon as possible.

Patients with elevated total bilirubin at baseline due to hepatic infiltration by follicular lymphoma (FL), Gilbert's Syndrome, or hemolysis:

The threshold to qualify for repeat laboratory tests is defined as elevation of hepatic enzymes based on the above criteria, combined with concurrent elevation of total bilirubin above baseline.

In addition:

- obtain a detailed history of current symptoms, concurrent diagnoses, and medical history according to the DILI checklist (see Tables 1 and 2 below);
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the DILI checklist (see Tables 1 and 2 below);
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the DILI checklist (see Tables 1 and 2 below);

and report these via the eCRF.

Clinical chemistry

- Alkaline phosphatase, albumin, prothrombin time or International Normalized Ratio, creatine kinase, creatine kinase muscle-brain, coeruloplasmin, α-1 antitrypsin, transferrin, amylase, lipase, fasting glucose, cholesterol, triglycerides, cholinesterase

Serology

- Hepatitis A (anti-IgM, total Ig), hepatitis B (hepatitis B surface antigen [HBsAg], Anti-HBs, DNA), hepatitis C (anti-hepatitis C virus [HCV], RNA if anti-HCV positive), hepatitis D (anti-IgM, total Ig), hepatitis E (anti-hepatitis E virus [HEV], anti-HEV IgM, RNA if anti-HEV IgM positive), anti-Smooth Muscle antibody (titer), anti-nuclear antibody (titer), anti-liver-kidney microsomes antibody, anti-mitochondrial antibody, Epstein Barr Virus (virus capsid antigen [VCA] IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)

Hormones, tumor marker

- Thyroid stimulating hormone

Hematology

- Complete blood count (including differential counts)

Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, eg, bile duct stones or neoplasm.

Initiate close observation of patients by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and or AST

abnormalities stabilize or return to normal, then according to the CTP. Depending on further laboratory changes, additional parameters identified, eg, by reflex testing, will be followed up based on medical judgment and GCP.

Assessment of drug-induced liver injury (DILI):

Source: Lee WM and Senior JR. Recognizing drug-induced liver injury: current problems, possible solutions. Toxicol Pathol. 2005;33(1):155-64.

The type of liver injury is determined first: hepatocellular, cholestatic or mixed (see Table 1).

Table 1: Determining the Type of Acute Liver Injury

Ratio (R) of serum activities of ALT/ALP, in xULN, measured together at time liver injury first recognized	
Hepatocellular	**R** ≥5, OR (ALT >2 × ULN and ALP in normal range)
Cholestatic	**R** ≤2, OR (ALP >2 × ULN and ALT in normal range)
Mixed	2 <**R** <5 AND (ALT >2 × ULN and ALP >ULN)

Checklist criteria are then scored according to Table 2.

Table 2: Abbreviated DILI checklist

Criteria	Explanation	Score
Time to onset of liver injury, from initial exposure to drug	Suggestive 2; compatible, 1; inconclusive, 0. (if no information, case insufficiently documented; if incompatible, unrelated)	0 to 2
Course of the reaction	Highly suggestive, 3; suggestive 2; compatible, 1; inconclusive or no data, 0; against a role for the drug, −2	−2 to 3
Known risk factors for DILI; Alcohol use; Age ≥ 55	None, 0; one validated risk factor, 1; two or more validated risk factors, 2	0 to 2
Concomitant drug exposure	None, no information, or incompatible time to onset, 0; time compatible but not known hepatotoxin, −1; time compatible and known hepatotoxin, −2; definitely caused by other agent, −3	0 to −3
Alternative nondrug cause	Ruled out (not hepatitis A, B, or C; not alcohol-induced [AST/ALT = 2]; no gall stones or biliary tract disease by ultrasound; no recent hypotension), 2; not fully investigated, some ruled out, 1 to −2, depending on how many; probable, −3	−3 to 2
Previous information on drug	Not known hepatotoxin, 0; published as hepatotoxic, 1; labeled as hepatotoxin, 2	0 to 2
Response to rechallenge	Positive, 3; compatible, 1; not done, not interpretable, 0; negative, −2	−2 to 3

APPENDIX 10: SCHEDULE OF ASSESSMENTS

1. Screening (Visit 1 – Study Days -30 to 0)

The following screening procedures will be performed within 30 days prior to the first day of blinded study drug administration unless otherwise stated.

- Informed consent (must be obtained prior to the patient undergoing any study specific procedures and may occur prior to the 30 day screening period).
- Review inclusion /exclusion criteria.
- Record screening visit in the IXRS.
- Confirm diagnosis of Grade 1-3a, CD20+ FL and ensure tissue or slide is available for the retrospective central pathology review (Appendix 2). If a biopsy has not been performed within the previous 24 months prior to screening visit, a new biopsy is required to confirm that the histology is unchanged.
- Evaluate FL signs and symptoms and ensure the patient is not experiencing B symptoms.
- Ensure the patient is Ann Arbor Stage II, III, or IVA (Appendix 5).
- Collect information for FLPI-2 (Appendix 3).
- Collection of demographic information.
- Medical and surgical history.
- Adverse events.
- Prior and current medications.
- Physical examination (PE) The PE should include assessment of general appearance, skin, head, neck, throat, lymph nodes, thyroid, abdomen, cardiovascular, neurological, musculoskeletal/extremities, and respiratory systems, as appropriate, and consistent with local standard of care. Body weight will be measured. Height will be measured at screening only. The PE must include lymph nodes, liver and spleen. Any specific signs or symptoms that are medically significant should be reported. Particular attention should be paid to 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).
- Vital signs, including systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature. To be measured after the patient has been in a sitting/lying down position for at least 5 minutes.

- ECOG performance status assessment
- 12-lead electrocardiogram (ECG).
- Laboratory testing including hematology, blood chemistry, urinalysis, serum β2 microglobulin, lactate dehydrogenase (LDH), and viral disease screening (hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody, and HIV testing)
- HBV testing - patients with occult or prior hepatitis B infection (defined as positive total HBcAb and negative HBsAg) only.
- TB screen (if required by local regulation or at the investigator's discretion) to be performed according to local practice and local regulatory guidance, unless obtained within 3 months prior to Day 1. A chest X-ray will be required for all patients with a positive TB test to confirm there is no active TB.
- Serum pregnancy test (human chorionic gonadotrophin; hCG) for women of childbearing potential. For definition of childbearing potential, refer to inclusion criterion 9 & 10.
- Contrast enhanced CT scan of neck, chest, abdomen and pelvis and any other areas known or suspected to be involved. A CT scan acquired up to 60 days prior to Day 1 may be used for screening provided that the scan is of sufficient quality according to central review. For Investigators who routinely use PET scans for assessment of their patients, a PET scan may be performed **in addition to** (not instead of) the CT scan at the Investigator's discretion. Combined PET-CT scans may be used only if performed with contrast, and if the resolution is sufficient to allow accurate and consistent comparison of lesion measurements with subsequent CT scans. Where the contrast product is contraindicated, an abdomen-pelvic magnetic resonance imaging scan (MRI) should be performed with a non-contrast chest CT scan.
- Bone marrow biopsy (biopsy specimen up to 60 days prior to Day 1 may be used for screening. To be performed locally and confirmed centrally. Patients with bone marrow biopsies demonstrating lymphoma within the previous year are not required to undergo a repeat bone marrow evaluation prior to study entry. Patients with a prior bone marrow biopsy performed more than 1 year before screening or negative for lymphoma, or with no bone marrow biopsy, will be required to undergo another bone marrow biopsy within 60 days of randomization.

2. Study Period

2.1. Day 1 (Visit 2)

- Review inclusion/exclusion criteria to ensure patient eligibility
- Randomization via IXRS (can be conducted up to 4 days prior to Day 1).
- Note: Randomization will be stratified based on low, intermediate, and high risk patients using the Follicular Lymphoma International Prognostic Index 2 (FLIPI-2).

It is critical that the FLIPI-2 is scored correctly and that this information is entered into the IXRS accurately.

- IXRS study drug assignment.
- PE including body weight.
- Vital signs.
- Prior and concomitant medications.
- Adverse events.
- Laboratory testing including hematology, blood chemistry, urinalysis, serum β2 microglobulin, and LDH.
- HBV DNA testing in patients with occult or prior hepatitis B infection (defined as positive total HBcAb and negative HBsAg) at screening.
- Urine pregnancy test for female patients of childbearing potential.
- PK / PD (CD19+ B-cell count) sampling at 0 hours (pre-dose), and at the end of infusion (± 10 minutes).
- IgG and IgM sampling.
- Immunogenicity sampling prior to dosing.
- Administration of pre-medications.
- Study drug administration.

2.2. Treatment Visits (Visits 3, 4, and 5 – Study Days 8, 15 and 22)

- PE including body weight.
- Vital signs.
- Concomitant medications.
- Adverse events.
- Laboratory testing including hematology, blood chemistry, and urinalysis.
- PK / PD (CD19+ B-cell count) sampling at 0 hours (pre-dose), and at the end of infusion (± 10 minutes)
- IgG and IgM sampling
- Immunogenicity sampling prior to dosing (Day 15 only).
- Contact IXRS.

- Administration of pre-medications.
- Study drug administration.

2.3. Follow-up Visits (Visit 6, 7, 8, 9 and 10 –Weeks 5, 12, 20, 28 and 36)

- Physical examination (PE).
- Vital signs.
- ECOG performance status assessment (Weeks 5 and 28 only).
- 12-lead ECG (Week 28 only).
- Concomitant medications.
- Adverse events.
- Laboratory testing including hematology, blood chemistry, urinalysis, serum β2 microglobulin, and LDH.
- HBV DNA testing in patients with occult or prior hepatitis B infection (defined as positive total HBcAb and negative HBsAg) at screening.
- Ann Arbor staging (Week 28 only).
- Contrast enhanced CT scan of neck, chest, abdomen and pelvis, and any other areas known or suspected to be involved. Assessment permitted up to 4 weeks prior to, or 2 weeks after the Week 28 visit. Optional PET or PET-CT scan in addition to CT scan. MRI where the contrast product is contraindicated. (Weeks 12 and 28)
- Bone marrow biopsy – second biopsy required only for patients with positive findings at screening, to confirm Complete Response (CR) based on investigator's review of CT scan (from Week 12 onwards).
- Serum pregnancy test for female patients of childbearing potential (Week 28 only).
- PK (not in week 36) / PD (CD19+ B-cell count) sampling.
- IgG and IgM sampling
- Immunogenicity sampling.

2.4. Week 52 / Early End of Study Visit (Visit 11 –Week 52)

- Contact IXRS
- Physical examination (PE).
- Vital signs, including systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature.

- 12-lead electrocardiogram (ECG).
- ECOG performance status assessment
- Concomitant medications.
- Adverse events.
- Laboratory testing including hematology, blood chemistry, urinalysis, serum β2 microglobulin, and lactate dehydrogenase (LDH).
- HBV DNA testing in patients with occult or prior hepatitis B infection (defined as positive total HBcAb and negative HBsAg) at screening.
- Serum pregnancy test (human chorionic gonadotrophin; hCG) for women of childbearing potential.
- PD (CD19+ B-cell count) sampling.
- IgG and IgM sampling.
- Immunogenicity sampling.

2.5. Early Treatment Discontinuation Visit

At an Early Treatment Discontinuation visit, the same assessments should be conducted as at Week 28 / Early End of Study, with the following additional assessments:

- Ann Arbor staging – only for patients who need to start a new treatment.
- Bone marrow biopsy – only for patients with positive findings at screening, to confirm CR based on investigator's review of CT scan
- CT scan (MRI scan where contrast is contraindicated) – only for patients who discontinue study drug early for any reason and need to start a new treatment before the Week 28 visit.

2.6. Unscheduled Visit

- Unscheduled visits should be scheduled as per Investigator discretion. Tests will be selected as per Investigator's discretion.

2.7. Phone Visit

As a measure to minimize lost to follow-up, a phone visit can be tried.

- ECOG performance status assessment
- Concomitant medications.
- Adverse events.

APPENDIX 11: DEFINITION OF PROGRESSION THAT WARRANTS INITIATION OF TREATMENT CHEMOTHERAPY/RADIOTHERAPY.

Modified based on the publication:

Ardeshna KM1, Qian W, Smith P, Braganca N, Lowry L, Patrick P, Warden J, Stevens L, Pocock CF, Miall F, Cunningham D, Davies J, Jack A, Stephens R, Walewski J, Ferhanoglu B, Bradstock K, Linch DC. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncol. 2014; 15: 424-35.

It is recognized that it is difficult to clearly define when disease progression is sufficient to warrant the initiation of chemotherapy or radiotherapy. The following is suggested guidance:

1. Development of symptomatic enlarged lymph nodes or spleen.

2. The development of B symptoms or severe pruritus.

3. Lymphomatous mass >7cm provided it has increased in size by at least 25%.

4. More than 3 sites with diameter >5cm.

5. The development of significant serous effusions, clinically or on CT (small, clinically non-evident effusions on CT scan are not an indication to start chemotherapy).

6. Hemoglobin <100g/L (10g/dL), absolute neutrophil count $<1.5x10^9$/L (1,500/mm^3), platelet $<100x\ 10^9$/L (100,000/mm^3) not attributable to other causes. If asymptomatic this should persist for >1 month.

7. Critical or near critical organ involvement or organ compression, e.g. ureteric obstruction, epidural compression.

8. A rising LDH is not in itself an indication to initiate therapy but may trigger further investigations.