ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 03/26/2015

# A Study of Rituximab (MabThera®/Rituxan®) in Patients With Rheumatoid Arthritis and Inadequate Response to Methotrexate (SCORE)

This study has been completed.

| | |
|---|---|
| Sponsor: | Hoffmann-La Roche |
| Collaborators: | |
| Information provided by (Responsible Party): | Hoffmann-La Roche |
| ClinicalTrials.gov Identifier: | NCT00578305 |

## Purpose

This 3 arm study assessed the efficacy of rituximab (MabThera®/Rituxan®) in the prevention of progression of structural joint damage in participants with active rheumatoid arthritis who had an inadequate clinical response to methotrexate. Participants were randomized to receive rituximab 500 mg intravenously (iv), rituximab 1000 mg iv, or placebo iv on days 1 and 15 every 24 weeks in the main study; all participants received concomitant methotrexate at a stable dose of 12.5-25 mg/week throughout the study. Further courses of rituximab were provided to eligible participants. Structural joint damage was assessed by magnetic resonance imaging (MRI) at baseline and at intervals during the study.

| Condition | Intervention | Phase |
|---|---|---|
| Rheumatoid Arthritis | Biological/Vaccine: Rituximab<br>Drug: Placebo<br>Drug: Methylprednisolone<br>Drug: Methotrexate<br>Drug: Folic acid or folate | Phase 3 |

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study
Official Title: A Randomized, Placebo Controlled, Multicenter Clinical Study Investigating Efficacy of Rituximab in the Inhibition of Joint Structural Damage Assessed by Magnetic Resonance Imaging in Patients With Rheumatoid Arthritis and Inadequate Response to Methotrexate

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Change in Magnetic Resonance Imaging (MRI) Erosion Score From Baseline to Week 24 [Time Frame: Baseline to Week 24] [Designated as safety issue: No]

  The erosion score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists. Each location was scored in 0.5 increments from 0 to 10 with each integer unit increment representing a 10% loss of articular bone using the following scale. 0.0=normal, no erosion; 0.5=1-5% erosion; 1.0=6-10% erosion; 1.5=11-15% erosion; 2.0=16-20% erosion; etc, up to 10.0=96-100% erosion. The individual scores were summed and normalized to a range of 0 to 100 with a higher score indicating more erosion. A negative change score indicates improvement.

Secondary Outcome Measures:

- Change in Magnetic Resonance Imaging (MRI) Erosion Score From Baseline to Weeks 12 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  The erosion score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists. Each location was scored in 0.5 increments from 0 to 10 with each integer unit increment representing a 10% loss of articular bone using the following scale. 0.0=normal, no erosion; 0.5=1-5% erosion; 1.0=6-10% erosion; 1.5=11-15% erosion; 2.0=16-20% erosion; etc, up to 10.0=96-100% erosion. The individual scores were summed and normalized to a range of 0 to 100 with a higher score indicating more erosion. A negative change score indicates improvement.
- Change in Magnetic Resonance Imaging (MRI) Synovitis Score From Baseline to Weeks 12, 24, and Week 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  The synovitis score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images of 3 wrist regions and 5 metacarpophalangeal joints in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists. Each location was scored in 0.5 increments from 0 to 3 with each integer unit increment representing a 33% enhancement of the maximum volume of enhancing tissue in the synovial compartment using the following scale: 0.0=normal, no synovitis; 0.5=1-17% estimated volume of enhancement; 1.0=18-33%; 1.5=34-50%; 2.0=51-67%; 2.5=68-83%; 3.0=84-100% estimated volume of enhancement. The individual scores were summed and normalized to a range of 0 to 100 with a higher score indicating more synovitis. A negative change score indicates improvement.
- Change in Magnetic Resonance Imaging (MRI) Osteitis Score From Baseline to Weeks 12, 24, and Week 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  The osteitis score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Each location was scored in 0.5 increments from 0 to 3 with each integer unit increment representing a 33% increase in the volume of the peripheral 1 cm of original (eroded + residual) articular bone using the following scale: 0.0=normal, no osteitis; 0.5=1-17% involvement of original articular bone; 1.0=18-33%; 1.5=34-50%; 2.0=51-67%; 2.5=68-83%; 3.0=84-100% involvement of original articular bone. The individual scores were summed and normalized to a range of 0 to 100 with a higher score indicating more synovitis. A negative change score indicates improvement.
- Percentage of Participants With no Newly Eroded Joints at Weeks 24 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  No newly eroded joints was defined as no new erosions in joints which were scored 0 at baseline. The erosion score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal

radiologists. Each location was scored in 0.5 increments from 0 to 10 with each integer unit increment representing a 10% loss of articular bone using the following scale. 0.0=normal, no erosion; 0.5=1-5% erosion; 1.0=6-10% erosion; 1.5=11-15% erosion; 2.0=16-20% erosion; etc, up to 10.0=96-100% erosion.

- Percentage of Participants With no Progression/no Worsening in Bone Erosion at Weeks 24 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  There were 2 definitions of no progression/no worsening in bone erosion. A participant met the criterion for definition 1 when there was a change in the magnetic resonance imaging erosion score ≤ 0. A participant met the criteria for definition 2 when there was either (1) no change from Baseline in the MRI erosion score, (2) an increase in erosion score and the size of the increase in score was smaller than the smallest detectable change, or (3) a drop in the erosion score. The erosion score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists.
- Percentage of Participants With Improvement in Synovitis at Weeks 24 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  There were 2 definitions of improvement in synovitis. A participant met the criterion for definition 1 when there was a drop in the magnetic resonance imaging synovitis score from Baseline > 0.5. A participant met the criterion for definition 2 when there was a drop in the magnetic resonance imaging synovitis score from Baseline > than the smallest detectable change. The synovitis score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI (RAMRIS) scoring system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists.
- Percentage of Participants With Improvement in Osteitis at Weeks 24 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  There were 2 definitions of improvement in osteitis. A participant met the criterion for definition 1 when there was a drop in the magnetic resonance imaging osteitis score from Baseline > 0.5. A participant met the criterion for definition 2 when there was a drop in the magnetic resonance imaging osteitis score from Baseline > than the smallest detectable change. The osteitis score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI (RAMRIS) scoring system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists.
- Change From Baseline in the Disease Activity Score 28 (DAS28) at Weeks 24 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  The DAS28 is a combined index for measuring disease activity in rheumatic arthritis (RA) and includes swollen and tender joint counts, C-reactive protein level (CRP), and general health (GH) status. The index is calculated with the following formula: DAS28 = (0.56 × √(TJC28)) + (0.28 × √(SJC28)) + (0.7 × log(CRO)) + (0.014 × GH), where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints, GH = a participant's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]). The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. A negative change score indicates improvement.
- Percentage of Participants With European League Against Rheumatism (EULAR) Good, Moderate, or no Response at Weeks 24 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  Change of the DAS28 score from Baseline was used to determine the EULAR responses. For a post-Baseline score ≤ 3.2, a change from Baseline of < -1.2 was a good response, < -0.6 to ≥ -1.2 was a moderate response, and ≥ -0.6 was no response. For a post-Baseline score > 3.2 to ≤ 5.1, a change from Baseline of < -0.6 was a moderate response and ≥ -0.6 was no response. For a post-Baseline score > 5.1, a change from Baseline < -1.2 was a moderate response and ≥ -1.2 was no response. A good response could not be achieved for post-Baseline scores > 3.2. DAS28=(0.56×√(TJC28))+(0.28×√(SJC28))+(0.7×log(CRP))+(0.014×GH), where TJC28=tender joint count (JC) and SJC28=swollen JC (28 joints), GH=a participant's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end=no disease activity, right end=maximum disease activity), and CRP=C-reactive protein level. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity.
- Percentage of Participants With Low Disease Activity (Disease Activity Score 28 [DAS28] ≤ 3.2) at Weeks 24 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

The percentage of participants who had low rheumatic arthritis disease activity at Weeks 24 and 52, as measured by a DAS28 score ≤ 3.2, is reported. DAS28 is calculated with the following formula: DAS28 = (0.56 × √(TJC28)) + (0.28 × √(SJC28)) + (0.7 × log(CRO)) + (0.014 × GH), where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints, GH = a participant's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]), and CRP = C-reactive protein level. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity.

- Percentage of Participants in Remission Response (Disease Activity Score 28 [DAS28] < 2.6) at Weeks 24 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  The percentage of participants in remission of their rheumatic arthritis at Weeks 24 and 52, as measured by a DAS28 score < 2.6, is reported. DAS28 is calculated with the following formula: DAS28 = (0.56 × √(TJC28)) + (0.28 × √(SJC28)) + (0.7 × log(CRO)) + (0.014 × GH), where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints, GH = a participant's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]), and CRP = C-reactive protein level. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity.
- Percentage of Participants With an Improvement of at Least 20%, 50%, or 70% in the American College of Rheumatology (ACR) Score (ACR20/50/70) From Baseline at Weeks 24 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  Improvement must be seen in tender and swollen joint counts (28 assessed joints; Joints were evaluated and classified as swollen or not swollen and tender or not tender based on pressure and joint manipulation upon physical examination) and in at least 3
- Percentage of Participants Achieving a Major Clinical Response at Week 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  A major clinical response was defined as an improvement of at least 70% in the American College of Rheumatology score from Baseline at Week 52. Improvement must be seen in tender and swollen joint counts (28 assessed joints) and in at least 3 of the following 5 parameters: Separate participant and physician assessments of participant disease activity in the previous 24 hours on a visual analog scale (VAS, the extreme left end of the line "no disease activity" [symptom-free and no arthritis symptoms] and the extreme right end "maximum disease activity"); participant assessment of pain in previous the 24 hours on a VAS (extreme left end of the line "no pain" and the extreme right end "unbearable pain"); Health Assessment Questionnaire-Disability Index (20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do); and C reactive protein level.
- Correlation of Magnetic Resonance Imaging Assessments and Clinical Outcome Measures [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  Correlation coefficients of magnetic resonance imaging erosion, synovitis, and osteitis scores and clinical outcome measures of swollen joint count (SJC), tender joint count (TJC), C-reactive protein level (CRP), erythrocyte sedimentation rate (ESR), a participant's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (GH), Disease Activity Score 28-C-reactive protein (DAS28-CRP), and Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) are reported. Not all of these variables were specified as primary or secondary Outcome Measures in the study protocol and were not individually analyzed.
- Change From Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Weeks 24 and 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

  The HAQ-DI assesses how well the patient is able to perform 8 activities: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. The patient answers 20 questions with 1 of 4 responses with the past week as the time frame: 0=without difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. The highest score for any question in a category determines the category score. The total score ranges from 0 (no disability) to 3 (completely disabled). A negative change score indicates improvement.
- Adverse Events (AEs), Laboratory Parameters, C-reactive Protein, ESR. [Time Frame: Throughout study] [Designated as safety issue: No]

Enrollment: 185
Study Start Date: November 2007
Primary Completion Date: November 2009
Study Completion Date: May 2013

| Arms | Assigned Interventions |
|---|---|
| Experimental: Rituximab 500 mg<br>Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. | Biological/Vaccine: Rituximab<br>Rituximab was supplied as a sterile liquid for iv administration.<br>Other Names:<br>MabThera®<br>Rituxan®<br>Drug: Methylprednisolone<br>Drug: Methotrexate<br>Drug: Folic acid or folate |
| Experimental: Rituximab 1000 mg<br>Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. | Biological/Vaccine: Rituximab<br>Rituximab was supplied as a sterile liquid for iv administration.<br>Other Names:<br>MabThera®<br>Rituxan®<br>Drug: Methylprednisolone<br>Drug: Methotrexate<br>Drug: Folic acid or folate |
| Placebo Comparator: Placebo<br>Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received | Drug: Placebo<br>Placebo was supplied as a sterile liquid in single-use vials for iv administration. |

| Arms | Assigned Interventions |
|---|---|
| a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. | Drug: Methylprednisolone<br>Drug: Methotrexate<br>Drug: Folic acid or folate |

Detailed Description:

There were 3 phases in the study: A 52 week long main study, a study extension phase, and a 48 week long safety follow-up phase.

The first course of treatment with placebo or rituximab was initiated on Day 1 of the 52 week long main study. A second course of treatment was initiated after Week 24, if the participant met eligibility criteria. After Week 52, eligible participants received further treatment courses at intervals ≥ 6 months in the study extension phase. No treatments were administered in the safety follow-up phase.

Participants had to meet the following eligibility criteria to receive rituximab in the study extension phase.

- Minimum of 24 weeks had passed since the first infusion of the last course of study medication.
- C-reactive protein-based Disease Activity Score 28 (DAS28-CRP) ≥ 2.6.
- Absolute neutrophil count not below 1.5 x 103/μL.
- Patient had not developed contraindications for receiving rituximab, such as:
    a. Any new or uncontrolled concomitant disease such as, but not limited to, cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine or gastrointestinal disorders.
    b. Primary or secondary immunodeficiency (history of, or currently active), including known history of HIV infection.
    c. Known active infection of any kind (excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization, or treatment with iv anti-infectives within 4 weeks prior to infusion or completion of oral anti-infectives within 2 weeks prior to infusion.
- Patient was not pregnant or breast feeding.
- Patients who entered the study and were found to be hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (HBcAb) positive, were to be negative for hepatitis B viral DNA (< 29 IU/mL) and were to have aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN) results within the last 12 weeks.

## Eligibility

Ages Eligible for Study: 18 Years to 80 Years

Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

### Criteria

Inclusion Criteria:

- Adult patients, 18-80 years of age.
- Active rheumatoid arthritis for ≥ 3 months and ≤ 10 years.
- Evidence of erosive disease and/or clinical synovitis in a signal joint.
- Inadequate response to 12.5-25 mg/week methotrexate for ≥ 12 weeks.

Exclusion Criteria:

- Rheumatic autoimmune disease or inflammatory joint disease other than rheumatoid arthritis. - Any surgical procedure within 12 weeks prior to baseline.
- Previous treatment with a biologic agent or with a B cell modulating or cell depleting therapy.

## Contacts and Locations

Locations

Argentina
Buenos Aires, Argentina, C1280AEB

Brazil
Goiania, GO, Brazil, 74110010
Curtiba, PR, Brazil, 80030-110
Porto Alegre, RS, Brazil, 90610-000
Sao Paulo, SP, Brazil, 04023-900

Canada, Manitoba
Winnipeg, Manitoba, Canada, R3E0W3

Canada, Newfoundland and Labrador
St John's, Newfoundland and Labrador, Canada, A1A 5E8

Canada, Ontario
Ottawa, Ontario, Canada, K1H 1A2
Ottawa, Ontario, Canada, K2G 6E2
Toronto, Ontario, Canada, M4N 3M5

Canada, Quebec
Montreal, Quebec, Canada, H3Z 2Z3
Montreal, Quebec, Canada, H2L 1S6
Montreal, Quebec, Canada, H1T 2M4
Quebec City, Quebec, Canada, G1V 3M7

Canada, Saskatchewan
Saskatoon, Saskatchewan, Canada, S7M 0Z9

Czech Republic
Brno, Czech Republic, 625 00
Ceské Budejovice, Czech Republic, 370 01
Praha, Czech Republic, 128 50

Denmark
- Hillerod, Denmark, 3400
- Hvidovre, Denmark, 2650
- København, Denmark, 2100

Estonia
- Tallinn, Estonia, 11312
- Tallinn, Estonia, 13419

France
- Montpellier, France, 34295
- Nice, France, 06202
- Orleans, France, 45032
- Toulouse, France, 31059

Germany
- Bad Aibling, Germany, 83043
- Berlin, Germany, 10117
- Dresden, Germany, 01307
- Erlangen, Germany, 91054
- Halle, Germany, 06120
- Hannover, Germany, 30625

Greece
- Athens, Greece, 115 27
- Patras, Greece, 265 04
- Thessaloniki, Greece, 54636

Latvia
- Riga, Latvia, 1002
- Riga, Latvia, 1038

Lithuania
- Vilnius, Lithuania, LT-08661

Netherlands
- Amsterdam, Netherlands, 1105 AZ

Norway
- Oslo, Norway, 0370

Romania
- Bucharest, Romania, 020475
- Cluj-napoca, Romania, 400006

Russian Federation
- Kazan, Russian Federation, 420097
- Moscow, Russian Federation, 115522
- Saint-Petersburg, Russian Federation, 195067
- Voronezh, Russian Federation, 394066

Serbia
- Belgrade, Serbia, 11000
- Niska Banja, Serbia, 18250

Spain
- Barcelona, Barcelona, Spain, 08003

Barcelona, Barcelona, Spain, 08907
Madrid, Madrid, Spain, 28046
Malaga, Malaga, Spain, 29010
Sevilla, Sevilla, Spain, 41009
Valencia, Valencia, Spain, 46017

Switzerland

Bern, Switzerland, 3010

Turkey

Adana, Turkey, 01330
Ankara, Turkey, 06018
Istanbul, Turkey, 34098
Izmir, Turkey, 35100

Investigators

| | | |
|---|---|---|
| Study Director: | Clinical Trials | Hoffmann-La Roche |

## More Information

| | |
|---|---|
| Responsible Party: | Hoffmann-La Roche |
| Study ID Numbers: | MA21056 |
| Health Authority: | Latvia: State Agency of Medicines |

# Study Results

## Participant Flow

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

| | Description |
|---|---|
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Double-blind Treatment Phase

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Started | 62 | 60 | 63 |
| Treated | 62 | 60 | 63 |
| Completed | 59 | 56 | 49 |
| Not Completed | 3 | 4 | 14 |

Extension Phase

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Started | 53 | 50 | 43 |
| Completed | 49 [1] | 49 [1] | 40 [1] |
| Not Completed | 4 | 1 | 3 |

[1] Some participants completed the study in this period and did not enter the safety follow-up period.

Safety Follow-up Phase

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Started | 57 [1] | 54 [1] | 54 [1] |
| Completed | 11 | 9 | 8 |

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Not Completed | 46 | 45 | 46 |

[1] Some participants entered safety follow-up directly from the double-blind treatment period.

## Baseline Characteristics

Analysis Population Description

Safety population: All participants who received any part of an infusion of the study drug during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Baseline Measures

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo | Total |
|---|---|---|---|---|
| Number of Participants | 62 | 60 | 63 | 185 |
| Age, Continuous [units: years] | 48.7 (11.10) | 50.7 (11.65) | 50.3 (11.94) | 49.9 (11.54) |

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo | Total |
|---|---|---|---|---|
| Mean (Standard Deviation) | | | | |
| Gender, Male/Female<br>[units: participants] | | | | |
| Female | 45 | 50 | 48 | 143 |
| Male | 17 | 10 | 15 | 42 |

## Outcome Measures

1. Primary Outcome Measure:

| | |
|---|---|
| Measure Title | Change in Magnetic Resonance Imaging (MRI) Erosion Score From Baseline to Week 24 |
| Measure Description | The erosion score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists. Each location was scored in 0.5 increments from 0 to 10 with each integer unit increment representing a 10% loss of articular bone using the following scale. 0.0=normal, no erosion; 0.5=1-5% erosion; 1.0=6-10% erosion; 1.5=11-15% erosion; 2.0=16-20% erosion; etc, up to 10.0=96-100% erosion. The individual scores were summed and normalized to a range of 0 to 100 with a higher score indicating more erosion. A negative change score indicates improvement. |
| Time Frame | Baseline to Week 24 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

| | Description |
|---|---|
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 59 | 58 | 60 |
| Change in Magnetic Resonance Imaging (MRI) Erosion Score From Baseline to Week 24<br>[units: Units on a scale]<br>Mean (Standard Deviation) | 0.13 (2.258) | 0.39 (1.807) | 1.33 (2.235) |

2. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change in Magnetic Resonance Imaging (MRI) Erosion Score From Baseline to Weeks 12 and 52 |
| Measure Description | The erosion score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists. Each location was scored in 0.5 increments from 0 to 10 with each integer unit increment representing a 10% loss of articular bone using the following scale. 0.0=normal, no erosion; 0.5=1-5% erosion; 1.0=6-10% erosion; 1.5=11-15% erosion; 2.0=16-20% erosion; etc, up to 10.0=96-100% erosion. The individual scores were summed and normalized to a range of 0 to 100 with a higher score indicating more erosion. A negative change score indicates improvement. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 60 | 62 | 63 |
| Change in Magnetic Resonance Imaging (MRI) Erosion Score From Baseline to Weeks 12 and 52<br>[units: Units on a scale]<br>Mean (Standard Deviation) | | | |
| Week 12 (n = 58, 58, 56) | 0.42 (1.693) | 0.13 (1.764) | 0.33 (4.122) |
| Week 52 (n = 56, 57, 58) | 0.11 (2.623) | -0.30 (2.372) | 3.02 (4.456) |

3. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change in Magnetic Resonance Imaging (MRI) Synovitis Score From Baseline to Weeks 12, 24, and Week 52 |
| Measure Description | The synovitis score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images of 3 wrist regions and 5 metacarpophalangeal joints in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists. Each location was scored in 0.5 increments from 0 to 3 with each integer unit increment representing a 33% enhancement of the maximum volume of enhancing tissue in the synovial compartment using the following scale: 0.0=normal, no synovitis; 0.5=1-17% estimated volume of enhancement; 1.0=18-33%; 1.5=34-50%; 2.0=51-67%; 2.5=68-83%; 3.0=84-100% estimated volume of enhancement. The individual scores were summed and normalized to a range of 0 to 100 with a higher score indicating more synovitis. A negative change score indicates improvement. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Change in Magnetic Resonance Imaging (MRI) Synovitis Score From Baseline to Weeks 12, 24, and Week 52<br>[units: Units on a scale]<br>Mean (Standard Deviation) | | | |
| Week 12 (n = 58, 58, 56) | -0.50 (1.701) | -1.15 (1.866) | -0.22 (2.050) |
| Week 24 (n = 61, 59, 59) | -1.14 (1.923) | -1.81 (2.289) | 0.20 (2.257) |
| Week 52 (n = 61, 59, 59) | -2.03 (2.562) | -2.73 (3.120) | -0.01 (2.700) |

4. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change in Magnetic Resonance Imaging (MRI) Osteitis Score From Baseline to Weeks 12, 24, and Week 52 |
| Measure Description | The osteitis score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Each location was scored in 0.5 increments from 0 to 3 with each integer unit increment representing a 33% increase in the volume of the peripheral 1 cm of original (eroded + residual) articular bone using the following scale: 0.0=normal, no osteitis; 0.5=1-17% involvement of original articular bone; 1.0=18-33%; 1.5=34-50%; 2.0=51-67%; 2.5=68-83%; 3.0=84-100% involvement of original articular bone. The individual scores were summed and normalized to a range of 0 to 100 with a higher score indicating more synovitis. A negative change score indicates improvement. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Change in Magnetic Resonance Imaging (MRI) Osteitis Score From Baseline to Weeks 12, 24, and Week 52<br>[units: Units on a scale]<br>Mean (Standard Deviation) | | | |
| Week 12 (n = 58, 58, 56) | -2.11 (5.049) | -1.88 (5.366) | -0.14 (3.940) |
| Week 24 (n = 61, 59, 59) | -2.91 (5.687) | -2.86 (5.976) | 0.07 (5.574) |
| Week 52 (n = 61, 59, 59) | -4.75 (7.413) | -3.83 (6.255) | -0.22 (6.390) |

5. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants With no Newly Eroded Joints at Weeks 24 and 52 |
| Measure Description | No newly eroded joints was defined as no new erosions in joints which were scored 0 at baseline. The erosion score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists. Each location was scored in 0.5 increments from 0 to 10 with each integer unit increment representing a 10% loss of articular bone using the following scale. 0.0=normal, no erosion; 0.5=1-5% erosion; 1.0=6-10% erosion; 1.5=11-15% erosion; 2.0=16-20% erosion; etc, up to 10.0=96-100% erosion. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Percentage of Participants With no Newly Eroded Joints at Weeks 24 and 52<br>[units: Percentage of participants] | | | |
| Week 24 | 77.4 | 73.3 | 55.5 |
| Week 52 | 77.4 | 40 | 60.3 |

6. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants With no Progression/no Worsening in Bone Erosion at Weeks 24 and 52 |
| Measure Description | There were 2 definitions of no progression/no worsening in bone erosion. A participant met the criterion for definition 1 when there was a change in the magnetic resonance imaging erosion score ≤ 0. A participant met the criteria for definition 2 when there was either (1) no change from Baseline in the MRI erosion score, (2) an increase in erosion score and the size of the increase in score was smaller than the smallest detectable change, or (3) a drop in the erosion score. The erosion score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI scoring (RAMRIS) system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

| | Description |
|---|---|
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Percentage of Participants With no Progression/no Worsening in Bone Erosion at Weeks 24 and 52<br>[units: Percentage of participants] | | | |
| Week 24 (Definition 1) | 50.0 | 51.7 | 33.3 |
| Week 24 (Definition 2) | 88.7 | 96.7 | 81.0 |
| Week 52 (Definition 1) | 48.4 | 55.0 | 27.0 |
| Week 52 (Definition 2) | 85.5 | 93.3 | 55.6 |

7. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants With Improvement in Synovitis at Weeks 24 and 52 |

| | |
|---|---|
| Measure Description | There were 2 definitions of improvement in synovitis. A participant met the criterion for definition 1 when there was a drop in the magnetic resonance imaging synovitis score from Baseline > 0.5. A participant met the criterion for definition 2 when there was a drop in the magnetic resonance imaging synovitis score from Baseline > than the smallest detectable change. The synovitis score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI (RAMRIS) scoring system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Percentage of Participants With Improvement in Synovitis at Weeks 24 and 52<br>[units: Percentage of participants] | | | |
| Week 24 (Definition 1) | 41.9 | 56.7 | 22.2 |
| Week 24 (Definition 2) | 41.9 | 56.7 | 22.2 |
| Week 52 (Definition 1) | 54.8 | 60.0 | 25.4 |
| Week 52 (Definition 2) | 54.8 | 60.0 | 25.4 |

8. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants With Improvement in Osteitis at Weeks 24 and 52 |
| Measure Description | There were 2 definitions of improvement in osteitis. A participant met the criterion for definition 1 when there was a drop in the magnetic resonance imaging osteitis score from Baseline > 0.5. A participant met the criterion for definition 2 when there was a drop in the magnetic resonance imaging osteitis score from Baseline > than the smallest detectable change. The osteitis score was determined according to the Outcome Measures in Rheumatology (OMERACT) rheumatoid arthritis MRI (RAMRIS) scoring system in magnetic resonance images with and without gadolinium of 15 anatomical locations in each wrist and 10 locations in each hand in the hand and wrist with the most arthritic activity. If there was no difference in disease activity between the hands, the dominant hand was used. Images were assessed by 2 experienced blinded musculoskeletal radiologists. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Percentage of Participants With Improvement in Osteitis at Weeks 24 and 52<br>[units: Percentage of participants] | | | |
| Week 24 (Definition 1) | 50.0 | 51.7 | 22.2 |
| Week 24 (Definition 2) | 50.0 | 51.7 | 22.2 |
| Week 52 (Definition 1) | 58.1 | 51.7 | 27.0 |
| Week 52 (Definition 2) | 58.1 | 51.7 | 27.0 |

9. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in the Disease Activity Score 28 (DAS28) at Weeks 24 and 52 |
| Measure Description | The DAS28 is a combined index for measuring disease activity in rheumatic arthritis (RA) and includes swollen and tender joint counts, C-reactive protein level (CRP), and general health (GH) status. The index is calculated with the following formula: DAS28 = (0.56 × √(TJC28)) + (0.28 × √(SJC28)) + (0.7 × log(CRO)) + (0.014 × GH), where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints, GH = a participant's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]). The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. A negative change score indicates improvement. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Change From Baseline in the Disease Activity Score 28 (DAS28) at Weeks 24 and 52<br>[units: Units on a scale]<br>Mean (Standard Deviation) | | | |
| Week 24 (n = 63, 62, 59) | -1.714 (1.2204) | -1.683 (1.0158) | -0.752 (1.1834) |
| Week 52 (n = 63, 62, 59) | -2.055 (1.1844) | -1.801 (1.0443) | -0.747 (1.2557) |

10. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants With European League Against Rheumatism (EULAR) Good, Moderate, or no Response at Weeks 24 and 52 |
| Measure Description | Change of the DAS28 score from Baseline was used to determine the EULAR responses. For a post-Baseline score ≤ 3.2, a change from Baseline of < -1.2 was a good response, < -0.6 to ≥ -1.2 was a moderate response, and ≥ -0.6 was no response. For a post-Baseline score > 3.2 to ≤ 5.1, a change from Baseline of < -0.6 was a moderate response and ≥ -0.6 was no response. For a post-Baseline score > 5.1, a change from Baseline < -1.2 was a moderate response and ≥ -1.2 was no response. A good response could not be achieved for post-Baseline scores > 3.2. DAS28=(0.56×√(TJC28))+(0.28×√(SJC28))+(0.7×log(CRP))+(0.014×GH), where TJC28=tender joint count (JC) and SJC28=swollen JC (28 joints), GH=a participant's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end=no disease activity, right end=maximum disease activity), and CRP=C-reactive protein level. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Percentage of Participants With European League Against Rheumatism (EULAR) Good, Moderate, or no Response at Weeks 24 and 52<br>[units: Percentage of participants] | | | |
| Week 24 - No response | 33.9 | 22.0 | 58.7 |
| Week 24 - Moderate response | 37.1 | 42.4 | 22.2 |
| Week 24 - Good response | 29.0 | 35.6 | 19.0 |
| Week 52 (n = 63, 62, 59) - No response | 21.0 | 13.6 | 60.3 |
| Week 52 (n = 63, 62, 59) - Moderate response | 45.2 | 49.2 | 31.7 |
| Week 52 (n = 63, 62, 59) - Good response | 33.9 | 37.3 | 7.9 |

11. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants With Low Disease Activity (Disease Activity Score 28 [DAS28] ≤ 3.2) at Weeks 24 and 52 |
| Measure Description | The percentage of participants who had low rheumatic arthritis disease activity at Weeks 24 and 52, as measured by a DAS28 score ≤ 3.2, is reported. DAS28 is calculated with the following formula: DAS28 = (0.56 × √(TJC28)) + (0.28 × √(SJC28)) + (0.7 × log(CRO)) + (0.014 × GH), where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints, GH = a participant's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]), and CRP = C-reactive protein level. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Percentage of Participants With Low Disease Activity (Disease Activity Score 28 [DAS28] ≤ 3.2) at Weeks 24 and 52<br>[units: Percentage of participants] | | | |
| Week 24 | 33.9 | 36.7 | 19.0 |
| Week 52 | 37.1 | 38.3 | 9.5 |

12. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants in Remission Response (Disease Activity Score 28 [DAS28] < 2.6) at Weeks 24 and 52 |
| Measure Description | The percentage of participants in remission of their rheumatic arthritis at Weeks 24 and 52, as measured by a DAS28 score < 2.6, is reported. DAS28 is calculated with the following formula: DAS28 = (0.56 × √(TJC28)) + (0.28 × √(SJC28)) + (0.7 × log(CRO)) + (0.014 × GH), where TJC28 = tender joint count and SJC28 = swollen joint count, each on 28 joints, GH = a participant's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (left end = no disease activity [symptom-free and no arthritis symptoms], right end = maximum disease activity [maximum arthritis disease activity]), and CRP = C-reactive protein level. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

| | Description |
|---|---|
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Percentage of Participants in Remission Response (Disease Activity Score 28 [DAS28] < 2.6) at Weeks 24 and 52<br>[units: Percentage of participants] | | | |
| Week 24 | 21.0 | 28.3 | 12.7 |
| Week 52 | 25.8 | 25.0 | 7.9 |

13. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants With an Improvement of at Least 20%, 50%, or 70% in the American College of Rheumatology (ACR) Score (ACR20/50/70) From Baseline at Weeks 24 and 52 |
| Measure Description | Improvement must be seen in tender and swollen joint counts (28 assessed joints; Joints were evaluated and classified as swollen or not swollen and tender or not tender based on pressure and joint manipulation upon physical examination) and in at least 3 |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Percentage of Participants With an Improvement of at Least 20%, 50%, or 70% in the American College of Rheumatology (ACR) Score (ACR20/50/70) From Baseline at Weeks 24 and 52<br>[units: Percentage of participants] | | | |
| Week 24 - ACR20 response | 51.6 | 51.7 | 28.6 |
| Week 24 - ACR50 response | 24.2 | 26.7 | 11.1 |
| Week 24 - ACR70 response | 11.3 | 8.3 | 1.6 |
| Week 52 - ACR20 response | 67.7 | 68.3 | 28.6 |

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Week 52 - ACR50 response | 37.1 | 35.0 | 14.3 |
| Week 52 - ACR70 response | 17.7 | 16.7 | 6.3 |

14. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants Achieving a Major Clinical Response at Week 52 |
| Measure Description | A major clinical response was defined as an improvement of at least 70% in the American College of Rheumatology score from Baseline at Week 52. Improvement must be seen in tender and swollen joint counts (28 assessed joints) and in at least 3 of the following 5 parameters: Separate participant and physician assessments of participant disease activity in the previous 24 hours on a visual analog scale (VAS, the extreme left end of the line “no disease activity” [symptom-free and no arthritis symptoms] and the extreme right end “maximum disease activity”); participant assessment of pain in previous the 24 hours on a VAS (extreme left end of the line “no pain” and the extreme right end “unbearable pain”); Health Assessment Questionnaire-Disability Index (20 questions, 8 components: dressing/ grooming, arising, eating, walking, hygiene, reach, grip, and activities, 0=without difficulty to 3=unable to do); and C reactive protein level. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

| | Description |
|---|---|
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Percentage of Participants Achieving a Major Clinical Response at Week 52<br>[units: Percentage of participants] | 6.5 | 6.7 | 1.6 |

15. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Correlation of Magnetic Resonance Imaging Assessments and Clinical Outcome Measures |
| Measure Description | Correlation coefficients of magnetic resonance imaging erosion, synovitis, and osteitis scores and clinical outcome measures of swollen joint count (SJC), tender joint count (TJC), C-reactive protein level (CRP), erythrocyte sedimentation rate (ESR), a participant's global assessment of disease activity in the previous 24 hours on a 100 mm visual analog scale (GH), Disease Activity Score 28-C-reactive protein (DAS28-CRP), and Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) are reported. Not all of these variables were specified as primary or secondary Outcome Measures in the study protocol and were not individually analyzed. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Correlation of Magnetic Resonance Imaging Assessments and Clinical Outcome Measures<br>[units: Correlation coefficient] | | | |
| Erosion score and SJC - Week 24 | 0.341 | 0.425 | 0.446 |
| Erosion score and SJC - Week 52 | 0.287 | 0.234 | 0.355 |
| Synovitis score and SJC - Week 24 | 0.329 | 0.389 | 0.566 |
| Synovitis score and SJC - Week 52 | 0.168 | 0.188 | 0.574 |
| Osteitis score and SJC - Week 24 | 0.407 | 0.354 | 0.370 |
| Osteitis score and SJC - Week 52 | 0.265 | 0.192 | 0.398 |
| Erosion score and TJC - Week 24 | 0.364 | 0.115 | 0.298 |

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Erosion score and TJC - Week 52 | 0.275 | 0.067 | 0.425 |
| Synovitis score and TJC - Week 24 | 0.336 | 0.174 | 0.282 |
| Synovitis score and TJC - Week 52 | 0.142 | 0.036 | 0.421 |
| Osteitis score and TJC - Week 24 | 0.355 | 0.118 | 0.288 |
| Osteitis score and TJC - Week 52 | 0.245 | 0.048 | 0.371 |
| Erosion score and CRP - Week 24 | 0.185 | -0.024 | 0.006 |
| Erosion score and CRP - Week 52 | 0.055 | 0.098 | 0.352 |
| Synovitis score and CRP - Week 24 | 0.030 | 0.090 | 0.192 |
| Synovitis score and CRP - Week 52 | -0.077 | 0.085 | 0.311 |
| Osteitis score and CRP - Week 24 | -0.031 | -0.057 | 0.040 |
| Osteitis score and CRP - Week 52 | 0.005 | -0.010 | 0.119 |
| Erosion score and ESR - Week 24 | 0.321 | 0.136 | 0.197 |
| Erosion score and ESR - Week 52 | 0.127 | 0.188 | 0.314 |
| Synovitis score and ESR - Week 24 | 0.182 | 0.214 | 0.358 |
| Synovitis score and ESR - Week 52 | 0.185 | 0.248 | 0.360 |
| Osteitis score and ESR - Week 24 | 0.044 | 0.043 | 0.148 |
| Osteitis score and ESR - Week 52 | -0.041 | 0.116 | 0.205 |
| Erosion score and GH - Week 24 | 0.206 | 0.043 | 0.326 |
| Erosion score and GH - Week 52 | 0.063 | -0.009 | 0.316 |
| Synovitis score and GH - Week 24 | 0.186 | 0.221 | 0.206 |
| Synovitis score and GH - Week 52 | -0.026 | -0.037 | 0.286 |
| Osteitis score and GH - Week 24 | 0.274 | 0.122 | 0.205 |
| Osteitis score and GH - Week 52 | 0.106 | 0.052 | 0.136 |
| Erosion score and DAS28-CRP - Week 24 | 0.420 | 0.198 | 0.457 |
| Erosion score and DAS28-CRP - Week 52 | 0.238 | 0.127 | 0.498 |
| Synovitis score and DAS28-CRP - Week 24 | 0.393 | 0.349 | 0.437 |
| Synovitis score and DAS28-CRP - Week 52 | 0.149 | 0.150 | 0.500 |

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Osteitis score and DAS28-CRP - Week 24 | 0.380 | 0.209 | 0.351 |
| Osteitis score and DAS28-CRP - Week 52 | 0.139 | 0.143 | 0.356 |
| Erosion score and DAS28-ESR - Week 24 | 0.429 | 0.255 | 0.439 |
| Erosion score and DAS28-ESR - Week 52 | 0.244 | 0.180 | 0.473 |
| Synovitis score and DAS28-ESR - Week 24 | 0.398 | 0.332 | 0.438 |
| Synovitis score and DAS28-ESR - Week 52 | 0.198 | 0.147 | 0.514 |
| Osteitis score and DAS28-ESR - Week 24 | 0.353 | 0.231 | 0.353 |
| Osteitis score and DAS28-ESR - Week 52 | 0.108 | 0.172 | 0.356 |

16. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Change From Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Weeks 24 and 52 |
| Measure Description | The HAQ-DI assesses how well the patient is able to perform 8 activities: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. The patient answers 20 questions with 1 of 4 responses with the past week as the time frame: 0=without difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. The highest score for any question in a category determines the category score. The total score ranges from 0 (no disability) to 3 (completely disabled). A negative change score indicates improvement. |
| Time Frame | Baseline to Week 52 |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized participants and received any part of an infusion of study medication during the main study.

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

| | Description |
|---|---|
| Rituximab 1000 mg | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Measured Values

| | Rituximab 500 mg | Rituximab 1000 mg | Placebo |
|---|---|---|---|
| Number of Participants Analyzed | 62 | 60 | 63 |
| Change From Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Weeks 24 and 52<br>[units: Units on a scale]<br>Mean (Standard Deviation) | | | |
| Week 24 (n = 63, 62, 59) | -0.425 (0.5606) | -0.439 (0.4770) | -0.194 (0.5849) |
| Week 52 (n = 63, 62, 59) | -0.520 (0.5873) | -0.417 (0.4450) | -0.177 (0.5943) |

17. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Adverse Events (AEs), Laboratory Parameters, C-reactive Protein, ESR. |
| Measure Description | |
| Time Frame | Throughout study |
| Safety Issue? | No |

Outcome Measure Data Not Reported

## Reported Adverse Events

| | |
|---|---|
| Time Frame | [Not specified] |
| Additional Description | Safety population: All participants who received any part of an infusion of the study drug during the main study.<br>Some participants entered the safety follow-up period directly from the double-blind treatment period. |

Reporting Groups

| | Description |
|---|---|
| Rituximab 500 mg - Double-blind Treatment Phase | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg - Double-blind Treatment Phase | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo - Double-blind Treatment Phase | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 500 mg - Extension Phase | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

| | Description |
|---|---|
| Rituximab 1000 mg - Extension Phase | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo - Extension Phase | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 500 mg - Safety Follow-up Phase | Participants received rituximab 500 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Rituximab 1000 mg - Safety Follow-up Phase | Participants received rituximab 1000 mg iv on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants received further treatment courses on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |
| Placebo - Safety Follow-up Phase | Participants received placebo intravenously (iv) on Day 1 and Day 15 of the main study. Participants received a second course of treatment on Day 1 and Day 15 after Week 24 of the main study, if they met eligibility criteria (see the Detailed Description). Participants were switched to receive rituximab 1000 mg iv on Day 1 and Day 15 at intervals of ≥ 6 months after Week 52 in the study extension phase, if they met eligibility criteria (see the Detailed Description). Throughout the study, participants received methylprednisolone 100 mg iv prior to infusion of the investigational drug, methotrexate 7.5 to 25 mg/week orally or parenterally, and folic acid or folate ≥ 5 mg/week orally. |

Serious Adverse Events

| | Rituximab 500 mg - Double-blind Treatment Phase | Rituximab 1000 mg - Double-blind Treatment Phase | Placebo - Double-blind Treatment Phase | Rituximab 500 mg - Extension Phase | Rituximab 1000 mg - Extension Phase | Placebo - Extension Phase |
|---|---|---|---|---|---|---|
| | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) |
| Total | 3/62 (4.84%) | 4/60 (6.67%) | 5/63 (7.94%) | 3/50 (6%) | 5/47 (10.64%) | 2/41 (4.88%) |
| Blood and lymphatic system disorders | | | | | | |
| Neutropenia [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 1/50 (2%) | 0/47 (0%) | 0/41 (0%) |
| Cardiac disorders | | | | | | |
| Acute coronary syndrome [A] † | 0/62 (0%) | 0/60 (0%) | 1/63 (1.59%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Gastrointestinal disorders | | | | | | |
| Colonic polyp [A] † | 0/62 (0%) | 0/60 (0%) | 1/63 (1.59%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Intestinal diverticulum [A] † | 0/62 (0%) | 0/60 (0%) | 1/63 (1.59%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| General disorders | | | | | | |
| General physical health deterioration [A] † | 0/62 (0%) | 0/60 (0%) | 1/63 (1.59%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Hepatobiliary disorders | | | | | | |
| Cholecystitis acute [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 1/41 (2.44%) |
| Cholelithiasis [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 1/41 (2.44%) |
| Infections and infestations | | | | | | |
| Appendicitis [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 1/50 (2%) | 0/47 (0%) | 0/41 (0%) |
| Bronchitis [A] † | 0/62 (0%) | 1/60 (1.67%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Erysipelas [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 1/41 (2.44%) |
| Omphalitis [A] † | 0/62 (0%) | 1/60 (1.67%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Respiratory tract infection viral [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 1/47 (2.13%) | 0/41 (0%) |
| Soft tissue infection [A] † | 1/62 (1.61%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Metabolism and nutrition disorders | | | | | | |

| | Rituximab 500 mg - Double-blind Treatment Phase | Rituximab 1000 mg - Double-blind Treatment Phase | Placebo - Double-blind Treatment Phase | Rituximab 500 mg - Extension Phase | Rituximab 1000 mg - Extension Phase | Placebo - Extension Phase |
|---|---|---|---|---|---|---|
| | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) |
| Hyperglycemia [A] † | 1/62 (1.61%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Musculoskeletal and connective tissue disorders | | | | | | |
| Back pain [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 1/47 (2.13%) | 0/41 (0%) |
| Knee deformity [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 1/47 (2.13%) | 0/41 (0%) |
| Rheumatoid arthritis [A] † | 0/62 (0%) | 0/60 (0%) | 2/63 (3.17%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | | | | |
| Cervix carcinoma Stage 0 [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Colorectal cancer [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 1/47 (2.13%) | 0/41 (0%) |
| Papillary serous endometrial carcinoma [A] † | 0/62 (0%) | 1/60 (1.67%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Prostate cancer [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 1/47 (2.13%) | 0/41 (0%) |
| Nervous system disorders | | | | | | |
| Lumbar radiculopathy [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 1/50 (2%) | 0/47 (0%) | 0/41 (0%) |
| Pregnancy, puerperium and perinatal conditions | | | | | | |
| Omphalorrhexis [A] † | 0/62 (0%) | 1/60 (1.67%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Renal and urinary disorders | | | | | | |
| Renal colic [A] † | 1/62 (1.61%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Reproductive system and breast disorders | | | | | | |
| Breast mass [A] † | 0/62 (0%) | 0/60 (0%) | 0/63 (0%) | 0/50 (0%) | 1/47 (2.13%) | 0/41 (0%) |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Bronchitis chronic [A] † | 0/62 (0%) | 1/60 (1.67%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (11.2)

| | Rituximab 500 mg - Safety Follow-up Phase | Rituximab 1000 mg - Safety Follow-up Phase | Placebo - Safety Follow-up Phase |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 0/57 (0%) | 1/54 (1.85%) | 0/54 (0%) |
| Blood and lymphatic system disorders | | | |
| Neutropenia [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Cardiac disorders | | | |
| Acute coronary syndrome [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Gastrointestinal disorders | | | |
| Colonic polyp [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Intestinal diverticulum [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| General disorders | | | |
| General physical health deterioration [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Hepatobiliary disorders | | | |
| Cholecystitis acute [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Cholelithiasis [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Infections and infestations | | | |
| Appendicitis [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Bronchitis [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Erysipelas [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Omphalitis [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Respiratory tract infection viral [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Soft tissue infection [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Metabolism and nutrition disorders | | | |
| Hyperglycemia [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |

| | Rituximab 500 mg - Safety Follow-up Phase | Rituximab 1000 mg - Safety Follow-up Phase | Placebo - Safety Follow-up Phase |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Knee deformity [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Rheumatoid arthritis [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cervix carcinoma Stage 0 [A] † | 0/57 (0%) | 1/54 (1.85%) | 0/54 (0%) |
| Colorectal cancer [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Papillary serous endometrial carcinoma [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Prostate cancer [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Nervous system disorders | | | |
| Lumbar radiculopathy [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Pregnancy, puerperium and perinatal conditions | | | |
| Omphalorrhexis [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Renal and urinary disorders | | | |
| Renal colic [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Reproductive system and breast disorders | | | |
| Breast mass [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchitis chronic [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (11.2)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

| | Rituximab 500 mg - Double-blind Treatment Phase | Rituximab 1000 mg - Double-blind Treatment Phase | Placebo - Double-blind Treatment Phase | Rituximab 500 mg - Extension Phase | Rituximab 1000 mg - Extension Phase | Placebo - Extension Phase |
|---|---|---|---|---|---|---|
| | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) | Affected/ At Risk (%) |
| Total | 24/62 (38.71%) | 24/60 (40%) | 20/63 (31.75%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Immune system disorders | | | | | | |
| Rheumatoid arthritis [A] † | 2/62 (3.23%) | 1/60 (1.67%) | 6/63 (9.52%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Infections and infestations | | | | | | |
| Bronchitis [A] † | 4/62 (6.45%) | 5/60 (8.33%) | 2/63 (3.17%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Oral herpes [A] † | 1/62 (1.61%) | 3/60 (5%) | 0/63 (0%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Viral infection [A] † | 4/62 (6.45%) | 3/60 (5%) | 2/63 (3.17%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Musculoskeletal and connective tissue disorders | | | | | | |
| Arthralgia [A] † | 4/62 (6.45%) | 0/60 (0%) | 1/63 (1.59%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Back pain [A] † | 1/62 (1.61%) | 4/60 (6.67%) | 1/63 (1.59%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Nervous system disorders | | | | | | |
| Headache [A] † | 4/62 (6.45%) | 0/60 (0%) | 1/63 (1.59%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Nasopharyngitis [A] † | 2/62 (3.23%) | 3/60 (5%) | 2/63 (3.17%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Upper respiratory tract infection [A] † | 2/62 (3.23%) | 4/60 (6.67%) | 1/63 (1.59%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |
| Vascular disorders | | | | | | |
| Hypertension [A] † | 0/62 (0%) | 1/60 (1.67%) | 4/63 (6.35%) | 0/50 (0%) | 0/47 (0%) | 0/41 (0%) |

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA (11.2)

| | Rituximab 500 mg - Safety Follow-up Phase | Rituximab 1000 mg - Safety Follow-up Phase | Placebo - Safety Follow-up Phase |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Immune system disorders | | | |
| Rheumatoid arthritis [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Infections and infestations | | | |
| Bronchitis [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Oral herpes [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Viral infection [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Back pain [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Nervous system disorders | | | |
| Headache [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasopharyngitis [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Upper respiratory tract infection [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |
| Vascular disorders | | | |
| Hypertension [A] † | 0/57 (0%) | 0/54 (0%) | 0/54 (0%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (11.2)

## 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.

Results Point of Contact:

Name/Official Title: Medical Communications
Organization: Hoffmann-La Roche
Phone: 800 821-8590
Email: genentech@druginfo.com