# Statistical Analysis Plan

## AGB002

**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**

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| Final V1.0 | 10Sep2019 | | Not Applicable – First Version |
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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ADA | Anti-drug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| ATC | anatomical therapeutic chemical |
| 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 |
| AUEC | Area under the PD variable-time effect curve |
| $AUEC_{0\text{-}168}$ | truncated AUEC over the dosing interval |
| $AUEC_{0\text{-}WX}$ | area under the PD variable-time effect curve from time 0 to Week X |
| BMI | Body mass index |
| BSA | body surface area |
| CI | confidence interval |
| $C_{max}$ | maximum concentration |
| CMH | Cochran-Mantel-Haenszel |
| CR | complete response |
| CSR | clinical study report |
| CT | computerized/computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| $C_{trough}$ | trough concentration |
| CV | Coefficient of Variation |
| DSMB | Data Safety Monitoring Board |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| ENR | Enrolled Set |
| EOS | End of Study |

| | |
|---|---|
| FAS | Full Analysis Set |
| FL | follicular lymphoma |
| FLIPI-2 | Follicular lymphoma international prognostic index 2 |
| IUDR | Imputation Using Drop-out Reason |
| i.v. | intravenous(ly) |
| IWG | International Working Group |
| LTBFL | low tumor burden follicular lymphoma |
| MAR | missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple Imputation |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| NED | No evidence of disease |
| NRI | non-responder imputation |
| ORR | overall response rate |
| PD | pharmacodynamic(s) |
| PD | progressive disease |
| PDS | Pharmacodynamic Analysis Set |
| PET | positron emission tomography |
| PK | pharmacokinetic(s) |
| PKS | Pharmacokinetic Analysis Set |
| PML | progressive multifocal leukoencephalopathy |
| PP | Per-protocol |
| PR | partial response |
| PT | Preferred Term |
| RAN | Randomized Set |
| $RAUC_{0\text{-}168}$ | accumulation ratio for $AUC_{0\text{-}168}$ |
| $RC_{max}$ | accumulation ratio for $C_{max}$ |
| RDI | Relative dose intensity |
| SAE | serious adverse event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |

| | |
|---|---|
| SD | stable disease |
| SEM | Standard error of the mean |
| SOC | System Organ Class |
| TEAE | treatment-emergent AE |
| TTE | time to event |
| ULN | upper limit of normal |
| US | United States |
| User ID | user identification |
| WHO-DD | World Health Organization-Drug Dictionary |

# 1. Introduction

This document describes the rules and conventions to be used in the presentation and analysis of pharmacokinetics (PK), efficacy, safety, pharmacodynamics (PD), and immunogenicity data for Protocol AGB002. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. The following analyses will be performed for this study: data and safety monitoring board (DSMB) analyses, analysis for Week 12, for inclusion in week 28 clinical study report (CSR), analysis for Week 28 (Week 28 CSR) and Week 52 (Week 52 CSR) which is an addendum of Week 28 CSR.

This statistical analysis plan (SAP) is based on protocol version amendment 03, dated 03Nov2017.

# 2. Study Design and Study Objective

## 2.1. STUDY OBJECTIVE

### 2.1.1. PRIMARY OBJECTIVE

The primary objective of the study is 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).

### 2.1.2. SECONDARY OBJECTIVE

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.

## 2.2. STUDY DESIGN

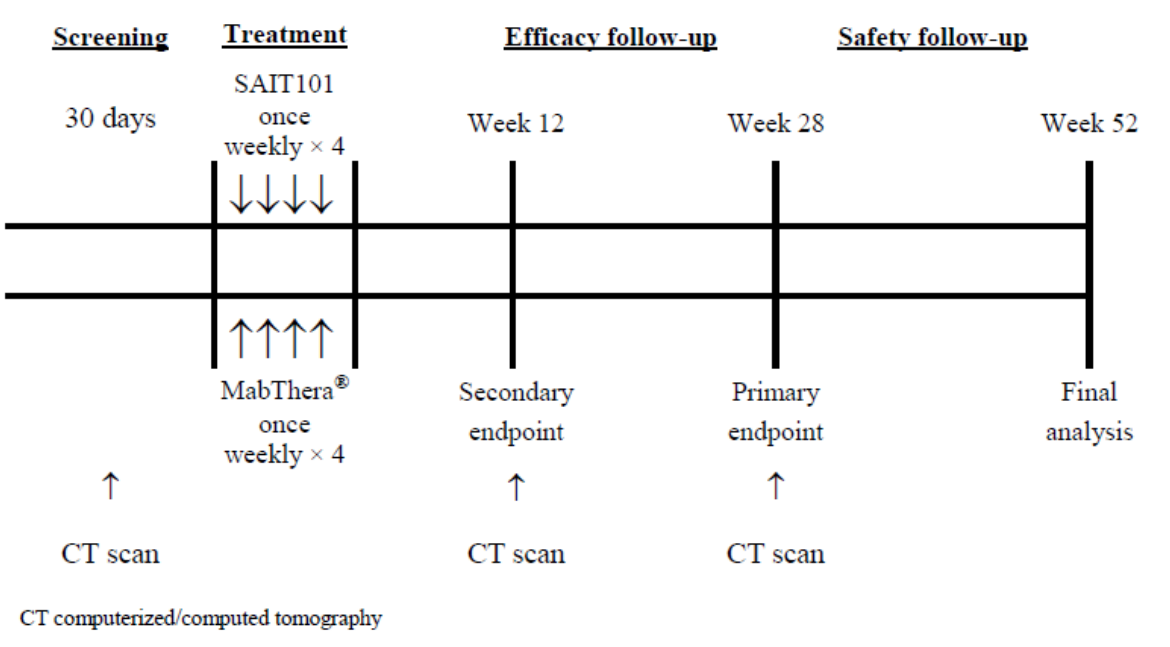
This is a multi-center, randomized, double-blind, parallel-group study to evaluate the efficacy, safety, and immunogenicity of SAIT101 versus MabThera® in asymptomatic patients with low tumor burden follicular lymphoma. This study will take place globally across approximately 165 study sites in order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

Eligible patients will be randomized to receive either SAIT101 or MabThera® monotherapy as an i.v. infusion once a week for 4 weeks. Randomization will be stratified by inclusion in the PK/PD sub-population and follicular lymphoma international prognostic index 2 (FLIPI-2) score. 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.

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 follicular lymphoma (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 computerized/ computed tomography (CT) scan, should be performed before the start of the new treatment. Patient who discontinue the study treatment will be followed-up until Week 52 (End of study - EOS) for safety and immunogenicity. 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 EOS visit before they are formally withdrawn. Once a patient is withdrawn from the study, no further assessments can be conducted.

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

**Figure 1.** Study Design from Protocol




## 2.3. SAMPLE SIZE CALCULATION

Response rate of MabThera® 4 weekly dosing in low tumor burden follicular lymphoma was assessed in Ardeshna et al. 2014, Kahl et al. 2014 and Colombat et al. based on systematic literature search. The Ardeshna study was the only randomized trial which compared the treatment of MabThera® alone with the 'watch & wait' (W&W). The month 7 response rate on MabThera® monotherapy was estimated to be 77% with 95% confidence interval (CI) (66%-85%), considering 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%, equivalence can be declared if the response rate in the SAIT101 arm is more than 49%. As above, the estimated margin should be set less than ±17.0%.

In the reference study, the month 7 response rate in MabThera® monotherapy was estimated to be 77% with 95% CI (66%-85%) and response rate of W&W group was estimated to be 6%, giving an estimated difference in overall response rate (ORR) of 71% with 95% CI (59%-79%). 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 MabThera® 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, Ps, is 0.770 and the Test expected proportion, Pt, is 0.770; results are based on 1,000 simulations using the Newcombe-Wilson score method to construct the CI.

Thus, 154 patients in each group are able to satisfy the primary analysis of ORR, given an 83% probability of declaring equivalence in the full analysis set (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, 147 patients in each group will give 80% probability of demonstrating equivalence in the PPS.

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 MabThera® 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%). The maximum difference in the upper and lower 95% CI of ORRs is ±15.0%, which is smaller than the margin ±16.0%, and this estimated ORR with 95% CI for SAIT101 is considered to exclude a clinically relevant. difference versus MabThera.

**Pharmacokinetic/ Pharmacodynamic sub-population**

For PK, assuming a coefficient of variation (CV) of 38% in both $AUC_{0\text{-}168}$, based on Regazzi et al. 2005 and assuming no true difference between SAIT101 and MabThera® 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 procedures, 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.

## 2.4. 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. The block size(s) of the randomization will be documented in the Week 28 CSR.

## 2.5. SCHEDULE OF EVENTS

The schedule of events is provided in Table 1 in the protocol.

## 2.6. CHANGES TO ANALYSIS FROM PROTOCOL

The following updates were made:

- The PK and PD analysis sets were updated to include subjects that received at least one dose of the study drug. The PD analysis set were updated to only include subjects that have at least one measured PD variable (CD19+ B-cell count). IgM and IgG were removed from the definition of the PDS since those PD variables are measured in all subjects in the safety analysis set.
- The following criteria was not considered for the exclusion of patients from the Per Protocol Set (PPS):
    - Patient did not have available response assessment at Week 28

# 3. Planned Analyses

The following analyses will be performed for this study:

## 3.1. DATA AND SAFETY MONITORING BOARD (DSMB)

It is anticipated, there will be at least 4 DSMB meetings for reviewing safety data in this study, with timing of review meetings based on first 24 patients, 50% of patients at Week 4, all patients at Week 24 and Week 36. Analysis for DSMB meetings will be described in a separate DSMB SAP. The fourth DSMB is optional and will be confirmed if needed after the third DSMB. For additional details on DSMB meetings, please refer to the DSMB charter dated 07Oct2016.

## 3.2. FINAL ANALYSIS

The study will be unblinded at Week 28 for the primary endpoint analysis and a CSR will be prepared based on data up-to and including Week 28for all patients. The investigators and patients will remain blinded to treatment assignment during the post Week 28 follow up period.

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 .

### 3.3. EXPLORATORY ANALYSIS

Additional exploratory subgroup analyses, i.e., in addition to the analyses described in this SAP, may be performed as ad hoc analyses as deemed necessary. The subgroups to be used for this analysis may be based on, but not limited to, the results of analysis of PK, PD, efficacy, safety, immunogenicity and concomitant medication.

## 4. Analysis Sets and Protocol Deviations

Analysis sets or exclusions therein will be determined through review of clinical database and protocol deviations prior to database lock and the unblinding of the study. A blinded data review meeting will be set up then to decide on the final allocation rules to assign patients to the analysis sets. Agreement and sponsor authorization of patient inclusion in/exclusion from each Analysis Set will be obtained prior to the unblinding of the study for final analysis.

Analysis sets will be listed by patient.

### 4.1. ENROLLED SET [ENR]

The Enrolled Set (ENR) consists of all patients who provided informed consent for this study.

### 4.2. RANDOMIZED SET [RAN]

The Randomized Set (RAN) consists of all screened patients who received a randomization number. For analyses and displays based on RAN, patients will be classified according to the treatment they were assigned at randomization.

### 4.3. FULL ANALYSIS SET [FAS]

The Full Analysis Set (FAS) consists of all RAN patients in accordance with the intended treatment arm, regardless of the treatment actually received. However, patients who do not qualify for randomization and are inadvertently randomized into the study will be excluded from the FAS, provided these patients do not receive study drug. The FAS will

be considered as the primary analysis sets for the primary efficacy endpoint and one of the analysis sets for other efficacy endpoints.

The Full Analysis Set for exploratory analysis (FASEXP) consists of all FAS patients who had their tumor assessment measured by positron emission tomography computerized tomography (PET-CT) scan.

## 4.4. SAFETY ANALYSIS SET [SAF]

The Safety Analysis Set (SAF) consists of all RAN patients who received at least one dose of study drug. Patients will be analyzed according to the treatment received. SAF is used as the basis for all safety analyses.

If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis.

## 4.5. PER PROTOCOL SET [PPS]

The Per Protocol set (PPS) consists of all 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 PPS 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, this is subject to evaluation of the clinical relevance of the treatment intake

Major protocol deviations and/or the situation that lead to exclusion from the PPS will be specified and authorized prior to unblinding the treatment arms. Efficacy endpoints will also be summarized on the PPS.

The Per Protocol set for exploratory analysis (PPSEXP) consists of all the PPS patients who had their tumor measured by positron emission tomography computerized tomography (PET-CT) scan.

## 4.6. PHARMACOKINETIC ANALYSIS SET [PKS]

The PKS will include all patients who receive at least one 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 (see section **Error! Reference source not found.**).

Patients in the PKS will be analyzed according to the treatment received.

## 4.7. PHARMACODYNAMIC ANALYSIS SET [PDS]

The PDS will include all patients who receive at least one dose of study drug, have at least one measured PD variables (CD19+ B cell count) at a scheduled time point post-dose, and have no major protocol deviations or violations thought to significantly affect the PD of the drug (see section **Error! Reference source not found.**).

Patients in the PDS will be analyzed according to the treatment received.

## 4.8. PROTOCOL DEVIATIONS

Criteria defining protocol deviations are referenced in the Protocol Deviation Guidance and Protocol Deviation Specification. The Protocol Deviation specification will be developed according to the guidance and updated whenever a new version of the guidance is released. Additional updates before unblinding may be added in the case of protocol deviations which are not specified in the guidance but are reported from sites and classified as critical/major following assessment

All Critical/Major protocol deviations captured by programming or reported protocol deviations from sites, will be transferred to the biostatistics (BIOS) group by the project manager in IQVIA via email, will be summarized by category of deviation (e.g. Inclusion criteria) and treatment group using the RAN; and all protocol deviations, minor and major, will be listed (indicating which deviations are minor and which are major).

Protocol deviations do not lead to patient withdrawal unless they indicate a significant risk to the patient's safety. Protocol deviations leading to patient exclusion from the specific analysis sets (except for PK set and PD set) will be determined based on blinded data review prior to database lock.

#### 4.8.1. DEVIATIONS RELATED TO PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

Changes to procedures or events, which impact the quality of the PK and PD data, will be considered significant protocol deviations/events for the PK/PD analysis and will be described within the CSR body text. These changes or events will include any circumstances that could alter the evaluation of the PK and PD. Examples include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing on the day of PK and PD sampling. In the case of a significant protocol deviation or event, PK and PD data collected during the affected treatment period will be excluded from the study results but will be included in the by-patient listings. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant protocol deviations. A common example of a non-significant protocol deviation is deviations from blood sample collection times.

Deviations will be reviewed in a blinded manner prior to database lock. Based on this review, patients or PK/PD data points will be excluded from the analyses as deemed appropriate. Deviations or events with the potential to affect PK/PD results will be listed, as will the excluded data points.

# 5. General Considerations

All patients will be tabulated according to their initial treatment group regardless of any dose adjustment during study conduct.

## 5.1. STUDY DAY

Study Day in days will be calculated from the date of the first study drug administration (Day 1)and will be used to show the start/stop day of assessment or event.

If the date of the event is on or after the first study drug date then:

- Study Day = date of event – first study drug date + 1.

If the date of the event is prior to the first study drug date, then:

- Study Day = date of event – first study drug date.

In the situation where the event date is partial or missing, the date will appear partial or

missing in the listings and Study Day will be calculated after proper imputation has been carried out as described in APPENDIX 1.

## 5.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to first study drug date after informed consent is obtained (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-reference, but AEs and medications commencing on the reference start date will be considered post-reference.

Baseline for PD is defined as the value of CD19+ B-cell count, IgG, and IgM level at pre-dose on Day 1.

## 5.3. RETESTS AND UNSCHEDULED VISITS DATA

Generally, data recorded at the nominal visit will be presented for by-visit summaries.

Unscheduled measurements will not be included in by-visit summaries, but will contribute to the best/worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the latest available measurement of non-PK/PD assessments for that visit will be used for by-visit summaries.

If the patient discontinued treatment during the study after Day 1 and the next visit data is missing, then early termination data, i.e. early treatment discontinuation visit data, will be mapped to the next available visit number for by-visit summaries. Otherwise, early termination data will not be mapped.

Listings will include scheduled, phone visit, unscheduled, retest and early study discontinuation data in chronological order. Listings will include all scheduled, unscheduled, retest, early discontinuation and phone visit data.

## 5.4. STATISTICAL TESTS

The default significant level will be 0.05 for statistical tests; the two-sided 95% CIs will be calculated, unless if specified otherwise.

### 5.5. COMMON CALCULATIONS

For quantitative measurements, change from Baseline at Visit X will be calculated as:

Change at Visit X= Test Value at Visit X – Baseline Value

The time from Date of Event A to Date of Event B (years) is calculated as:

- (Date of Event B - Date of Event A + 1)/365.25.

The time from Date of Event A to Date of Event B (months) is calculated as:

- (Date of Event B - Date of Event A + 1)/30.4375.

### 5.6. SOFTWARE VERSION

All derivations (except PK and PD parameter calculations), statistical analyses, summaries and listings will be generated using SAS® Version 9.4 or higher.

Pharmacokinetic and PD parameters will be calculated by non-compartmental model using Phoenix WinNonlin® 6.4 or higher (Pharsight Corporation, a Certara Company, Princeton, New Jersey), and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Graphics may be prepared using the same versions of SAS®, or Phoenix WinNonlin®, or with SigmaPlot® 12.5, or higher (Systat Software, Inc., San Jose, California).

## 6. Statistical Considerations

### 6.1. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally.

Center pooling will be carried out across all centers for use in statistical summaries for this study.

### 6.2. MISSING DATA

Partial date will be imputed for the identification of treatment-emergent adverse events (TEAEs), prior/concomitant medication, calculation of demographic information and

medical history. Rules will be discussed in Appendix 1 of this SAP.

Main efficacy data will be handled in Section 15.1.2 and 15.2.2 of this SAP.

Missing PK concentrations will be handled as described in Section 13.

Unless otherwise specified, missing data will not be imputed in this study.

### 6.3. MULTIPLE COMPARISONS/ MULTIPLICITY

No multiple comparison adjustment for any pharmacokinetic inferential analyses is planned since the significance level is specified by the regulators, and therefore the power calculations account for the two comparisons planned. No multiple comparison adjustment will be used for primary efficacy analysis, since there is only one primary efficacy analysis for Overall Response Rate (ORR) at Week 28.

### 6.4. DATA EXTRACTION RULE

For the Week 28 CSR, only data up to the target visit will be included for reporting purpose. For example, at the Week 28 CSR, the cut-off date will be each patient's last assessment date at the Week 28 visit (or date of withdrawal if withdrawn before Week 28) or CT scans within 14 days, whichever comes last. For example, if one patient had CT scans 10 days after their Week 28 visit, his/her cut-off date will be the date of Week 28 visit+10; if a patient didn't have CT scans within 14 days of their Week 28 visit, his/her cut-off date will be the last assessment date of the Week 28 visit. The cut-off date for each patient may be different. Specific data extraction rules are described in Appendix 2.

## 7. Output Presentations

The TLF templates provided with this SAP describe the conventions for the presentation of data in outputs, and the format and content of the summary tables, figures and listings.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

## 8. Disposition and Withdrawals

The number of patients who were screened (enrolled) will be presented. Patient disposition and withdrawals will be presented by treatment group and overall. The number

and percentage of patients who were randomized, who were randomized in error, who were treated and who were not treated, who completed the study, discontinued study drug with reason for discontinuation, and withdrew early from the study by reason for withdrawal will be presented.

Protocol deviations (as defined in section 4.8) will be presented by treatment group for the RAN.

Number (%) of patients in the analysis sets and excluded from each analysis set will be summarized by treatment group and reason for the RAN.

# 9. Demographic and other Baseline Characteristics

Patient demographics and baseline characteristics will be summarized by treatment group and overall for the RAN and FAS. If the FAS is the same as the RAN, then only the RAN will be summarized. Continuous variables will be summarized with descriptive statistics (n, mean, SD, median, minimum and maximum). Categorical variables will be summarized with counts and percentages.

The following demographics and baseline characteristics will be summarized appropriately for the study:

Demographics

- Age (years) – calculated to date of Informed Consent
- Age group – 18-60 years, >60 years
- Gender – Female, Male
- Ethnicity– Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown
- Race – American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Unknown, Not Reported
- Weight (kg) at Baseline
- Height (cm) at Baseline
- Body Mass Index (BMI) ($kg/m^2$) – derived as weight (kg)/(height (m))$^2$
- Body Surface Area (BSA) ($m^2$) – Collected from eCRF, derived using the Du Bios

formula, given as BSA= 0.20247 x height $(m)^{0.725}$ x weight $(kg)^{0.425}$

Baseline Characteristics

- Disease duration (years) – calculated the first diagnosis date of LTBFL relative to date of informed consent
- Childbearing potential – Yes, No
- Risk groups according to FLIPI-2 score – Low risk, Intermediate risk, High risk

The FLIPI-2 includes five adverse prognostic factors as below, and risk groups will be graded with presenting a number of risk factors (from 0 to 5).

| 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 |

| Risk Group | Number of Adverse Factors |
|---|---|
| Low risk | 0-1 |
| Intermediate risk | 2 |
| High risk | 3-5 |

- ECOG performance status – 0, 1
- Ann Arbor Stage – I, II, III, IV with appropriate modifier appended if available (e.g., IE)
- Type of Ann Arbor Staging – CS, PS
- Histological confirmation of LTBFL diagnosis information will be listed
- Anti-drug antibody (ADA) status at baseline (positive, negative)

# 10. Medical and Surgical History and Continuing Medical Condition

Medical and surgical history, continuing medical conditions will be coded using Medical Dictionary for Regulatory Activities central coding dictionary, Version 22.0 (MedDRA 22.0), and summarized by system organ class (SOC) and preferred term (PT) for the RAN. Continuing medical condition was identified the items with 'Ongoing with treatment' or 'Ongoing without treatment' status in the Medical History page of the eCRF. SOCs will be presented alphabetically; PTs will be sorted within SOC in descending order of subject frequency across both treatments (Total). If the frequency of the PT is tied, the PTs will be sorted alphabetically.

# 11. Medications and Procedures

**Medications**

Prior and/or concomitant medications will be coded using WHO DRUG dictionary DDE B2 format Mar 01, 2018 and Anatomical Therapeutic Chemical (ATC) Classification**.**

See Appendix 1 for the handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started prior to and finished prior to the first dose of study drug.
- 'Concomitant' medications are medications which started on or after the first dose of study drug, or started prior to the first dose of study drug and ended on or after the first dose of study drug or are ongoing at the end of the study.

A medication will be considered as either 'Prior' or 'Concomitant'.

Prior medication and concomitant medications will be summarized by ATC pharmacological sub-class (4th level) for the SAF. ATCs will be presented alphabetically; PTs will be sorted within ATC in descending order of subject frequency across both treatments (Total). If the frequency of the PT is tied, the PTs will be sorted alphabetically. All medications used will be listed.

**Procedure**

Prior cancer-related surgery or procedure, as reported on the eCRF 'Prior cancer-related surgery or procedure' page, will be coded using MedDRA 22.0, and summarized by SOC and PT for the SAF. SOCs will be presented alphabetically; PTs will be sorted within SOC in descending order of subject frequency across both treatments (Total). If the frequency of the PT is tied, the PTs will be sorted alphabetically. Details of the cancer-related surgery or procedure will be listed in listings.

See Appendix 1 for the handling of partial dates for procedure.

# 12. Study Medication Exposure

## 12.1. STUDY DRUG ADMINISTRATION

Duration of exposure to study drug in days, number of administrations and total dose administrated (mg), dose intensity (mg/m$^2$/day), relative dose intensity (RDI), any dose interruption will be summarized by treatment group with descriptive statistics using the SAF.

Exposure duration (days) will be calculated according to the following algorithm.

- If the last date the patient took study drug was known;
    - Exposure duration (days) = last study drug date – first study drug date + 1,
- If the last date the patient took study drug was unknown, but the visit that the patient took last study drug was known;
    - Exposure duration (days) = the visit date of last study drug – first study drug date + 1,
- If the last date the patient took study drug was unknown and the visit that the patient took last study drug was also unknown;
    - If the last visit before the patient discontinued or withdrew is after Week 4 visit OR the patient completed the study, then Exposure duration (days) = date of Week 4 visit – first study drug date + 1
    - If the last visit before the patient discontinued or withdrew is before Week 4 visit, then Exposure duration (days) = the last visit date – first study drug

date + 1

Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

Dose intensity is derived from the following definitions:

- Dose Intensity (mg/ $m^2$/day) = sum of actual dose level administered (mg/ $m^2$) / duration of exposure (days), where the actual dose level administrated = administrated actual total dose (mg) in that cycle / BSA for dose calculation in that cycle ($m^2$) from electronic case report form (eCRF).

RDI is based on the actual dose intensity and the planned dose intensity and will be calculated as follows:

- RDI (%) = $\frac{\text{actual dose intensity}}{\text{planned dose intensity}} \times 100$

Where the planned dose intensity can be calculated following below algorithm:

Planned dose intensity (mg/ $m^2$/day) =4*375(mg/$m^2$)/ 28

Study drugs administration data will be listed.

### 12.2. INFUSION PRE-MEDICATION

'Infusion pre-medication' is either corticosteroids, analgesic or antipyretic, or anti-histamine administrated before the start of each study drug infusion.

Infusion pre-medication data will be listed.

## 13. Pharmacokinetics

### 13.1. SERUM CONCENTRATION DATA

A listing of PK blood sample collection times and derived sampling time deviations, as well as rituximab concentrations will be provided. Serum concentrations of rituximab will be listed and summarized by treatment and by study week, study day, and nominal time point using appropriate descriptive statistics, such as number of data (n), mean, standard deviation (SD), percentage coefficient of variation (CV%), minimum, median, and

maximum. Concentrations excluded from analyses will be flagged in the listings. Unscheduled assessments will be listed but not included in summary statistics. Analyte concentrations which fall below limit of quantification (BLQ) will be set to zero and missing concentration values will be omitted for all concentration summaries. For PK parameter summaries, $C_{trough}$ values that are BLQ will be treated as the lower limit of quantification (LLOQ)/2.

Plots of individual and mean serum rituximab concentration-time profiles will be presented by treatment, Week/Day, and nominal time point on both linear and semi-logarithmic scales.

Additional graphical presentations of PK data may be added at the discretion of the PK scientist.

## 13.2. PHARMACOKINETIC PARAMETERS

For PK parameter calculations on Week 1, predose samples that are BLQ or missing will be assigned a numerical value of zero. Any anomalous concentration values observed at predose over the 1st dosing interval will be identified in the study report and used for the computation of PK parameters. Pharmacokinetic parameters will be computed if the anomalous concentration is not greater than 5% of the observed maximum concentration ($C_{max}$). If the anomalous concentration is greater than 5% of $C_{max}$, the PK parameters for the given patient will be calculated and reported in the listing, but excluded from statistical summaries and analyses. On week 4, predose sample that is BLQ will be assigned a numerical value of zero. Missing predose sample will be set to missing.

The following PK parameters will be calculated for rituximab for each treatment by non-compartmental methods using actual elapsed time from dosing, if possible.

| | |
|---|---|
| $AUC_{0\text{-}168,w1}$ | Area under the serum concentration-time curve (AUC) over the 1st dosing interval on Week 1 from time zero (predose) to the time prior to the 2nd dose (168 hours postdose) (µg·h/mL), calculated by linear up/log down trapezoidal summation. This parameter will only be calculated if at least the 2 postdose concentrations (the end of infusion and Week 2 predose) are available and evaluable. |
| $AUC_{0\text{-}168,w4}$ | Area under the serum concentration-time curve (AUC) over the 4th dosing interval on Week 4 from time zero (predose) to 168 hours postdose (µg·h/mL), calculated by linear up/log down trapezoidal summation. This parameter will only be calculated if all 3 concentrations (predose, the end of infusion, and Week 5) are available and evaluable. |
| $C_{max,w1}$ | Maximum serum concentration (µg/mL) over the 1st dosing interval on Week 1, obtained directly from the observed concentration versus time data. This |

| | |
|---|---|
| | parameter will only be reported if the end-of-infusion concentration is available and evaluable. |
| $C_{max,w4}$ | Maximum serum concentration (µg/mL) over the 4th dosing interval on Week 4, obtained directly from the observed concentration versus time data. This parameter will only be reported if the end-of-infusion concentration is available and evaluable. |
| $t_{max,w1}$ | Time of maximum concentration (h) over the 1st dosing interval on Week 1, obtained directly from the observed concentration versus time data. Calculations will follow conventions of $C_{max,w1}$. |
| $t_{max,w4}$ | Time of maximum concentration (h) over the 4th dosing interval on Week 4, obtained directly from the observed concentration versus time data. Calculations will follow conventions of $C_{max,w4}$. |
| $C_{trough}$ | Concentrations at predose on Days 8, 15, and 22 (µg/mL) and the time equivalent to the predose on Day 29, obtained directly from the observed concentration versus time data. |
| RAUC | Accumulation ratio, calculated for $AUC_{0-168}$ as ($AUC_{0-168,w4}/AUC_{0-168,w1}$). |
| $RC_{max}$ | Accumulation ratio, calculated for $C_{max}$ as ($C_{max,w4}/ C_{max,w1}$). |

The following deviations related to time of sample collections will be considered for calculation of the above parameters. $AUC_{0-168}$ or/and $C_{max}$ will be calculated and reported, but not included in summary and inferential statistical analyses if:

- The end of infusion sample is collected more than 10 minutes early or after the end-of-infusion, $AUC_{0-168}$ and $C_{max}/t_{max}$ will be calculated and reported, but not included in summary and inferential statistical analyses.

- 168 hour postdose sample (i.e. predose of following infusion) is collected more than 1 calendar day early or late for Week 1 and Week 4, $AUC_{0-168}$ will be calculated and reported, but not included in summary and inferential statistical analyses. The trough concentration on Day 29 will not be included in any summaries if the sample is collected more than 1 calendar day early or late.

- Dose on Week 4 is more than 1 calendar day outside the scheduled time, data will be carefully evaluated if inclusion of $AUC_{0-168}$, $C_{max}$, $t_{max}$, and trough concentration on Day 29 in summaries and/or inferential analyses is warranted.

- Dose is missed either on Week 2 and/or Week 3, Week 4 PK parameters will be calculated and reported but not included in summaries and/or inferential analyses.

$AUC_{0-168,w1}$ and $AUC_{0-168,w4}$ will be considered as primary PK endpoints and the other parameters will be secondary.

All primary and secondary PK parameters will be listed and summarized by treatment and study week using n, mean, SD, standard deviation, CV%, minimum, median, maximum, and geometric mean, geometric CV%, except that $t_{max}$ will be reported with n, minimum, median, and maximum only.

The additional following summaries of PK parameters will be generated:

- By treatment and region (EU, Other including US)
- By treatment and age category (18-60 years and >60 years)
- By treatment and sex
- By treatment and overall ADA status.

The geometric means of the primary PK parameters ($AUC_{0\text{-}168,w1}$ and $AUC_{0\text{-}168,w4}$) will be compared between SAIT101 and MabThera® using analysis of variance on the loge-transformed parameters with fixed effect for treatment. No covariates will be included. 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 if 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 $C_{max,w1}$, $C_{max,w4,}$ and $C_{trough}$ (Day 29) parameters using the same methods.

A sensitivity analysis will be performed for the above PK comparisons, in which the above comparison will be replicated, with the addition of the following covariates to the statistical model: age, sex, overall ADA status, body weight at baseline.

Scatter plots of individual and geometric mean primary PK parameters $AUC_{0\text{-}168,w1}$, $AUC_{0\text{-}168,w4}$, $C_{max,\ w1}$ and $C_{max,w4}$ will be presented. Additional, graphical presentations of PK data may be added at the discretion of the PK scientist, if further illustration of the PK results is deemed appropriate.

# 14. Pharmacodynamics

## 14.1. PHARMACODYNAMIC CONCENTRATION DATA

Listings of PD blood sample collection times , derived sampling time deviations, as well as levels of observed PD variables (CD19+ B cell count, IgG, and IgM) will be provided.

Change from baseline PD variables will be calculated as (observed [measured] postdose value minus baseline value). Percent change from baseline will be calculated as 100 x [(observed post-dose value minus baseline value)/baseline]. Baseline is defined as the CD19+ B-cell count, IgG and IgM data at predose on Day 1.

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

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

The relationship of CD19+ B cell counts versus drug concentrations will be explored by scatter plot.

## 14.2. PHARMACODYNAMIC PARAMETERS

For PD parameter calculations, predose samples that are BLQ for observed value will be assigned a numerical value of zero for calculation of change from baseline variables. For subjects with missing (i.e., non-evaluable samples) predose samples, change and percent change from baseline will not be calculated and PD parameters will not be reported. Any other observed BLQ values will be assigned as zero and any other observed missing values will be set to missing.

The following parameters, area under the PD variable-time effect curve (AUEC), will be calculated from the change from baseline CD19+ B cell count-time data by linear trapezoidal method using actual elapsed time from dosing. The PD parameters will be derived using SAS® or Phoenix WinNonlin®.

| | |
|---|---|
| $AUEC_{0\text{-}168,w1}$ | Area under the PD variable-time effect curve (AUEC) (cells·day/µL) over the 1st dosing interval on Week 1 from time zero (predose) to the time prior to the 2nd dose (168 hours postdose) |
| $AUEC_{0\text{-}168,w2}$ | AUEC (cells·day/µL) over the 2nd dosing interval on Week 2 from time zero (predose) to the time prior to the 3rd dose (168 hours postdose) |
| $AUEC_{0\text{-}168,w3}$ | AUEC (cells·day/µL) over the 3rd dosing interval on Week 3 from time zero (predose) to the time prior to the 4th dose (168 hours postdose) |

| | |
|---|---|
| $AUEC_{0\text{-}168,w4}$ | AUEC (cells·day/μL) over the 4th dosing interval on Week 4 from time zero (predose) to 168 hours postdose |
| $AUEC_{0\text{-}w12}$ | AUEC (cells·day/μL) from time zero (predose) on Week 1 to the time point on Week 12 |
| $AUEC_{0\text{-}w28}$ | AUEC (cells·day/μL) from time zero (predose) on Week 1 to the time point on Week 28 |
| $AUEC_{0\text{-}w52}$ | AUEC (cells·day/μL) from time zero (predose) on Week 1 to the time point on Week 52 |

For AUEC calculations, the actual measurement time at the end off the partial area, was used for calculation (ie, no adjustments were made for any time deviations at this scheduled sampling time point). If the change from baseline at those respective timepoints was missing, the respective PD parameters were set to missing. All AUEC parameters will also be normalized to the time interval observed by dividing by the observed interval length. Negative partial areas will be calculated into the AUEC as observed, without exclusion or modification.

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

The means for CD19+ B cell AUECs will be descriptively compared between SAIT101 and MabThera® using analysis of covariance that includes a fixed effect for treatment. 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.

# 15. Exploratory Analysis of ADA on PK and PD

An exploratory statistical assessment of the impact of overall ADA status (positive or negative) on PK across treatments will be completed by adding this covariate to the model used in the primary statistical analysis.

Overall ADA status will be defined as ADA positive if a positive ADA result occurred at any timepoint up to Week 28 (for Week 28 analysis for PK and PD and for final analysis for PK only) or up to Week 52 (for PD, final analysis). Subjects without a positive ADA result at any timepoint are considered ADA negative.

The ratio of geometric means for ADA positive/ADA negative will be reported with the 90%

CI for this ratio. Descriptive statistics for rituximab concentrations and the primary PK parameters will also be presented by ADA status. Mean PK profiles will be plotted by treatment and ADA status on linear and semi-log concentration scales.

The impact of ADA on PD (observed CD19+ B cell counts) will be explored graphically. Mean PD profiles will be plotted by treatment and overall ADA status on a linear scale.

# 16. Efficacy Outcomes

## 16.1. PRIMARY EFFICACY

### 16.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is the difference in Overall Response Rate (ORR) at Week 28, approximately 24 weeks after the completion of study treatment.

ORR is defined as the proportion of patients with complete response (CR) or partial response (PR) as assessed by central imaging review per IWG criteria 2007 until Week 28 after the start of treatment. ORR will be evaluated for each patient separately from the date of first administration of trial medication (i.e. Day 1) until either progression, death or up to Week 28 (i.e. study day 204 =190+14), whichever happens earlier. Per protocol, 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).

Patients who start subsequent anticancer therapy will typically have progressed or stopped treatment due to unacceptable toxicity. A CT scan should be conducted at their early treatment discontinuation visit. In the case where a patient starts subsequent anti-cancer therapy but the ORR evaluation period of that patient is still ongoing, the patient's ORR will be evaluated only until the start of subsequent anti-cancer therapy.

Unscheduled assessments recorded during the evaluation period for ORR will be taken into account for determination of ORR. Tumor assessments started on study day 204 but not completed on study day 204 will be fully included in the evaluation of best ORR.

The primary endpoint will be analyzed as described in section 16.1.3 and sensitivity analyses for the primary efficacy analysis will be performed as described in section 16.1.4.

### 16.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

The imputation of ORR will follow Imputation Using Drop-out Reason (IUDR). The imputation rules for the IUDR imputation of ORR will be as follows:

Following the start of a new treatment for FL, either due to lack of efficacy or treatment-related toxicity reasons (i.e. treatment failure requiring tumor targeting treatment for FL other than the protocol-defined treatment or death due to progressive disease), patients without a response assessment at Week 28 will be considered as non-responders.

Overall tumor assessments by central imaging review will be assessed as CR, PR, stable disease (SD), progressive disease (PD), Unknown, and No Evidence of Disease (NED). Missing or non-evaluable response assessments (i.e. UNK and NED) will not be imputed and will be considered as non-responders.

Missing responses unrelated to treatment (i.e. withdrawal by patient, pregnancy) will 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 for treatment related or not (i.e. lost to follow-up).

### 16.1.3. ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary test for statistical equivalence will be performed with respect to SAIT101 versus MabThera® for patients in the FAS. The primary hypothesis is based on the difference in ORR at Week 28 between the two treatments. The 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 contained within the equivalence margin of [-16.0%, 16.0%] by Cochran-Mantel-Haenszel (CMH) tests. The adjusted proportion difference in ORR and its 95% Newcombe-Wilson CI will be calculated using weighted CMH with stratification factor FLIPI-2 (low, intermediate and high risk).

Descriptive statistics will be presented for the ORR as well as the overall tumor assessment (CR, PR, SD, PD) at planned time points by treatment groups. In addition, a listing of target, non-target and new lesions assessed per IWG criteria 2007 by visit will be also presented.

A bar-chart plot presenting the overall tumor response rate (CR, PR, SD and PD) and the ORR at Week 12 and Week 28, by treatment group, will also be provided.

### 16.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

To assess the robustness of the primary efficacy result, the sensitivity analyses included in Table will be performed.

**Table 1 – Primary analysis and sensitivity analyses for the primary efficacy endpoint**

| Analyses for primary endpoint | Analysis Set | Analysis Method | Stratification factors included | Imputation method for missing value at Week 28 |
|---|---|---|---|---|
| Primary analysis | FAS | 95% Newcombe-Wilson CI using the CMH weighted method | FLIPI-2 score group | IUDR |
| Sensitivity analysis 1-1 | FAS | Same as primary | Same as primary | No imputation |
| Sensitivity analysis 1-2 | PPS | Same as primary | Same as primary | NA |
| Sensitivity analysis 2-1 | FAS | 95% Newcombe-Wilson CI | None | Same as primary |
| Sensitivity analysis 2-2 | PPS | 95% Newcombe-Wilson CI | None | NA |
| Sensitivity analysis 3 | FAS | Same as primary | Same as primary | NRI |
| Sensitivity analysis 4 | FAS | Same as primary | Same as primary | MI |

| | | | | |
|---|---|---|---|---|
| Sensitivity analysis 5-1 | FAS | Logistic regression model along with Delta method | Same as primary | Same as primary |
| Sensitivity analysis 5-2 | PPS | Logistic regression model along with Delta method | Same as primary | NA |

NRI= Non-responder imputation, MI= multiple imputation; IUDR= imputation using drop-out reason (NRI for missing due to treatment-related reason, MI using logistic regression assuming ignorable missing at random (MAR) for missing due to reasons unrelated to treatment, and no imputation when the reasons are unknown whether they are related to treatment or not).

## 16.2. SECONDARY EFFICACY

### 16.2.1. SECONDARY EFFICACY VARIABLE(S) & DERIVATION(S)

**ORR at Week 12**

The Overall Response Rate (ORR) at Week 12 will be derived as described in section 16.1.1, i.e., similar to the primary endpoint (ORR at Week 28).

**Time to event (TTE)**

The time to event (TTE) is defined as the time from the date of randomization to the date when an event occurs; the following are considered as an event: disease progression evaluated based on tumor assessment done by central imaging review vendor, death due to any cause, or the start of new treatment for FL, whichever comes first.

**Table 2. Outcome and event dates for TTE**

| No. | Situation | Date of Event or Censoring | Outcome |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 1 | No baseline tumor assessment or no post-baseline tumor assessment* | Date of first study drug administration | Censored |
| 2 | No progression and no death and no new anticancer treatment | Date of last evaluable tumor assessment (from "Overall Lesion Assessment" CRF page) | Censored |
| 3 | Documented progression | Date of first documented progression# | Event |
| 4 | Death without progression | Date of death | Event |
| 5 | New anticancer treatment started prior to documented disease progression or death on study | Date of first date of new anticancer treatment | Event |

* No baseline tumor assessment means no any target identified and no non-target lesions present at screening captured from "Lesion Assessment with CT Scan" CRF page; no post-baseline means without any assessments by CT scans and evaluated by central review as defined by the IWG Criteria 2007 after study treatment administered.

# Earliest lesion assessment date among target, non-target and new lesions at which visit identified as disease progression by central reviewer.

**Tumor response (CR, PR, SD, PD) at Week 12 and Week 28**

Tumor response (CR, PR, SD, and PD) will be evaluated by central imaging assessment at Week 12 and Week 28 as defined by the IWG Criteria 2007.

### 16.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE(S)

All analyses of secondary efficacy variables will be based on available data. No missing data will be imputed.

### 16.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLE(S)

The ORR at Week 12 will be presented for each treatment group and the difference between treatment groups in ORR at Week 12 will be analyzed using the same method as the primary efficacy endpoint. The adjusted difference rate and corresponding 95% CI will be presented.

Descriptive statistics will be presented for the ORR and the overall tumor assessment (CR, PR, SD, PD) at Week 12 by treatment groups.

A bar-chart plot presenting the overall tumor response rate (CR, PR, SD and PD) and the ORR by treatment group will be provided for Week 12. A listing of the week 12 response assessments will also be presented.

For TTE, 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, i.e. FLIPI-2 (low, intermediate and high risk). The occurrence of the events considered for the TTE and the TTE will be presented in a listing.

## 16.3. EXPLORATORY EFFICACY

**Subgroups**

The primary efficacy endpoint will be repeated for each of the following subgroup categories as exploratory efficacy analyses based on the FAS and the PPS.

- Region – EU, Others (including US)
- Age group – 18-60 years, >60 years
- Gender – Female, Male
- ADA status – Positive at any time up to Week 28, Negative at all time points

The same statistical method (as defined in Section 16.1.3) will be used for each subgroup category. The adjusted proportion difference in ORR and corresponding 95% CI according to the primary analysis will also be presented in a Forest plot. The interaction p-value for the subgroups being examined will be calculated based upon the full set of data (not subset for each subgroup category being examined), and will be based on primary CMH

model to which the variable for the subgroup being examined will be added as an additional stratification factor The p-value will be calculated using Gail-Simon Test for Qualitative Interactions, specifying that we are interested in the subgroup variable risk differences .

As mentioned in section 3.3, additional exploratory subgroup analyses may be performed as ad hoc analyses if deemed necessary. The subgroups to be used for this analysis may be based on, but not limited to, the results of analysis of PK, PD, efficacy, safety, immunogenicity and concomitant medication.

**Tumor response from IWG Criteria 2014, Lugano Classification**

For patients who have their tumors additionally measured by positron emission tomography computerized tomography (PET-CT) scan, tumor response (CR, PR, SD, and PD) assessed centrally as defined by the IWG Criteria 2014, Lugano Classification, will be descriptively summarized and TTE will also be calculated using the same method as for TTE in efficacy analyses, except based on the FASEXP and PPSEXP sets.

# 17. Safety Outcomes

All outputs for safety outcomes will be based on the SAF.

There will be no statistical comparisons between the treatment groups for safety data.

## 17.1. ADVERSE EVENTS

Adverse events (AEs) will be coded using MedDRA 22.0.

A TEAE will be defined as any AE with an onset date (and time if applicable) on or after the date (and time if applicable) of first dose of study drug until Week 52, or the EOS visit, if earlier. AEs with increased severity during the treatment period will be considered as TEAEs whether already present during the pre-treatment period or not. Pre-existing AEs before the treatment period with no increase in severity during the treatment period will not be considered as TEAEs.

See Appendix 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

For AE table summary, patients will be counted at most once for each PT and each SOC.

SOCs will be presented alphabetically; PTs will be sorted within SOC in descending order of subject frequency across both treatments (Total). If the frequency of the PT is tied, the PTs will be sorted alphabetically.

AEs occurring between consent and first dose and AEs with an onset more than 60 days after the end of treatment, i.e., last study drug date + 1 days (as defined in section 12.1 of this SAP), will not be summarized (unless they are related or AESIs), but they will be listed. All AEs will be listed.

**TEAEs**

Incidence of TEAEs will be summarized by the number and percentage of patients experiencing events by SOC and PT.

**Severity**

Severity will be assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03. A TEAE with a missing NCI-CTCAE severity grade will be classified as missing. If a patient reports a TEAE more than once within that SOC/PT, the AE with the maximum NCI-CTCAE severity grade will be used in the corresponding severity summaries. TEAEs will be summarized separately by SOC, PT, and severity group.

**Relationship to Study Drug (Causality)**

The causal relationship between the study drug and the AE should be defined as unrelated or related. TEAEs with a missing relationship to study drug will be regarded as "related" to study drug. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

A summary of related TEAEs starting on the day of the infusion or the day after the infusion will be presented.

**TEAEs Leading to Discontinuation of Study Drug**

TEAEs leading to permanent discontinuation of study drug are identified by choosing 'Drug permanently withdrawn' in the question 'Action taken with study drug' on the Adverse Events page of the eCRF, and will be summarized by SOC and PT.

**TEAEs Leading to Study Drug Interruption**

TEAEs leading to study drug interruption are identified by choosing 'Drug interrupted' in

the question 'Action taken with study drug' on the Adverse Events page of the eCRF, and will be summarized by SOC and PT.

**Serious Adverse Events**

Serious adverse events (SAEs) are identified by choosing 'Yes' in the question 'Is the adverse event serious' on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared, and all SAEs will be listed.

**TEAEs Leading to Death**

TEAEs leading to death are identified by choosing 'Yes' in the question 'Resulted in death' on the Adverse Events page of the eCRF. TEAEs leading to death will be summarized by SOC and PT, and listed.

**TEAEs of Special Interest (AESI)**

AESIs to be considered in this study are: progressive multifocal leukoencephalopathy (PML), hepatitis reactivation, infusion reactions, anaphylactic reactions, mucocutaneous reactions and serious infections (see study protocol section 6.4 for more details). These group terms are each separately identified on the eCRF.

The incidence of TEAEs of special interest are identified by choosing 'Yes' in the question 'Is this event an AESI (Adverse Event of Special Interest)' on the Adverse Events page of the eCRF. TEAEs of special interest will be summarized by SOC and PT, and listed. Additionally, TEAEs of special interest to infusion reactions will be summarized by SOC and PT.

**TEAEs Related to Immune-response**

The incidence of TEAEs related to immune-response are identified by choosing 'Yes' in the question 'Is this AE 'immune-response-related' of the Adverse Events page of the eCRF. TEAEs related to immune-response will be summarized by SOC and PT, and listed.

All AEs will be listed.

## 17.2. DEATH

Information relating to patients who die during the study is recorded on the Death Information page of the eCRF. The information will be presented in a summary table and a data listing.

## 17.3. LABORATORY EVALUATIONS

Results from the laboratory test will be included in the reporting of this study for hematology (including erythrocyte sedimentation rate), clinical chemistry (including C-reactive protein and rheumatoid factor), virology, and urinalysis parameters.

Presentations will use SI Units (where applicable). Unit conversions will be performed by Data Management (DM) in the database where necessary.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification, or "> X", i.e. above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements).
- Shift table of incidence of abnormal values (abnormal low, normal, abnormal high), based on normal range, from baseline to each post-baseline visit for hematology, clinical chemistry, and urinalysis parameters.
- Abnormalities by visit and overall abnormalities incidence result will be summarized, and further break down by high/low abnormalities. Patients will be counted at most once for a high or low abnormality for hematology and chemistry parameters.
    - Overall abnormal: Patient with at least one abnormal (high or low) result in post-baseline visit regardless the baseline result.
    - Overall normal: Patient without any abnormal result in all post-baseline visits regardless the baseline result.
- Listing of all laboratory test values (hematology and chemistry) with the abnormal values flagged with H (high) or L (low).

The following figures will be provided for laboratory data:

- Actual values by visit will be presented using a box plot for hematology and clinical chemistry. Mean +/- SEM by visit will be provided for hematology and clinical chemistry.

- Shift from Baseline for hematology and clinical chemistry.
    - For liver function tests (LFTs), the reference tick marks will be 3x ULN, 5x ULN and 10x ULN. Possible Hy's Law cases will be listed.
    - For other hematology and chemistry, the reference tick marks will be: 3x LLN, 2x LLN, 1x LLN, 1x ULN, 2x ULN and 3x ULN

**Laboratory Normal Ranges**

Quantitative laboratory measurements will be compared with the relevant laboratory normal ranges in SI units:

- Abnormal high: Higher than the laboratory reference range upper limit.
- Normal: Within the laboratory reference range (upper and lower limit included).
- Abnormal low: Lower than the laboratory reference range lower limit.

## 17.4. 12-LEAD ECG EVALUATION

The following summaries will be provided for ECG data:

- Incidence of ECG evaluation results by visit
- Listing of all ECG evaluation results.

## 17.5. VITAL SIGNS

The following vital signs measurements will be reported for this study:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse (beats/min)
- Body Temperature (°C)
- Respiratory Rate (breaths/min)

- Weight (kg)

The following summaries will be provided for vital signs and weight data:

- Actual and change from baseline by visit and time point
- Shift table of incidence of significant abnormal values (low, normal, high), based on the criteria listed as below, from baseline to each post-baseline visit.
- Abnormalities by visit and overall abnormalities incidence result will be summarized and presented for all parameters, and further broken down by high/low abnormalities. Patients will be counted at most once for a high or low abnormality for each vital sign parameter.
    - Overall abnormal: Patient with at least one abnormal (abnormal high or abnormal low) result in post-baseline visit regardless of the baseline result.
    - Overall normal: Patient without any abnormal result in all post-baseline visits regardless of the baseline result.

A Listing of vital signs will be provided with results meeting clinically significant abnormal criteria marked as High (H) or Low (L)

**Vital Signs Specific Derivations**

For Body Temperature (°C), the oral, axillary and tympanic routes will be considered as equivalent and no conversions will be applied. The conversion from Fahrenheit to Celsius will be made as follows:

- T(°C) = (T(°F) - 32) × 5/9: degrees Celsius (°C), degrees Fahrenheit (°F)

**Vital Signs Clinically Significant Abnormal Criteria**

Clinically significant abnormal quantitative vital signs measurements will be identified in accordance with the following clinically significant abnormal criteria:

**Table 3 : Clinically Significant Abnormal Criteria of Vital Signs**

| Variable | Unit | Visit | Low | High |
|---|---|---|---|---|
| Systolic | mmHg | Baseline | < 90 mmHg | > 180 mmHg |

| | | | | |
|---|---|---|---|---|
| blood pressure | | Post-baseline | ≤ 90 mmHg AND change from baseline ≤ -20 mmHg | ≥ 180 mmHg AND change from baseline ≥ 20 mmHg |
| Diastolic blood pressure | mmHg | Baseline | < 50 mmHg | > 110 mmHg |
| | | Post-baseline | ≤ 50 mmHg AND change from baseline ≤ -15 mmHg | ≥ 105 mmHg AND change from baseline ≥ 15 mmHg |
| Pulse | beats/min | Baseline | < 50 beats/min | > 120 beats/min |
| | | Post-baseline | ≤ 50 beats/min AND change from baseline ≤ -15 beats/min | ≥ 120 beats/min AND change from baseline ≥ 15 beats/min |
| Body temperature | ˚C | Baseline | < 35.0 ˚C | > 38.3 ˚C |
| | | Post-baseline | ≤ 35.0 ˚C AND change from baseline ≤ -1.1 ˚C | ≥ 38.3 ˚C AND change from baseline ≥ 1.1 ˚C |
| Respiratory rate | breaths/min | Baseline | ≤ 10 breaths/min | ≥ 24 breaths/min |
| | | Post-baseline | ≤ 10 breaths/min | ≥ 24 breaths/min |
| Weight | kg | Baseline | None | None |
| | | Post-baseline | percentage change from baseline ≤ -7.0 % | percentage change from baseline ≥ 7.0 % |

## 17.6. B CELL RECOVERY

B cell recovery is defined as “peripheral B cell counts that have returned to at least 50% baseline values or higher or equal to the lower limit of normal”. Note that B-cell counts need to be depleted (defined as CD19+ B cell count below 20 cells/μL) for each subject before recovery is assessed. The incidence of B cell recovery and CD19+ B cell count per patient will be summarized at each visit and overall, by treatment group. Listings for B cell recovery data and CD19+ B cell count by patient will be provided. A plot for proportion of patients achieving B cell recovery over time by treatment group will be displayed.

## 17.7. OTHER SAFETY ASSESSMENTS

The following data will be listed only:

- Abnormal physical examination
- Pregnancy test
- TB test
- HBV testing
- New anti-lymphoma treatment

- ECOG Performance Score

# 18. Immunogenicity Outcomes

The immunogenicity analyses will be performed using the SAF.

## 18.1. ADA

The incidence of ADA and neutralizing antibody at Day 1 pre-dose and at Weeks 2 pre-dose, 3 pre-dose, 4 pre-dose, Week 5, 12, 20, 28, 36, and 52 (EOS) will be summarized by treatment group and visit.

- Incidence (%)= number of subjects with specific assessment result/ number of subject with available assement results * 100%

ADA and neutralizing antibody results by visit as well as the overall positive of ADA and neutralizing antibody from Day 1 will be summarized. Patients with at least one positive result up to Week 28 (or Week 52) from (and including) Day 1 will be considered as overall positive; Otherwise, patients without any positive result up to Week 24 (or Week 52) from (and including) Day 1 will be considered as overall negative.

For each treatment group, the proportion of response, 95% CI for the proportion, proportion difference between SAIT101 and MabThera®, standard deviation, and 95% CI for the proportion difference will be reported. The Wilson Score method will be used to calculate 95% CI.

- Response:
  - ADA positive
  - ADA negative
  - Neutralizing antibody positive
  - Neutralizing antibody negative

Listings for ADA assessments by patient will be provided.

# APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings. However, in general, when calculating relative days, partial dates with missing day only will be assumed to be 15th of the month, earliest possible date for start date (i.e. 1st of the month) and latest possible date for stop date (i.e. 31st of the month); and partial dates with both missing day and month will be assumed to be 1st January for start date or 31st December for stop date.

Algorithm for Treatment-Emergent Adverse Events:

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If start date/time < first IP taken date/time, then not TEAE<br>If start date/time >= first IP taken date/time, then TEAE |
| | Partial | If start date/time < first IP taken date/time, then not TEAE<br>If start date/time >= first IP taken date/time, then TEAE |
| | Missing | If start date/time < first IP taken date/time, then not TEAE<br>If start date/time >= first IP taken date/time, then TEAE |
| | | |
| Partial, but known components show that it cannot be on or after first IP taken date | Known | Not TEAE |
| | Partial | Not TEAE |
| | Missing | Not TEAE |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| | | |
| Partial, could be on or after first IP taken date | Known | If stop date/time < first IP taken date/time, then not TEAE<br><br>If stop date/time >= first IP taken date/time, then TEAE |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>If stop date/time < first IP taken date/time, then not TEAE<br><br>If stop date/time >= first IP taken date/time, then TEAE |
| | Missing | Assumed TEAE |
| | | |
| Missing | Known | If stop date/time < first IP taken date/time, then not TEAE<br><br>If stop date/time >= first IP taken date/time, then TEAE |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>- If stop date/time < first IP taken date/time, then not TEAE<br><br>- If stop date/time >= first IP taken date/time, then TEAE |
| | Missing | Assumed TEAE |

Algorithm for Prior/Concomitant Medications:

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If start date < first IP taken date, then:<br>If stop date < first IP taken date, assign as prior<br>Else if stop date >= first IP taken date, assign as Concomitant.<br>If start date >= first IP taken date, assign as concomitant |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If start date < first IP taken date, then:<br>If stop date < first IP taken date, assign as prior<br>Else if stop date >= first IP taken date, assign as Concomitant.<br>If start date >= first IP taken date, assign as concomitant |
| | Missing | Assign as concomitant |
| | | |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Partial | Known | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br><br>If start date < first IP taken date, then:<br><br>If stop date < first IP taken date, assign as prior<br><br>Else if stop date >= first IP taken date, assign as Concomitant.<br><br>If start date >= first IP taken date, assign as concomitant |
| | Partial | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>If start date < first IP taken date, then:<br><br>If stop date < first IP taken date, assign as prior<br><br>Else if stop date >= first IP taken date, assign as Concomitant.<br><br>If start date >= first IP taken date, assign as concomitant |
| | Missing | Assign as concomitant |
| | | |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Missing | Known | No imputation for missing start date<br><br>If stop date < first IP taken date, assign as prior<br><br>Others assign as concomitant |
| | Partial | No imputation for missing start date; impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>If stop date < first IP taken date assign as prior<br><br>Others assign as concomitant |
| | Missing | Assign as concomitant |

# APPENDIX 2. DATA EXTRACTION RULE

a. **AE** domain: take all AEs if AE start date (imputed date will be used if partial date available) <= cut-off date

If AE start date <= cut-off date < AE end date (i.e., resolved after cut-off date), then the AE will be considered as “Ongoing” for reporting. AE outcome will programming changed as “NOT RECOVERED/NOT RESOLVED”

b. **CM** domain: take all CMs if CM start date (imputed date will be used if partial date available) <= cut-off date

If CM start date <= cut-off date < CM end date (i.e., medication ended after cut-off date), then the CM will be considered as “Ongoing” for reporting.

h. **Other** domains:

Use --DTC or –STDTC depending on domain

Take all data if –DTC or --STDTC <= cut-off date

# APPENDIX 3. PROTOCOL DEVIATION SPECIFICATION

| Deviation code | DVDECOD (Category) | *****Sample***** DVTERM (PD Description) | Additional Description for PD detection | Study Part | Timepoint | DVCAT | program/ Source data verification? | Excluded from the PP | Excluded from the PP2 | Excluded from the PK | Excluded from the PD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I01 | Eligibility and Entry Criteria | Male or female age out of range (< 18 or >80 years) at Screening | | A, B | Screening | Major | program | Yes | Yes | | |
| E01 | Eligibility and Entry Criteria | Previous usage of any biological agents including any TNF-alpha inhibitor prior to Randomisation | Refer ATC CODE for prohibited medication to get this PD | | Week 0 (Randomisation) | Major | program | Yes | Yes | | |
| D01 | Withdrawal Criteria | Subject still receive IPs even though serious infection including active TB or opportunistic infection | from adverse event data; if not, source data verification | | All visits from Randomisation | Major | program and manual review | No | No | | |
| C01 | Study Procedures Criteria | More than 6 weeks from Screening to randomisation (+1 week window allowed if the subject is still eligible at the Randomisation for ESR/CRP and major safety lab) | More than 6 weeks from Screening to randomisation (+1 week window allowed if the subject is still eligible at the Randomisation for ESR/CRP and major safety lab) | | Week 0 (Randomisation) | Major | program and manual review | Yes | Yes | | |
| C02 | Study Procedures Criteria | Week 24/Visit8 window deviation (out of +- 5 days) | Week 24/Visit 8 window deviation (out of +- 5 days) | | Week 24/Visit 8 | Major | program and manual review | No | No | | |
| C18 | Study Procedures Criteria | ACR component (CRP) assessed after IP injection at Randomisation | ACR component (CRP) assessed after IP injection at Week 0 (Randomisation) regardless IP time is unknown or missing | | Week 0 | Major | Source data verification | Yes | Yes | | |
| C20 | Study Procedures Criteria | Chest x-ray assessed earlier than 3 months prior to Screening or after Randomisation; If >100 days prior to Screening or after Randomisation, exlcude from PPS1 and PPS2 | Chest x-ray assessed earlier than 3 months prior to Screening or after Randomisation; If >100 days prior to Screening or after Randomisation, exlcude from [illegible] | | Week 0 | Major | program and source data verification | Yes, If >100 days prior to Screening or after Randomisation | Yes, If >100 days prior to Screening or after Randomisation | | |