Statistical Analysis Plan

AGB001

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

ClinicalTrials.gov Identifier: NCT02819726

Version Number and Date: V2.0, 13Feb2019

Statistical Analysis Plan Signature Page

Statistical Analysis Plan V2.0 (Dated 13Feb2019) for Protocol AGB001 Version Amendment 04 (Dated 27Apr2017).

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
V1.0	28Dec2017		Not Applicable – First Version
Draft V1.01	12Jul2018		1. Updated protocol version from amendment 05 (dated 19Oct2017) to amendment 04 (dated 27Apr2017), as Archigen decided to revert protocol version for the study. 2. Removed all Part C and extension study due to protocol version revert. 3. Updated unit of duration of MTX from weeks to months. 4. Updated planned dose intensity from "133.3334 mg/day for subjects who completed both infusions of the course" to "Planned Dose Intensity for every course (mg/day) = 2000 mg/15 days = 133.3334 mg/day for subjects who completed both infusions for the course.in Part A or Part B, and for subjects who only received for the first administration in Part A or Part B, subjects' planned dose intensity will be 1000 mg/1 day = 1000 mg/day" in section 12.1. 5. Removed the extreme studentized deviate test from detecting outliers. 6. Updated formula of DAS28-ESR from "0.56 x √ (TJC28) + 0.28* √ (SJC28) + 0.7* ln(ESR+1) + 0.14*GH" to "0.56 x √ (TJC28) + 0.28* √ (SJC28) + 0.7* ln(ESR) + 0.014*GH" 7. Added detail and SAS code (Appendix 4) for multiple imputation for missing at random in section 15.1.4. 8. Added reference and SAS code (Appendix 5) for logistic regression described in section 15.2.3. 9. Added detail for definition of baseline in section 5.2, i.e. "For joint assessments, patient's global assessments, physician's global assessments, CRP and ESR, both date and time will be considered for defining baseline.". 10. Updated definition of depletion of CD19+ B cell count to "CD19+ B cell count below the

			limit of quantification (20 cells/µL)" due the assay limit of 20 cells/ µL/ 11. Updated PKAS to only include subjects with at least one primary PK parameter 12. Updated handling of BLQ values prior to C_{max}; BLQ values are set to missing rather than setting BLQ values prior to C_{max} to zero, which is more applicable for oral dosing, where a lag time for detection of quantifiable concentrations may be observed. 13. Added rules for exclusion of PK parameters 14. Updated handling of missing data for Change from Baseline calculation of CD19+ B cell counts
Draft v1.02	07Sep2018		Section 3.1: Added "Other analyses may be added in case they're thought to affect DSMB safety review, however no statistical inference will be included in order to avoid an inflation of the type I error.", "DSMB4 will include all safety analyses and immunogenicity and PK/PD without any statistical inference." Section 5.2: Added vital sign for considering both date and time while defining baseline Section 9: Updated wording for HAQ-DI categories Section 15.1.2: Added medical review for potential outliers and outliers will be confirmed during blinded data review meeting prior to database lock and unblinding
Draft v1.02	27Dec2018		Section 8: Per sponsor comments on dry run delivery, added specification of "adequate response" and "inadequate response" for analysis by Week52, i.e. adequate response: met all eligibility requirements for retreatment, which will be captured from "Re-treatment" of CRF Section 8-Completed of Part B: added detail to clarify, i.e. required to receive complete study treatment of Part B Typo revision of "captured"
Draft v1.03	15Jan2019		Removed DSMB4 and W24 CSR. Section 2.6 updated. Section 3.2 and 3.3: Updated Analysis for Week 24 CSR (Part A) and for Week 52 CSR (Part B) into one final analysis, due to W24 CSR

			canceled and no unblinded at W24. Section 4.3-FAS: Per agreement during blinded data review meeting 1, omit criteria of eligible for Part A or not while excluding patients from the FAS. Section 4.5-PP: Per agreement during blinded data review meeting 1, if patients who were ineligible for Part A, they will be excluded from the PP set. Section 9: added tables for baseline characteristics by site 10703 and other sites. Section 13.2: Added two impact analyses added. Section 15.2.2 adjustment of ESR: If ESR=0, it will be adjusted as ln (ESR+1) while calculating DAS28-ESR, i.e. ln(1)=0 Section 15.3.3: added line chart for changes from baseline of DAS28-CRP and bar chart for ACR20/50/70, which already existed in SHELL. Section 15.3.3.: added above two figures for site 10703 per sponsor request. Section 15.2.7: an impact analysis was added for site 10703 to evaluate impact of the site on the main efficacy analysis.
Draft 1.04	31Jan2019		Section 4.5: Updated definition of PP set and omitted PP2 set. Section 8: Updated disposition summary per agreement on BDR1 meeting Section 15.2.5: Added comparison for MabThera vs Rituxan as one of exploratory analysis Section 15.2.6: Removed sensitivity analyses due to protocol deviation Section 15.2.7: had been adjusted to 15.2.6 in main context Section 16.1: Updated definition of TEAE, i.e. no limit of end date Section 11.1 and Appendix 1: prior and concomitant are derived by answer of CRF (Was the medication/therapy taken prior to the study? Yes=prior, No=concomitant)
Draft 1.05	12Feb2019		Section 2.6: Added immunogenicity analyses. Section 4: Added clarification for PK and PD analysis sets. Section 9: Updated analysis for demographic and other baseline characteristics for overall

			total (Site 10703/ All sites except site 10703/ Overall) Section 15: Added description for all three comparisons (SAIT101 vs MabThera®, SAIT101 vs Rituxan®, MabThera® vs Rituxan®) for efficacy endpoints per sponsor request. Section 15.2.5: Updated sentence to make it clear. Section 17: Added analysis of proportion, 95%CI, difference, 95%CI for difference per sponsor request.
2.0	13Feb2019		Section 15.1.2: Added detail, i.e. “If there are any confirmed outliers, then analysis will be performed with and without the outlier(s) to see how the outliers affect study results as sensitivity analysis after unblinding. If there is no confirmed outlier, then box plot and the sensitivity analysis will not be performed after unblinding for final analysis.”

Table of Contents

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 AGB001. 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 analysis for third data and safety monitoring board (DSMB) analysis and additional if needed, analysis for period till Week 52 (Week 52 CSR).

This statistical analysis plan (SAP) is based on protocol version amendment 04, dated 27Apr2017.

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 PK of SAIT101 versus rituximab licensed in the European Union (hereafter designated MabThera®, brand name in EU) versus rituximab licensed in the United States (hereafter designated Rituxan®, brand name in US) in patients with rheumatoid arthritis (RA).

2.1.2. SECONDARY OBJECTIVE

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

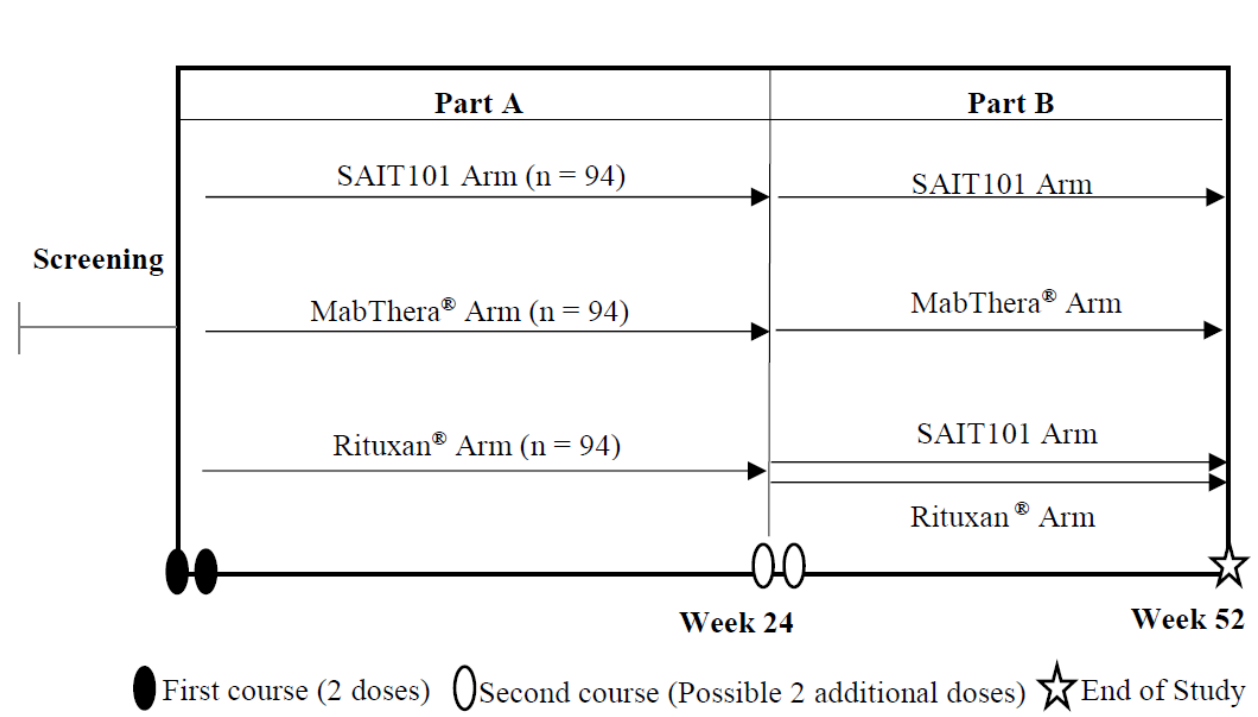
2.2. STUDY DESIGN

This is a multicenter, randomized, double-blind and parallel group study in patients with RA. It consists of Part A up to 24 weeks followed by Part B up to Week 52 that also collects transition data in patients eligible for a second course of treatment.

The regular study duration of the study per individual patient will be 52 weeks from the start date of the first course. To prevent missing data in important supportive efficacy and safety analysis, patients who discontinued study treatment, will also attend all visits until Week 52.

It is planned to randomize approximately 282 patients at approximately 70 investigative centers globally.

Figure 1. Study Design from Protocol



2.3. SAMPLE SIZE CALCULATION

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

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

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

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

2.4. RANDOMIZATION

In Part A, patients will be randomized in a 1:1:1 ratio to receive the first course of SAIT101 (n=94) versus Rituxan® (n=94) versus MabThera® (n=94). The first course includes two intravenous (i.v.) 1,000 mg study drug infusions: one on Day 1 (Visit 2) and the second on Day 15 (Visit 5).

In Part B, eligible patients in the SAIT101 arm or MabThera® arm will receive the second course of SAIT101 treatment or MabThera®, respectively, at Week 24 and Week 26, however, in the Rituxan® arm will be randomized in a 1:1 ratio to receive SAIT101 or Rituxan® treatment at Weeks 24 and 26. The second course includes two 1,000 mg i.v. infusions (one at Week 24 and the second infusion at Week 26 [14 days later]) of study drug.

At Week 24, patients will be evaluated for further course of the infusion, i.e. Part B.

2.5. SCHEDULE OF EVENTS

The schedule of events is provided in Table 2 in the protocol.

2.6. CHANGES TO ANALYSIS FROM PROTOCOL

Summary for Change from Baseline in DAS28-ESR at Week 8, 16, 24, 36 and 52 will be added. Comparison between SAIT101 and Rituxan® will be added as exploratory analyses in section 15.2.5.

Definition of depletion in CD19+ B cell count was updated from CD19+ B cell count below 14/μL to CD19+ B cell count below 20/μL, because the assay limit reported by the central laboratory is 20 cells/μL.

To evaluate differences among Mexican site 10703 and all other sites between baseline characteristics, additional tables of baseline characteristics will be added by site 10703 vs other sites in section 9.

Two additional impact analyses will be added for PK in section 13.2 and one will be added for main efficacy analysis in section 15.2.7.

The study will be unblinded until Week 52, instead of Week 24 in protocol, per sponsor decision.

There will be no interim analysis and CSR prepared based on the 24-week data of all patients. Analysis of Part A and Part B will be combined into one final analysis.

Additional analyses for immunogenicity have been added in section 17, per sponsor decision.

3. Planned Analyses

The following analyses will be performed for this study:

3.1. DATA AND SAFETY MONITORING BOARD (DSMB)

There will be at least 3 DSMB meetings for reviewing safety data in this study. Analysis for first and second DSMB meetings will be described in a separate DSMB SAP; while the third (all patients at week 26) and onward will be based on this SAP where analyses described in section 8-12 and 16 will be performed. Other analyses may be added in case they are thought to affect DSMB safety review, however no statistical inference will be included in order to avoid an inflation of the type I error.

The first DSMB analysis will be considered as Interim Analysis of 10 patients per group (30 patients in total) of safety data collected up to Week 4 whose safety report will be submitted to regulatory. For additional details on DSMB meetings, please refer to the DSMB charter dated 26Jan2017.

3.2. FINAL ANALYSIS (W52 CSR)

The analysis of primary, secondary and exploratory endpoints, including PK/PD, efficacy, safety and

immunogenicity, will be performed per protocol based on procedures outlined in this SAP based on the 52-week data of all patients.

The study will be unblinded only at Week 52 and a Week 52 CSR (W52 CSR) will be prepared based on the 52-week data of all patients.

The analysis for W52 CSR will be performed by IQVIA Biostatistics following sponsor authorization of this Statistical Analysis Plan, database lock and sponsor authorization of analysis sets.

3.3. EXPLORATORY ANALYSES

The exploratory analyses will be described in following sections, for those analyses which are not described in this SAP will be performed as ad hoc analysis after unblinding, if needed. The subgroups to be used will be based on 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 subjects to the analysis sets.

Note that the PK/PD parameter analysis will be only performed after data base lock. A blinded data review meeting of PK/PD data will be done to decide the final allocation rules to assign subjects to the PK and PD analysis sets. The PK scientist will only be unblinded once the PK/PD parameter analysis has been finalized.

Analysis sets will be listed by subject.

4.1. ENROLLED SET [ENR]

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

4.2. RANDOMIZED SET [RAN]

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

4.3. FULL ANALYSIS SET [FAS]

The Full Analysis Set (FAS) of the study consists of all RAN patients in accordance with the intended treatment arm, regardless of the treatment actually received. The FAS will be one of the populations used for the efficacy endpoints.

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 during Part A or Part B. Subjects will be analyzed according to the treatment received. The SAF is used as the basis for all safety analyses up to Week 52.

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

4.5. PER PROTOCOL SET [PP]

The Per Protocol Set (PP) consists of all RAN patients who received at least both infusions of study drug in Part A and continued study assessments up to Week 24. Patients with any critical and/or major protocol deviations that affect the efficacy assessments will be assessed for inclusion in the set. Patients may be excluded from the PP set if they did not meet key eligibility criteria, were taking prohibited concomitant medication, received the wrong study drug, or other situations that may affect the efficacy assessments.

Protocol deviations or the situation that leads to exclusion from the PP will be specified and authorized prior to unblinding the treatment arms. Efficacy endpoints will also be summarized on the PP.

4.6. PHARMACOKINETIC ANALYSIS SET [PKS]

The PK analysis set will include all patients who receive both planned doses of SAIT101 or MabThera® or Rituxan® in Part A (i.e., first course), have at least one estimable primary PK parameter value and have no major protocol deviations or events thought to significantly affect the PK of the drug.

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

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

4.7. PHARMACODYNAMIC ANALYSIS SET [PDS]

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

Subjects 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. Protocol Deviation specification will be developed according to the guidance and updated whenever new version of the guidance is released. Additional update before unblinding may be added in case of the protocol deviations are not specified in the guidance but are reported from sites and classified critical/major.

All Critical/Major protocol deviations captured by programing or reported protocol deviations from sites, which will be transferred to the biostatistics (BIOS) group by 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 will be listed.

Protocol deviations do not lead to subject withdrawal unless they indicate a significant risk to the subject's safety. Protocol deviations leading to subject exclusion from the specific analysis set (except for PK set and PD set) will be pre-defined at Protocol Deviation Specification and get approval prior to database lock.

4.8.1. DEVIATIONS RELATED TO PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

Changes to the procedures or events, which impact the quality of the PK and PD data, will be considered significant protocol deviations and will be described within the CSR body text. These changes or events will include any circumstances that will alter the evaluation of the PK and PD.

Examples of protocol deviations that are important for PK and actions to be taken are discussed in Section 13.

In the case of a significant protocol deviation or event, PK and PD data collected during the affected treatment period will be excluded from summaries and analyses but included in by-subject 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. In general, a common example of a non-significant protocol deviation is deviations from blood sample collection times.

5. General Considerations

All patients will be tabulated according to their initial treatment group for analyses when all study team are blinded; while for final analysis (W52 CSR), both initial first and second courses of study treatment group will be considered, regardless of any dose adjustment during study conduct.

5.1. STUDY DAY

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

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. For vital sign, joint assessments, patient's global assessments, physician's global assessments, CRP and ESR, both date and time will be considered for defining baseline.

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 for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early study discontinuation data.

5.4. STATISTICAL TESTS

The default significant level will be 0.05 for statistical tests; the two-sided 90% confidence intervals (CI) will be calculated for PK analyses and 95% CI for efficacy analyses, 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.

Noncompartmental PK parameter calculations will be performed using Phoenix WinNonlin® 6.4 or higher, and/or SAS® Version 9.4 or higher. Graphics may be prepared using the same versions of SAS®, or Phoenix WinNonlin®, or with SigmaPlot® 12.5, or higher.

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. MULTIPLE COMPARISON/MULTIPLICITY

No multiple comparison adjustment will be used for main efficacy analysis, since there is only one main efficacy analysis for change from baseline at Week 24. No multiple comparison adjustment will be used either for the PK analyses since the significance level is pre-specified at 10% (two-sided) to show equivalence within pre-specified limits, and the overall power for the PK equivalence assessment accounts for the multiple testing.

6.3. 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 data for will be handled as described in Section 13 for PK and Section 14 for PD.

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

6.4. DATA EXTRACTION RULE

For DSMB, only data up to the DSMB target time point will be included. Specific data extraction rules are described in Appendix 3.

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 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 screen failure. For the patients who were randomized, summaries will be presented for the number and percentage of patients as follows:

Analyses by Week 24:

- Met eligibility of Part A or not
  - Received any infusion in Part A
  - Not received any infusion in Part A
- 1st Randomized
- Received at least one infusion of study drug
- Prematurely discontinued treatment during Part A
  - Prematurely stopped and not restarted the first infusion (by reason for premature discontinuation of study treatment, which will be catprured from “End of Treatment” of CRF)
  - Only completed the first infusion (by resaon for premature discontinuation of study treatment, which will be catprured from “End of Treatment” of CRF)
  - Prematurely stopped and not restarted the second infusion (by reason for premature discontinuation of study treatment, which will be catprured from “End of Treatment” of CRF)
  - Prematurely stopped, then restarted, but not completed the second infusion (by reason for premature discontinuation of study treatment, which will be catprured from “End of Treatment” of CRF)
- Withdrew early from Part A of the study
  - Lost to follow-up

  - Study terminted by sponsor
  - Trial site terminated by sponsor
  - Withdrawal of content
  - Other
  - Missing
- Completed Part A of the study-- received assessments at Week 24 without study treatment discontinuation (required to receive two complete study infusions of Part A) or study withdrawal during Part A

Analyses by Week 52:

- All items for analyses by Week 24 above
- Met eligibility of Part B or not (which will be captured from “Re-treatment” of CRF)
  - Received any infusion in Part B
  - Not received any infusion in Part B
- Re-randomized
- Received at least one infusion of study drug during Part B
- Prematurely discontinued treatment during Part B
  - Prematurely stopped and not restarted the first infusion (by reason for premature discontinuation of study treatment, which will be captured from “End of Treatment” of CRF)
  - Only completed the first infusion (by reason for premature discontinuation of study treatment, which will be captured from “End of Treatment” of CRF)
  - Prematurely stopped and not restarted the second infusion (by reason for premature discontinuation of study treatment, which will be captured from “End of Treatment” of CRF)
  - Prematurely stopped, then restarted, but not completed the second infusion (by reason for premature discontinuation of study treatment, which will be catprured from “End of Treatment” of CRF)
- Withdrew early from Part B of the study
  - Lost to follow-up
  - Study terminted by sponsor
  - Trial site terminated by sponsor
  - Withdrawal of content
  - Other
  - Missing
- Completed Part B of the study—received assessments at Week 52 without study treatment discontinuation (required to receive two complete study infusions of Part B) or study withdrawal during Part B
- Completed the study—received at least the first course of study drug and assessments at Week 52

Protocol deviations (as defined in section 4.10) will be presented by treatment group for the RAN.

Number (%) of subjects in the analysis sets and exclusion reason will be summarized by treatment group for the RAN.

9. Demographic and other Baseline Characteristics

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

To evaluate differences among Mexican site 10703 and all other sites between baseline characteristics,

additional analyses of baseline characteristics will be added.

- Overall total (all treatments) for site 10703
- Overall total (all treatments) for all sites except site 10703
- Overall total (all sites/treatments)

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
- BMI (kg/m^2) at Baseline – derived as weight (kg)/(height (m))^2

Baseline Characteristics

- Disease duration (years) – calculated initial diagnosis date of RA relative to date of informed consent
- Childbearing potential – Yes, No
- Duration of Methotrexate (MTX) use (months) – calculated relative to date of Day 1; MTX identified using the following Prefered Term: "METHOTREXATE", “METHOTREXATE SODIUM"
- Number of previous disease-modifying anti-rheumatic drugs (DMARDs) except MTX – 0, 1, 2, 3, More than 3

DMARDs will be coded using WHO DRUG dictionary DDE Mar 01, 2016 or higher and identified using the following Anatomical Therapeutic Chemical Classification (ATCC) code: L04AA, A07EC, M01CA, M01CB, M01CC, M01CX, J01AA, P01BA

- Baseline rheumatoid factor
- Baseline anti-CCP antibodies
- Baseline C-reactive protein (CRP) (mg/L)
- Baseline erythrocyte sedimentation rate (ESR) (mm/hr)
- Baseline swollen joint count (SJC)
- Baseline tender joint count (TJC)
- Baseline patient global assessments VAS score (mm)
- Baseline physician global assessment VAS score (mm)
- Baseline patient pain assessment VAS score (mm)
- Baseline HAQ-DI score
- Baseline DAS28-CRP score
- Baseline DAS28-ESR score

The HAQ-DI questionnaire contains 20 questions classified into 8 categories (dressing & grooming, arising, eating, walking, hygiene, reach, grip, and activities) with 2 to 3 questions for each category. The scoring for each result should be as below: 0 = Without ANY Difficulty; 1 = With SOME Difficulty; 2 = With MUCH Difficulty; 3 = UNABLE To Do.

The HAQ-DI score will be calculated as follows:

1) Determine the highest score among 2 to 3 questions for 8 categories

2) Adjust for use of aids/devices and/or help from another person excluding ‘Other’ items - Increase the score

of 0 or 1 to 2, but if the score is 2, it remains 2 and if the score is 3, it remains 3

Any aids or devices	Category
Cane, Walker, Crutches, Wheelchair	Walking
Devices used for dressing	Dressing & Grooming
Built up or special utensils	Eating
Special or built up chair	Rising
Raised toilet seat, Bathtub seat, Bathtub bar, Long-handled appliances in bathroom	Hygiene
Long-handled appliances for reach	Reach
Jar opener	Grip
Errands and chores	Common Daily Activities

3) If score can't be determined in more than 2 categories, then HAQ-DI score will be considered as missing, i.e. at least score for 6 of 8 categories.

4) HAQ-DI score is calculated as the summed category scores divided by the number of categories answered (range 6-8).

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 19.0 (MedDRA 19.0) or higher, 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.

11. Medications and Procedures

11.1. MEDICATIONS

Prior and/or concomitant medications will be coded using WHO DRUG dictionary DDE Mar 01, 2016 or higher and Anatomical Therapeutic Chemical Classification (ATCC).

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

Medications will be considered as "prior", if answer of "Was the medication/therapy taken prior to the study?" are yes, and if answers are no then they will be considered as concomitant medications.

'Rescue' medication is defined as the use of non-biologic DMARDs, after Week 16 of the study and is identified as 'Rescue medication' for 'Indication' on eCRF. Patients with any rescue medication are summarized by visit and treatment group. Time to first incidence of rescue medication after Week 16 of the study will be estimated for each treatment group and presented using Kaplan-Meier methods. Kaplan-Meier plots will also be presented.

In addition, percentiles of time without rescue medication will be presented.

The following formula will use to calculate the time-to-event variable in weeks = floor ((event occur date - date of first study drug + 1)/(7))

Prior medication, concomitant medications and rescue medications will be summarized will be summarized by Anatomic Therapeutic Chemical (ATC) pharmacological sub-class (4th level) for the SAF. All medication used will be listed.

11.2. PROCEDURE

General surgery or procedure received 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 weeks from Day 1, number of patients completed for each administration visit, number of administrations, cumulative dose (mg) from Day 1, dose intensity (mg/day) by course, relative dose intensity (RDI) by course, will be summarized by treatment group with descriptive statistics using the SAF. A plot will be prepared to visually present the patient distribution of exposure duration by treatment based on the SAF.

Exposure duration will be calculated according to the following algorithm.

- Exposure duration (weeks) = (last study drug date – first study drug date + 1)/7, Interruptions, compliance, and dose changes are not taken into account for duration of exposure.
- Exposure duration for each course (days) = last infusion date of the course – first infusion date of the course + 1

Dose intensity is derived from the following definitions by course:

- Dose Intensity for 1st course (mg/day) = sum of actual dose administered for the 1st course (mg) / exposure duration for 1st course (days) = sum of actual dose administered for the 1st course (mg) / (last infusion date of the 1st course – first infusion date of the 1st course + 1) (days) .

Dose intensity for 2nd, 3rd and 4th course will follow similar rule as the 1st course above.

RDI is based on the actual dose intensity and the planned dose intensity and will be calculated by course 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 for every course (mg/day) = 2000 mg/15 days = 133.3334 mg/day for subjects who completed both infusions in Part A or Part B, and for subjects who only received for the first administration in Part A or Part B, subjects' planned dose intensity will be 1000 mg/1 day = 1000 mg/day.

Administration of study drugs will be listed.

Partial date convention

Partial dates will be assumed to be latest possible date of specific visit planned to have study drug infusion, e.g. first infusion of the 2nd course will be assumed as the latest assessment date in Week 24 visit.

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.

Administration of infusion pre-medication will be listed in listing.

13. Pharmacokinetics Analysis

The PK data collected in Part A and Part B (up through Week 24) will be analyzed according to the treatment administered.

Serum concentrations of rituximab at the time points pre-defined in the study protocol will be measured by a validated method and used for the PK analysis.

Treatment of PK data affected by important protocol deviations and/or events will include the following:

- Randomized study drug not administered or not fully administered, or wrong trial drug administered: In case a dose is not administered or fully administered, any parameters for this subject, if calculated, for this dose and the subsequent dose will not be included in descriptive and/or inferential statistics; the subject will not be part of the PK analysis set per definition. In case of wrong trial drug being administered, patients will be analyzed and included according to the actual treatment they received (rather than the planned treatment), unless there are other additional factors or changes involved that would impact PK.
- Dose is administered outside of the time window provided in protocol (i.e., visit window of ±1 day [i.e. 24 hours] for dose on Day 15): Due to the long half-life and extended duration of blood sampling collections, the impact of sampling time deviations on $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}inf)}$-related parameters, and $AUC_{(0\text{-}last)}$ would be considered negligible and those parameters will generally not be excluded from descriptive and/or inferential statistics. Similarly, $C_{max,d2}$ will not be excluded.
- Total duration of infusion not available (i.e., start and/or stop time of infusion missing): Any concentrations or PK parameters based fully or partially on the affected dose will be evaluated at the BDRM.
- Interruption of infusion: Due to the long half-life of the drug, interruptions are expected to have minimal impact on PK parameters that are susceptible to infusion interruptions, as long as the full dose is administered. No parameters will be excluded based on infusion interruptions.
- Pharmacokinetic samples at important phases of the PK disposition curve collected outside the protocol-defined window and/or missing: Important phases include time points around the end-of-infusion, the last sampling time point, and the trough concentration collected prior to dosing on Day 15.
    - End-of-infusion (EOI) and EOI+1h sample Dose 1 and/or 2: If both samples are missing, profiles are not evaluable for AUC and related parameters as well as the affected C_{max}/t_{max}. If both samples are collected outside of the protocol specified sampling window, data will be assessed during the BDRM to assess whether exclusion of PK parameters is warranted.
    - 336 hours after the 1st dose (i.e., predose second dose on Day 15): See section 13.2 below, for how such deviation at the end of the dosing interval will be treated for calculation of $AUC_{(0\text{-}d15)}$. In general, if this sample is missing or collected outside of a window of 312 to 360 hours postdose for the 336-hour time point, profiles are not evaluable for C_{trough}. The impact on $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}inf)}$-related parameters, and $AUC_{(0\text{-}last)}$ is considered negligible and those parameters will generally not be excluded from descriptive and/or inferential statistics.
    - Week 24 sample (=t_{last}): If the Week 24 sample is missing or is collected outside of the protocol-specified visit window of ±3 days, $AUC_{(0\text{-}t)}$ is not evaluable with the exception if the sample prior to the last sample is already BLQ as the missing sample will be inconsequential for profile evaluation.

- Non-critical PK samples collected outside of the protocol-defined window: Actual times will be used for PK parameter calculation. If a chronic pattern of deviation is noted, it will be evaluated individually and discussed at the BDRM.
- Non-critical PK samples not collected: Missing data will be treated as missing data and no parameters will be excluded unless the missing data impact the objective acceptance criteria for elimination rate related parameters.
- Sample processing errors that might render a subject's bioanalytical data to be inaccurate: Data affected by these errors will be evaluated during PK parameter analysis to determine whether or not they can be included in the PK analysis. If warranted, this may be discussed during the BDRM

An additional statistical analysis will be performed excluding subjects with major GCP violations (i.e. GCP violations observed at site 10703) (see Section **Error! Reference source not found.**).

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 summarized for each treatment by study day and nominal time point using appropriate descriptive statistics such as number of data (n), mean, SD, CV%, minimum, median, and maximum. Concentrations that are below the limit of quantification (BLQ) will be treated as zero for the computation of descriptive statistics and missing concentration values will be omitted for all concentration summaries. End-of-infusion samples that have been taken prior to the sample taken 3 hour after the start of infusion, will be excluded from descriptive statistics but included in PK parameter analysis (using actual time). Samples with significant deviations from the planned time, as determined by the pharmacokineticist, may be excluded from the calculation of descriptive statistics; these will include samples, which are taken outside a window of 312 to 360 hours at the 336-hour nominal sampling time (i.e., predose sample on Day 15).

A subject listing of all concentration-time data for each treatment will be presented. Concentrations excluded from analyses will be flagged in the listings. Unscheduled assessments will be listed but not included in summary statistics. Plots of arithmetic mean concentration-time data (±SD) will be presented for each treatment on linear and semi-logarithmic scales. Individual subject concentration-time data will be graphically presented on 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 following the first dose, predose samples that are BLQ or missing will be assigned a numerical value of zero. Any anomalous concentration values observed at predose 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 subject will be calculated and reported in the listing, but excluded from statistical summaries and analyses. For the second dose, a predose sample that is BLQ will be assigned a numerical value of zero. Missing predose samples will be set to missing.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points prior to C_{max} will be set to missing. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from

the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

The following PK parameters will be estimated for SAIT101, MabThera® and Rituxan® by noncompartmental methods using actual elapsed time, where possible.

$AUC_{(0\text{-}t)}$ Area under the serum concentration-time curve from time zero (immediately predose on Day 1) to time of last quantifiable concentration (µg·h/mL), calculated by linear up/log down trapezoidal summation.

$AUC_{(0\text{-}inf)}$ Area under the serum concentration-time curve from zero (immediately predose on Day 1) extrapolated to infinite time (µg·h/mL), calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0\text{-}last)} + C_{last}/\lambda_z$. For presenting data purpose, symbol $AUC_{(0\text{-}inf)}$ instead of $AUC_{(0\text{-}\infty)}$ will be used in all PK analysis and reporting.

$AUC_{(0\text{-}d15)}$ Area under the serum concentration-time curve from zero (immediately predose on Day 1) until Day 15 prior to infusion (µg·h/mL), calculated by linear up/log down trapezoidal summation.

Actual time/concentration on Day 15 will be used for the calculation of this parameter unless the parameter is derived by interpolation (see below);

- A window of 312 to 360 hours postdose for the 336-hour (Day 15) time point (which has been selected as a window that would not create an influence of more than ±5% on the AUC) will be used as an acceptance criterion, for calculation using actual time/concentration on Day 15, and for inclusion of this parameter in descriptive and inferential statistics;
- If the 336-hour sample was collected after 360 hours (i.e., outside the defined time window) but prior to the second dose, then a log-linear interpolation will be used to derive the concentration at 336 hours for computation of $AUC_{(0\text{-}d15)}$;
- If the 336-hour sample is missing or was collected before 312 hours, the $AUC_{(0\text{-}d15)}$ will be set to missing.

$AUC_{(w2\text{-}w24)}$ Area under the serum concentration-time curve from Week 2 (predose) to Week 24 (µg·h/mL), calculated by linear up/log down trapezoidal summation.

$AUC_{(0\text{-}w12)}$ Area under the serum concentration-time curve from zero (predose) to Week 12 (µg·h/mL), calculated by linear up/log down trapezoidal summation.

C_{trough} Trough (predose) concentration (µg/mL) prior to second infusion on Day 15, obtained directly from the observed concentration versus time data.

- If the sample was collected outside of a window of 312 to 360 hours postdose, C_{trough} will be excluded for descriptive and inferential statistics.

$C_{max,dose1}$ Maximum serum concentration (µg/mL) over the 1st dosing interval, 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.

$C_{max,dose2}$ Maximum serum concentration (µg/mL) over the 2nd dosing interval, 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.

$t_{max, dose1}$	Time of maximum concentration (h) post-infusion over the 1st dosing interval, obtained directly from the observed concentration versus time data.
$t_{max, dose2}$	Time of maximum concentration (h) post-infusion over the 2nd dosing interval, obtained directly from the observed concentration versus time data.
λ_z	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination.
$t_{1/2}$	Apparent terminal half-life (h), determined as $\ln 2/\lambda_z$.
CL	Systemic clearance after intravenous dosing (L/h), calculated as dose (1st + 2nd dose) divided by $AUC_{(0\text{-}inf)}$.
V_D	Volume of distribution following intravenous dosing (L), calculated as dose (1st + 2nd dose) divided by $[\lambda_z \cdot AUC_{(0\text{-}inf)}]$

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized.

$t_{1/2}$, Interval	The time interval (h) of the log-linear regression to determine λ_z.
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z. A minimum of 3 data points will be used for determination.
R_{sq}	Goodness-of-fit statistic for calculation of λ_z (Regression coefficient).
$\%AUC_{ex}$	Percentage of $AUC_{(0\text{-}inf)}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{(0\text{-}inf)} \times 100]$.

The following criteria will be assessed:

- if $AUC_{(0\text{-}t)}$ is less than 80.0% of $AUC_{(0\text{-}\infty)}$ (i.e. $\%AUC_{ex}$>20.0%), the data will be flagged in the listing.
- if predose concentration is greater than 5% of $C_{max,dose1}$ for a subject, the concentration data and parameters for this subject will be flagged in the listing and excluded from summary statistics.

For partial areas from interval time 1 (t1) to time 2 (t2), if t2 is missing, $AUC_{(t1\text{-}t2)}$ will not be calculated.

Pharmacokinetic parameters will be listed and summarized by treatment using descriptive statistics (n, mean, SD, CV%, minimum, median, maximum, geometric mean, and 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 (US, EU, Other)
- By treatment and age category (18-60 years and >60 years)
- By treatment and sex
- By treatment and ADA status at baseline.

The PK parameters, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}d15)}$, $C_{max,dose2}$ after the second infusion on Day 15, and C_{trough}, before the second infusion on Day 15 will be considered the co-primary PK endpoints. All other PK endpoints will be regarded as secondary.

A statistical comparison of the $\log_e$-transformed primary parameters between treatments will be based on an analysis of variance model. No covariates will be included. The difference in least squares means between the

test (SAIT101) and the reference (MabThera® or Rituxan®) treatments and the associated 90% CI will be calculated. Comparison between the reference treatments will also be performed. Back transformation will provide the ratio of geometric means between treatments and 90% CI for this ratio. Equivalence will be concluded if the 90% CI for the ratio of geometric means of test/reference for primary endpoints are completely contained within the acceptance interval of 0.80 to 1.25. Least-squares geometric means will be also presented for each treatment with corresponding 95% CIs. BLQ values for C_{trough} will be treated as LOQ/2 for all statistical comparison. Line plots will be generated to visually display all comparisons for all primary parameters.

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

An exploratory statistical assessment of the impact of baseline ADA status (Positive or Negative) will be completed by adding this fixed effect to the model used in the primary statistical analysis. The ratio of geometric means for ADA positive/ADA negative will be reported with the 90% CI for this ratio.

Scatter plots of individual and geometric mean PK parameters $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}d15)}$, $C_{max,dose2}$ after the second infusion on Day 15 and C_{trough} before the second infusion on Day 15 versus treatment 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.

Additional impact analyses will be performed to evaluate the impact of site 10703 on the primary analysis, and the statistical significance of any PK differences associated with this site. The first impact analysis will entail repeating the primary analysis above but excluding site 10703. The second impact analysis will entail adding two fixed effects to the primary model: Site1073 (Yes/No), Site10703 x Treatment interaction, and testing both effects at the two-sided 5% significance level. The type 3 p-values will be reported for all effects in this model, but no treatment or site comparison estimates will be made.

13.3. EXPLORATORY ANALYSIS OF ADA ON PHARMACOKINETICS

The impact of ADA on PK will be explored graphically. Mean drug concentration-time plots for subjects with positive ADA at baseline and for subjects without positive ADA at baseline will be presented separately in both linear and semi-logarithmic scales.

Comparative descriptive statistics for the primary PK parameters will be presented as well.

14. Pharmacodynamics Analysis

Part A and combination of Part A and B will be analyzed.

Serum/plasma levels of PD variables at the time points pre-defined in the study protocol will be measured by validated methods and used for the PD analyses.

14.1. PHARMACODYNAMIC CONCENTRATION DATA

A listing of PD blood sample collection times and derived sampling time deviations 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 change from baseline/baseline). Baseline is defined as the value observed on Day 1 (immediately before the start of the first infusion in Part A) or screening (for IgG, IgM, IgA).

Observed, change from baseline, and percent change from baseline in CD19+ B-cell counts, will be listed and summarized by study part, treatment, and scheduled visit using descriptive statistics (n, mean, SD, CV%, minimum, median, and maximum). Data from unscheduled visits will be listed but not summarized.

Depletion of CD19+ B-cell counts (defined as a CD19+ B cell count below 20/μL) will be summarized with incidence by scheduled visit up to Week 52. Time to B-cell depletion (calculated as first time CD19+ B cell count below the limit of quantification (20 cells/μL) minus time of first dosing, rounded to nearest whole day) and duration of CD19+ B cell depletion (calculated as time of first return to non-depletion minus time of first depletion rounded to the nearest whole day) will be summarized for subjects in Part A. Time to B-Cell depletion will be summarized, and presented with Kaplan Meier curves and estimates of median depletion time with corresponding 95% CI. Duration thereof will be summarized only.

Observed and change from baseline in IgG, IgM, and IgA levels as well as CRP levels will be listed and summarized up to W24 CSR while for W52 CSR and onwards analysis, both initial first and second courses of study treatment groups will be considered using descriptive statistics described above.

Analyte CD19+ B cell count, IgG, IgM, IgA, and CRP data which fall below quantifiable concentrations will be set to zero for all summaries while missing values will be omitted.

Plots of serial mean and individual observed, change from baseline and percent change from baseline for CD19+ B-cell counts over time by treatment on linear scale will be provided: 1) up to Week 24; 2) from Week 24 to Week 52.

14.2. PHARMACODYNAMIC PARAMETERS

For PD parameter calculations, predose samples that are BLQ for observed values 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.

If calculable, the area under the depletion-time curve (AUEC) of CD19+ B cell count, will be calculated for change from baseline CD19+ B cell-time data by linear trapezoidal method using actual elapsed time from dosing. Negative partial areas will be calculated into the AUEC as observed, without exclusion or modification. All AUC parameters will be normalized to the time interval observed by dividing by the observed interval length.

$AUEC_{(0\text{-}d15)}$	AUEC (count·h) from time zero (predose immediately prior to 1st infusion) until Day 15 prior to infusion
$AUEC_{(0\text{-}w24)}$	AUEC (count·h) from time zero (predose immediately prior to 1st infusion) to Week 24

For both these parameters, the actual measurement time on Day 15 and Week 24 (predose), respectively, will be used for calculation (i.e., no adjustments will be made for any time deviations at this scheduled sampling time point). If the change from baseline value at those respective timepoints is missing, the respective parameters will be set to missing. The PD parameters will be summarized by treatment using n, mean, SD, CV%, minimum, median, maximum, and 95% CIs.

Pharmacodynamic parameters $AUEC_{(0\text{-}d15)}$ and $AUEC_{(0\text{-}w24)}$ will be compared between SAIT101 and both MabThera® and Rituxan® using analysis of covariance that includes a fixed effect for treatment and a covariate for baseline CD19+ B cell value. Least-squares mean for each treatment will be presented for each treatment with corresponding 95% CIs. The difference in least-squares means (SAIT101-MabThera® and SAIT101-Rituxan® and MabThera®-Rituxan) will be presented with corresponding 90% CIs.

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

14.3. EXPLORATORY ANALYSIS OF ADA ON PHARMACODYNAMICS

The impact of ADA on PD (CD19+ B cells) will be explored graphically. Mean CD19+ B cell count-time plots for subjects with positive ADA at baseline and for subjects without positive ADA at baseline will be presented on linear scale.

15. Efficacy Outcomes

All comparison for main and secondary efficacy variables between SAIT101 and MabThera® will be repeated for MabThera® and Rituxan® and SAIT101 and Rituxan® as exploratory analyses.

15.1. MAIN EFFICACY

15.1.1. MAIN EFFICACY VARIABLE & DERIVATION

The main efficacy variable is the change from Baseline in DAS28-CRP at Week 24. The change from baseline in DAS28-CRP at Visit 24 will be calculated as follows:

Change at Visit 24= Value of DAS28-CRP at Visit 24 – Baseline value of DAS28-CRP

DAS28-CRP assessments consisted of tender joint counts (TJC), swollen joint counts (SJC) and C-reactive Protein (CRP). Formula is listed as follow or a calculator is available online at the following website: http://www.das-score.nl/das28/DAScalculators/dasculators.html.

- DAS28-CRP = [0.56 x √(TJC28) + 0.28* √(SJC28) + 0.36* ln(CRP+1)] x 1.10 + 1.15

TJC28: Tender Joint Count (28 joints); SJC28: Swollen Joint Count (28 joints); CRP(mg/L).

28 joints include proximal interphalangeal joints (10 joints), metacarpophalangeal joints (10 joints), wrists (2 joints), elbows (2 joints), shoulders (2 joints) and knees (2 joints).

DAS28-CRP will be considered missing if any of the three components is missing.

15.1.2. MISSING DATA AND OUTLIER METHODS FOR MAIN EFFICACY VARIABLE

All analyses of main efficacy variables will be based on available data. No missing data will be imputed and no outlier will be excluded.

For the sensitive analysis to main efficacy analysis, missing data for DAS28-CRP prior to Week 24 will be imputed and outlier will be handled as described in Section 15.1.4.

If there is any doubt of outlier, a box plot will be used for detecting potential outliers among all subjects, i.e. values higher than Q3+1.5*IQR or lower than Q1-1.5*IQR (Q1=25th quartile, Q3=75th quartile, IQR=Q3-Q1.). The potential outliers among all subjects will be reviewed by medical and be confirmed during blinded data review meeting and prior to database lock and unblinding. If there are any confirmed outliers, then analysis will be performed with and without the outlier(s) to see how the outliers affect study results as sensitivity analysis after unblinding. If there is no confirmed outlier, then box plot and the sensitivity analysis will not be performed after unblinding for final analysis.

15.1.3. ANALYSIS OF MAIN EFFICACY VARIABLE

The primary objective of this study is to demonstrate equivalence in the SAIT101 and MabThera® in DAS28-CRP change from Baseline at Week 24. The equivalence between the two treatment groups will be declared if the two-sided 95% confidence interval (CI) of the difference in change from baseline in DAS28-CRP between SAIT101 and MabThera® is entirely contained within the equivalence margin of [-0.6, 0.6].

An analysis of co-variance (ANCOVA) model of change from baseline in DAS28-CRP at Week 24 with treatment group as factors and the baseline DAS28-CRP value as a covariate will be used to test the treatment difference of SAIT101 versus MabThera®. Least squares mean (LSM), standard error and two-sided 95% confidence interval for change from baseline will be reported for each treatment group. For the treatment difference, the LSM difference, standard error, and two-sided 95% confidence interval will be reported for both FAS and PP.

Value of DAS28-CRP and its change from baseline will also be listed.

15.1.4. Sensitivity Analysis of Main Efficacy Variable

If there is any statistical outlier, a sensitivity analysis will be performed for the main efficacy without outlier(s) to see whether the outlier(s) affect study results.

All sensitivity analyses below will be performed for the main efficacy variable of DAS28-CRP change from baseline at Week 24.

A sensitivity analysis will be performed for the main efficacy with the addition of the following covariates to the statistical model: Region (EU, US, Other), age, sex, ADA status at baseline (positive, negative), body weight at baseline, and baseline DAS28-CRP based on the FAS and PP. Besides, another sensitivity analysis will be performed for main efficacy with the treatment interaction term and baseline DAS28-CRP based on the FAS and PP.

The same analysis with the main efficacy analysis will be repeated for the PP and FAS with imputed DAS28-CRP for those of subjects withdrew before 24 weeks to explore the robustness of the results. The missing data imputation methods in detail are as follows:

- Last Observation Carried Forward (LOCF) approach will be applied. For all patients withdrawn from study for any reason, the last non-missing observation before withdrawal will be carried forward to the subsequent endpoint visit for evaluation. Enrolled patients without at least one post-baseline observation will not be included for evaluation.
- Baseline-observation-carried-forward (BOCF) approach will be applied regardless of any withdrawal reason. Enrolled patients without at least one baseline observation will not be included for evaluation.
- For patients with missing DAS28-CRP at Week 24 due to treatment-related reasons, i.e. treatment discontinuation for receiving rescue therapy OR adverse events OR lack of efficacy before Week24, the patients will be considered as DAS28-CRP non-responders at Week 24 and the BOCF approach will be applied. Otherwise, no impuation will be applied.
- For patients with missing DAS28-CRP at Week 24 due to treatment-related reasons, i.e. treatment discontinuation for receiving rescue therapy OR adverse events OR lack of efficacy before Week24, the BOCF approach will be applied. Otherwise, multiple impuation for missing at random approach will be applied. In order to preserve any observed difference between treatment groups, best change will be assumed to be missing at random (MAR). Robustness of the main efficacy conclusion to the missing at random assumption will be evaluated by sensitivity analyses that will take account the reasons for withdrawal.

15.1.4.1. Multiple imputation for missing at random

Monotone missing data structure will be created as follows: intermediate (non-monotone) missing data will be multiply imputed using the Markov chain Monte Carlo (MCMC) method and assuming MAR and multivariate normality. Transformation of data will only be used if there is a clear deviation from normality. The SAS procedure PROC MI with the MCMC option will be used with seed number=12345.

Then, each component will be imputed with treatment group, DAS28-CRP at baseline and data at previous visit from all DAS28-CRP components as covariates.

Imputation will be repeated 100 times. The DAS28-CRP will then be calculated for each of the multiply imputed data sets from the imputed components. Results will be combined using MIANALYZE SAS procedure with the Rubin's rules. Please refer to Appendix 4 for detail SAS code.

15.2. OTHER EFFICACY

15.2.1. SECONDARY EFFICACY VARIABLE(S) & DERIVATION(S)

Change from Baseline in DAS28-CRP at Week 8, 16, 36, and 52

Change from baseline in DAS28-CRP at week 8, 16, 36 and 52 will be derived with the similar criteria in Section 15.1.1 of this analysis plan.

ACR20 response rates at Week 8, 16, 24, 36, and 52

ACR20 response is defined as at least a 20% improvement from baseline if meet the criteria below. A subject will be classified as having achieved an ACR20 response (ACR20 = 1) if the following 3 conditions are satisfied.

$\frac{Swollent\ Joint\ Count\ at\ visit\ X - Swollent\ Joint\ Count\ at\ baseline}{Swollent\ Joint\ Count\ at\ baseline} \leq -0.2$ and

$\frac{Tender\ Joint\ Count\ at\ visit\ X - Tender\ Joint\ Count\ at\ baseline}{Tender\ Joint\ Count\ at\ baseline} \leq -0.2$ and

At least 3 of following conditions are satisfied.

- $\frac{Patient's\ Pain\ at\ visit\ X - Patient's\ Pain\ at\ baseline}{Patient'sPain\ at\ baseline} \leq -0.2$
- $\frac{Patient's\ Global\ at\ visit\ X - Patient's\ Global\ at\ baseline}{Patient's\ Global\ at\ baseline} \leq -0.2$
- $\frac{Physician\ Global\ at\ visit\ X - Physician\ Global\ at\ baseline}{Physician\ Global\ at\ baseline} \leq -0.2$
- $\frac{HAQ-DI\ at\ visit\ X - HAQ-DI\ at\ baseline}{HAQ-DI\ at\ baseline} \leq -0.2$
- $\frac{CRP\ at\ visit\ X - CRP\ at\ baseline}{CRP\ at\ baseline} \leq -0.2$

ACR50 response rates at Weeks 8, 16, 24, 36, and 52

ACR50 response is defined as at least a 50% improvement from baseline if meet the criteria mentioned in ACR20 above with using 0.5 instead of 0.2.

ACR70 response rates at Week 8, 16, 24, 36, and 52

ACR70 response is defined as at least a 70% improvement from baseline if meet the criteria mentioned in ACR20 above with using 0.7 instead of 0.2.

Individual components of the ACR improvement criteria on Day 1 and at Week 8, 16, 24, 36, and 52

- Swollen and tender joint count (66/68)
- Patient's assessment of pain
- Physician's global assessment of disease activity
- Patient's global assessment of disease activity
- Patient's assessment of disability (HAQ-DI)
- C-reactive protein level.

Major clinical response

Major clinical response is ACR70 response for 24 consecutive weeks. Subjects who are ACR70 responders at Week 8, 16 and 24 will be classified as a major clinical responder at Week 24; responders at Week 24, 36 and 52 will be as a major responder at Week 52.

Change from Baseline in DAS28-ESR at Week 8, 16, 24, 36, and 52

- DAS28-ESR = 0.56 x √(TJC28) + 0.28* √(SJC28) + 0.7* ln(ESR) + 0.014*GH
- Change at Visit 24 = Value of DAS28-ESR at Visit 24 – Baseline value of DAS28-ESR

Where ESR: The Erythrocyte Sedimentation Rate (in mm/h); GH: The patient global health assessment (from 0=best to 100=worst).

If ESR=0, it will be adjusted as ln(ESR+1) while calculating DAS28-ESR, i.e. ln(1)=0.

Clinical remission at Weeks 8, 16, 24, 36, and 52

Clinical remission is defined as score of Simplified Disease Activity Index (SDAI) smaller than 3.3. SDAI is calculated as following formula.

- SDAI = TJC28 + SJC28 + PtG (cm) +PyG (cm) + CRP (mg/dl)

Where TJC28 means the number of tender joints (0-28), SJC28 means the number of swollen joints (0-28), CRP means the C-Reactive Protein concentration, PtG means Patient's global assessment (from 0=best to 10=worst, 10 cm=100mm), PyG means Physician's global assessment (from 0=best to 10=worst , 10 cm=100mm).

SDAI will be considered as missing if any of the above five components is missing.

Proportion of patients with European League against Rheumatism (EULAR) response at Weeks 8 16, 24, 36, and 52

The EULAR response will be derived using the DAS28-CRP. To be classified as responders, patients should have a significant change in DAS (at least >0.6 from Baseline) and also low current disease activity. Subjects will be classified as either good, moderate or non-responder based on the following table:

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

15.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

All analyses of other secondary efficacy variables will be based on available data. No missing data will be imputed. For sensitivity analysis of ACR response, Missing ACR responses will be treated as non-responders.

15.2.3. Analysis of Secondary Efficacy Variable(s)

For all continuous efficacy variables including DAS28, each component of the ACR criteria, change from baseline of DAS28 will be summarized descriptively by treatment group and visit using n, mean, standard

deviation, median, minimum, and maximum; and analyzed as main efficacy variable by using ANCOVA model with each baseline value as covariate.

Categorical efficacy variables, such as proportion of patients with ACR20/50/70 response, major clinical response, clinical remission and EULAR response will be summarized descriptively by treatment group and visit using counts and proportions; and the Wilson Score method will be used to calculate 95% CI. All summaries of secondary efficacy variables and comparison between SAIT101 and MabThera® will be based on FAS and PP. A logistic regression method (Reeve, 2016; Appendix 5) will be employed with baseline DAS28 as covariate. All efficacy variables will be listed.

To visualize results of efficacy variables, a line chart will be developed by treatment group and visit at Week 8,16, 24, 36 and 52 for changes from baseline in DAS28-CRP based on FAS and PP; a bar chart will be created for ACR20/50/70 response by treatment groups and the visits based on FAS and PP. Besides, to evaluate impact of Mexican site 10703, the above two charts for site 10703 will be created.

15.2.4. Subgroup Analyses

The main efficacy endpoint will be repeated on following subgroups as exploratory analyses based on the FAS and the PP.

- Region – EU, US, Others
- Age group – 18-60 years, >60 years
- Gender – Female, Male
- CRP at baseline – <10, ≥10
- ADA status at baseline – Positive, Negative
- TJC≥8 and SJC≥8 at baseline

Secondary endpoints of ACR20 at Week 24 and DAS28-ESR at Week 24 will be repeated as exploratory analysis based on the FAS and the PP.

15.2.5. Exploratory Analyses for comparison between SAIT101 and Rituxan, MabThera and Rituxan

All comparison for main and secondary efficacy variables between SAIT101 and MabThera® will be repeated for MabThera® and Rituxan® and SAIT101 and Rituxan® as exploratory analyses.

15.2.6. Impact Analysis for Mexican Site 10703

An impact analysis will be performed to evaluate the impact of site 10703 on the main efficacy analysis. The impact analysis will entail adding two fixed effects to the primary model: Site10703 (Yes/No), Site10703 x Treatment interaction, and testing both effects at the two-sided 5% significance level.

16. 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.

16.1. ADVERSE EVENTS

AEs will be coded using MedDRA 19.0 or higher.

For an AE change from non-serious AE to be a serious AE, it will be treated as a continuous event and count for once only in AE summary.

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. 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 Preferred Term (PT) and each System Organ Class (SOC).

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 is classified as mild/moderate/severe (increasing severity) per eCRF. A TEAE with a missing severity will be classified as missing. If a subject reports a TEAE more than once within that SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

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 subject 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.

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 Adverse Drug Reaction (TEADRs)

An adverse drug reaction (ADR) is identified by choosing 'Related' in the question 'Causal relationship to study drug' on the Adverse Events page of the eCRF. TEAEs with a missing relationship to study drug will be regarded as "related". TEADRs will be summarized by SOC and PT, and listed.

TEAEs of Special Interest (AESI)

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. Besides, 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.

16.2. 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. 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.
- 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 each laboratory parameter.
- Overall abnormalities from Day 1: Patients with at least one abnormal (abnormal high or abnormal low) result up to Week 24, 52 after Day 1 will be considered as overall abnormal; Otherwise, patient without any abnormal result up to Week 24, 52 after Day 1 will be considered as overall normal.

Listing of all laboratory test values with the abnormal values flagged out with H (high) or L (low).

Laboratory Normal Ranges

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

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

Drug-Induced Liver Injury (DILI)

Drug-induced liver injury will be assessed through the number of possible Hy's law cases as following:

- ALT or AST > 3 × ULN, and
- ALP < 2 × ULN, and
- Total bilirubin ≥ 2 × ULN

All parameters above should be measured at the same visit. The possible Hy's law cases will be summarized and listed by treatment groups.

16.3. 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.

16.4. 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
- Shift table of incidence of abnormal values (abnormal low, normal, abnormal high), based on pre-defined abnormalities criteria, from baseline to each post-baseline visit
- 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 each laboratory parameter.
- Overall abnormalities from Day 1: Patients with at least one abnormal (abnormal high or abnormal low) result up to Week 24, 52 after Day 1 will be considered as overall abnormal; Otherwise, patient without any abnormal result up to Week 24, 52 after Day 1 will be considered as overall normal.

Vital Signs Specific Derivations

For Body Temperature (°C), conversions to oral route will be made as follows:

- Tympanic: +0.5°C
- Oral: No Adjustment
- 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: Clinically Significant Abnormal Criteria of Vital Signs

Variable	Unit	Visit	Low	High
Systolic blood pressure	mmHg	Baseline	< 90 mmHg	> 180 mmHg
		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 %

16.5. B CELL RECOVERY

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

16.6. OTHER SAFETY ASSESSMENTS

The following observations will be provided for listing only:

- Abnormal physical examination
- Chest X-ray
- QuantiFERON Gold test
- Pregnancy test
- HBV testing
- Virology Screen test

17. Immunogenicity Outcomes

The immunogenicity analyses and comparison will be performed using the SAF.

The incidence of Human anti-chimeric antibodies (HACA) and neutralizing antibody at Day 1 predose and at Weeks 1, 2, 4, 12, 16, 24, 36 and 52 will be summarized by treatment group and visit.

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

Overall positive of HACA and neutralizing antibody from Day 1 will be summarized. Patients with at least one positive result up to Week 24, 52 after Day 1 will be considered as overall positive; Otherwise, patient without any positive result up to Week 24, 52 after Day 1 will be considered as overall negative.

For the treatment difference among treatment groups listed below, the proportion, 95% CI for the proportion, proportion difference, standard deviation, and 95% CI for the proportion difference will be reported. The Wilson Score method will be used to calculate 95% CI.

- Response:
  - HACA possitive
  - HACA negative
  - Neutralizing antibody positive
  - Neutralizing antibody negative
- Treatment groups:
  - Rituxan®- Rituxan® (reference group)
  - Rituxan®- SAIT101
  - SAIT101-SAIT101
  - MabThera®-MabThera®

Listings for immunogenicity assessment data by subject will be provided.

18. Reference

Ratitch, B., & O'Kelly, M. (2011). Implementation of pattern-mixture models using standard SAS/STAT procedures. PharmaSUG, Paper-SP04.

Reeve R. Confidence interval of difference of proportions in logistic regression in presence of covariates. Statistical Methods in Medical Research. 2016. DOI : 10.1177/0962280216631583

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 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 < first IP taken date, then not TEAE If start date >= first IP taken date, then TEAE
	Partial	If start date < first IP taken date, then not TEAE If start date >= first IP taken date, then TEAE
	Missing	If start date < first IP taken date, then not TEAE If start date >= first IP taken date, 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
Partial, could be on or after first IP taken date	Known	If stop date < first IP taken date, then not TEAE If stop date >= first IP taken date, 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: If stop date < first IP taken date, then not TEAE If stop date >= first IP taken date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < first IP taken date, then not TEAE If stop date >= first IP taken date, 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: - If stop date < first IP taken date, then not TEAE

START DATE	STOP DATE	ACTION
		- If stop date >= first IP taken date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior/Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	
	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)
	Missing	
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)
	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)
	Missing	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)
Missing	Known	No imputation for missing start date
	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)
	Missing	

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.

c. **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 PPS1 and PPS2		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		

APPENDIX 4. DETAIL OF MULTIPLE IMPUTATION FOR MISSING AT RANDOM

```
proc mi data = formi2 nimpute = 100 seed = 12345 out = bocfmi1 minimum = 0;
    by trt01pn trt01p;
    var param1_1 param2_1 param3_1
        param1_2 param2_2 param3_2
        param1_3 param2_3 param3_3
        param1_4 param2_4 param3_4;
    mcmc chain = multiple impute = monotone;
run;

proc sort data = bocfmi1;
    by _imputation_ trt01pn usubjid;
run;

proc mi data = bocfmi1 out = bocfmi2 nimpute = 1 seed = 12345 minimum = 0;
    by _imputation_;
    var trt01pn param1_1 param2_1 param3_1
                param1_2 param2_2 param3_2
                param1_3 param2_3 param3_3
                param1_4 param2_4 param3_4;
    monotone regression;
run;


****Get LS means and CI;
%macro m_ancova_mi(trtn = , outn = , avar = );

ods output SolutionF = _pval_mi Diffs = _lsmeand_mi LSMeans = _lsmean_mi;

proc mixed data = ADBOCFMI;
by _imputation_;
where &trt.n in (&trtn.);
class &trt.n;
model &avar. = &trt.n avalb / solution;
lsmeans &trt.n / cl pdiff ;
run;

      proc mianalyze parms(classvar = full) = _lsmean_mi;
            class &trt.n;
            modeleffects &trt.n;
            ods output parameterestimates = lsmean_&outn.;
        run;

        proc mianalyze parms(classvar = full) = _lsmeand_mi;
            class &trt.n;
            modeleffects &trt.n;
            ods output parameterestimates = lsmeand_&outn.;
        run;

        proc mianalyze parms = _pval_mi;
            class &trt.n;
            modeleffects &trt.n avalb;
            ods output parameterestimates = pval_&outn.;
        run;
```

```
    %mend m_ancova_mi;

    ****<AVAL>;
    ****<SAIT101 vs MabThera>;
%m_ancova_mi(trtn = 1 2, outn = 1, avar = aval);
```

APPENDIX 5. DETAIL OF PORPORTION DIFFERENCE IN LOGISTICS REGRESSION

The analysis of the observed proportion difference will be based on logistic regression with subsequent transformation of the estimated parameters to the difference in proportions. The estimates from the logistic regression are on the logit scale, and the difference in proportions will be calculated as the difference between the predicted probabilities in the treatment groups on the original scale.

The method of Reeve for calculating the confidence interval will now be described in detail. We will parameterize the model in the form

$$L(E(Y_i)) = \beta_0 + \gamma\tau_i + \beta_1 x_{i1} + \ldots + \beta_k x_{ik}.$$

$$z = b_0 + b_1 x_1^* + \cdots + b_k x_k^*$$

g= γ the treatment group effect.

Let b_0, g, b_1, …, b_k, be the maximum likelihood estimates for the parameters. Then the estimator for the difference in proportions between the treatment groups can be estimated as

$$\Delta p = h(b_0 + g + b_1 x_1^* + \cdots + b_k x_k^*) - h(b_0 + b_1 x_1^* + \cdots + b_k x_k^*),$$

x_k^* is the mean value of x_{ik} over the i-subjects.

where $h = L^{-1}$. For ease of exposition, define $z = b_0 + b_1 x_1^* + \ldots + b_k x_k^*$, and define $p_\tau = h(z + g\tau)$ for $\tau = 0$ or 1. We then have $\Delta p = p_1 - p_0$. Then confidence limits x_A for A = 0.025 or 0.975 for 95% CIs and for A= 0.05 or 0.95 for 90% CIs is given by xA = FΔp(A), where FΔp(A) denotes the cumulative distribution function of Δp. This distribution function may be calculated directly using a Monte Carlo method, by simulating K realizations of (g, z) from the appropriate bivariate Normal distribution, and for each realization calculating the statistic T(g, z) = h(g + z) – h(z). Let $\theta \equiv (\bar{g}, \bar{z})$, and R the Cholesky decomposition of Var θ. If X is a K × 2 matrix, each element of which is independent, normally distributed with mean 0 and variance 1, Θ = XR + θ follows the appropriate (g, z) distribution. The cumulative density function of T(g, z) can then be generated, and the appropriate tail probabilities found.

The analysis will consist of the following two steps: (take ACR20 for example)

Step 1: Calculation of difference in proportion based on adjusted proportion

The adjusted difference of proportion in each group is estimated from the logistic regression on the logit scale. The difference in proportions is calculated as the difference between the probabilities predicted by the model for both treatment groups on the original scale.

Details:

The statistical model for the analysis of the ACR20 will be:

(M2) Logit (E{ACR20}) = treatment + baseline DAS28-CRP

The following SAS code will be used:

```
PROC GENMOD DATA= ACR20_central;
CLASS TRT;
MODEL response (event='Y') = TRT base-DAS28-CRP / dist=bin  link=logit;
      lsmeans TRT / ilink;
run;
```

The population adjusted natural scaled proportion are the estimates produced by the LSMEANS statement.

Step 2: Calculation of confidence intervals based on cumulative distribution function method of Reeve

The respective risk-difference confidences intervals are calculated using the risk difference (calculated in Step 1) and the cumulative distribution function method of Reeve with 1,00 simulations.

Details:

The difference in proportions is produced in Step 1.
The confidence intervals for the estimated difference in proportions are produced using the cumulative distribution function method of Reeve.

For completeness, the 95% and 90% CI for risk difference will also be calculated for ACR20.

The SAS code to implement the method is provided next page and require as input:

1. Variance (g) is directly provided by SAS PROC GENMOD Empirical Standard Error Estimates.

2. $Cov(b_i, b_j)$ *and* $Cov(\gamma, b_i)$ $\forall i, j \in [0; k]$ are directly provided by SAS PROC GENMOD Covariance Matrix (Empirical).

3. Variance (z) will be calculated using the formula:

$$Var(z) = Var\left(b_0 + b_1 x_1^* + \cdots + b_k x_k^*\right) = \sum_{i,j=0}^{k} x_i^* x_j^* Cov(b_i, b_j) \; where \; x_0^* = 1$$

4. Covariance (g,z) will be calculated using the formula:

$$Cov(g,z) = Cov\left(\gamma, b_0 + b_1 x_1^* + \cdots + b_k x_k^*\right) = \sum_{i=0}^{k} x_i^* \, Cov(\gamma, b_i)$$

Then VarTheta is equal to $\begin{pmatrix} Var(g) & Cov(g,z) \\ Cov(g,z) & Var(z) \end{pmatrix}$

Reference: Reeve R. Confidence interval of difference of proportions in logistic regression in presence of covariates. Statistical Methods in Medical Research. 2016. DOI : 10.1177/0962280216631583

SAS CODE FOR DIFFERENCE IN PROPORTION CIS

```
%macro m_prop_diff(trtn = , outn = );

    ****Get difference and SE CI;
    ods output RiskDiffCol1 = _riskdiff PdiffCLs = _diffcl;

    proc freq data = adeff1;
        where &trt.n in (&trtn.);
        by paramcd param paramn avisitn avisit;
        table &trt.n * aval / riskdiff(column = 1 cl = wilson equal var =
sample);
    run;

    data diff1_&outn.;
        set _riskdiff(in = a where = (strip(lowcase(row)) = "difference"))
            _diffcl(in = b);
        by paramcd param paramn avisitn avisit;
        length col4 $200;
        if a then do;
            seq = 3;
            if not missing(risk) and not missing(ase) then col4 = strip(put(risk
* 100, 8.1))||" ("||strip(put(ase * 100, 8.2))||")";
            if compress(scan(col4, 1, "(")) = "-0.0" then col4 = tranwrd(col4, "-
", "");
        end;
        if b then do;
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            seq = 4;
            if not missing(lowercl) and not missing(uppercl) then col4 =
"("||strip(put(lowercl * 100, 8.2))||", "||strip(put(uppercl * 100, 8.2))||")";
        end;
        subseq = &outn.;
    run;

    ****Get adjusted difference and SE;
    ods output LSMeans = _lsmean parameterestimates = est covb = covb diffs =
diff;

    proc genmod data = adeff1;
        where &trt.n in (&trtn.);
        by paramcd param paramn avisitn avisit;
        class &trt.n / param = GLM ref = last;
        model aval(event = '1') = &trt.n das28c_b / dist = binomial link = logit
covb;
        lsmeans &trt.n / ilink cl diff = all obsmargins;
    run;

    data diff2_&outn.;
        set _lsmean;
        by paramcd param paramn avisitn avisit;
        length col4 $200;
        mu_lag = lag(mu);
        if first.avisit then mu_lag = .;
        else if last.avisit then do;
            diff = mu_lag - mu;
            col4 = put(diff * 100, 8.1);
            if compress(col4) = "-0.0" then col4 = tranwrd(col4, "-", "");
            output;
        end;
    run;
/*%macro mtest;*/
    ****CI;
    **Get param info;
    proc sql noprint;
        select count(distinct paramn) into : paramnum from adeff1;
        select distinct paramn into : par1 - : par%sysfunc(compress(&paramnum.))
from adeff1;
    quit;

    **Get visit info;
    proc sql noprint;
        select count(distinct avisitn) into : vsnum from adeff1;
        select distinct avisitn into : vs1 - : vs%sysfunc(compress(&vsnum.)) from
adeff1;
    quit;

    **Do loop for all visits;
    %do j = 1 %to &vsnum.;

        proc sql noprint;
            select count(*) into : obsnum from diff
            where avisitn = &&vs&j.. and int(probz) ne 1
            ;
            select count(*) into : obsnum2 from est
```

```
            where avisitn = &&vs&j.. and strip(level1) = "1" and not
missing(probchisq) and round(probchisq, 0.001) < 1
            ;
        quit;
        %put &obsnum. &obsnum2.;

        %if &obsnum2. > 0 %then %do;

            data covb1;
                set covb;
                where avisitn = &&vs&j..;
            run;

            data est1;
                set est;
                where avisitn = &&vs&j..;
            run;

            proc sql noprint;
                  create table listx as
                  select 1 as mx0, mean(das28c_b) as mx1, paramn
                  from adeff1
                where &trt.n in (&trtn.) and avisitn = &&vs&j..
                group by paramn
                ;
            quit;

            proc transpose data = listx out = listx_t(drop = _name_);
                by paramn;
                  var mx0 mx1;
            run;

            data covbx;
                  set covb1;
                  if rowname = "Prm2" then delete;
                  drop prm2 rowname paramcd param avisit;
            run;

            **Do loop for each param;
            %do i = 1 %to &paramnum.;

                proc sql noprint;
                  select count(*) into: num from covbx
                    where paramn = &&par&i..;
                quit;

                  data Plistx;
                        set listx;
                    where paramn = &&par&i..;
                        drop paramn;
                run;

                  data Pcovbx;
                        set covbx;
                    where paramn = &&par&i..;
                        drop paramn avisitn;
                run;
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```
                    data Pcovb1;
                          set covb1;
                      where paramn = &&par&i..;
                          drop paramn avisitn;
                    run;

                    data Plistx_t;
                          set listx_t;
                      where paramn = &&par&i..;
                          drop paramn;
                    run;

                    proc fcmp;
                          array mat1[1,&num.]/nosymbols;
                          rc=read_array('Plistx',mat1);

                          array mat2[&num.,&num.]/nosymbols;
                          rc=read_array('Pcovbx',mat2);

                          array mat3[&num.,1]/nosymbols;
                          rc=read_array('Plistx_t',mat3);

                          array res1[1,&num.];
                          call mult(mat1,mat2,res1);

                          array result[1,1];
                          call mult(res1,mat3,result);

                          rc= write_array('varZ',result);
                    quit;


                    proc sql noprint;
                      select put(result1,best12.) into: varz from varz;
                    quit;

                    %put Varz is: &varz.;

                    data cov_g;
                        set Pcovb1;
                        keep prm2;
                        if rowname="Prm2" then delete;
                    run;

                  proc fcmp;
                      array mat1[1,&num.]/nosymbols;
                      rc=read_array('Plistx',mat1);

                      array mat2[&num.,1]/nosymbols;
                      rc=read_array('cov_g',mat2);

                      array mat3[1,1];
                      call mult(mat1,mat2,mat3);
                      rc=write_array('covGZ',mat3);
                  quit;
```

```
                proc sql noprint;
                    select put(mat31,best12.) into: covgz from covgz;
                    select put(prm2, best12.) into: varg from Pcovb1 where
rowname="Prm2";
                quit;

                proc fcmp;
                    array varcov[2,2] (&varg.,&covgz.,&covgz., &varz.);
                    rc=write_array('varcov',varcov);
                    put varcov=;
                quit;

                data prod_z;
                    set est1;
                    where paramn = &&par&i..;
                    length newvar $20;
                    newvar=strip(parameter)||strip(level1);
                run;

                  proc transpose data=prod_z out=prodz_t;
                        var estimate;
                        id newvar;
                  run;

                  data prodz_t;
                        set prodz_t;
                        X0=intercept;
                        X1=das28c_b;
                        keep x:;
                  run;

                  proc fcmp;
                        array mat1[1,&num.]/nosymbols;
                        rc=read_array('prodz_t',mat1);
                        array mat3[&num.,1]/nosymbols;
                        rc=read_array('Plistx_t',mat3);
                        array zres[1,1];
                        call mult(mat1,mat3,zres);
                        rc=write_array('zres',zres);
                  run;

                  proc sql noprint;
                        select put(estimate,best12.) into: g from est1 where
level1="1" and paramn=&&par&i..;
                        select put(zres1,   best12.) into: z from zres;
                  quit;

                  %put  estimate of g and z :  &g. &z. ;

                  %let K=1000000;
                  %let alpha=0.05;

                  proc IML;
                        theta={&G. &Z.}; print theta;
                        vartheta={&VARG. &COVGZ. , &COVGZ. &VARZ.}; print
vartheta;
                        Xc = t(root(Vartheta));
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```
                        call randseed(456);
                        X = j(&K.,2);
                        call randgen(X,"Normal");
                        X1=X[,1];
                        X2=X[,2];
                        create X var{X1 X2}; append;
                        close X;
                        Y=X*Xc;
                        G=Y[,1]+Theta[1,1];
                        Z=Y[,2]+Theta[1,2];
                        DELTA=(1/(1+exp(-(G+Z))))-(1/(1+exp(-Z)));
                        call sort(DELTA);
                        LOW=DELTA[round(&k.*(&alpha./2))]; print low;
                        UP=DELTA[&K.-round(&k.*(&alpha./2))]; print up;
                        create uplow var{low up};append;
                    quit;

                proc sql noprint;
                    select count(*) into : ulobsnum from uplow;
                quit;

                %if &ulobsnum. > 0 %then %do;
                  data uplow&j._&i.;
                        set uplow;
                        paramn  = &&par&i..;
                        avisitn = &&vs&j..;
                  run;
                %end;
                %else %do;
                  data uplow&j._&i.;
                        paramn  = &&par&i..;
                        avisitn = &&vs&j..;
                        low = .;
                        up = .;
                        output;
                  run;
                %end;

            %end;

        %end;

        %else %do i = 1 %to &paramnum.;

            data uplow&j._&i.;
                  paramn  = &&par&i..;
                avisitn = &&vs&j..;
                low = .;
                up = .;
                output;
            run;

        %end;

    %end;

    data diffci_&outn.;
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```
        set %do i = 1 %to &vsnum.;
                %do j = 1 %to &paramnum.;
                    uplow&i._&j.
                %end;
            %end;
        ;
        length col4 $200;
        if not missing(low) and not missing(up) then col4 = "("||strip(put(low *
100, 8.2))||", "||strip(put(up * 100, 8.2))||")";
    run;
/*%mend; %mtest;*/
    proc datasets library=work memtype=data nolist;
        delete uplow varcov zres prodz_t varcov varz plistx pcovbx pcovb1
plistx_t cov_g covgz varcov
        %do i = 1 %to &vsnum.;
            %do j = 1 %to &paramnum.;
                uplow&i._&j.
            %end;
        %end;
        ;
    quit;

    **Set all together;
    data stat_f;
        set diff1_&outn. (in = a)
            diff2_&outn. (in = b)
            diffci_&outn.(in = c);
        if b then seq = 5;
        if c then seq = 6;
        if missing(subseq) then subseq = &outn.;
    run;

    proc sort data = stat_f;
        by paramn avisitn subseq seq;
    run;

    data dummy;
        %do i = 1 %to &paramnum.;
            %do j = 1 %to &vsnum.;
                paramn = &&par&i..;
                avisitn = &&vs&j..;
                subseq = &outn.;
                do seq = 3 to 6;
                    output;
                end;
            %end;
        %end;
    run;

    data stat&outn.;
        merge dummy(in = a)
              stat_f;
        by paramn avisitn subseq seq;
        if a;
        if missing(col4) then do;
            if seq in (3 5) then col4 = "-(-)";
            else col4 = "(-, -)";
```

```
        end;
/*        else if seq in (4 6) and missing(col4) then col4 = "(- , -)";*/
    run;

%mend m_prop_diff;
```