2.0 SYNOPSIS

Name of Sponsor/Company: Archigen Biotech Limited

Name of Finished Product: SAIT101 (proposed rituximab biosimilar)

Name of Active Ingredient: Rituximab

Title of Study:

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

Investigators:

Sixty-six Investigators at study centers that consented at least 1 subject.

Study Centers:

Sixty-six study centers in 11 countries (Bosnia, Bulgaria, Czech Republic, Germany, Hungary, India, South Korea, Mexico, Poland, Spain, and United States) consented at least 1 subject.

Publication (Reference):

None

Study Period:	**Phase of Development:**
First Subject Enrolled: 11 October 2016 Last Subject Completed: 07 November 2018	Phase I/III

Background and Rationale for the Study:

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterized by inflammation in the synovium of joints, which is associated with progressive joint destruction, and depending on the severity, may be accompanied by systemic manifestations including lung disease, rheumatoid nodules, and effects on the cardiovascular system. B lymphocytes (B-cells) are thought to contribute considerably to the pathogenesis of RA. Rituximab is a genetically engineered recombinant chimeric human/murine antibody directed against the CD20 antigen. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis. Rituximab is marketed under the brand name Rituxan® in the United States of America (USA) and MabThera® outside the USA. SAIT101 is a proposed biosimilar product of rituximab.

Objectives:

Primary Objective:

The primary objective of the study was to compare the pharmacokinetics (PK) of SAIT101 (proposed rituximab biosimilar) versus rituximab licensed in the European Union (EU) (hereafter designated as MabThera, brand name in EU) versus rituximab licensed in the USA (hereafter designated as Rituxan, brand name in USA) in subjects with RA.

Secondary Objectives:

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

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Methodology:

This was a multicenter, randomized, double-blind, parallel group study to compare the PK, PD, safety, efficacy, tolerability, and immunogenicity of SAIT101 versus MabThera versus Rituxan in subjects with RA. This study consisted of Part A up to 24 weeks followed by Part B up to week 52. Part B also collected transition data in subjects treated with Rituxan who were eligible for a second course of treatment.

The study duration was 52 weeks.

Subjects with RA who had an inadequate response to at least 3 months' treatment (according to the approved treatment and dosage) or intolerance (at Investigator's discretion and/or experience of severe adverse event [AE] or toxicity such as infusion related reaction, hypersensitivity, anaphylaxis or severe toxicity) to anti-tumor necrosis factor (TNF) therapy participated in the study. All the screening assessments were performed within 30 days prior to randomization on Day 1 (visit 2, baseline), except in subjects who required prophylaxis of latent tuberculosis or a washout of current anti-TNF medication or other biologic and non-biologic disease-modifying antirheumatic drugs (DMARDs), (except methotrexate [MTX]). For these subjects, the screening period was extended to allow for the washout required but would not exceed beyond 60 days. In these subjects, all screening assessments were performed within 30 days prior to randomization with the exception of the informed consent and chest X-ray.

Part A - First Course:

Subjects were randomized in a 1:1:1 ratio into 3 different groups and received 1 course of SAIT101 (n = 98) versus Rituxan (n = 98) versus MabThera (n = 98). Eligible subjects moved from Part A to Part B of the study at week 24.

Each subject received the first course which included 2 intravenous (i.v.) 1000 mg study treatment infusions: the first infusion was on Day 1 (visit 2) and the second infusion on Day 15 (visit 5). Subjects received an antipyretic and an antihistamine, eg, paracetamol and diphenhydramine or equivalent before each infusion, plus 100 mg i.v. methyl prednisone prior to each infusion. The Day 1 infusion rate (both first and second courses) of SAIT101, or MabThera or Rituxan was 50 mg/hour; after the first 30 minutes, it was escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. If there was no infusion related reaction on Day 1, the Day 15 infusion (both first and second courses) was started at 100 mg/hour and increased by 100 mg/hour increments at 30 minutes intervals, to a maximum of 400 mg/hour. On Day 1 and Day 15 (first and second infusions), blood PK samples and PD samples (CD19+ B-Cell) were collected before and 3 hours after the start of infusion of the study treatment and immediately (within 10 minutes) before and 1 hour after the end of infusion and at 48 hours after the start of each infusion (Days 3 and 17).

Pharmacokinetic/PD samples were also taken at weeks 1, 4, 8, 12, 16, 20, and 24. Blood PD samples were additionally collected at weeks 36 and 52.

At week 24, subjects were evaluated for a second course of treatment. Subjects with an inadequate response (<50% improvement from baseline in both the swollen joint count [SJC] and tender joint counts [TJC]) at week 24 (visit 12), received the second course of two i.v. 1000 mg infusions (first infusion at week 24 and the second infusion at week 26 [14 days later]) of the study treatment.

Part B - Second Course:

Eligible subjects in the SAIT101 group received the second course of SAIT101 treatment at week 24 and week 26.

Eligible subjects in the MabThera group received the second course of MabThera treatment at week 24 and week 26.

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Eligible subjects in the Rituxan group were randomized in a 1:1 ratio and received either SAIT101 or Rituxan treatment at week 24 and week 26. For each course of infusion, the subjects received two i.v. doses of 1000 mg (10 mg/mL) SAIT101 or Rituxan or MabThera infusion. Drug infusions took place under the close supervision of an experienced physician, and in an environment where full resuscitation facilities were immediately available. All subjects were followed up for safety up to 52 weeks from the start date of the first infusion. Subjects visited the study center approximately every 12 weeks during Part B, from the start date of the second course of infusions. To prevent missing data in important supportive efficacy and safety analysis, subjects who were not eligible for the second course of treatment or who discontinued study treatment also attended all the visits until week 52.
Number of Subjects (Planned and Analyzed): Planned: Approximately 282 patients were to be randomized into the study, at approximately 70 investigative centers Analyzed: A total of 450 subjects were enrolled at 66 study centers, of which 294 subjects were randomized in a 1:1:1 ratio to receive 1 course of SAIT101 (n = 98) versus Rituxan (n = 98) versus MabThera (n = 98). A total of 294 subjects were randomized to Part A and 220 subjects to Part B of the study, of which 251 subjects completed the study.
Diagnosis and Main Criteria for Inclusion and Exclusion: Male and female subjects aged between 18 and 80 years with severe RA who had an inadequate response to at least 3 months' treatment (according to the approved treatment and dosage) or intolerance (at Investigator's discretion and/or experienced intolerable AEs or toxicity such as infusion related reaction, hypersensitivity, anaphylaxis or severe toxicity) to anti-TNF therapy participated in the study. Subjects were required to be on a stable weekly dose of MTX, 7.5 to 25 mg/week for at least 12 weeks, including the last 4 weeks prior to Day 1 (lower doses of MTX <10 mg/week were only permitted if subjects had documented evidence of intolerance to higher doses of MTX). Subjects who were pregnant, breastfeeding, or planning a pregnancy during the treatment period or 12 months after the last infusion of study treatment, subjects with class IV RA as per Classification of Global Functional Status in RA, and who had current inflammatory joint disease other than RA were excluded from the study.
Test Product, Dose and Mode of Administration, Batch Number: SAIT101 1000 mg (10 mg/mL) for i.v. infusion. In **Part A**, each subject received 1 course of two i.v. 1000 mg study treatment infusions: First infusion on Day 1 and the second infusion on Day 15. In **Part B**, subjects with an inadequate response (<50% improvement from baseline in SJC and TJCs at week 24 [visit 12]) received a further course of two i.v. 1000 mg drug infusions: First infusion at week 24 and the second infusion at week 26. • Eligible subjects in the SAIT101 group received the second course of SAIT101 treatment at week 24 and week 26. Batch numbers of the test product (SAIT101) are: 1035274, 1035275, 1035276, 1035277

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Comparator Drug, Dose and Mode of Administration, Batch Number:

Rituxan or MabThera 1000 mg (10 mg/mL) by i.v. infusion

In **Part A**, each subject received 1 course of two i.v. 1000 mg study treatment infusions: First infusion on Day 1 and the second infusion on Day 15.

In **Part B**, subjects with an inadequate response (<50% improvement from baseline in swollen and tender joint counts at week 24 [visit 12]) received a further course of two i.v. 1000 mg drug infusions: First infusion at week 24 and the second infusion at week 26.

- Eligible subjects in the MabThera group received additional MabThera treatment at week 24 and week 26.
- Eligible subjects in the Rituxan arm were randomized in a 1:1 ratio and received SAIT101 or Rituxan treatment at week 24 and week 26.

Batch numbers of the comparator drugs are:

Rituxan: 660696, 3063889, 3122526, 3141694

MabThera: N7089B05, N7091B01, N7103B06, N7138B03

Duration of Study:

Total study duration was up to 52 weeks for each subject, including baseline, Part A, and Part B

Criteria for Evaluation/Endpoint:

Pharmacokinetics

The PK parameters area under the concentration-time curve (AUC) from time zero to the last quantifiable concentration [$AUC_{(0\text{-}t)}$], AUC from time zero to infinity [$AUC_{(0\text{-}\infty)}$], AUC from time zero to Day 15 prior to infusion [$AUC_{(0\text{-}d15)}$], AUC from week 2 to week 24 [$AUC_{(w2\text{-}w24)}$], AUC from time zero to week 12 [$AUC_{(0\text{-}w12)}$], trough concentration before the second infusion on Day 15 (C_{trough}), maximum concentration after the first infusion ($C_{max,dose1}$), maximum concentration after the second infusion on Day 15 ($C_{max,dose2}$), time to maximum concentration after the first infusion ($t_{max,\ dose1}$), time to maximum concentration postinfusion on Day 15 ($t_{max,\ dose2}$), apparent terminal rate constant (λ_z), terminal half-life ($t_{1/2}$), systemic clearance (CL), and volume of distribution (V_D) were estimated for rituximab by noncompartmental methods using actual elapsed time from dosing, where possible.

Pharmacodynamics

The CD19+ B-cell count at the preinfusion on Day 1 was used as baseline. The PD variables depletion of CD19+ B-cell count up to week 24, time needed to B-cell depletion, duration of CD19+ B-cell depletion, percent CD19+ B-cell count versus baseline, area under the depletion-time curve of CD19+ B-cell count change at Day 15 and week 24 ($AUEC_{(0\text{-}d15)}$ and $AUEC_{(0\text{-}w24)}$, respectively), change from baseline in CD19+ B-cell count during the study period, change from baseline in immunoglobulin (Ig) IgG, IgM, and IgA levels, and change from baseline in C-reactive protein (CRP) levels at weeks 8, 16, 24, 36, and 52 were presented.

Efficacy

The main efficacy variable was the change from baseline in Disease Activity Score (DAS) based on a 28-joint count (DAS28)-CRP at week 24. The DAS28-CRP assessments consisted of TJC, SJC, and CRP.

The other efficacy variables included the change from baseline in DAS28-CRP, American College of Rheumatology 20% response criteria (ACR20), American College of Rheumatology 50% response criteria

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(ACR50), American College of Rheumatology 70% response criteria (ACR70) individual components of the ACR improvement criteria, change from baseline in DAS28- erythrocyte sedimentation rate (ESR) at week 8, 16, 24, 36, and 52; major clinical response; proportion of subjects with European League against Rheumatism (EULAR) response at weeks 8, 16, 24, 36, and 52 were estimated. The ACR20, ACR50, ACR70 were assessed by TJC, SJC, CRP, ESR, Visual Analogue Scale (VAS), and Health Assessment Questionnaire-Disability Index (HAQ-DI).

Immunogenicity (Human Anti-Chimeric Antibody and Neutralizing Antibody)

Human anti-chimeric antibodies (HACAs) (also referred to as anti-drug antibody [ADA]) and neutralizing antibody were assessed at Day 1 predose and at weeks 1, 2, 4, 12, 16, 24, 36, and 52. Serum samples in which HACA were detected, were analyzed for neutralizing antibody

Safety:

The subject's safety is evaluated based on Serious AEs (SAEs), AEs, treatment-emergent adverse events (TEAEs), adverse drug reactions (ADRs), vital signs, clinical laboratory parameters including hematology, chemistry, and urinalysis, physical findings, concomitant medications, incidence of rescue medication (where rescue medication is defined as the use of non-DMARDs after week 16 of the study), and B-cell recovery measured by a CD19+ B-cell count after week 24.

Statistical Methods:

Pharmacokinetic Analyses

Descriptive statistics were used to summarize serum rituximab concentration and PK parameter data by treatment.

Plots of the mean and individual serum rituximab concentrations over time by treatment were provided.

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

The statistical analyses of the $\log_e$-transformed primary PK parameters were based on an analysis of variance (ANOVA) model. The differences in least-squares (LS) means between each of the 3 pairs (SAIT101 vs. MabThera, SAIT101 vs. Rituxan, and MabThera vs. Rituxan) and the associated 90% confidence interval (CI) were determined. Back transformation provided the ratio of geometric means and 90% CIs for these ratios. Equivalence was concluded if the 90% CIs for the ratios of geometric means of primary PK parameters were completely contained within the acceptance interval of 80% and 125%.

A sensitivity analysis was performed for the above comparisons, with the addition of age, weight, sex, and ADA status at baseline as covariates.

Mean drug concentration-time plots for subjects with positive ADA at baseline and for subjects without positive ADA at baseline were presented to assess the impact of ADA on PK.

Pharmacodynamic Analyses

Observed, change from baseline, and percent change from baseline in CD19+ B-cell counts, PD parameters based on change from baseline and percent of baseline CD19+ B-cell counts, depletion incidence for CD19+ B-cell counts, time needed to B-cell depletion, duration of CD19+ B-cell depletion and IgG, IgM, IgA, and CRP levels were summarized using descriptive statistics.

Pharmacodynamic parameters $AUEC_{(0\text{-}d15)}$ and $AUEC_{(0\text{-}w24)}$ based on change from baseline and percent of baseline CD19+ B-cell counts were compared between SAIT101 and both MabThera and Rituxan using

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analysis of covariance that included a fixed effect for treatment and a covariate for baseline CD19+ B-cell value. Least-squares means for each treatment were presented with corresponding 95% CIs. The difference in LS means (SAIT101-MabThera and SAIT101-Rituxan and MabThera-Rituxan) were presented with corresponding 90% CIs.

Plots of mean and individual observed, change from baseline, and percent change from baseline CD19+ B-cell counts over time by treatment were provided.

To assess the impact of ADA on PD, the mean CD19+ B-cell count-time plots for subjects with positive ADA at baseline and for subjects without positive ADA at baseline were presented.

Efficacy Analyses

The change from baseline in DAS28-CRP at week 24 was considered as the main efficacy endpoint.

Two-sided 95% CI for the difference between SAIT101 and MabThera, in DAS28-CRP change from baseline at week 24 was computed from an analysis of covariance using baseline DAS28-CRP as covariate and treatment as model factors. Equivalence was concluded if the 95% CI for the mean difference for main endpoint was completely within the equivalence margin of −0.6 to 0.6. Both Per-Protocol Set (PPS) and Full Analysis Set (FAS) were considered as the efficacy analysis population and no missing data were imputed for the efficacy analyses in FAS.

Continuous variables were summarized using N, mean, standard deviation (SD), minimum, median, and maximum. Categorical variables were summarized using frequency counts and percentages.

Immunogenicity Analyses

Incidence of HACA and neutralizing antibody and summary of counts of antibodies per subject prior to first dose on Day 1 and at week 1, 2, 4, 12, 16, 24, 36, and 52 were summarized overall and by treatment group.

Safety Analyses

All reported terms for AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA 21.1). No statistical testing was performed for AEs. For all AE and SAE tables, subjects were counted at most once for each Preferred Term (PT) and each System Organ Class (SOC). Adverse events were summarized by the number and percentage of subjects experiencing events by SOC, PT, and severity.

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

The incidence of B-cell recovery and CD19+ B-cell count per subject was summarized at each visit, overall and by treatment group.

Interim Analysis

An interim analysis was performed with the safety data of 10 subjects per group (30 subjects in total), collected up to week 4.

Sample Size

A percentage coefficient of variation (CV%) ranging from 26.3% to 37.3% for the 5 co-primary parameters was assumed for this study based on a recent study in RA subjects treated with rituximab (REFLEX study).

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When the evaluable sample size in each group is 84, a 3 group design had 81% power to reject both the null hypothesis that the ratio of test to standard geometrics means was below 0.800, and the null hypothesis that the ratio of test to standard geometrics means was above 1.250 (ie, that the test and standard were not equivalent), in favor of the alternative hypothesis, that the means of the 2 groups were equivalent, assuming that the expected ratio of means was 1.000, the CV% for the standard was 0.330, that data were analyzed in the log scale using ANOVA and that each 1-sided test was made at the 5% level. Each of the 15 hypotheses tests (5 co-primary endpoints × 3 pairwise comparisons) were powered at 98% to 99% to yield 81% study-wide power.

A total of 282 subjects (94 subjects per group) were planned to be randomized in order to yield a minimum of 84 subjects per group to account for a presumed 10% withdrawal.

A total of 94 subjects in the SAIT101 group and MabThera group provided 96% probability of declaring equivalence in FAS with each 1-sided test at 2.5% level, accounting for a presumed 1.0 SD of DAS28 from an earlier study, and the equivalence margin of −0.6 to 0.6 chosen as half of a clinical meaningful improvement of 1.2 in DAS28. Considering 18% withdrawal from the REFLEX study, approximately 77 subjects per group provided approximately 91% probability of declaring equivalence in the PPS.

Summary – Conclusions:

Disposition and Demography:

This was a multicenter, randomized, double-blind, parallel group study conducted in 11 countries to compare the PK, PD, safety, efficacy, tolerability, and immunogenicity of SAIT101 versus MabThera versus Rituxan in subjects with RA. A total of 294 subjects were randomized to Part A and 220 subjects to Part B of the study of which 251 subjects completed the study.

The mean age of all subjects was 51.8 years (ranging from 21 to 79 years). There were a higher proportion of females 240 (81.6%) vs males 54 (18.4%) who participated in the study.

Pharmacokinetic Results:

Rituximab exposure and disposition PK parameters were comparable for all 3 treatment groups. Median t_{max} was comparable across all 3 treatments with the median ranging between 4.500 to 5.167 hours following infusion 1 and 4.167 to 4.250 hours following infusion 2. Geometric mean $t_{1/2}$ estimates were similar for all treatments and ranged between 303.7 and 319.7 hours. Similarly, CL and V_D were comparable between treatments.

Pharmacokinetic equivalence was demonstrated for all treatment comparisons (SAIT101 versus MabThera, SAIT101 versus Rituxan, and MabThera versus Rituxan) for the primary PK parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-d15)}$, and $C_{max,dose2}$ with the 90% CIs being fully contained within the standard acceptance limits for equivalence (80.00% to 125.00%). For C_{trough}, the comparison of SAIT101 versus Rituxan also demonstrated equivalence, but for the SAIT101 versus MabThera and MabThera versus Rituxan comparison, the 90% CIs extended either below or above the standard acceptance limits. Similar results were observed for the sensitivity analysis, which included age, weight, sex, and ADA status at baseline as covariates.

The results of the assessment of PK equivalence for the primary PK parameters are summarized in the table below.

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Parameter (units)	Treatment	n	GLS Mean	Statistical Comparisons GLS Mean Ratio (90% CI) (%)		
				SAIT101/ MabThera	SAIT101/ Rituxan	MabThera/ Rituxan
$AUC_{(0-t)}$ (h*µg/mL)	SAIT101	79	144500	95.33 (87.07, 104.37)	93.48 (85.54, 102.15)	98.06 (89.49, 107.45)
	MabThera	70	151600			
	Rituxan	76	154600			
$AUC_{(0-\infty)}$ (h*µg/mL)	SAIT101	93	152300	94.07 (86.91, 101.81)	94.39 (87.21, 102.16)	100.35 (92.68, 108.65)
	MabThera	91	161900			
	Rituxan	91	161300			
$AUC_{(0-d15)}$ (h*µg/mL)	SAIT101	91	42950	96.31 (90.52, 102.46)	98.65 (92.64, 105.05)	102.43 (96.14, 109.14)
	MabThera	88	44600			
	Rituxan	83	43540			
$C_{max, dose\ 2}$ (µg/mL)	SAIT101	94	406.0	94.93 (89.03, 101.23)	98.75 (92.61, 105.30)	104.03 (97.54, 110.95)
	MabThera	93	427.7			
	Rituxan	93	411.1			
C_{trough} (µg/mL)	SAIT101	83	60.35	89.08 (77.20, 102.79)	102.56 (88.72, 118.56)	115.13 (99.51, 133.21)
	MabThera	81	67.75			
	Rituxan	77	58.84			

Abbreviations: CI: Confidence interval; GLS: Geometric least-squares
The statistical comparison of the $\log_e$-transformed primary parameters between treatments is based on an analysis of variance model with fixed effect for treatment.
Source: Table 14.3.6-3.1

In an impact analysis excluding two subjects with unusual C_{trough} concentrations, pharmacokinetic equivalence was demonstrated for all primary PK parameters for all treatment comparisons.

Pharmacodynamic Results:

CD19+ B-cells rapidly depleted and a long duration of depletion (median of >166 days based on truncated data at week 24) was observed across all treatment groups. The proportion of subjects with CD19+ B-cell count depletion was comparable across treatment groups in Part A of the study up to week 20. At week 24, the proportion of subjects with depletion was 71.4% (SAIT101), 78.0% (MabThera) and 84.7% (Rituxan).

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In Part A, the mean observed, change and percent change from baseline CD19+ B-cell count versus time profiles were comparable across all 3 treatment groups. Mean CD19+ B-cell count decreased by greater than 85% of baseline by the end of infusion on Day 1 for all treatments. The majority of subjects had not recovered by week 24 when recovery was defined as either CD19+ B-cell counts returned to baseline or the lower limit of normal of 110 cells/μL. Overall from Day 1 until week 24, a comparable proportion of subjects recovered (5.4% [SAIT101], 4.3% [MabThera], and 3.3% [Rituxan]).

In Part B, the arithmetic mean CD19+ B-cell count versus time profiles were generally comparable for treatment groups receiving a second course of therapy in Part B with sustained depletion of CD19+ B-cell counts up to week 52. CD19+ B-cell counts started to recover for subjects who were not receiving a second course of therapy in Part B.

There was no apparent difference in CD19+ B-cell depletion for SAIT101, MabThera or Rituxan based on change from baseline CD19+ B-cell PD parameter data. The 90% CIs for the difference in change from baseline and normalized change from baseline $AUEC_{(0\text{-}d15)}$ and $AUEC_{(0\text{-}w24)}$ between treatments included the value 0. Similarly, no statistical difference was observed for $AUEC_{(0\text{-}d15)}$ based on percent of baseline data. However, statistically significant treatment differences (at the level of 0.10) were observed for the SAIT101 versus MabThera and SAIT101 versus Rituxan comparison for $AUEC_{(0\text{-}w24)}$ based on percent of baseline data.

The mean Ig and CRP concentrations were decreased throughout the study with no apparent treatment differences.

Efficacy Results:

The efficacy parameters were summarized using the FAS population and analyses in the PPS were used as supportive analysis to confirm the robustness of the results in the FAS.

Treatment equivalence was achieved between SAIT101, MabThera, and Rituxan for the main efficacy endpoint of DAS28-CRP at week 24, as demonstrated by 95% CI of the treatment difference being contained within the predefined equivalence range of − 0.6 to 0.6. The DAS28-CRP values were within the specified margin at all timepoints (weeks 8, 16, 36, and 52). The results of sensitivity analyses using last observation carried forward (LOCF), baseline-observation-carried-forward (BOCF), BOCF with multiple imputation, BOCF without imputation methods revealed that the results were similar to the results from the analysis of covariance (ANCOVA) model analysis. Results in the subgroups were comparable to the results in the overall population.

The DAS28-ESR values were within the specified margin at all timepoints (weeks 8, 16, 24, 36 and 52). The results of ANCOVA analysis and subgroup analysis of DAS28-ESR at week 24, revealed similar results to the DAS28-CRP analysis. Hence the DAS-28-ESR results support the results from DAS28-CRP and further confirmed that the treatment groups did not differ significantly.

ACR20 response rates were around the expected response rates based on previous studies with rituxan, and the number of subjects with improvement in response rates did not differ significantly in all 3 treatment groups. The results of the subgroup analysis were comparable to the results in overall population. The 95% CIs for the LS mean difference included 0 at all timepoints, indicating that the treatments did not differ significantly with respect to the ACR20 response rate.

The time course of improvement in ACR50 and ACR70 response rates at week 8, 16, 24, 36, and week 52 was similar to ACR20 response and was comparable between treatments. Improvement in individual components of the ACR improvement criteria from baseline was similar to ACR response rate. ACR20, ACR50, and ACR70 response rates are around the expected response rates based on previous studies with rituxan, and the 3 treatment groups showed similar results.

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The number of subjects with good EULAR response was comparable across all 3 treatment groups. Clinical remission was noted in very small number of subjects (<5 at week 24 and ≤5 at week 52).

Immunogenicity Results:

There was no difference in the proportions of patients experiencing adverse drug reactions overall; 14/48 (29.2%) for subjects who had a least 1 positive HACA result and 69/246 (28.0%) in subjects who had no positive HACA results.

Only 1/32 subjects in the Rituxan-SAIT101 single transition group who was not HACA positive following completion of dosing with Rituxan and prior to dosing with SAIT101 tested positive for HACA following dosing with SAIT101.

Safety Results:

The safety analysis was assessed using the safety analyses set population.

A total of 217 subjects (73.8%) experienced at least one AE during the study. A total of 213 subjects had 584 TEAEs (68 [69.4%subjects in the SAIT101 group, 70 [71.4%] subjects in the MabThera group and 75 [76.5%] subjects in the Rituxan group). The incidence of TEAEs were similar among the 3 treatment groups.

The most frequently reported primary SOCs were infections and infestations with an overall incidence of 32.0% (33.7% SAIT101 versus 28.6% MabThera versus 33.7% Rituxan). At the PT level, the most frequently reported AEs were urinary tract infection (13.3% SAIT101 versus 4.1% MabThera versus 8.2% Rituxan); upper respiratory tract infection (5.1% SAIT101 versus 8.2% MabThera versus 5.1% Rituxan), and nasopharyngitis (7.1% SAIT101 versus 3.1% MabThera versus 7.1% Rituxan). The incidence of AEs and the frequency of occurrence were similar among all 3 treatment groups.

The majority of the TEAEs reported in the study were considered as mild in severity. The percentage of subjects with mild and moderate TEAEs were comparable across the 3 treatment groups.

A total of 33 SAEs were reported in 27 (9.2%) subjects (7 [7.1%] subjects in each SAIT101 and MabThera group, and 13 [13.3%] subjects in the Rituxan group) during the study. The incidence of SAEs was similar in the SAIT101 and MabThera group but was higher in the Rituxan group. One subject from the Rituxan group died during the study period.

There were no clinically meaningful changes in mean values from baseline to assessment timepoints for hematology, clinical chemistry, and urinalysis parameters across the treatment groups. Analyses of vital sign and physical findings did not reveal any clinically relevant difference across the treatment groups.

Of the total 294 subjects, one subject (0.3%) used rescue medication (hydroxychloroquine) after week 16 of the study.

Conclusion:

Pharmacokinetic equivalence was demonstrated for the SAIT101 versus Rituxan comparison for all primary PK parameters. For the SAIT101 versus MabThera and MabThera versus Rituxan comparisons, all PK parameters except for C_{trough} were also within the predefined equivalence margins. An impact analysis demonstrated that this result may be driven by two subjects with unusual C_{trough} values; after exclusion of these subjects all primary PK parameters were within the standard acceptance limits for equivalence for all treatment comparison. Generally, the difference between MabThera and SAIT101 or Rituxan C_{trough} observed in the primary analysis, was considered to be clinically unimportant when evaluated in conjunction with all the other PK parameters, PD, efficacy and safety assessments, which all showed similarity between treatment arms.

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Name of Finished Product: SAIT101 (proposed rituximab biosimilar)

Name of Active Ingredient: Rituximab

There was no apparent difference in CD19+ B-cell counts for SAIT101, MabThera, or Rituxan based on change from baseline CD19+ B-cell PD parameter data.

CD19+ B-cell depletion was rapid and a long duration of depletion (median of >166 days based on truncated data at week 24) was observed across all treatment groups. Comparable proportions of patients achieved B-cell depletion across all treatment groups.

The majority of patients, in comparable proportions across each treatment, showed no B-cell recovery by week 24 and no clear difference between treatment arms was evident.

Therapeutic equivalence was demonstrated between SAIT101, MabThera and Rituxan based on change from baseline in DAS28-CRP at week 24. This is supported by the other efficacy parameters assessed.

No clinically relevant differences in immunogenicity assessments were noted in this study between the treatments evaluated, including immunogenicity assessments after a single transition to from Rituxan to SAIT101.

No clinically relevant differences in the adverse event profile, laboratory testing, vital signs or ECG evaluation were noted in this study between the treatments evaluated.

In summary, bioequivalence of SAIT101 to the marketed drugs was concluded based on PK, PD, efficacy, safety, and immunogenicity in subjects with RA.

Date and Version of Report: 24 July 2019, Version 1.0.