



Clinical trial results:

A Randomized, Double-blind, Parallel Group, Multicenter Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy of SALT101 versus MabThera® versus Rituxan® in Patients with Rheumatoid Arthritis (RA).

Summary

EudraCT number	2014-005368-13
Trial protocol	DE HU ES CZ IT
Global end of trial date	07 November 2018

Results information

Result version number	v1 (current)
This version publication date	13 November 2019
First version publication date	13 November 2019
Summary attachment (see zip file)	AGB001 CSR Synopsis (agb-001-synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	AGB001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02819726
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Archigen Biotech Limited
Sponsor organisation address	1 Francis Crick Avenue, Cambridge, United Kingdom, CB2 0AA
Public contact	Medical Director, Archigen Biotech Limited, +44 2037495000, info@archigenbio.com
Scientific contact	Medical Director , Archigen Biotech Limited, +44 2037495000, info@archigenbio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2018
Global end of trial reached?	Yes
Global end of trial date	07 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and applicable laws and regulations.

Background therapy: -

Evidence for comparator:

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

Rituximab was initially developed and was approved under the trade name Rituxan® by the United States Food and Drug Administration (USFDA) in 1997. Rituxan was co-developed and marketed in the United States of America (USA) under the brand name Rituxan. It is marketed outside the USA by Roche under the brand name MabThera®.

Both Mabthera and Rituxan were used as comparators in this clinical study to explore the biosimilarity of SAIT101 in RA to these licenced products.

Actual start date of recruitment	11 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 57
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	United States: 28

Country: Number of subjects enrolled	Mexico: 69
Country: Number of subjects enrolled	Bosnia and Herzegovina: 7
Country: Number of subjects enrolled	India: 46
Worldwide total number of subjects	294
EEA total number of subjects	130

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	222
From 65 to 84 years	72
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a global study conducted in 66 study centres. The first patient entered the study on 11 October 2019 and the date of the last patients last study visit was 07 November 2019.

Pre-assignment

Screening details:

All the screening assessments were performed within 30 days prior to randomization on Day 1 (visit 2, baseline). A total of 463 patients were screened for the study and 294 were randomised to study treatment (i.e. there were 169 screen failures).

Period 1

Period 1 title	Part A
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

This was a double-blind study. Subjects, Investigators, the Joint Assessor, and other site personnel remained blinded throughout the entire study period except for the study Pharmacist or designee. The IXRS was used to manage randomization to the treatment groups in a blinded manner.

Arms

Are arms mutually exclusive?	Yes
Arm title	SAIT101

Arm description:

1000 mg iv SAIT101 on Days 1 and 5 (Part A)

Arm type	Experimental
Investigational medicinal product name	SAIT101
Investigational medicinal product code	
Other name	Biosimilar rituxumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The selected dose of SAIT101 test product, 1000 mg (10 mg/mL) was as per the authorized dosing schedule and the dose administered during the conduct of this study was within the therapeutic range for the treatment or prevention of RA.

The Day 1 infusion rate (on both week 0 and week 24) of SAIT101 was started at 50 mg/hour; after the first 30 minutes, it was escalated in 50 mg/hour incremented every 30 minutes, to a maximum of 400 mg/hour.

Arm title	MabThera
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Arm description:

1000 mg iv MabThera on Day 1 and 15 (Part B). 1000 mg iv Mabthera on Week 24 and 26 (Part B) for edible subjects.

Arm type	Active comparator
Investigational medicinal product name	Mabthera
Investigational medicinal product code	
Other name	Rituximab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg iv MabThera on Day 1 and 15 (Part A). 1000 mg iv MabThera on Week 24 and 26 for eligible

subjects.

Arm title	Rituxan
Arm description: 1000 mg iv Rituxan on Days 1 and 15 (Part A) and 1000 mg iv Rituxan on Weeks 24 and 26 (Part B) for eligible subjects.	
Arm type	Active comparator
Investigational medicinal product name	Rituxan
Investigational medicinal product code	
Other name	Rutuximab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The comparator drugs Rituxan are approved by FDA and European Medicines Agency, respectively for the treatment of RA at dose of two 1000 mg infusions on Day 1 and Day 15.

The Day 1 infusion rate (on both week 0 and week 24) of Rituxan was started at 50 mg/hour; after the first 30 minutes, it was escalated in 50 mg/hour incremented every 30 minutes, to a maximum of 400 mg/hour.

Number of subjects in period 1	SAIT101	MabThera	Rituxan
Started	98	98	98
Completed	92	88	87
Not completed	6	10	11
Consent withdrawn by subject	3	5	6
Lost to follow-up	-	1	-
Protocol deviation	3	4	5

Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

This was a double-blind study. Subjects, Investigators, the Joint Assessor, and other site personnel remained blinded throughout the entire study period except for the study Pharmacist or designee. The IXRS was used to manage randomization to the treatment groups in a blinded manner.

Arms

Are arms mutually exclusive?	Yes
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Arm title	SAIT101
Arm description: 1000 mg iv SAIT101 on Days 1 and 5 (Part A)	
Arm type	Experimental
Investigational medicinal product name	SAIT101
Investigational medicinal product code	
Other name	Biosimilar rituxumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The selected dose of SAIT101 test product, 1000 mg (10 mg/mL) was as per the authorized dosing schedule and the dose administered during the conduct of this study was within the therapeutic range for the treatment or prevention of RA.

The Day 1 infusion rate (on both week 0 and week 24) of SAIT101 was started at 50 mg/hour; after the first 30 minutes, it was escalated in 50 mg/hour incremented every 30 minutes, to a maximum of 400 mg/hour.

Arm title	MabThera
Arm description: 1000 mg iv MabThera on Day 1 and 15 (Part A). 1000 mg iv Mabthera on Week 24 and 26 (Part B) for edible subjects.	
Arm type	Active comparator
Investigational medicinal product name	Mabthera
Investigational medicinal product code	
Other name	Rituxamab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg iv MabThera on Day 1 and 15 (Part A). 1000 mg iv MabThera on Week 24 and 26 for eligible subjects.

Arm title	Rituxan
Arm description: 1000 mg iv Rituxan on Days 1 and 15 (Part A) and 1000 mg iv Rituxan on Weeks 24 and 26 (Part B) for eligible subjects.	
Arm type	Active comparator
Investigational medicinal product name	Rituxan
Investigational medicinal product code	
Other name	Rutuximab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The comparator drugs Rituxan are approved by FDA and European Medicines Agency, respectively for the treatment of RA at dose of two 1000 mg infusions on Day 1 and Day 15.

The Day 1 infusion rate (on both week 0 and week 24) of Rituxan was started at 50 mg/hour; after the first 30 minutes, it was escalated in 50 mg/hour incremented every 30 minutes, to a maximum of 400 mg/hour.

Number of subjects in period 2^[1]	SAIT101	MabThera	Rituxan
Started	73	70	98
Completed	69	62	87
Not completed	4	8	11
Consent withdrawn by subject	2	3	6
Lost to follow-up	1	2	-
Protocol deviation	1	3	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: SAIT101 Arm: 19 patients completing Part A were not eligible for Part B

MabThera Arm: 19 patients completing Part A were not eligible for Part B

Rituxan arm: 10 patients participating in Part A were not eligible for Part B

Baseline characteristics

Reporting groups

Reporting group title	SAIT101
Reporting group description: 1000 mg iv SAIT101 on Days 1 and 5 (Part A)	
Reporting group title	MabThera
Reporting group description: 1000 mg iv MabThera on Day 1 and 15 (Part B). 1000 mg iv Mabthera on Week 24 and 26 (Part B) for edible subjects.	
Reporting group title	Rituxan
Reporting group description: 1000 mg iv Rituxan on Days 1 and 15 (Part A) and 1000 mg iv Rituxan on Weeks 24 and 26 (Part B) for eligible subjects.	

Reporting group values	SAIT101	MabThera	Rituxan
Number of subjects	98	98	98
Age categorical Units: Subjects			
Adults (18-60 years)	76	75	71
Adults (>60 years)	22	23	27
Age continuous Units: years			
arithmetic mean	50.9	52.5	52.1
standard deviation	± 12.41	± 10.87	± 12.09
Gender categorical Units: Subjects			
Female	79	81	80
Male	19	17	18
Race Units: Subjects			
American Indian or Alaskan Native	24	20	21
Asian	18	19	24
Native Hawaiian or Other Pacific Islander	0	0	0
Black of African American	2	0	1
White	52	56	52
More than one race	2	3	0
Unknown or not reported	0	0	0
Anti-drug Antibody (ADA) Status Units: Subjects			
ADA Positive	2	1	4
ADA Negative	96	97	94
Disease Duration Units: Years			
arithmetic mean	9.8	11.2	9.3
standard deviation	± 6.73	± 7.72	± 7.10
C-Reactive Protein (CRP) Units: mg/L			
arithmetic mean	19.5	15.3	16.2

standard deviation	± 28.99	± 20.63	± 17.91
Erythrocyte Sedimentation Rate (ESR) Units: mm/hr			
arithmetic mean	51.0	47.5	51.5
standard deviation	± 26.58	± 22.87	± 23.35
Swollen Joint Count (SJC66) Units: Number analysed			
arithmetic mean	15.2	15.2	13.0
standard deviation	± 7.97	± 7.01	± 6.19
Tender Joint Count (TJC68) Units: Tender Joint Count			
arithmetic mean	21.7	22.6	20.0
standard deviation	± 11.08	± 13.66	± 10.84
Patient Global Assessment Visual Analogue Scale (VAS) Score Units: mm			
arithmetic mean	68.9	67.6	70.8
standard deviation	± 15.87	± 17.53	± 17.04
Physicain Global Assessment VAS Score Units: mm			
arithmetic mean	71.0	69.4	69.8
standard deviation	± 14.3	± 15.9	± 14.32
Patient Pain Assessment VAS Score Units: mm			
arithmetic mean	67.0	68.8	70.7
standard deviation	± 18.71	± 20.02	± 19.06
Health Assessment questionnaire Disability Index (HAQ-DI) Units: Score			
arithmetic mean	1.7	1.7	1.6
standard deviation	± 0.57	± 0.64	± 0.64
Disease Activity Score (DAS-28-CRP)			
Disease activity score based on a 28-joint count-C-Reactive Protein (DAS-28-CRP)			
Units: Score			
median	5.28	5.29	5.17
standard deviation	± 0.890	± 0.807	± 0.833
Disease Activity Score (DAS-28-ESR)			
Disease activity score based on a 28-joint count - Erythrocyte Sedimentation Rate (DAS-28-ESR).			
Units: Score			
arithmetic mean	6.54	6.53	6.48
standard deviation	± 0.844	± 0.781	± 0.758
Height Units: cm			
arithmetic mean	162.6	161.3	163.3
standard deviation	± 9.29	± 8.79	± 8.37
Weight Units: kg			
arithmetic mean	73.0	71.9	71.6
standard deviation	± 17.62	± 16.94	± 17.99
Body Mass Index (BMI) Units: kg/m2			
arithmetic mean	27.5	27.5	26.7

standard deviation	± 5.48	± 5.46	± 5.95
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Reporting group values	Total		
Number of subjects	294		
Age categorical Units: Subjects			
Adults (18-60 years)	222		
Adults (>60 years)	72		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	240		
Male	54		
Race Units: Subjects			
American Indian or Alaskan Native	65		
Asian	61		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	3		
White	160		
More than one race	5		
Unknown or not reported	0		
Anti-drug Antibody (ADA) Status Units: Subjects			
ADA Positive	7		
ADA Negative	287		
Disease Duration Units: Years arithmetic mean standard deviation	-		
C-Reactive Protein (CRP) Units: mg/L arithmetic mean standard deviation	-		
Erythrocyte Sedimentation Rate (ESR) Units: mm/hr arithmetic mean standard deviation	-		
Swollen Joint Count (SJC66) Units: Number analysed arithmetic mean standard deviation	-		
Tender Joint Count (TJC68) Units: Tender Joint Count arithmetic mean			

standard deviation	-		
Patient Global Assessment Visual Analogue Scale (VAS) Score Units: mm arithmetic mean standard deviation	-		
Physicain Global Assessment VAS Score Units: mm arithmetic mean standard deviation	-		
Patient Pain Assessment VAS Score Units: mm arithmetic mean standard deviation	-		
Health Assessment questionnaire Disability Index (HAQ-DI) Units: Score arithmetic mean standard deviation	-		
Disease Activity Score (DAS-28-CRP)			
Disease activity score based on a 28-joint count-C-Reactive Protein (DAS-28-CRP)			
Units: Score median standard deviation	-		
Disease Activity Score (DAS-28-ESR)			
Disease activity score based on a 28-joint count - Erythrocyte Sedimentation Rate (DAS-28-ESR).			
Units: Score arithmetic mean standard deviation	-		
Height Units: cm arithmetic mean standard deviation	-		
Weight Units: kg arithmetic mean standard deviation	-		
Body Mass Index (BMI) Units: kg/m2 arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	SAIT101
Reporting group description: 1000 mg iv SAIT101 on Days 1 and 5 (Part A)	
Reporting group title	MabThera
Reporting group description: 1000 mg iv MabThera on Day 1 and 15 (Part B). 1000 mg iv Mabthera on Week 24 and 26 (Part B) for edible subjects.	
Reporting group title	Rituxan
Reporting group description: 1000 mg iv Rituxan on Days 1 and 15 (Part A) and 1000 mg iv Rituxan on Weeks 24 and 26 (Part B) for eligible subjects.	
Reporting group title	SAIT101
Reporting group description: 1000 mg iv SAIT101 on Days 1 and 5 (Part A)	
Reporting group title	MabThera
Reporting group description: 1000 mg iv MabThera on Day 1 and 15 (Part A). 1000 mg iv Mabthera on Week 24 and 26 (Part B) for edible subjects.	
Reporting group title	Rituxan
Reporting group description: 1000 mg iv Rituxan on Days 1 and 15 (Part A) and 1000 mg iv Rituxan on Weeks 24 and 26 (Part B) for eligible subjects.	

Primary: Area under the concentration time curve from Time 0 to the last quantifiable concentration (AUC0-t)

End point title	Area under the concentration time curve from Time 0 to the last quantifiable concentration (AUC0-t)
End point description:	
End point type	Primary
End point timeframe: Base line (time zero = pre-dose Day 1) to the time of the last quantifiable plasma concentration.	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	70	76	
Units: h*µg/mL				
geometric mean (geometric coefficient of variation)	144500 (± 34.2)	151600 (± 33.2)	154600 (± 35.6)	

Attachments (see zip file)	Primary PK Forest Plots (SAIT101 v MabThera).PNG Primary PK Forest Plots (SAIT101 v Rituxan).PNG Primary PK Forest Plots (MabThera v Rituxan).PNG
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Statistical analyses

Statistical analysis title	SAIT101:MabThera (AUC0-t)
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Statistical analysis description:

GLS Mean Ratio of AUC(0-t) SAIT101 vs MabThera. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment

Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	equivalence ^[1]
Parameter estimate	GLS Mean Ratio
Point estimate	95.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.07
upper limit	104.37

Notes:

[1] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Statistical analysis title	SAIT101:Rituxan (AUC0-t)
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Statistical analysis description:

GLS Mean Ratio of AUC(0-t) SAIT101 vs Rituxan.

The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment

Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	equivalence ^[2]
Parameter estimate	GLS Mean Ratio
Point estimate	93.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	85.54
upper limit	102.15

Notes:

[2] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Statistical analysis title	MabThera:Rituxan (AUC0-t)
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Statistical analysis description:

GLS Mean Ratio of AUC(0-t) MabThera vs Rituxan. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed

effect for treatment

Comparison groups	MabThera v Rituxan
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	equivalence ^[3]
Parameter estimate	GLS Mean Ratio
Point estimate	98.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	89.49
upper limit	107.45

Notes:

[3] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Primary: Area under the concentration time curve from Time 0 to the last quantifiable concentration (AUC0 ∞)

End point title	Area under the concentration time curve from Time 0 to the last quantifiable concentration (AUC0 ∞)
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End point description:

End point type	Primary
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End point timeframe:

Baseline (time zero = pre-dose Day 1) to infinity (∞).

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	91	91	
Units: h* μ g/mL				
geometric mean (geometric coefficient of variation)	152300 (\pm 34.6)	161900 (\pm 32.2)	161300 (\pm 33.3)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera (AUC0- ∞)
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Statistical analysis description:

GLS Mean Ration of (AUC0- ∞) SAIT101 vs MabThera. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.

Comparison groups	SAIT101 v MabThera
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Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	equivalence ^[4]
Parameter estimate	GLS Mean Ratio
Point estimate	94.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	86.91
upper limit	101.81

Notes:

[4] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Statistical analysis title	SAIT101:Rituxan (AUC0-∞)
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Statistical analysis description:

GLS Mean Ration of (AUC0-∞) SAIT101 vs Rituxan. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.

Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	equivalence ^[5]
Parameter estimate	GLS Mean Ratio
Point estimate	94.39
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.21
upper limit	102.16

Notes:

[5] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Statistical analysis title	MabThera:Rituxan (AUC0-∞)
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Statistical analysis description:

GLS Mean Ration of (AUC0-∞) MabThera vs Rituxan. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.

Comparison groups	MabThera v Rituxan
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	equivalence ^[6]
Parameter estimate	GLS Mean Ratio
Point estimate	100.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	92.68
upper limit	108.65

Notes:

[6] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Primary: Area under the concentration time curve from Time 0 to Dat 15 (AUC0-D15))

End point title	Area under the concentration time curve from Time 0 to Dat 15 (AUC0-D15))
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End point description:

End point type	Primary
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End point timeframe:

Baseline (pre-dose, Day 1) to pre-dose Day 15 (Part A).

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	88	83	
Units: h*µg/mL				
geometric mean (geometric coefficient of variation)	42950 (± 26.7)	44600 (± 25.6)	43540 (± 24.1)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera (AUC0-D15)
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Statistical analysis description:

GLS Mean Ration of (AUC0-D15) SAIT101 vs MabThera. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.

Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	equivalence ^[7]
Parameter estimate	GLS Mean Ratio
Point estimate	96.31
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.52
upper limit	102.46

Notes:

[7] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Statistical analysis title	SAIT101:Rituxan (AUC0-D15)
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Statistical analysis description:

GLS Mean Ration of (AUC0-D15) SAIT101 vs Rituxan. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.

Comparison groups	SAIT101 v Rituxan
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Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	equivalence ^[8]
Parameter estimate	GLS Mean Ratio
Point estimate	96.31
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.52
upper limit	102.46

Notes:

[8] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Statistical analysis title	MabThera:Rituxan (AUC0-D15)
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Statistical analysis description:

GLS Mean Ratio of (AUC0-D15) MabThera vs Rituxan. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.

Comparison groups	MabThera v Rituxan
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	equivalence ^[9]
Parameter estimate	GLS Mean Ratio
Point estimate	102.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	96.14
upper limit	109.14

Notes:

[9] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Primary: Maximum Plasma Concentration (Cmax) after Day 15 infusion

End point title	Maximum Plasma Concentration (Cmax) after Day 15 infusion
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End point description:

End point type	Primary
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End point timeframe:

Cmax value after Day 15 infusion (Dose 2)

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	93	93	
Units: µg/mL				
geometric mean (geometric coefficient of variation)	406.0 (± 28.3)	427.7 (± 28.3)	411.1 (± 24.5)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera (Cmax)
Statistical analysis description: GLS Mean Ratio of Cmax SAIT101 vs MabThera. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	equivalence ^[10]
Parameter estimate	GLS Mean Ratio
Point estimate	94.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	89.03
upper limit	101.23

Notes:

[10] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Statistical analysis title	SAIT101:Rituxan (Cmax)
Statistical analysis description: GLS Mean Ratio of Cmax SAIT101 vs Rituxan. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	equivalence ^[11]
Parameter estimate	GLS Mean Ratio
Point estimate	94.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	89.03
upper limit	101.23

Notes:

[11] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Statistical analysis title	MabThera:rituxan (Cmax)
Statistical analysis description: GLS Mean Ratio of Cmax SAIT1MabThera vs Rituxan. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.	
Comparison groups	MabThera v Rituxan

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	equivalence ^[12]
Parameter estimate	GLS Mean Ratio
Point estimate	104.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	97.54
upper limit	110.95

Notes:

[12] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Primary: Trough concentration (C_{trough}) before the second infusion on Day 15

End point title	Trough concentration (C _{trough}) before the second infusion on Day 15
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End point description:

End point type	Primary
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End point timeframe:

Immediately before the second infusion of treatment on Day 15 (dose 2).

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	81	77	
Units: µg/mL				
geometric mean (geometric coefficient of variation)	60.35 (± 40.3)	67.75 (± 36.2)	58.84 (± 97.9)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera (C _{trough})
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Statistical analysis description:

GLS Mean Ratio of C_{trough} SAIT101 vs MabThera. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.

Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	equivalence ^[13]
Parameter estimate	GLS Mean Ratio
Point estimate	89.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	77.2
upper limit	102.79

Notes:

[13] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Statistical analysis title	SAIT101:Rituxan (Ctrough)
Statistical analysis description: GLS Mean Ratio of Ctrough SAIT101 vs MabThera. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	equivalence ^[14]
Parameter estimate	GLS Mean Ratio
Point estimate	102.56
Confidence interval	
level	90 %
sides	2-sided
lower limit	88.72
upper limit	118.56

Notes:

[14] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Statistical analysis title	MabThera:Rituxan (Ctrough)
Statistical analysis description: GLS Mean Ratio of Ctrough MabThera vs Rituxan. The standard comparison of the log-transformed primary parameters between treatments is based on an analysis of variance (ANOVA) model with fixed effect for treatment.	
Comparison groups	MabThera v Rituxan
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	equivalence ^[15]
Parameter estimate	GLS Mean Ratio
Point estimate	115.13
Confidence interval	
level	90 %
sides	2-sided
lower limit	99.51
upper limit	133.21

Notes:

[15] - Standard acceptance limits for bioequivalence (80.00% to 125.00%) for the treatment comparisons.

Primary: Change from Baseline in DAS28-CRP at Week 24

End point title	Change from Baseline in DAS28-CRP at Week 24
End point description: Change from Baseline (Day 1) in the Disease Activity Score 28 C-reactive protein score (DAS28-CRP) at Week 24.	
End point type	Primary
End point timeframe: Baseline (Day 1) to Week 24.	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	87	85	
Units: Score on a scale				
least squares mean (standard deviation)	-0.991 (\pm 1.1735)	-0.832 (\pm 0.8483)	-0.861 (\pm 0.9488)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera (DAS28-CRP)
Statistical analysis description:	
Change from Baseline in DAS28-CRP at Week 24 SAIT101 vs MabThera. Least square means and confidence intervals (CIs) were estimated from an ANCOVA model containing treatment group as a factor and baseline DAS28-CRP value as a covariate. ANCOVA model contains treatment group only.	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	equivalence ^[16]
P-value	= 0.2402
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.422
upper limit	0.106
Variability estimate	Standard error of the mean
Dispersion value	0.134

Notes:

[16] - The equivalence between 2 study treatments would be declared if the two-sided 95% CI of the difference in change from baseline in DAS28-CRP at week 24 in entirely contained within the equivalence margin of [-0.6,0.6].

Statistical analysis title	SAIT101:Rituxan (DAS28-CRP)
Statistical analysis description:	
Change from Baseline in DAS28-CRP at Week 24 SAIT101 vs Rituxan. Least square means and confidence intervals (CIs) were estimated from an ANCOVA model containing treatment group as a factor and baseline DAS28-CRP value as a covariate. ANCOVA model contains treatment group only.	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	equivalence ^[17]
P-value	= 0.1346
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.469
upper limit	0.063
Variability estimate	Standard error of the mean
Dispersion value	0.135

Notes:

[17] - The equivalence between 2 study treatments would be declared if the two-sided 95% CI of the difference in change from baseline in DAS28-CRP at week 24 in entirely contained within the equivalence margin of [-0.6,0.6].

Statistical analysis title	Mabthera:Rituxan (DAS28-CRP)
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Statistical analysis description:

Change from Baseline in DAS28-CRP at Week 24 MabThera vs Rituxan. Least square means and confidence intervals (CIs) were estimated from an ANCOVA model containing treatment group as a factor and baseline DAS28-CRP value as a covariate. ANCOVA model contains treatment group only.

Comparison groups	MabThera v Rituxan
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	equivalence ^[18]
P-value	= 0.7429
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.04

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.314
upper limit	0.224
Variability estimate	Standard error of the mean
Dispersion value	0.137

Notes:

[18] - The equivalence between 2 study treatments would be declared if the two-sided 95% CI of the difference in change from baseline in DAS28-CRP at week 24 in entirely contained within the equivalence margin of [-0.6,0.6].

Primary: Clinical Remission Response (CRR) at Weeks 8, 16, 24, 36 and 52

End point title	Clinical Remission Response (CRR) at Weeks 8, 16, 24, 36 and 52
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End point description:

Efficacy endpoint: Clinical remission response (CRR) defined by the Simplified Disease Activity Index (SDAI) <3.3 at weeks 8, 16, 24, 36 and 52 (EOS).

End point type	Primary
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End point timeframe:

Baseline (Day 1) to Week 52 (EOS)

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	92	91	
Units: Score on a scale				
number (confidence interval 95%)				
CRR Week 8	0 (0.00 to 3.97)	0 (0.00 to 4.01)	0 (0.00 to 4.05)	
CRR Week 16	0 (0.00 to 4.01)	1 (0.19 to 5.84)	0 (0.00 to 4.05)	
CRR Week 24	0 (0.00 to 4.09)	1 (0.20 to 6.23)	0 (0.00 to 4.37)	
CRR Week 36	2 (0.61 to 7.74)	0 (0.00 to 4.48)	1 (0.21 to 6.51)	
CRR Week 52 (EOS)	1 (0.19 to 5.90)	2 (0.63 to 7.91)	2 (0.64 to 8.09)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera CRR Week 52
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Statistical analysis description:

Clinical Remission Response at Week 52 (EOS) SAIT101 vs MabThera. Clinical remission is defined as score of Simplified Disease Activity Index (SDAI) smaller than 3.3. The 95% CIs for clinical remission rate and treatment difference were derived using the Wilson Score method. The adjusted difference and its 95% CI are from a logistic regression model containing treatment group as a factor and baseline DAS28-CRP as a covariate.

Comparison groups	MabThera v SAIT101
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	3.9
Variability estimate	Standard error of the mean
Dispersion value	1.92

Statistical analysis title	SAIT101:Rituxan CRR Week 52
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Statistical analysis description:

Clinical Remission Response at Week 52 (EOS) SAIT101 vs Rituxan. Clinical remission is defined as score of Simplified Disease Activity Index (SDAI) smaller than 3.3. The 95% CIs for clinical remission rate and treatment difference were derived using the Wilson Score method. The adjusted difference and its 95% CI are from a logistic regression model containing treatment group as a factor and baseline DAS28-CRP as a covariate.

Comparison groups	SAIT101 v Rituxan
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Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.07
upper limit	3.86
Variability estimate	Standard error of the mean
Dispersion value	1.95

Statistical analysis title	MabThera:Rituxan CRR Week 52
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Statistical analysis description:

Clinical Remission Response at Week 52 (EOS) MabThera vs Rituxan. Clinical remission is defined as score of Simplified Disease Activity Index (SDAI) smaller than 3.3. The 95% CIs for clinical remission rate and treatment difference were derived using the Wilson Score method. The adjusted difference and its 95% CI are from a logistic regression model containing treatment group as a factor and baseline DAS28-CRP as a covariate.

Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.05
upper limit	5.83
Variability estimate	Standard error of the mean
Dispersion value	2.27

Secondary: Area Under the Concentration Time Curve Week 2 to Week 24 (AUC(w2-24))

End point title	Area Under the Concentration Time Curve Week 2 to Week 24 (AUC(w2-24))
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End point description:

End point type	Secondary
End point timeframe:	
Week 2 to Week 24	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	61	65	
Units: h*µg/mL				
geometric mean (geometric coefficient of variation)	107300 (± 41.1)	109200 (± 40.0)	116000 (± 40.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Time Curve Day 0 to Week 12 (AUC(0-w12))

End point title	Area Under the Concentration Time Curve Day 0 to Week 12 (AUC(0-w12))
End point description:	
End point type	Secondary
End point timeframe:	
Pre-dose Day 1 (Baseline) to Pre-dose Week 12 (AUC(0-w12))	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	89	92	
Units: h*µg/mL				
geometric mean (geometric coefficient of variation)	148500 (± 33.1)	157400 (± 30.3)	155900 (± 33.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) Dose 1

End point title	Maximum Plasma Concentration (Cmax) Dose 1
End point description:	
End point type	Secondary
End point timeframe:	
Cmax post-infusion on Day 15.	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	92	91	
Units: Hours				
median (inter-quartile range (Q1-Q3))	5.167 (3.00 to 6.50)	5.167 (3.00 to 358.75)	4.500 (3.00 to 6.75)	

Attachments (see zip file)	PK Scatterplots Cmax, D2 and Ctrough.PNG
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Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Tmax) Dose 2

End point title	Maximum Plasma Concentration (Tmax) Dose 2
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End point description:

End point type	Secondary
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End point timeframe:

Post-infusion Day 24.

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	93	93	
Units: hours				
median (inter-quartile range (Q1-Q3))	4.167 (2.92 to 5.50)	4.167 (0.00 to 48.08)	4.250 (2.92 to 23.50)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Terminal Rate Constant (λ_z)

End point title	Apparent Terminal Rate Constant (λ_z)
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End point description:

End point type	Secondary
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End point timeframe:

First Dosing Period (Part A)

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	91	92	
Units: Hours				
least squares mean (standard deviation)	0.002358 (\pm 0.00061132)	0.002283 (\pm 0.00067311)	0.002240 (\pm 0.00059435)	

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic Clearance (CL)

End point title	Systemic Clearance (CL)
End point description:	
End point type	Secondary
End point timeframe:	
First Dosing Period (Part A)	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	91	91	
Units: L/day				
geometric mean (geometric coefficient of variation)	0.01314 (\pm 34.6)	0.01235 (\pm 29.0)	0.01240 (\pm 33.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (VD)

End point title	Volume of Distribution (VD)
End point description:	
End point type	Secondary
End point timeframe:	
First Dosing Period	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	91	91	
Units: Litres				
geometric mean (geometric coefficient of variation)	5.757 (± 28.0)	5.635 (± 23.6)	5.727 (± 22.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-Life (T1/2)

End point title	Terminal Half-Life (T1/2)
End point description:	
End point type	Secondary
End point timeframe:	
First Dosing Interval	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	91	92	
Units: Hours				
geometric mean (geometric coefficient of variation)	303.7 (± 26.1)	316.1 (± 29.0)	319.7 (± 26.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in DAS28-CRP at Weeks 8, 16, 36 and 52

End point title	Change From Baseline in DAS28-CRP at Weeks 8, 16, 36 and 52
End point description:	
Efficacy endpoint: Change from baseline (Day 1) in DAS28-CRP at weeks 8, 16, 36 and 52 (End of Study). DAS28-CRP was calculated using the following equation: $[0.56 \times \text{Square Root (SQRT)} (\text{tender 28 joint count}) + 0.28 \times \text{SQRT}(\text{swollen 28 joint count}) + 0.36 \times \ln(\text{CRP} + 1)] \times 1.10 + 1.15$.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to Week 52 (End of study).	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	97	98	
Units: Score on a scale				
least squares mean (standard deviation)				
Day 1 (Baseline)	5.281 (± 0.8899)	5.288 (± 0.8073)	5.170 (± 0.8326)	
Week 8	4.405 (± 1.0189)	4.324 (± 1.1132)	4.252 (± 1.1393)	
Week 16	4.001 (± 1.1116)	4.155 (± 0.9750)	4.100 (± 1.0044)	
Week 24	4.300 (± 1.0331)	4.463 (± 1.0648)	4.443 (± 0.9774)	
Week 36	3.552 (± 1.1452)	3.823 (± 0.9290)	3.716 (± 1.0684)	
Week 52 (EOS)	3.660 (± 1.2636)	3.754 (± 1.3037)	3.518 (± 1.1276)	

Attachments (see zip file)	Change in Baseline in DAS28-CRP.PNG
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Statistical analyses

Statistical analysis title	SAIT101:MabThera (Change in DAS28-CRP at Week 52)
Statistical analysis description:	
GLS Means Difference SAIT101 vs MabThera in DAS29-CRP score Day 1 to Week 52 (EOS). Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and Baseline DAS28-CRP value as a covariate. ANCOVA model contains treatment group only.	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6068
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.428
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.172

Statistical analysis title	SAIT101:Rituxan (Change in DAS28-CRP at Week 52)
Statistical analysis description:	
LS Means Difference SAIT101 vs Rituxan DAS29-CRP score Day 1 to Week 52 (EOS). Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and Baseline DAS28-CRP value as a covariate. ANCOVA model contains treatment group only.	
Comparison groups	SAIT101 v Rituxan

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.599
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.249
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.172

Statistical analysis title	Mabthera:Rituxan (Change in DAS28-CRP at Week 52)
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Statistical analysis description:

LS Means Difference MabThera vs Rituxan DAS29-CRP score Day 1 to Week 52 (EOS). Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and Baseline DAS28-CRP value as a covariate. ANCOVA model contains treatment group only.

Comparison groups	MabThera v Rituxan
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3053
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.165
upper limit	0.532
Variability estimate	Standard error of the mean
Dispersion value	0.175

Secondary: American College of Rheumatology 20% Response Criteria (ACR20) Response Rates at Weeks 8, 16, 24, 36 and 52

End point title	American College of Rheumatology 20% Response Criteria (ACR20) Response Rates at Weeks 8, 16, 24, 36 and 52
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End point description:

Efficacy endpoint: American College of Rheumatology (ACR) 20% response criteria (ACR20) response rates at weeks 8, 16, 24, 36 and 52

End point type	Secondary
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End point timeframe:

Week 8 to week 52 (End of Study)

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	93	92	
Units: ACR20 Reponse Rate				
number (confidence interval 95%)				
Week 8	39 (31.70 to 51.10)	33 (26.51 to 45.61)	44 (37.91 to 57.91)	
Week 16	50 (43.18 to 62.95)	54 (48.48 to 68.21)	53 (47.98 to 67.84)	
Week 24	36 (28.79 to 49.35)	31 (26.37 to 46.11)	34 (29.68 to 50.10)	
Week 36	63 (59.87 to 78.49)	47 (46.52 to 67.46)	58 (58.00 to 78.69)	
Week 52 (EOS)	60 (53.75 to 72.82)	49 (44.18 to 64.34)	59 (55.98 to 75.26)	

Attachments (see zip file)	ACR20 Repsonses (%).PNG
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Statistical analyses

Statistical analysis title	SAIT101:MabThera ACR20 Reponse Rate at Week 52
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Statistical analysis description:

ACR20 Response Rate difference at Week 52 (EOS) assessment SAIT101 vs MabThera. The 95% CIs for ACR response rate and difference were derived using the Wilson Score method.

Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Response Rate Difference
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.74
upper limit	23.03
Variability estimate	Standard error of the mean
Dispersion value	7.22

Statistical analysis title	SAIT101:Rituxan ACR20 Reponse Rate at ...
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Statistical analysis description:

ACR20 Response Rate difference at Week 52 (EOS) assessment SAIT101 vs Rituxan. The 95% CIs for ACR response rate and difference were derived using the Wilson Score method.

Comparison groups	SAIT101 v Rituxan
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Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Response Rate Difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.95
upper limit	11.22
Variability estimate	Standard error of the mean
Dispersion value	7.05

Statistical analysis title	MabThera:Rituxan ACR20 Reponse Rate at ...
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Statistical analysis description:

ACR20 Response Rate difference at Week 52 (EOS) assessment MabThera vs Rituxan. The 95% CIs for ACR response rate and difference were derived using the Wilson Score method.

Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Response Rate Difference
Point estimate	-11.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.47
upper limit	2.45
Variability estimate	Standard error of the mean
Dispersion value	7.26

Secondary: American Collage of Rheumatology 50% Response Criteria (ACR50) Response Rates and American Collage of Rheumatology 70% Response Criteria (ACR70) at Weeks 8, 16, 24, 36 and 52

End point title	American Collage of Rheumatology 50% Response Criteria (ACR50) Response Rates and American Collage of Rheumatology 70% Response Criteria (ACR70) at Weeks 8, 16, 24, 36 and 52
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End point description:

Efficacy endpoint: American Collage of Rheumatology 50% response criteria (ACR50) response rates and American Collage of Rheumatology 70% response criteria (ACR70) at weeks 8, 16, 24, 36 and 52.

End point type	Secondary
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End point timeframe:

Week 8 to week 52 (EOS)

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	98	98	
Units: ACR20 Response Rate				
number (confidence interval 95%)				
ACR50 Week 8	13 (8.17 to 22.02)	11 (6.73 to 19.95)	14 (9.29 to 23.94)	
ACR70 Week 8	2 (0.58 to 7.35)	2 (0.59 to 7.51)	2 (0.60 to 7.58)	
ACR50 Week 16	17 (11.61 to 27.07)	16 (11.00 to 26.40)	14 (9.39 to 24.18)	
ACR70 Week 16	9 (5.12 to 17.20)	4 (1.70 to 10.65)	5 (2.37 to 12.22)	
ACR50 Week 24	15 (10.14 to 25.17)	8 (4.73 to 17.11)	5 (2.51 to 12.90)	
ACR70 Week 24	8 (4.47 to 16.23)	2 (0.63 to 8.00)	3 (1.19 to 9.76)	
ACR50 Week 36	37 (31.51 to 51.44)	19 (15.37 to 33.38)	25 (21.31 to 40.69)	
ACR70 Week 36	19 (13.95 to 30.63)	6 (3.40 to 15.06)	12 (8.47 to 23.59)	
ACR50 Week 52 (EOS)	35 (28.14 to 47.33)	25 (19.58 to 37.80)	30 (24.74 to 44.02)	
ACR70 Week 52 (EOS)	23 (16.89 to 34.05)	13 (8.64 to 23.16)	17 (12.28 to 28.48)	

Attachments (see zip file)	ACR50 Responses (%).PNG ACR70 Responses (%).PNG
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Statistical analyses

Statistical analysis title	SAIT101:MabThera (ACR50) Reponse Rate at Week 52
Statistical analysis description:	
ACR50 Response Rate Difference SAIT101 vs MabThera at Week 52 (EOS). The 95% CIs for ACR response rate and difference were derived using the Wilson Score method. The adjusted difference and its 95% confidence intervals are from a logistic regression model containing treatment group as a factor and baseline DAS28-CRP value as a covariate.	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Response Rate Difference
Point estimate	9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.07
upper limit	22.46
Variability estimate	Standard error of the mean
Dispersion value	6.87

Statistical analysis title	SAIT101:Rituxan (ACR50) Reponse Rate at Week 52
Statistical analysis description:	
ACR50 Response Rate Difference SAIT101 vs Rituxan at Week 52 (EOS). The 95% CIs for ACR response rate and difference were derived using the Wilson Score method. The adjusted difference and its 95% confidence intervals are from a logistic regression model containing treatment group as a factor and baseline DAS28-CRP value as a covariate.	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Response Rate Difference
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.22
upper limit	17.03
Variability estimate	Standard error of the mean
Dispersion value	7.07

Statistical analysis title	MabThera:Rituxan (ACR70) Reponse Rate at Week 52
Statistical analysis description:	
ACR70 Response Rate Difference MabThera vs Rituxan at Week 52 (EOS). The 95% CIs for ACR response rate and difference were derived using the Wilson Score method. The adjusted difference and its 95% confidence intervals are from a logistic regression model containing treatment group as a factor and baseline DAS28-CRP value as a covariate.	
Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Response Rate Difference
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.68
upper limit	6.41
Variability estimate	Standard error of the mean
Dispersion value	5.58

Statistical analysis title	SAIT101:MabThera (ACR70) Reponse Rate at Week 52
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Statistical analysis description:

ACR70 Response Rate Difference SAIT101 vs MabThera at Week 52 (EOS). The 95% CIs for ACR response rate and difference were derived using the Wilson Score method. The adjusted difference and its 95% confidence intervals are from a logistic regression model containing treatment group as a factor

and baseline DAS28-CRP value as a covariate.

Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Response Rate Difference
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.52
upper limit	21.22
Variability estimate	Standard error of the mean
Dispersion value	5.78

Statistical analysis title	SAIT101:Rituxan (ACR70) Reponse Rate at Week 52
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Statistical analysis description:

ACR70 Response Rate Difference SAIT101 vs Rituxan at Week 52 (EOS). The 95% CIs for ACR response rate and difference were derived using the Wilson Score method. The adjusted difference and its 95% confidence intervals are from a logistic regression model containing treatment group as a factor and baseline DAS28-CRP value as a covariate.

Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Response Rate Difference
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.69
upper limit	17.13
Variability estimate	Standard error of the mean
Dispersion value	6.08

Secondary: Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Swollen Joint Count (SJC) and Tender Joint Count (TJC) (the 66/68 Joint Count System)

End point title	Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Swollen Joint Count (SJC) and Tender Joint Count (TJC) (the 66/68 Joint Count System)
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End point description:

Efficacy endpoint: Individual components of the ACR improvement criteria on Day 1 and at weeks 8, 16, 24, 36 and 52: Swollen Joint Count (SJC) and tender joint count (TJC) (the 66/68 joint count system). SJC and TJC assess the level of skeletal disease involvement. the 66/68 Joint Count evaluates 66 joints for swelling and 68 joints for tenderness.

End point type	Secondary
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End point timeframe:

Baseline (Day 1 to Week 52 (EOS))

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	97	98	
Units: Swollen Joint Count				
least squares mean (standard deviation)				
Swollen Joint Count Day 1	15.2 (± 7.97)	15.2 (± 15.2)	13.0 (± 6.19)	
Swollen Joint Count Week 8	8.6 (± 7.11)	8.4 (± 6.62)	7.7 (± 5.92)	
Swollen Joint Count Week 16	6.5 (± 4.86)	7.8 (± 7.20)	7.0 (± 5.37)	
Swollen Joint Count Week 24	8.5 (± 5.13)	10.0 (± 5.85)	10.0 (± 6.19)	
Swollen Joint Count Week 36	4.8 (± 6.21)	5.4 (± 5.72)	5.7 (± 5.49)	
Swollen Joint Count Week 52 (EOS)	5.2 (± 6.53)	6.5 (± 9.46)	4.6 (± 5.04)	
Tender Joint Count Day 1	21.7 (± 11.08)	22.6 (± 13.66)	20.0 (± 10.84)	
Tender Count Count Week 8	13.9 (± 9.94)	14.0 (± 9.94)	13.5 (± 10.69)	
Tender Count Count Week 16	11.1 (± 10.24)	12.5 (± 8.36)	11.8 (± 9.09)	
Tender Count Count Week 24	13.6 (± 9.79)	15.6 (± 11.94)	15.2 (± 11.62)	
Tender Count Count Week 36	8.3 (± 9.10)	10.9 (± 10.68)	9.6 (± 10.81)	
Tender Count Count Week 52 (EOS)	9.3 (± 9.34)	11.9 (± 15.18)	9.4 (± 11.41)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera Swollen Joint Count (Week 52)
Statistical analysis description:	
Swollen Joint Count (SJC) Week 52 (EOS) assessment SAIT101 vs MabThera. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate.	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1997
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.23
upper limit	0.671
Variability estimate	Standard error of the mean
Dispersion value	0.991

Statistical analysis title	SAIT101:Rituxan Swollen Joint Count (Week 52)
Statistical analysis description:	
Swollen Joint Count (SJC) Week 52 (EOS) assessment SAIT101 vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate.	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9098
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.074
upper limit	1.848
Variability estimate	Standard error of the mean
Dispersion value	0.996

Statistical analysis title	MabThera:Rituxan Swollen Joint Count (Week 52)
Statistical analysis description:	
Swollen Joint Count (SJC) Week 52 (EOS) assessment MabThera vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate.	
Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.248
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.817
upper limit	3.15
Variability estimate	Standard error of the mean
Dispersion value	1.008

Statistical analysis title	SAIT101:MabThera Tender Joint Count (Week 52)
Statistical analysis description:	
Tender Joint Count (TJC) Week 52 (EOS) assessment SAIT101 vs MabThera. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate.	
Comparison groups	SAIT101 v MabThera

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1931
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.909
upper limit	0.996
Variability estimate	Standard error of the mean
Dispersion value	1.5

Statistical analysis title	SAIT101:Rituxan Tender Joint Count (Week 52)
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Statistical analysis description:

Tender Joint Count (TJC) Week 52 (EOS) assessment SAIT101 vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate.

Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6068
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.722
upper limit	2.184
Variability estimate	Standard error of the mean
Dispersion value	1.5

Statistical analysis title	Mabthera:Rituxan Tender Joint Count (Week 52)
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Statistical analysis description:

Tender Joint Count (TJC) Week 52 (EOS) assessment MabThera vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate.

Comparison groups	Rituxan v MabThera
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Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4352
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.805
upper limit	4.18
Variability estimate	Standard error of the mean
Dispersion value	1.52

Secondary: Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Physicians Global Assessment of Disease Activity (Assessed on 1 to 100 mm Visual Analog Scale [VAS])

End point title	Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Physicians Global Assessment of Disease Activity (Assessed on 1 to 100 mm Visual Analog Scale [VAS])
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End point description:

Efficacy endpoint: Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Physicians global assessment of disease activity (assessed on 1 to 100 mm Visual Analog Scale [VAS]). Where 0 = no disease activity and 100 = maximum disease activity.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to Week 52 (EOS)

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	97	97	98	
Units: Score on a scale				
least squares mean (standard error)				
Disease Activity Day 1	71.0 (± 14.30)	69.4 (± 15.00)	69.8 (± 14.32)	
Disease Activity Week 8	45.6 (± 20.75)	43.2 (± 23.86)	44.6 (± 23.28)	
Disease Activity Week 16	39.2 (± 20.94)	39.0 (± 20.97)	42.3 (± 20.89)	
Disease Activity Week 24	47.9 (± 22.28)	47.8 (± 20.25)	49.0 (± 22.45)	
Disease Activity Week 36	30.3 (± 21.56)	36.3 (± 21.71)	31.4 (± 20.69)	
Disease Activity Week 52 (EOS)	31.1 (± 21.67)	35.1 (± 23.49)	31.2 (± 22.95)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera Disease Activity (Week 52)
Statistical analysis description:	
Week 52 (EOS) Physician's Disease Activity Assessment SAIT101 vs MabThera. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline)	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2008
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-4.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.541
upper limit	2.226
Variability estimate	Standard error of the mean
Dispersion value	3.242

Statistical analysis title	SAIT101:Rituxan Disease Activity (Week 52)
Statistical analysis description:	
Week 52 (EOS) Physician's Disease Activity Assessment SAIT101 vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline)	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9047
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.771
upper limit	5.994
Variability estimate	Standard error of the mean
Dispersion value	3.242

Statistical analysis title	Mabthera:Rituxan Disease Activity (Week 52)
Statistical analysis description:	
Week 52 (EOS) Physician's Disease Activity Assessment MabThera vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline)	
Comparison groups	Rituxan v MabThera

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2498
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	3.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.665
upper limit	10.204
Variability estimate	Standard error of the mean
Dispersion value	3.268

Secondary: Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Participants Assessment of Pain (Assessed on 1 to 100 mm Visual Analog Scale [VAS])

End point title	Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Participants Assessment of Pain (Assessed on 1 to 100 mm Visual Analog Scale [VAS])
End point description:	
Efficacy endpoint: Individual Components of the ACR Improvement Criteria on Day 1 (Baseline) and at Weeks 8, 16, 24, 36 and 52 (EOS): Participants assessment of pain (assessed on 1 to 100 mm Visual Analog Scale [VAS])	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to Week 52	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	98	97	
Units: Score on a scale				
least squares mean (standard deviation)				
Assessment of Pain Day 1	67.0 (± 18.71)	68.8 (± 20.02)	68.8 (± 19.27)	
Assessment of Pain Week 8	48.4 (± 22.79)	50.4 (± 22.40)	47.9 (± 23.03)	
Assessment of Pain Week 16	42.7 (± 23.34)	44.6 (± 20.91)	44.4 (± 22.91)	
Assessment of Pain Week 24	49.3 (± 24.15)	51.6 (± 21.44)	51.8 (± 23.58)	
Assessment of Pain Week 36	36.8 (± 24.56)	44.9 (± 23.78)	41.6 (± 23.46)	
Assessment of Pain Week 52 (EOS)	41.2 (± 24.34)	43.2 (± 24.42)	44.5 (± 26.10)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera Assessment of Pain (Week 52)
Statistical analysis description:	
Patients Assessment of Pain Week 52 (EOS) SAIT101 vs MabThera. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline).	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other ^[19]
P-value	= 0.7322
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.0302
upper limit	5.841
Variability estimate	Standard error of the mean
Dispersion value	3.592

Notes:

[19] - Efficacy endpoint: Individual Components of the ACR Improvement Criteria on Day 1 (Baseline) and at Weeks 8, 16, 24, 36 and 52 (EOS): Participants assessment of pain (assessed on 1 to 100 mm Visual Analog Scale [VAS])

Statistical analysis title	SAIT101:Rituxan Assessment of Pain (Week 52)
Statistical analysis description:	
Patients Assessment of Pain Week 52 (EOS) SAIT101 vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline).	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other ^[20]
P-value	= 0.5418
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.347
upper limit	4.92
Variability estimate	Standard error of the mean
Dispersion value	3.623

Notes:

[20] - Efficacy endpoint: Individual Components of the ACR Improvement Criteria on Day 1 (Baseline) and at Weeks 8, 16, 24, 36 and 52 (EOS): Participants assessment of pain (assessed on 1 to 100 mm Visual Analog Scale [VAS])

Statistical analysis title	MabThera:Rituxan Assessment of Pain (Week 52)
Statistical analysis description:	
Patients Assessment of Pain Week 52 (EOS) MabThera vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline).	

Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other ^[21]
P-value	= 0.7869
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.136
upper limit	6.169
Variability estimate	Standard error of the mean
Dispersion value	3.633

Notes:

[21] - Efficacy endpoint: Individual Components of the ACR Improvement Criteria on Day 1 (Baseline) and at Weeks 8, 16, 24, 36 and 52 (EOS): Participants assessment of pain (assessed on 1 to 100 mm Visual Analog Scale [VAS])

Secondary: Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Participants Global Assessment of Disease Activity (Assessed on 1 to 100 mm VAS)

End point title	Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Participants Global Assessment of Disease Activity (Assessed on 1 to 100 mm VAS)
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End point description:

Efficacy endpoint: Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Participants global assessment of disease activity (assessed on 1 to 100 mm VAS). Patients rate how their Rheumatoid Arthritis has affected them, where 0 = very well and 100 = very poor.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to Week 52 (EOS)

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	97	97	97	
Units: Score on a scale				
least squares mean (standard deviation)				
Disease Activity Day 1	68.9 (± 15.87)	67.6 (± 17.53)	70.8 (± 17.04)	
Disease Activity Week 8	46.9 (± 22.57)	49.1 (± 22.98)	48.5 (± 22.93)	
Disease Activity Week 16	43.9 (± 21.47)	44.4 (± 21.63)	44.2 (± 22.82)	
Disease Activity Week 24	50.8 (± 21.16)	51.1 (± 20.49)	53.1 (± 21.90)	
Disease Activity Week 36	35.7 (± 22.63)	42.7 (± 22.54)	42.5 (± 23.70)	
Disease Activity Week 52 (EOS)	41.4 (± 23.02)	42.4 (± 24.10)	43.1 (± 23.93)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera Disease Activity (Week 52)
Statistical analysis description: Week 52 (EOS) Participants Disease Activity Assessment SAIT101 vs MabThera. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline)	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7097
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.062
upper limit	5.496
Variability estimate	Standard error of the mean
Dispersion value	3.443

Statistical analysis title	SAIT101:Rituxan Disease Activity (Week 52)
Statistical analysis description: Week 52 (EOS) Participants Disease Activity Assessment SAIT101 vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline)	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6683
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.28
upper limit	5.317
Variability estimate	Standard error of the mean
Dispersion value	3.453

Statistical analysis title	MabThera:Rituxan Disease Activity (Week 52)
Statistical analysis description: Week 52 (EOS) Participants Disease Activity Assessment MabThera vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and	

baseline value as a covariate. Change from Study Day 1 (Baseline)

Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9548
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.078
upper limit	6.682
Variability estimate	Standard error of the mean
Dispersion value	3.494

Secondary: Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Participants Assessment of Disability (Health Assessment Questionnaire-Disability Index [HAQ-DI])

End point title	Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Participants Assessment of Disability (Health Assessment Questionnaire-Disability Index [HAQ-DI])
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End point description:

Efficacy analysis: Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: Participants assessment of disability (Health Assessment Questionnaire-Disability Index [HAQ-DI 0-3]). The HAQ-DI questionnaire assesses the participants ability to function in daily life (8 categories) plus a pain VAS ranging from 0 (no pain) to 100 (Severe pain).

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to week 52.

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	98	97	
Units: Score on a scale				
least squares mean (standard deviation)				
HAQ-DI Day 1	1.610 (± 0.5728)	1.605 (± 0.67065)	1.585 (± 0.6421)	
HAQ-DI Week 8	1.168 (± 0.6318)	1.314 (± 0.6919)	1.176 (± 0.6398)	
HAQ-DI Week 16	1.129 (± 0.5775)	1.246 (± 0.9463)	1.152 (± 0.6668)	
HAQ-DI Week 24	1.209 (± 0.6071)	1.335 (± 0.6382)	1.294 (± 0.6594)	
HAQ-DI Week 36	0.994 (± 0.6220)	1.182 (± 0.6883)	1.061 (± 0.6247)	
HAQ-DI Week 52 (EOS)	1.027 (± 0.6208)	1.207 (± 0.7025)	1.190 (± 0.7116)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera HAQ-DI (Week 52)
Statistical analysis description: Week 52 (EOS) HAQ-DI score (0-3) SAIT101 vs MabThera. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline).	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0505
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.339
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.086

Statistical analysis title	SAIT101:Rituxan HAQ-DI (Week 52)
Statistical analysis description: Week 52 (EOS) HAQ-DI score (0-3) SAIT101 vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline).	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1141
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3079
upper limit	0.033
Variability estimate	Standard error of the mean
Dispersion value	0.086

Statistical analysis title	MabThera:Rituxan HAQ-DI (Week 52)
Statistical analysis description: Week 52 (EOS) HAQ-DI score (0-3) MabThera vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline).	
Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7111
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.139
upper limit	0.204
Variability estimate	Standard error of the mean
Dispersion value	0.087

Secondary: Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: C-reactive Protein (CRP) Level

End point title	Individual Components of the ACR Improvement Criteria on Day 1 and at Weeks 8, 16, 24, 36 and 52: C-reactive Protein (CRP) Level
End point description: Efficacy analysis: Individual Components of the ACR Improvement Criteria on Day 1 (Baseline) and at Weeks 8, 16, 24, 36 and 52 (EOS): C-reactive protein (CRP) level	
End point type	Secondary
End point timeframe: Baseline (Day 1) to week 52	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	98	98	
Units: Score on a scale				
least squares mean (standard deviation)				
CRP Day 1	19.5 (± 28.99)	15.3 (± 20.63)	16.2 (± 17.91)	
CRP Week 8	12.5 (± 15.78)	12.3 (± 20.29)	10.4 (± 12.78)	
CRP Week 16	8.5 (± 11.78)	7.2 (± 9.02)	7.3 (± 6.90)	
CRP Week 24	9.5 (± 14.54)	8.3 (± 14.40)	7.9 (± 10.35)	
CRP Week 36	8.0 (± 20.33)	7.0 (± 10.38)	7.1 (± 9.72)	
CRP Week 52 (EOS)	9.8 (± 14.14)	9.1 (± 14.93)	7.4 (± 11.34)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera CRP level Week 52
Statistical analysis description: Week 52 (EOS) C-Reactive Protein Sait101 vs MabThera. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline).	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8183
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.113
upper limit	3.253
Variability estimate	Standard error of the mean
Dispersion value	1.871

Statistical analysis title	SAIT101:MabThera CRP level Week 52
Statistical analysis description: Week 52 (EOS) C-Reactive Protein Sait101 vs MabThera. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline).	
Comparison groups	SAIT101 v Rituxan v MabThera
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8183
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.113
upper limit	3.253
Variability estimate	Standard error of the mean
Dispersion value	1.871

Statistical analysis title	SAIT101:Rituxan CRP level Week 52
Statistical analysis description: Week 52 (EOS) C-Reactive Protein Sait101 vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline).	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4186
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.164
upper limit	5.191
Variability estimate	Standard error of the mean
Dispersion value	1.868

Statistical analysis title	MabThera:Rituxan CRP level Week 52
Statistical analysis description: Week 52 (EOS) C-Reactive Protein MabThera vs Rituxan. Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline value as a covariate. Change from Study Day 1 (Baseline).	
Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3035
Method	ANCOVA
Parameter estimate	LS Means Difference
Point estimate	1.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.768
upper limit	5.655
Variability estimate	Standard error of the mean
Dispersion value	1.885

Secondary: Change From Baseline DAS28-erythrocyte Sedimentation Rate (ESR) at Weeks 8, 16, 24, 36 and 52

End point title	Change From Baseline DAS28-erythrocyte Sedimentation Rate (ESR) at Weeks 8, 16, 24, 36 and 52
End point description:	
Efficacy endpoint: Change from baseline (Day 1) in DAS28-erythrocyte sedimentation rate (ESR) at weeks 8, 16, 24, 36 and 52 (EOS). DAS28-ESR was calculated using the following equation: $[0.56 * \text{SQRT}(\text{tender 28 joint count}) + 0.28 * \text{SQRT}(\text{swollen 28 joint count}) + 0.7 * \ln(\text{ESR})] + 0.014 * \text{patient global health assessment}$.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to week 52 (EOS)	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	96	96	
Units: Score on scale				
least squares mean (standard deviation)				
DAS28-ESR Day 1	6.537 (± 0.8440)	6.533 (± 0.7810)	6.480 (± 0.7577)	
DAS28-ESR Week 8	5.330 (± 1.0649)	5.315 (± 1.2478)	5.235 (± 1.2578)	
DAS28-ESR Week 16	4.861 (± 1.1876)	5.059 (± 1.1682)	4.957 (± 1.1802)	
DAS28-ESR Week 24	5.216 (± 1.2510)	5.410 (± 1.2344)	5.432 (± 1.1891)	
DAS28-ESR Week 36	4.319 (± 1.2798)	4.689 (± 1.0077)	4.499 (± 1.1980)	
DAS28-ESR Week 52 (EOS)	4.435 (± 1.4375)	4.485 (± 1.4390)	4.391 (± 1.3947)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera DAS28-ESR (Week 52)
Statistical analysis description:	
DAS28-ESR score SAIT101 vs MabThera at Week 52 (EOS). Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline DAS28-ESR value as a covariate. ANCOVA model contains treatment group only.	
Comparison groups	MabThera v SAIT101
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9249
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.375
upper limit	0.413

Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	SAIT101:Rituxan DAS28-ESR (Week 52)
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Statistical analysis description:

DAS28-ESR score SAIT101 vs Rituxan at Week 52 (EOS). Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline DAS28-ESR value as a covariate. ANCOVA model contains treatment group only.

Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8209
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.351
upper limit	0.421
Variability estimate	Standard error of the mean
Dispersion value	0.201

Statistical analysis title	MabThera:Rituxan DAS28-ESR (Week 52)
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Statistical analysis description:

DAS28-ESR score MabThera vs Rituxan at Week 52 (EOS). Least square means and confidence intervals were estimated from an ANCOVA model containing treatment group as a factor and baseline DAS28-ESR value as a covariate. ANCOVA model contains treatment group only.

Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8962
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.376
upper limit	0.301
Variability estimate	Standard error of the mean
Dispersion value	0.205

Secondary: Major Clinical Response (Continuous ACR70) for at Least 24 Weeks

End point title	Major Clinical Response (Continuous ACR70) for at Least 24 Weeks
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End point description:

Efficacy endpoint: Major clinical response (continuous ACR70) from Baseline (Day 1) for at least 24 weeks

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to Week 24

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	86	85	
Units: Score on a scale				
number (confidence interval 95%)				
Major Clinical Response Week 24	1 (0.19 to 5.90)	0 (0.00 to 4.28)	0 (0.00 to 4.32)	
Major Clinical Repsonse Week 52 (EOS)	2 (0.62 to 7.83)	0 (0.00 to 4.53)	1 (0.22 to 6.75)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera Major Clinical Response Week 52
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Statistical analysis description:

Week 24 Major Clinical Response SAIT101 vs MabThera. The 95% CIs for major clinical response rate and treatment difference were derived using the Wilson Score method. The adjusted difference and its 95% CI are from a logistic regression model containing treatment group as a factor and baseline DAS28-CRP as a covariate.

Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Differnce (%)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	7.83
Variability estimate	Standard error of the mean
Dispersion value	1.57

Statistical analysis title	SAIT101:Rituxan Major Clinical Response Week 52
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Statistical analysis description:

Week 52 (EOS) Major Clinical Response SAIT101 vs Rituxan. The 95% CIs for major clinical response rate and treatment difference were derived using the Wilson Score method. The adjusted difference and

its 95% CI are from a logistic regression model containing treatment group as a factor and baseline DAS28-CRP as a covariate.

Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference (%)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.74
upper limit	6.67
Variability estimate	Standard error of the mean
Dispersion value	2

Statistical analysis title	MabThera:rituxan Major Clinical Response Week 52
Statistical analysis description:	
Week 52 (EOS) Major Clinical Response MabThera vs Rituxan. The 95% CIs for major clinical response rate and treatment difference were derived using the Wilson Score method. The adjusted difference and its 95% CI are from a logistic regression model containing treatment group as a factor and baseline DAS28-CRP as a covariate.	
Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference (%)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.75
upper limit	3.39
Variability estimate	Standard error of the mean
Dispersion value	1.24

Secondary: Proportion of Participants With European League Against Rheumatism (EULAR) Response at Weeks 8, 16, 24 36 and 52

End point title	Proportion of Participants With European League Against Rheumatism (EULAR) Response at Weeks 8, 16, 24 36 and 52
End point description:	
Efficacy endpoint: Proportion of participants with European League Against Rheumatism (EULAR) response (defined as good response, moderate response or no response) at weeks 8, 16, 24 36 and 52 (EOS). EULAR (European League Against Rheumatism) response was classified using the individual amount of change in the DAS28-CRP score. The DAS28-CRP was classified into 3 categories: low disease activity (≤ 3.2), moderate disease activity (> 3.2 and ≤ 5.1) and high disease activity (> 5.1). Good response was defined as >1.2 improvement in the DAS28-CRP from baseline with low disease activity.	
End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 52 (EOS)

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	92	93	
Units: Score on a scale				
number (confidence interval 95%)				
Week 8 Good	12 (7.54 to 21.21)	14 (9.29 to 23.94)	12 (7.54 to 21.21)	
Week 8 Good or Moderate	30 (23.62 to 42.30)	33 (26.82 to 46.05)	33 (25.51 to 45.61)	
Week 16 Good	20 (14.38 to 30.90)	12 (7.62 to 21.43)	13 (8.45 to 22.69)	
Week 16 Good or Moderate	44 (37.47 to 57.36)	42 (35.85 to 55.80)	33 (26.82 to 46.05)	
Week 24 Good	12 (7.71 to 21.65)	7 (3.95 to 15.69)	7 (4.05 to 16.04)	
Week 24 Good or Moderate	30 (24.17 to 43.14)	26 (21.28 to 40.19)	23 (18.76 to 37.34)	
Week 36 Good	27 (21.51 to 40.13)	15 (11.41 to 28.01)	27 (23.13 to 42.72)	
Week 36 Good or Moderate	58 (54.15 to 73.56)	50 (50.00 to 70.82)	54 (53.62 to 73.70)	
Week 52 (EOS) Good	34 (27.80 to 47.16)	31 (26.37 to 46.11)	32 (27.41 to 47.27)	
Week 52 (EOS) Good or Moderate	59 (53.95 to 73.18)	50 (46.98 to 67.33)	63 (62.23 to 80.71)	

Statistical analyses

Statistical analysis title	SAIT101:MabThera EULAR 'Good' Week 52
Statistical analysis description:	
Week 52 EULAR score 'Good' SAIT101 vs MabThera. EULAR (European League Against Rheumatism) response was classified using the individual amount of change in the DAS28-CRP score. The 95% CIs for EULAR response rate and treatment difference were derived using the Wilson Score method.	
Comparison groups	SAIT101 v MabThera
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.59
upper limit	15.1
Variability estimate	Standard error of the mean
Dispersion value	7.19

Statistical analysis title	SAIT101:Rituxan EULAR 'Good' Week 52
Statistical analysis description:	
Week 52 EULAR score 'Good' SAIT101 vs MabThera. EULAR (European League Against Rheumatism) response was classified using the individual amount of change in the DAS28-CRP score. The 95% CIs for EULAR response rate and treatment difference were derived using the Wilson Score method.	
Comparison groups	SAIT101 v Rituxan
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	10.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.75
upper limit	14.03
Variability estimate	Standard error of the mean
Dispersion value	7.21

Statistical analysis title	Mabthera:Rituxan EULAR 'Good' Week 52
Statistical analysis description:	
Week 52 EULAR score 'Good' SAIT101 vs MabThera. EULAR (European League Against Rheumatism) response was classified using the individual amount of change in the DAS28-CRP score. The 95% CIs for EULAR response rate and treatment difference were derived using the Wilson Score method.	
Comparison groups	Rituxan v MabThera
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.14
upper limit	12.91
Variability estimate	Standard error of the mean
Dispersion value	7.29

Secondary: Pharmacodynamic Endpoint: Depletion of B-lymphocyte Antigen CD19 (CD19+) B-cell Count up to Week 24

End point title	Pharmacodynamic Endpoint: Depletion of B-lymphocyte Antigen CD19 (CD19+) B-cell Count up to Week 24
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End point description:

Pharmacodynamic endpoint: proportion of participants (n) with depletion of CD19+ B-cell count up to week 24 (Pharmacodynamic analysis set).

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to Week 24 (Day 161)	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	96	94	
Units: Subjects	45	46	50	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Endpoint: Time Needed to CD19+ B-cell Depletion

End point title	Pharmacodynamic Endpoint: Time Needed to CD19+ B-cell Depletion
End point description:	
Pharmacodynamic endpoint: Time needed to CD19+ B-cell depletion in Part A (calculated as the first time CD19+ B-cell count below 20/ μ L minus time of first dosing in days rounded to 2 decimals)	
End point type	Secondary
End point timeframe:	
Various	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	93	93	
Units: Days				
least squares mean (standard deviation)	1.524 (\pm 2.6274)	2.847 (\pm 9.1286)	2.223 (\pm 9.0833)	

Attachments (see zip file)	Caplan-Meier time curve of B-Cell Depletion.PNG
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Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CD19+ B-Cell Depletion

End point title	Duration of CD19+ B-Cell Depletion
End point description:	
Pharmacodynamic endpoint: Duration of CD19+ B-Cell depletion. Only subjects that returned to non-	

depletion at or before Week 24 were included).

End point type	Secondary
End point timeframe:	
Various	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	26	21	
Units: Days				
least squares mean (standard deviation)	78.444 (\pm 77.5290)	85.856 (\pm 73.4460)	77.290 (\pm 72.0557)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of CD19+ B-Cell Count Verses Baseline

End point title	Percentage of CD19+ B-Cell Count Verses Baseline
End point description:	Pharmacodynamic endpoint: percentage of CD19+ B-Cell count verses Baseline (Day 1). Recovery was defined as either CD19+ B-Cell count returned to Baseline or the lower limit of normal of 100 cell/ μ L at Week 24.
End point type	Secondary
End point timeframe:	
Various	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93	93	90	
Units: Subjects	5	4	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Time Curve of CD19 B-cell Count Change at Day 15 and Week 24

End point title	Area Under the Concentration Time Curve of CD19 B-cell Count Change at Day 15 and Week 24
End point description:	Pharmacodynamic endpoint. Area under the concentration time curve of CD19 B-cell count change at Day 15 (AUEC0-d15) and week 24 (AUEC0-w24) based on change from baseline and percent of baseline

values.

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to Day 15 and week 24	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	76	73	
Units: Cells*day/ μ				
least squares mean (confidence interval 95%)				
AUEC(0-d15)	-2650.0 (-2786.0 to -2513.9)	-2672.1 (-2804.9 to -2539.3)	-2719.4 (-2855.3 to -2583.6)	
AUEC(0-d24)	-32707.6 (-33128.1 to -32287.1)	-33018.3 (-33440.4 to -32596.2)	-33003.7 (-33442.8 to -32564.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD19+ B-cell Count During the Study Period

End point title	Change From Baseline in CD19+ B-cell Count During the Study Period
End point description:	
Pharmacodynamic endpoint: Descriptive statistics (mean [SD]) of the change from baseline in CD19+ B-cell count during the study period (Day 15 [AUEC(0-d15)] and Week 24 [AUEC(0-w24)])	
End point type	Secondary
End point timeframe:	
Baseline (Day1) to Day 15 and Week 24	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	76	73	
Units: Cells*day/ μ L				
least squares mean (standard deviation)				
AUEC(0-d15)	-2729 (\pm 1915.3)	-2935 (\pm 2222.1)	-2367 (\pm 1978.1)	
AUEC90-w24)	-33500 (\pm 23881)	-36410 (\pm 22883)	-28500 (\pm 20878)	

Statistical analyses

Secondary: Change From Baseline in Immunoglobulin (Ig) G, IgM and IgA Levels

End point title	Change From Baseline in Immunoglobulin (Ig) G, IgM and IgA Levels
End point description:	
Pharmacodynamic endpoint: Descriptive statistics (mean [SD]) of the change from baseline in CD19+ B-cell count during the study period (Day 15 [AUEC(0-d15)] and Week 24 [AUEC(0-w24)])	
End point type	Secondary
End point timeframe:	
Screening to Week 52 (EOS)	

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	96	93	
Units: Mg/dL				
least squares mean (standard deviation)				
IgG Screening	1231.0 (± 299.36)	1230.1 (± 365.54)	1203.4 (± 373.29)	
IgG Week 8	1108.0 (± 242.20)	1080.6 (± 279.75)	1038.5 (± 290.01)	
IgG Week 16	1105.2 (± 232.51)	1075.7 (± 277.51)	1038.5 (± 290.01)	
IgG Week 24	1114.6 (± 251.78)	1077.2 (± 265.55)	1023.2 (± 278.70)	
IgG Week 52 (EOS)	1102.0 (± 272.44)	1081.1 (± 285.13)	999.9 (± 232.03)	
IgM Screening	164.3 (± 76.06)	167.9 (± 100.16)	159.0 (± 81.36)	
IgM Week 8	137.5 (± 71.38)	132.6 (± 83.58)	128.9 (± 68.50)	
IgM Week 16	123.7 (± 61.08)	124.9 (± 85.71)	117.0 (± 60.44)	
IgM Week 24	123.3 (± 62.37)	117.1 (± 80.96)	109.9 (± 73.11)	
IgM Week 36	111.7 (± 56.89)	108.0 (± 77.79)	99.7 (± 56.38)	
IgM Week 52 (EOS)	109.6 (± 56.80)	107.6 (± 77.00)	95.2 (± 52.57)	
IgA Screening	321.11 (± 269.22)	283.4 (± 134.80)	342.9 (± 153.24)	
IgA Week 8	293.6 (± 176.04)	264.4 (± 121.41)	316.5 (± 146.15)	
IgA Week 16	301.8 (± 204.18)	253.0 (± 111.58)	312.7 (± 151.87)	
IgA Week 24	279.8 (± 119.87)	263.0 (± 121.15)	307.7 (± 147.92)	
iGA Week 36	283.8 (± 204.12)	259.2 (± 116.55)	297.1 (± 146.85)	
IgA Week 52 (EOS)	269.4 (± 116.74)	254.7 (± 115.38)	297.8 (± 138.63)	
IgG week 36	1076.6 (± 246.62)	1060.9 (± 305.12)	976.6 (± 249.11)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in C-reactive Protein (CRP) Levels at Weeks 8, 16, 24, 36 and 52

End point title	Change From Baseline in C-reactive Protein (CRP) Levels at Weeks 8, 16, 24, 36 and 52
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End point description:

Pharmacodynamic endpoint: Change from baseline (Day 1) in C-reactive protein (CRP) levels (mg/dL) at weeks 8, 16, 24, 36 and 52 (EOS)

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to Week 52 (EOS)

End point values	SAIT101	MabThera	Rituxan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	96	93	
Units: Mg/dL				
least squares mean (standard deviation)				
CRP Day 1	19.5 (± 29.5)	15.5 (± 20.76)	16.1 (± 17.64)	
CRP Week 8	12.5 (± 15.78)	12.3 (± 20.29)	10.4 (± 12.85)	
CRP Week 16	8.5 (± 11.78)	7.2 (± 9.02)	7.3 (± 6.90)	
CRP Week 24	9.5 (± 14.54)	8.3 (± 14.40)	7.9 (± 10.35)	
CRP Week 36	8.0 (± 10.33)	7.0 (± 10.38)	7.1 (± 9.72)	
CRP Week 52 (EOS)	9.8 (± 14.28)	9.1 (± 15.01)	7.3 (± 11.33)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were collected from each subjects from the start of the first infusion of study drug on Day 1 until the Week 52 Data cut-off.

Adverse event reporting additional description:

After the subject signed the Informed Consent form (ICF), but prior to the initiation of study drug, only serious adverse events (SAEs) caused by a protocol mandated procedure were reported (e.g. SAEs related to invasive procedures such as biopsies).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	SAIT101 Arm
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Reporting group description:

SAIT101 Arm (Safety Analysis Set)

Reporting group title	MabThera Arm
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Reporting group description:

Mabthera Arm (Safety Analysis Set)

Reporting group title	Rituxan Arm
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Reporting group description:

Rituxan Arm (Safety Analysis Set)

Serious adverse events	SAIT101 Arm	MabThera Arm	Rituxan Arm
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 98 (7.14%)	7 / 98 (7.14%)	13 / 98 (13.27%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			

subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia	Additional description: One subject in the MabThera group experienced the treatment-emergent SAE of anemia on study day 58 of treatment, which was reported as severe and considered as related to study treatment.		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia	Additional description: One subject in the SAIT101 group experienced the treatment-emergent SAE of febrile neutropenia on study day 68 of treatment, which was reported as moderate in intensity and considered related to study treatment.		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Interstitial lung disease			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B reactivation			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			

subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural hematoma			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SAIT101 Arm	MabThera Arm	Rituxan Arm
Total subjects affected by non-serious adverse events subjects affected / exposed	72 / 98 (73.47%)	70 / 98 (71.43%)	75 / 98 (76.53%)
Injury, poisoning and procedural complications Urinary tract infection subjects affected / exposed occurrences (all)	13 / 98 (13.27%) 14	4 / 98 (4.08%) 6	8 / 98 (8.16%) 10
Infusion related reaction subjects affected / exposed occurrences (all)	2 / 98 (2.04%) 2	2 / 98 (2.04%) 2	7 / 98 (7.14%) 8
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	2 / 98 (2.04%) 2	5 / 98 (5.10%) 5	2 / 98 (2.04%) 2
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	8 / 98 (8.16%) 9	3 / 98 (3.06%) 3
Gastrointestinal disorders Gastritis subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	1 / 98 (1.02%) 1	5 / 98 (5.10%) 5
Musculoskeletal and connective tissue disorders Rheumatoid arthritis subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 7	6 / 98 (6.12%) 6	6 / 98 (6.12%) 7
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 98 (7.14%) 9	3 / 98 (3.06%) 4	7 / 98 (7.14%) 7
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 5	8 / 98 (8.16%) 10	5 / 98 (5.10%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2015	Amendment 3 dated 02 June 2016 implemented the following changes: <ul style="list-style-type: none">• correction of errors for text from previous versions• correction of grammatical errors• addition of missing words/text and deletion of certain text
26 October 2015	Amendment 1 dated 26 October 2015 implemented the following changes: <ul style="list-style-type: none">• revised the criteria of study population• clarified study design• terminology for premedication was updated• clarified the definition for clinical remission• clarified inclusion and exclusion criteria• revised text for subject withdrawal and updated the discontinuation criteria• addition of text related to interim analysis• modified schedule of assessments• pharmacodynamic variables were clarified• updated the washout period for prior medications• administrative changes were made, correction of errors for text from previous versions and addition/deletion of certain text to clarify the important points
19 May 2016	Amendment 2 dated 19 May 2016 implemented the following changes: <ul style="list-style-type: none">• criteria of study population and phase of study development were revised• modified the study design of MabThera group in Part B• updated the terminology for premedication• addition of text related to week 4 interim analysis, and criteria for unblinding at week 24 was clarified• modified the inclusion criteria for the dose of MTX given as a current treatment for RA• main criteria of evaluation were clarified by specifying the study endpoints• withdrawn subjects were included in the PK analysis if the eligibility criteria for PK data set were met• modified the text related to primary safety concerns associated with rituximab• updated the text related to study treatment formulation Archigen Biotech Limited• updated the absolute neutrophil count and platelet count prior to second course of study treatment• clarified the management of hepatitis reactivation and other infections during rituximab therapy• revisions were made in inclusion and exclusion criteria text for clarity• subjects who lacked efficacy could be included in the PK and efficacy analysis. subjects receiving rescue therapy prior to week 24 were considered not to be eligible for second course of infusion• modified schedule of assessments• criteria for SAE, ADR, and AESI, and reporting of AE and SAE were clarified• added text for PML and mucocutaneous reactions• updated criteria for diagnosing anaphylaxis• added text for changes in clinical laboratory assessment results• updated the text for sample size and analysis sets, handling missing values and outliers• clarified the text for study treatment preparation and disposal of unused study treatments• revisions in text made to clarify the important points• correction of grammatical, typo and certain editorial and consistency errors

27 April 2017	<p>Amendment 4 dated 27 April 2017 implemented the following changes:</p> <ul style="list-style-type: none"> • name of finished product terminology updated as proposed biosimilar to rituximab • Sixty days of screening time needed for prophylaxis of latent TB were allowed • assessments to be done within 30 days of screening period was clarified • unnecessary restriction in time duration for premedication intake was deleted • eligibility criteria on latent TB was clarified • sampling time point was clarified • time point of second interim safety analysis was changed to align with DSMB review timepoint • inclusion criteria related to contraception and pregnancy testing was changed as per clinical trial facilitation group guidance • immunogenicity sampling at immune-response-related was added for intensive monitoring • serious AE collection changed to collect minimally required information by ICH E6 R2 (2015. 6. 11) • clarified that any AE were followed up to resolution • revisions in text made to clarify the important points • correction of certain editorial and consistency errors
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported