ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 03/10/2015

ClinicalTrials.gov ID: NCT00502853

Study Identification

Unique Protocol ID:	ML21081
Brief Title:	A Pilot Study of MabThera (Rituximab) Evaluated by MRI in Patients With Rheumatoid Arthritis.
Official Title:	Pilot Study to Evaluate the Effect of Mabthera in Combination With MTX in the Inhibition of Progression of Synovitis, Bone Marrow Edema, and Erosions Evaluated by Magnetic Resonance Imaging (MRI) in the Hand of Patients With Rheumatoid Arthritis.
Secondary IDs:	

Study Status

Record Verification:	March 2015
Overall Status:	Completed
Study Start:	October 2007
Primary Completion:	July 2010 [Actual]
Study Completion:	July 2010 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	No

IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: unknown Board Name: Comitato Etico A.O. Universitaria San Martino Board Affiliation: Unknown Phone: +39 010 5555021 Email: comitato.etico@hsanmartino.it
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Italy: Ethics Committee

Study Description

Brief Summary:	This single arm study will measure the effect of MabThera in combination with methotrexate on the progression of synovitis, the extent of bone marrow edema, and the number of erosions in the wrist and hand of patients with rheumatoid arthritis, using a new MRI technique. Patients will receive MabThera 1000mg i.v. on days 1 and 15, in combination with a stable dosage of 10-25mg/week methotrexate throughout the duration of the study. Further courses of MabThera will be provided to eligible patients. MRI will be performed 1-2 weeks before treatment initiation, and repeated 1 and 6 months after the first MabThera infusion. The anticipated time on study treatment is 1-2 years, and the target sample size is <100 individuals.
Detailed Description:	

Conditions

Conditions:	Rheumatoid Arthritis
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 4
Intervention Model:	Single Group Assignment
Number of Arms:	1
Masking:	Open Label
Allocation:	Non-Randomized

Endpoint Classification: Safety/Efficacy Study

Enrollment: 10 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1	Drug: rituximab [MabThera/Rituxan] 1000mg iv on days 1 and 15 Drug: Methotrexate 10-25mg/week

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age: 75 Years

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- adult patients, 18-75 years of age;
- rheumatoid arthritis for >=3 months and <=10 years;
- inadequate response to methotrexate (12.5-25mg/week) for >=3 months;
- evidence of erosive disease and/or clinical synovitis in a signal joint.

Exclusion Criteria:

- autoimmune rheumatic diseases other than RA;
- surgical operations on bones/joints in 12 weeks prior to baseline visit;
- concomitant treatment with biologic agents;
- previous treatment with more than one biologic agent approved for RA, or with cell-depleting therapies.

Contacts/Locations

Study Officials: Clinical Trials
Study Director

Hoffmann-La Roche

Locations: Italy
Genova, Italy, 16132

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Rituximab Plus (+) Methotrexate (MTX)	Participants received rituximab 1000 milligrams (mg) intravenously (IV) and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg per week (mg/week) by mouth or parenterally. Nonresponsive participants (defined as Disease Activity Score Based on 28-Joint Count and C-Reactive Protein [DAS28-CRP] score of greater than [>]2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Overall Study

	Rituximab Plus (+) Methotrexate (MTX)
Started	10
Completed	10
Not Completed	0

Baseline Characteristics

Analysis Population Description
Safety population: all participants who received any part of an infusion of study drug.

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Baseline Measures

	Rituximab + MTX
Number of Participants	10
Age, Continuous [units: years] Mean (Standard Deviation)	52.42 (15.681)
Gender, Male/Female [units: participants]	
Female	6
Male	4

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Synovitis Score
Measure Description	Extension and degree of synovitis in wrist according to RAMRIS score developed by OMERACT. Synovitis is an area in synovial compartment that shows above normal post-gadolinium enhancement of a thickness greater than width of normal synovium. Synovitis is assessed in 3 wrist regions (distal radioulnar joint; radiocarpal joint; intercarpal and carpometacarpal joints) and in each metacarpophalangeal (MCP) joint. 1st carpometacarpal joint and 1st MCP joint are not scored. Score 0 is normal, and 1–3 (mild, moderate, severe) are by thirds of the presumed maximum volume of enhancing tissue in the synovial compartment. Total synovitis score=the sum of the individual scores (3 wrist regions [range 0-9] or 4 MCP joints [range 0-12]) for an overall range of 0–21, where 0=no damage and maximum score [9, 12, or 21]=most severe damage. Change in synovitis = Follow-up synovitis score - baseline score.
Time Frame	Baseline, Week 4, and Week 24
Safety Issue?	No

Analysis Population Description

The Safety Population included all participants who received any portion of the rituximab dose and was used for efficacy and safety analyses.

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Synovitis Score [units: units on a scale] Mean (Standard Deviation)	
Baseline	3.4 (1.58)
Week 4	2.3 (2.75)
Change at Week 4	-1.1 (2.38)
Week 24	2.4 (1.74)
Change at Week 24	-1.0 (1.73)

Statistical Analysis 1 for Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Synovitis Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline to Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1776
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Synovitis Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline to Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1215
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Synovitis Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2246
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	-0.1606
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.1231
	Estimation Comments	[Not specified]

2. Primary Outcome Measure:

Measure Title	OMERACT RAMRIS Bone Edema Score
Measure Description	Extension and degree of bone edema in the wrist according to the RAMRIS score developed by OMERACT. Bone edema is a lesion within the trabecular bone, with ill-defined margins and signal characteristics consistent with increased water content. Each bone (wrists: carpal bones, distal radius, distal ulna, metacarpal bases; MCP joints: metacarpal heads, phalangeal bases) is scored separately. The scale of 0–3 was based on the proportion of bone with edema, as follows: 0=no edema; 1=1 percent (%) to 33% of bone was edematous; 2 = 34%–66% of bone was edematous; and 3= 67%–100% of bone was edematous. Total bone edema score=sum of the individual scores for an overall range of 0–69, where 0=no edema and 69=most severe edema. Change in bone edema = follow-up bone edema score - baseline score.
Time Frame	Baseline, Weeks 4 and 24
Safety Issue?	No

Analysis Population Description

Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
OMERACT RAMRIS Bone Edema Score [units: units on a scale] Mean (Standard Deviation)	
Baseline	23.2 (13.56)
Week 4	23.8 (15.68)
Change at Week 4	0.6 (14.52)
Week 24	24.0 (14.66)
Change at Week 24	0.8 (16.77)

Statistical Analysis 1 for OMERACT RAMRIS Bone Edema Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline to Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8989
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for OMERACT RAMRIS Bone Edema Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline to Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8834
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for OMERACT RAMRIS Bone Edema Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8841
	Comments	[Not specified]

	Method	Other [Random coefficient model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	0.1357
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.9051
	Estimation Comments	[Not specified]

3. Primary Outcome Measure:

Measure Title	OMERACT RAMRIS Erosion Score
Measure Description	MRI bone erosion measures a sharply marginated bone lesion, with correct juxta-articular localization and typical signal characteristics, which is visible in 2 planes with a cortical break seen in at least 1 plane. Each bone (wrists: carpal bones, distal radius, distal ulna, metacarpal bases; MCP joints: metacarpal heads, phalangeal bases) scored separately. Scale is 0–10 based on proportion of eroded bone compared to assessed bone volume (0=no erosion; 1=1%–10% of bone eroded; 2=11%–20%, etc). For long bones, assessed bone volume is from articular surface (or best estimated position if absent) to depth of 1 centimeter (cm); in carpal bones it is the whole bone. Total erosion score=sum of individual scores for an overall range of 0–230, where 0=no erosion and 230=most severe erosion. Change in erosion=Follow-up erosion score - baseline score.
Time Frame	Baseline, Week 4, and Week 24
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
OMERACT RAMRIS Erosion Score [units: units on a scale]	

	Rituximab + MTX
Mean (Standard Deviation)	
Baseline	7.9 (3.67)
Week 4	8.1 (3.63)
Change at Week 4	0.2 (1.14)
Week 24	9.1 (4.38)
Change at Week 24	1.2 (2.39)

Statistical Analysis 1 for OMERACT RAMRIS Erosion Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline to Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5911
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for OMERACT RAMRIS Erosion Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline to Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1475
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for OMERACT RAMRIS Erosion Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1463
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	0.1786
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.1123
	Estimation Comments	[Not specified]

4. Primary Outcome Measure:

Measure Title	Early Enhancement Rate (REE)
Measure Description	A low cost, low field dedicated extremity MRI unit was used, which is specifically designed for the examination of peripheral joints. In addition to the standard OMERACT-RAMRIS scoring system, additional data were elaborated by using “dynamic” MRI, i.e. Contrast-Enhanced Dynamic MRI (DCE-MRI). This method evaluates the diffusion of the contrast mean in a series of very short sequences thus providing a diffusion curve which is proportionate to the extent of inflammation in the synovial membrane. Numerical parameters used with this method are the slope in the initial phase (rate of early enhancement - REE) and its “steady state” condition (relative enhancement - RE). REE per second during the first 55 seconds was calculated according to the formula REE55 = (S55-S0)/(S0x55)x100%. The REE shows the slope of the curve of contrast uptake tangential to the α angle and is steeper if inflammation is higher.
Time Frame	Baseline, Weeks 4 and 24
Safety Issue?	No

Analysis Population Description

Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Early Enhancement Rate (REE) [units: percent per second] Mean (Standard Deviation)	
Baseline	0.356 (0.2651)
Week 4	0.489 (0.5110)
Change at Week 4	0.150 (0.4106)
Week 24	0.363 (0.2615)
Change at Week 24	-0.012 (0.3227)

Statistical Analysis 1 for Early Enhancement Rate (REE)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3358
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Early Enhancement Rate (REE)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.9158
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Early Enhancement Rate (REE)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.8877
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Slope
	Estimated Value	0.003418
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.02345
	Estimation Comments	[Not specified]

5. Primary Outcome Measure:

Measure Title	Relative Enhancement (RE) Score

Measure Description	A low cost, low field dedicated extremity MRI unit was used, which is specifically designed for the examination of peripheral joints. In addition to the standard OMERACT-RAMRIS scoring system, additional data were elaborated by using “dynamic” MRI (DCE-MRI). This method evaluates the diffusion of the contrast mean in a series of very short sequences thus providing a diffusion curve which is proportionate to the extent of inflammation in the synovial membrane. Numerical parameters used with this method are the slope in the initial phase (REE) and its “steady state” condition (RE).
Time Frame	Baseline, Weeks 4 and 24
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Relative Enhancement (RE) Score [units: percent] Mean (Standard Deviation)	
Baseline	66.978 (42.3981)
Week 4	57.889 (51.9276)
Change at Week 4	-3.812 (34.3034)
Week 24	40.075 (21.6891)
Change at Week 24	-34.450 (32.9609)

Statistical Analysis 1 for Relative Enhancement (RE) Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7624
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Relative Enhancement (RE) Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0212
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Relative Enhancement (RE) Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0712
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	-4.2681
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.0529
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Ritchie Articular Index Scores
Measure Description	The Ritchie Articular Index is a graded assessment of tenderness in 26 joint regions. The sum of the grades of tenderness (0=not tender, 1=tender, 2=tender and causes wince, and 3 tender, causes wince and effort to withdraw) elicited by applying firm pressure over the joint margin of articular joints (such as shoulders, elbow, wrists, hips). The scores ranged from 0 (no tenderness) to 78 (most severe tenderness).
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Ritchie Articular Index Scores [units: units on a scale] Mean (Standard Deviation)	
Baseline	20.7 (8.30)
Week 4	16.9 (9.49)
Change at Week 4	-3.8 (6.78)
Week 12	9.5 (6.72)

	Rituximab + MTX
Change at Week 12	-11.2 (6.11)
Week 24	11.7 (9.60)
Change at Week 24	-9.0 (6.50)

Statistical Analysis 1 for Ritchie Articular Index Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1101
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Ritchie Articular Index Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0003
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Ritchie Articular Index Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0018
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 4 for Ritchie Articular Index Scores

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0023
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Slope
	Estimated Value	-2.0857
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.4965
	Estimation Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Health Assessment Questionnaire - Disability Index (HAQ-DI) Score

Measure Description	The Stanford HAQ-DI is a participant-reported questionnaire specific for rheumatoid arthritis (RA). It consist of 20 items referring to eight component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. Each item within a domain was scored on a 4-point Likert scale from 0 to 3: 0 = no difficulty; 1 = some difficulty; 2 = much difficulty; 3 = unable to do. The highest score reported by the participant for a domain determined the score for that domain. The overall disability index is computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty.
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description

Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Health Assessment Questionnaire - Disability Index (HAQ-DI) Score [units: units on a scale] Mean (Standard Deviation)	
Baseline	1.788 (0.6848)
Week 4	1.471 (0.7976)
Change at Week 4	-0.316 (0.3687)
Week 12	0.838 (0.6668)
Change at Week 12	-0.950 (0.7997)
Week 24	0.888 (0.7008)
Change at Week 24	-0.900 (0.6503)

Statistical Analysis 1 for Health Assessment Questionnaire - Disability Index (HAQ-DI) Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0240
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Health Assessment Questionnaire - Disability Index (HAQ-DI) Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0045
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Health Assessment Questionnaire - Disability Index (HAQ-DI) Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0018
	Comments	[Not specified]

	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 4 for Health Assessment Questionnaire - Disability Index (HAQ-DI) Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0019
	Comments	[Not specified]
	Method	Other [Random Coefficient Model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	-0.1964
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.04524
	Estimation Comments	[Not specified]

8. Secondary Outcome Measure:

Measure Title	Patient's Global Assessment of Pain
Measure Description	The participant’s assessment of their current level of pain on a 0 to 100 millimeter (mm) horizontal VAS. The left-hand extreme of the line was described as “no pain” and the right-hand as “unbearable pain”. The participant was asked to mark the line corresponding to their current level of pain and the distance from the left edge was recorded.
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description

Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Patient's Global Assessment of Pain [units: mm] Mean (Standard Deviation)	
Baseline	60.6 (22.75)
Week 4	49.0 (31.73)
Change at Week 4	-11.6 (20.38)
Week 12	34.7 (16.77)
Change at Week 12	-29.9 (28.27)
Week 24	22.7 (16.92)
Change at Week 24	-30.7 (23.69)

Statistical Analysis 1 for Patient's Global Assessment of Pain

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0074
	Comments	[Not specified]
	Method	Other [Random Coefficient Model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	-6.6294
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.8623
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Patient's Global Assessment of Pain

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1273
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Patient's Global Assessment of Pain

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0132
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 4 for Patient's Global Assessment of Pain

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1542
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

9. Secondary Outcome Measure:

Measure Title	DAS28 Score
Measure Description	DAS28 calculated from the number of swollen joints and tender joints using the 28-joints count, the erythrocyte sedimentation rate (ESR) (millimeters per hour [mm/hr]) and Patient's Global Assessment of Disease Activity (participant-rated arthritis activity assessment) with transformed scores ranging 0 to 10; higher scores indicated greater affectation due to disease activity. A DAS28 score of less than or equal to (≤) 3.2 = low disease activity, a DAS28 score of >3.2 to 5.1 = moderate to high disease activity.
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
DAS28 Score [units: units on a scale] Mean (Standard Deviation)	
Baseline	5.735 (0.8099)

	Rituximab + MTX
Week 4	5.261 (1.5552)
Change at Week 4	-0.474 (0.9250)
Week 12	4.307 (1.4552)
Change at Week 12	-1.587 (0.9743)
Week 24	4.400 (1.4263)
Change at Week 24	-1.335 (1.1425)

Statistical Analysis 1 for DAS28 Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1396
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for DAS28 Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0050
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for DAS28 Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0050
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 4 for DAS28 Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0054
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Slope
	Estimated Value	-0.2902
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.07966
	Estimation Comments	[Not specified]

10. Secondary Outcome Measure:

Measure Title	Erythrocyte Sedimentation Rate (ESR)

Measure Description	ESR was determined using the Westergren method. ESR measures how fast red blood cells (erythrocytes) fall to the bottom of a fine glass tube that is filled with the participant's blood. The higher the sedimentation rate the greater the inflammation.
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Erythrocyte Sedimentation Rate (ESR) [units: mm/hr] Mean (Standard Deviation)	
Baseline	72.6 (27.56)
Week 4	63.8 (26.63)
Change at Week 4	-15.6 (15.61)
Week 12	48.0 (26.12)
Change at Week 12	-30.2 (26.47)
Week 24	53.4 (18.34)
Change at Week 24	-19.1 (21.25)

Statistical Analysis 1 for Erythrocyte Sedimentation Rate (ESR)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0254
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Erythrocyte Sedimentation Rate (ESR)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0384
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Erythrocyte Sedimentation Rate (ESR)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0271
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 4 for Erythrocyte Sedimentation Rate (ESR)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0124
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	-4.7586
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.5278
	Estimation Comments	[Not specified]

11. Secondary Outcome Measure:

Measure Title	C-Reactive Protein (CRP)
Measure Description	CRP measured by milligrams per deciliter (mg/dL). High levels of CRP are indicators of active inflammation.
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
C-Reactive Protein (CRP) [units: mg/dL] Mean (Standard Deviation)	
Baseline	21.630 (24.1805)
Week 4	23.480 (22.7518)
Change at Week 4	1.850 (16.9261)
Week 12	10.929 (12.2432)
Change at Week 12	-10.929 (18.1919)
Week 24	23.410 (26.8998)
Change at Week 24	1.780 (36.7504)

Statistical Analysis 1 for C-Reactive Protein (CRP)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7376
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for C-Reactive Protein (CRP)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1631
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for C-Reactive Protein (CRP)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8816
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 4 for C-Reactive Protein (CRP)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8835
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	-0.2927
	Parameter Dispersion	Type: Standard Error of the mean

		Value: 1.9408
	Estimation Comments	[Not specified]

12. Secondary Outcome Measure:

Measure Title	Anti-Cyclic Citrullinated Peptide (Anti-CCP) Autoantibodies Count
Measure Description	Anti-CCP autoantibodies count measured by units per milliliter (U/mL). The anti-CCP autoantibodies bind antigenic determinants that contain the unusual amino acid citrulline. The anti-CCP antibody is a highly specific diagnostic test of RA (though with variable sensitivity) and a marker of joint damage with high prognostic significance.
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Anti-Cyclic Citrullinated Peptide (Anti-CCP) Autoantibodies Count [units: U/mL] Mean (Standard Deviation)	
Baseline	55.230 (33.3902)
Week 4	44.311 (28.4448)
Change at Week 4	-10.133 (18.0815)
Week 12	41.925 (32.2708)
Change at Week 12	-12.862 (16.7306)
Week 24	122.230 (247.7763)

	Rituximab + MTX
Change at Week 24	67.000 (247.0019)

Statistical Analysis 1 for Anti-Cyclic Citrullinated Peptide (Anti-CCP) Autoantibodies Count

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1312
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Anti-Cyclic Citrullinated Peptide (Anti-CCP) Autoantibodies Count

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0662
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Anti-Cyclic Citrullinated Peptide (Anti-CCP) Autoantibodies Count

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4133
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 4 for Anti-Cyclic Citrullinated Peptide (Anti-CCP) Autoantibodies Count

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6049
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	8.8196
	Parameter Dispersion	Type: Standard Error of the mean Value: 16.4534
	Estimation Comments	[Not specified]

13. Secondary Outcome Measure:

Measure Title	Rheumatoid Factor (RF) Immunoglobulin M (IgM) Concentrations
Measure Description	RF IgM concentrations measured by international units per milliliter (IU/mL). RF is an antibody reacting against the fragment, crystallizable (Fc) region of IgG. Quantitative measurements have shown a prognostic value in distinguishing between progressive and non-progressive disease in early RA, a correlation with radiologically determined joint damage, and relation with clinical improvement after disease-modifying anti-rheumatic treatment.
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Rheumatoid Factor (RF) Immunoglobulin M (IgM) Concentrations [units: IU/mL] Mean (Standard Deviation)	
Baseline	570.922 (827.0900)
Week 4	307.300 (337.9550)
Change at Week 4	-285.138 (530.8209)
Week 12	241.756 (357.8067)
Change at Week 12	-329.167 (499.0426)
Week 24	281.230 (337.6633)
Change at Week 24	-267.389 (529.7928)

Statistical Analysis 1 for Rheumatoid Factor (RF) Immunoglobulin M (IgM) Concentrations

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1725
	Comments	[Not specified]

	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Rheumatoid Factor (RF) Immunoglobulin M (IgM) Concentrations

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0832
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Rheumatoid Factor (RF) Immunoglobulin M (IgM) Concentrations

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1685
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 4 for Rheumatoid Factor (RF) Immunoglobulin M (IgM) Concentrations

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1331
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	-55.4458
	Parameter Dispersion	Type: Standard Error of the mean Value: 33.5821
	Estimation Comments	[Not specified]

14. Secondary Outcome Measure:

Measure Title	Total Immunoglobulin (Ig) Concentrations
Measure Description	Total Ig concentrations as measured by milligrams per milliliter (mg/mL).
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description

Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Total Immunoglobulin (Ig) Concentrations [units: mg/mL] Mean (Standard Deviation)	
Baseline	20.258 (6.7055)

	Rituximab + MTX
Week 4	17.786 (4.7033)
Change at Week 4	-1.602 (3.6846)
Week 12	17.296 (4.1845)
Change at Week 12	-2.336 (4.0998)
Week 24	18.354 (4.3432)
Change at Week 24	-1.042 (4.5527)

Statistical Analysis 1 for Total Immunoglobulin (Ig) Concentrations

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2938
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Total Immunoglobulin (Ig) Concentrations

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2216
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Total Immunoglobulin (Ig) Concentrations

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5670
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

15. Secondary Outcome Measure:

Measure Title	Hematocrit Concentration (%)
Measure Description	
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description
Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Hematocrit Concentration (%) [units: percentage] Mean (Standard Deviation)	

	Rituximab + MTX
Baseline	36.110 (2.2218)
Week 4	37.860 (1.4315)
Change at Week 4	1.750 (2.9497)
Week 12	37.512 (2.5798)
Change at Week 12	1.350 (4.3065)
Week 24	37.967 (2.6106)
Change at Week 24	1.667 (3.6695)

Statistical Analysis 1 for Hematocrit Concentration (%)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0934
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Hematocrit Concentration (%)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4047
	Comments	[Not specified]
	Method	Other [Student's t-test]

	Comments	[Not specified]

Statistical Analysis 3 for Hematocrit Concentration (%)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2101
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 4 for Hematocrit Concentration (%)

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1451
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Slope
	Estimated Value	0.3997
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.2506
	Estimation Comments	[Not specified]

16. Secondary Outcome Measure:

Measure Title	Percentage of Total B-lymphocytes
Measure Description	Concentration of all B-lymphocytes subtypes was assessed.
Time Frame	Baseline and Weeks 4, 12, and 24
Safety Issue?	No

Analysis Population Description

Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Percentage of Total B-lymphocytes [units: percentage of cells] Mean (Standard Deviation)	
Baseline	24.040 (10.2954)
Week 4	22.430 (8.0601)
Change at Week 4	-1.610 (7.1818)
Week 12	30.125 (12.0576)
Change at Week 12	5.562 (11.6748)
Week 24	24.133 (10.2802)
Change at Week 24	1.111 (7.7194)

Statistical Analysis 1 for Percentage of Total B-lymphocytes

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 4

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4963
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 2 for Percentage of Total B-lymphocytes

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 12
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2198
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 3 for Percentage of Total B-lymphocytes

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6773
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Statistical Analysis 4 for Percentage of Total B-lymphocytes

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Trend over time
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.5531
	Comments	[Not specified]
	Method	Other [Random coefficient model]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Slope
	Estimated Value	0.3688
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.5987
	Estimation Comments	[Not specified]

17. Secondary Outcome Measure:

Measure Title	Erosion Score - Right Hand
Measure Description	The erosion score per joint of the hands can range from 0 to 5. Erosions were scored 1 if they were discrete but clearly present, and 2 or 3 if they were larger, depending on the surface area of the joint involved. A score of 3 was given if the erosion was large and extended over the imaginary middle of the bone. A score of 5 was given if a complete collapse of the joint was present or if the full surface of the joint was affected. In each joint, individual erosions were summed up to a maximum of 5. The maximal erosion score for each hand was thus 80, considering the 16 areas for erosions per hand.
Time Frame	Baseline and Week 24
Safety Issue?	No

Analysis Population Description

Safety Population

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Erosion Score - Right Hand [units: units on a scale] Mean (Standard Deviation)	
Baseline	2.50 (2.972)
Week 24	2.19 (2.963)
Change at Week 24	-0.44 (1.741)

Statistical Analysis 1 for Erosion Score - Right Hand

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5002
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

18. Secondary Outcome Measure:

Measure Title	Erosion Score - Left Hand

Measure Description	The erosion score per joint of the hands can range from 0 to 5. Erosions were scored 1 if they were discrete but clearly present, and 2 or 3 if they were larger, depending on the surface area of the joint involved. A score of 3 was given if the erosion was large and extended over the imaginary middle of the bone. A score of 5 was given if a complete collapse of the joint was present or if the full surface of the joint was affected. In each joint, individual erosions were summed up to a maximum of 5. The maximal erosion score for each hand was thus 80, considering the 16 areas for erosions per hand.
Time Frame	Baseline and Week 24
Safety Issue?	No

Analysis Population Description

Safety Population; n=number of participants with values for analysis at the specified timepoints.

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	10
Erosion Score - Left Hand [units: units on a scale] Mean (Standard Deviation)	
Baseline (n=10)	1.90 (2.558)
Week 24 (n=8)	1.75 (2.619)
Change at Week 24 (n=8)	0.00 (0.707)

Statistical Analysis 1 for Erosion Score - Left Hand

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	1.0000
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

19. Secondary Outcome Measure:

Measure Title	Joint Space Narrowing - Right Hand
Measure Description	Joint space narrowing and joint subluxation or luxation are combined in a single score with a range of 0 to 4. A normal joint space was scored 0. A score of 2 was allowed to a focal narrowing of the joint or to a joint space not sufficiently narrowed to be scored 2. The score of 1 was not to be used when the reader was unsure whether there was joint space narrowing. A generalized narrowing leaving more than 50% of the original joint space present was scored 2. A generalized narrowing leaving less than 50% of the original joint space present was scored 3, and a subluxation of a joint was also scored 3. A bony ankylosis or a complete luxation of the joint was scored 4. A total of 13 joints were evaluated for narrowing and the scores were summed (13 times [x] 4 [maximum per joint]). Each sum was normalized to a scale of 0 (best possible outcome) to 100 (worst possible outcome).
Time Frame	Baseline and Week 24
Safety Issue?	No

Analysis Population Description

Safety Population; only participants with values at both Baseline and Week 24 were included in the analysis.

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	8
Joint Space Narrowing - Right Hand [units: units on a scale] Mean (Standard Deviation)	
Baseline	10.40 (7.859)
Week 24	10.13 (6.786)

	Rituximab + MTX
Change at Week 24	0.94 (6.609)

Statistical Analysis 1 for Joint Space Narrowing - Right Hand

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7002
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

20. Secondary Outcome Measure:

Measure Title	Joint Space Narrowing - Left Hand
Measure Description	Joint space narrowing and joint subluxation or luxation are combined in a single score with a range of 0 to 4. A normal joint space was scored 0. A score of 2 was allowed to a focal narrowing of the joint or to a joint space not sufficiently narrowed to be scored 2. The score of 1 was not to be used when the reader was unsure whether there was joint space narrowing. A generalized narrowing leaving more than 50% of the original joint space present was scored 2. A generalized narrowing leaving less than 50% of the original joint space present was scored 3, and a subluxation of a joint was also scored 3. A bony ankylosis or a complete luxation of the joint was scored 4. A total of 13 joints were evaluated for narrowing and the scores were summed (13 x 4 [maximum per joint]). Each sum was normalized to a scale of 0 (best possible outcome) to 100 (worst possible outcome).
Time Frame	Baseline and Week 24
Safety Issue?	No

Analysis Population Description

Safety Population; only participants with values at both Baseline and Week 24 were included in the analysis.

Reporting Groups

	Description
Rituximab + MTX	Participants received 1000 mg of Rituximab by IV infusion on Days 1 and 15 (considered to be one cycle). Participants also received 10-25 mg/week stable concomitant MTX by mouth or parenterally. Additional cycles of 2 infusions each could be administered provided the following: a minimum of 24 weeks had passed since the first infusion of the last course of study medication; the participant had a DAS28-CRP score of >2.6; the participant had a neutrophil count not below 1.5x10^3/µL; there was an absence of significant cardiac or pulmonary disease, primary or secondary immunodeficiency, and infections.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	8
Joint Space Narrowing - Left Hand [units: units on a scale] Mean (Standard Deviation)	
Baseline	8.45 (6.039)
Week 24	9.13 (6.004)
Change at Week 24	2.19 (5.694)

Statistical Analysis 1 for Joint Space Narrowing - Left Hand

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3132
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

21. Secondary Outcome Measure:

Measure Title	X-Rays: Right Hand Total Score

Measure Description	Right hand total scores as measured by X-rays examining erosion and joint space narrowing. Total score was calculated as the sum of the erosion score and the joint space narrowing score and scores ranged from 0 (best possible outcome) to 180 (worst possible outcome).
Time Frame	Baseline and Week 24
Safety Issue?	No

Analysis Population Description

Safety Population; only participants with values at both Baseline and Week 24 were included in the analysis.

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	8
X-Rays: Right Hand Total Score [units: units on a scale] Mean (Standard Deviation)	
Baseline	12.90 (9.433)
Week 24	12.31 (7.828)
Change at Week 24	0.50 (7.714)

Statistical Analysis 1 for X-Rays: Right Hand Total Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8597
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

22. Secondary Outcome Measure:

Measure Title	X-Rays: Left Hand Total Score
Measure Description	Left hand total scores as measured by X-rays examining erosion and joint space narrowing. Total score was calculated as the sum of the erosion score and the joint space narrowing score and ranged from 0 (best possible outcome) to 180 (worst possible outcome).
Time Frame	Baseline and Week 24
Safety Issue?	No

Analysis Population Description

Safety Population; only participants with values at both Baseline and Week 24 were included in the analysis.

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Measured Values

	Rituximab + MTX
Number of Participants Analyzed	8
X-Rays: Left Hand Total Score [units: units on a scale] Mean (Standard Deviation)	
Baseline	10.35 (7.192)
Week 24	10.88 (6.813)
Change at Week 24	2.19 (6.341)

Statistical Analysis 1 for X-Rays: Left Hand Total Score

Statistical Analysis Overview	Comparison Groups	Rituximab + MTX
	Comments	Change from Baseline at Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3617
	Comments	[Not specified]
	Method	Other [Student's t-test]
	Comments	[Not specified]

Reported Adverse Events

Time Frame	From baseline up to 24 weeks.
Additional Description	[Not specified]

Reporting Groups

	Description
Rituximab + MTX	Participants received rituximab 1000 mg IV and methylprednisolone 100 mg IV on Days 1 and 15 and MTX at a stable dose of 10-25 mg/week by mouth or parenterally. Nonresponsive participants (defined as DAS28-CRP score of >2.6) could have received additional infusions of rituximab 1000 mg (2 infusions, 14 days apart) provided a minimum of 24 weeks had passed since the first infusion of the last course of study medication.

Serious Adverse Events

	Rituximab + MTX
	Affected/At Risk (%)
Total	2/10 (20%)
Cardiac disorders	
Atrial fibrillation [A] *	1/10 (10%)
Infections and infestations	
Device related infection [A] *	1/10 (10%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Rituximab + MTX
	Affected/At Risk (%)
Total	10/10 (100%)
Endocrine disorders	
Hypothyroidism [A] *	1/10 (10%)
Gastrointestinal disorders	
Apical granuloma [A] *	1/10 (10%)
Infections and infestations	
Influenza [A] *	3/10 (30%)
Paronychia [A] *	1/10 (10%)
Pharyngitis [A] *	3/10 (30%)
Urinary tract infection bacterial [A] *	1/10 (10%)
Investigations	
Alanine aminotransferase increased [A] *	2/10 (20%)
Metabolism and nutrition disorders	
Diabetes mellitus [A] *	2/10 (20%)
Musculoskeletal and connective tissue disorders	
Back pain [A] *	1/10 (10%)
Neck pain [A] *	1/10 (10%)
Osteoarthritis [A] *	1/10 (10%)
Tenosynovitis stenosans [A] *	1/10 (10%)
Nervous system disorders	

	Rituximab + MTX
	Affected/At Risk (%)
Carpal tunnel syndrome [A] *	1/10 (10%)
Paraesthesia [A] *	1/10 (10%)
Renal and urinary disorders	
Haematuria [A] *	1/10 (10%)
Reproductive system and breast disorders	
Amenorrhoea [A] *	1/10 (10%)
Skin and subcutaneous tissue disorders	
Rash pruritic [A] *	1/10 (10%)
Rosacea [A] *	1/10 (10%)
Vascular disorders	
Hypertension [A] *	1/10 (10%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.0

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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