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A Study of Tocilizumab and Methotrexate Treatment Strategies (Adding Tocilizumab to Methotrexate Versus Switching to Tocilizumab) in Patients With Active Rheumatoid Arthritis With Inadequate Response to Prior Methotrexate Treatment

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT00810199

Purpose

This 2 arm study will compare 2 treatment strategies based on tocilizumab in combination with methotrexate or placebo in patients with moderate to severe rheumatoid arthritis. Patients receiving methotrexate treatment will be randomized to receive either a) tocilizumab 8 mg intravenous (iv) every 4 weeks + methotrexate orally (po) weekly or b) tocilizumab 8 mg iv every 4 weeks + placebo po weekly. After the first 24 weeks of blinded treatment, treatment adjustments (increase or decrease of treatment intensity) may be introduced at intervals, based on response. The anticipated time on study treatment is up to 3 years, and the target sample size is approximately 470 patients.

Condition	Intervention	Phase
Rheumatoid Arthritis	Drug: tocilizumab [RoActemra/Actemra] Drug: methotrexate Drug: placebo	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Safety/Efficacy Study
Official Title: Randomized Placebo-controlled Study of Two Treatment Strategies Based on Tocilizumab (TCZ) With or Without Methotrexate (MTX) and Possible Addition of Other Disease-modifying Anti-rheumatic Drugs (DMARDs) in Patients...

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Percentage of Participants With Disease Activity Score 28 Joints (DAS28) Remission at Week 24 [Time Frame: Week 24] [Designated as safety issue: No]
  The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. DAS28 Remission is defined as a DAS28 score < 2.6.

Secondary Outcome Measures:

- Percentage of Participants With American College of Rheumatology (ACR20) Response [Time Frame: Baseline, Weeks 24, 52, 104] [Designated as safety issue: No]
  ACR20 response is defined as a ≥ 20% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
- Percentage of Participants With ACR50 Response [Time Frame: Baseline, Weeks 24, 52, 104] [Designated as safety issue: No]
  ACR50 response is defined as a ≥ 50% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
- Percentage of Participants With ACR70 Response [Time Frame: Baseline, Weeks 24, 52, 104] [Designated as safety issue: No]
  ACR70 response is defined as a ≥ 70% improvement (reduction) compared with Baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
- Percentage of Participants With ACR90 Response [Time Frame: Baseline, Weeks 24, 52, 104] [Designated as safety issue: No]
  ACR90 response is defined as a ≥ 90% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
- Time to First ACR20 Response [Time Frame: 104 Weeks] [Designated as safety issue: No]
  Time in days from first administration of study drug until ACR20 response. ACR20 response is defined as a ≥ 20% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core

set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].

- Time to First ACR50 Response [Time Frame: 104 Weeks] [Designated as safety issue: No]
  Time in days from first administration of study drug until ACR50 response. ACR50 response is defined as a ≥ 50% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate).
- Time to First ACR70 Response [Time Frame: 104 Weeks] [Designated as safety issue: No]
  Time in days from first administration of study drug until ACR70 response. ACR70 response is defined as a ≥ 70% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
- Time to First ACR90 Response [Time Frame: 104 Weeks] [Designated as safety issue: No]
  Time in days from first administration of study drug until ACR90 response. ACR90 response is defined as a ≥ 90% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
- Area Under Curve (AUC) DAS28 [Time Frame: Baseline to Week 24] [Designated as safety issue: No]
  The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. AUC DAS28 was averaged over study days. Analysis of Covariance was adjusted for Baseline DAS28 as a covariate and treatment group and region as fixed factors. Higher calculated AUC values are worse (indicate higher disease activity).
- Percentage of Participants With Disease Activity Score 28 (DAS28) Remission [Time Frame: Week 52] [Designated as safety issue: No]
  The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. DAS28 Remission is defined as a DAS28 score < 2.6.
- Percentage of Participants With DAS28 Low Disease Activity (LDAS) [Time Frame: Weeks 24, 52] [Designated as safety issue: No]
  The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. LDAS is defined as DAS28 ≤ 3.2.

- Change From Baseline in DAS28 Score [Time Frame: Baseline, Weeks 24, 52] [Designated as safety issue: No]
  The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A higher value indicated higher disease activity. A negative change from Baseline indicated improvement.
- Percentage of Participants With Good or Moderate European League (EULAR) DAS28 Responses [Time Frame: Baseline, 24, 52] [Designated as safety issue: No]
  The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A negative change from Baseline indicated improvement. European League Against Rheumatism (EULAR) Good response: DAS28 ≤ 3.2 or a change from Baseline < -1.2. EULAR Moderate response: DAS28 > 3.2 to ≤ 5.1 or a change from Baseline < -0.6 to ≥ -1.2.
- Change From Baseline in Swollen Joint Count [Time Frame: Baseline, Weeks 24, 52] [Designated as safety issue: No]
  66 joints were assessed for swelling and joints are classified as swollen/not swollen giving a total possible swollen joint count score of 0 to 66. A negative change from Baseline indicated improvement.
- Change From Baseline in Tender Joint Count [Time Frame: Baseline, Weeks 24, 52] [Designated as safety issue: No]
  68 joints are assessed for tenderness and joints are classified as tender/not tender giving a total possible tender joint count score of 0 to 68. A negative change from Baseline indicated improvement.
- Change From Baseline in Patient Global Assessment of Disease Activity Visual Analog Scale (VAS) [Time Frame: Baseline, Weeks 24, 52] [Designated as safety issue: No]
  The patients global assessment of disease activity was assessed on a 0 to 100 millimeter (mm) horizontal visual analogue scale (VAS) by the patient. The left-hand extreme of the line equals 0 mm, and was described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme equals 100 mm, as "maximum disease activity" (maximum arthritis disease activity). A negative change from Baseline indicated improvement.
- Change From Baseline in Physician Global Assessment of Disease Activity Visual Analog Scale (VAS) [Time Frame: Baseline, Weeks 24, 52] [Designated as safety issue: No]
  The physician global assessment of disease activity was assessed using a 0 to 100 mm horizontal visual analogue scale (VAS) by the physician. The left-hand extreme of the line equals 0 mm, and is described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme equals 100 mm, as "maximum disease activity" (maximum arthritis disease activity). A negative change from Baseline indicated improvement.
- Change From Baseline in Patient Global Assessment of Pain (VAS) [Time Frame: Baseline, Weeks 24, 52] [Designated as safety issue: No]
  The patient assessed their pain using a 0 to 100 millimeter (mm) horizontal visual analogue scale (VAS). The left-hand extreme of the line equals 0 mm, and is described as "no pain" and the right-hand extreme equals 100 mm as "unbearable pain". A negative change from Baseline indicated improvement.
- Change From Baseline in Erythrocyte Sedimentation Rate (ESR) [Time Frame: Baseline, Weeks 24, 52] [Designated as safety issue: No]
  Blood was collected for Erythrocyte Sedimentation Rate (ESR) (a test that assesses tissue inflammation) and was analyzed at a local laboratory. ESR was measured in millimeters/hour (mm/hr). A reduction in the level is considered an improvement.
- Change From Baseline in C-Reactive Protein (CRP) [Time Frame: Baseline, Weeks 24, 52] [Designated as safety issue: No]
  Blood was collected for C-Reactive Protein (CRP) (a test for analysis of inflammatory and infectious disorders) and was analyzed at a central laboratory. The serum concentration of CRP was measured in milligrams/deciliter (mg/dL). A reduction in the level is considered an improvement.
- Change From Baseline in the Health Assessment Questionnaire Disability Index [Time Frame: Baseline, Weeks 24, 52] [Designated as safety issue: No]
  The Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) is a patient completed questionnaire specific for rheumatoid arthritis, consisting of 20 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. There are 4 possible responses for each question: 0=without any difficulty, 1=with some difficulty, 2=with much difficulty and 3=unable to do. The score for each of the domains is the highest (worst) score in each domain. A patient must have a domain score for at least 6 of 8 domains to calculate a valid HAQ-DI score which is the sum of domain scores, divided by the number of domains that have a score for a total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from Baseline indicated improvement.

- Change From Baseline in Total Genant Modified Sharp Scores (GSS) [Time Frame: Baseline, Weeks 24, 52, 104] [Designated as safety issue: No]
  Radiographs were taken of each hand and foot at Baseline, Weeks 24, 52 and104 and were evaluated using the Genant modified method according to Sharp. Erosion Score: A total of 14 locations in each hand and wrist and 6 joints in the foot were evaluated for erosion using an 8-point scale where 0=Normal to 3.5=very severe erosion. Joint Narrowing Score: A total of 13 locations in each hand and wrist and 6 joints in the foot were evaluated for joint narrowing score using a 9-point scale where 0=Normal to 4.0=definite ankylosis (stiffness or fixation of a joint). The maximum total erosion score in the hands is 98 and in the feet 42. The maximum scores for joint space narrowing (JSN) in the hands was104 and in the feet 48. The total score was the sum of scores for erosions and JSN. The maximum total modified GSS was 292. A lower number change from Baseline was better. Analysis of covariance model, with Baseline DAS28 as a covariate and treatment and site as fixed factors.
- Change From Baseline in Joint Space Narrowing Score [Time Frame: Baseline, Weeks 24, 52, 104] [Designated as safety issue: No]
  A total of 13 locations in each hand and wrist and 6 joints in the foot were evaluated for joint narrowing score using a 9-point scale where 0=Normal to 4.0=definite ankylosis (stiffness or fixation of a joint). The maximum scores for joint space narrowing (JSN) in the hands was 104 and in the feet 48 for a total possible score of 0 to 152. A lower change from Baseline indicated a better score. Analysis of covariance model included baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
- Change From Baseline in Erosion Score [Time Frame: Baseline, Weeks 24, 52, 104] [Designated as safety issue: No]
  A total of 14 locations in each hand and wrist and 6 joints in the foot were evaluated for erosion using an 8-point scale where 0=Normal to 3.5=very severe erosion. The maximum erosion score in the hands was 98 and in the feet 42 for a total possible score of 0 to 140. A lower number change from Baseline indicated a better score.
- Percentage of Participants Discontinuing Tocilizumab Due to Remission [Time Frame: Weeks 52, 104] [Designated as safety issue: No]
  The percentage of participants who stopped treatment with tocilizumab due to remission.
- Percentage of Participants Who Withdrew Due to Lack of Sufficient Therapeutic Response [Time Frame: Up to 3 years] [Designated as safety issue: No]
  Lack of Sufficient Therapeutic Response was defined as the patient not responding to the drug as expected.
- Percentage of Participants Who Withdrew Due to Safety Reasons [Time Frame: Up to 3 years] [Designated as safety issue: No]
  Safety reasons were defined as adverse events, intercurrent illness or death. An adverse event was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study were reported as adverse events.
- Change From Baseline in Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL) [Time Frame: Baseline, Weeks 24, 52, 104] [Designated as safety issue: No]
  The RAQoL is a disease specific patient-reported outcome measure that determines the effect rheumatoid arthritis has on a patient's quality of life consisting of 30 questions that are answered either yes=1 or no=0 for a total possible score ranging from 0 (best) to 30 (worst). A negative change from Baseline indicated improvement.
- Change From Baseline in Academic Medical Center (AMC) Linear Disability Scale (ALDS) [Time Frame: Baseline, Weeks 104] [Designated as safety issue: No]
  The Academic Medical Center (AMC) Linear Disability Score (ALDS) evaluates the participant's ability to perform activities of daily life consisting of 77 questions answered yes or no . The question difficulty and the patient's ability are arranged on a single hierarchical linear scale. ALDS scores range from 10 to 90 with a higher score representing higher functional status. A positive change from Baseline indicated improvement.
- Area Under the Curve (AUC) From Baseline to Week 24 for ACR Response [Time Frame: Baseline to Week 24] [Designated as safety issue: No]
  ACR response was defined as an improvement (reduction) compared with baseline for both total joint count-68 joints and swollen joint count-66 joints, and for three of five variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) where 0=no pain to 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where: 0=no disease activity to 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate]. Area under the curve for ACR response to Week 24 was averaged over study days. Analysis of covariance model includes treatment group, region and baseline DAS28 (≤ 5.5 and > 5.5) as fixed factors.
- Area Under the Curve (AUC) From Baseline to Week 52 for ACR Response [Time Frame: Baseline to Week 52] [Designated as safety issue: No]

ACR response was defined as an improvement (reduction) compared with baseline for both total joint count-68 joints and swollen joint count-66 joints, and for three of five variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) where 0=no pain to 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where: 0=no disease activity to 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].Area under the curve for ACR response to Week 52 averaged over study days. Analysis of covariance model includes treatment group, region and baseline DAS28 (<=5.5 and >5.5) as fixed factors.

- Time to Tocilizumab Remission [Time Frame: 104 Weeks] [Designated as safety issue: No]
  The time in days from initial study drug treatment to tocilizumab remission that occurred when the patient discontinued treatment with tocilizumab.
- Time to Drug-Free Remission [Time Frame: 104 Weeks] [Designated as safety issue: No]
  The time in days from initial study drug treatment to drug free remission that occurred when the participant was able to discontinue tocilizumab, methotrexate/placebo and open label disease-modifying antirheumatic drugs (DMARDS).
- Time to Flare After Tocilizumab Remission [Time Frame: 104 Weeks] [Designated as safety issue: No]
  The time in days to a flare (recurrence of disease symptoms) after the patient discontinued treatment with tocilizumab.
- Time to Restart of Treatment After Discontinuation/Remission [Time Frame: 104 Weeks] [Designated as safety issue: No]
  The time in days from treatment discontinuation or remission to the restart of treatment.

Enrollment: 556
Study Start Date: March 2009
Primary Completion Date: August 2010
Study Completion Date: January 2013

Arms	Assigned Interventions
Experimental: Tocilizumab + Methotrexate Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drugs (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of	Drug: tocilizumab [RoActemra/Actemra] tocilizumab 8 mg IV every 4 weeks. Other Names: RoActemra/Actemra Drug: methotrexate Approximately 15-17 mg methotrexate capsule orally once a week.

Arms	Assigned Interventions
remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.	
Placebo Comparator: Tocilizumab + Placebo Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.	Drug: tocilizumab [RoActemra/Actemra] tocilizumab 8 mg IV every 4 weeks. Other Names: RoActemra/Actemra Drug: placebo Placebo matching methotrexate capsule taken orally once a week.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- adult patients, ≥ 18 years of age;
- moderate to severe active rheumatoid arthritis (Disease Activity Score (DAS28) > 4.4);
- inadequate response to methotrexate;
- on a stable dose of ≥ 15mg/week methotrexate for at least 6 weeks.

Exclusion Criteria:

- prior treatment with a biologic;
- Rheumatoid arthritis (RA) functional class IV;
- known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections;
- evidence of active malignant disease.

Contacts and Locations

Locations

United States, California
Santa Monica, California, United States, 90404
Upland, California, United States, 91786
Whittier, California, United States, 90606
Whittier, California, United States, 90606

United States, Florida
Aventura, Florida, United States, 33180
Aventura, Florida, United States, 33180
Naples, Florida, United States, 34102
Orange Park, Florida, United States, 32073
Plantation, Florida, United States, 33317
Sarasota, Florida, United States, 34239
South Miami, Florida, United States, 33143
Tamarac, Florida, United States, 33321

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Eagan, Minnesota, United States, 55121

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Las Vegas, Nevada, United States, 89128

United States, Ohio
Mayfield, Ohio, United States, 44143
Middleburg Heights, Ohio, United States, 44130

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Oklahoma City, Oklahoma, United States, 73104

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West Reading, Pennsylvania, United States, 19611

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Greenville, South Carolina, United States, 29601

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Le Kremlin Bicetre, France, 94275
Le Mans, France, 72037
Marseille, France, 13385
Marseille, France, 13285
Monaco, France, 98012
Nantes, France, 44035
Nice, France, 06202
Paris, France, 75679
Paris, France, 75571
Pierre Benite, France, 69495
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Leiden, Netherlands, 2333 ZA
Maastricht, Netherlands, 6202 AZ
Nijmegen, Netherlands, 6525 GA
Utrecht, Netherlands, 3584 CX

Norway

Drammen, Norway, 3004
Gjettum, Norway, 1346
Kristiansand, Norway, 4604
Lillehammer, Norway, 2609
Moss, Norway, 1535
Oslo, Norway, 0319

Romania

- Bucharest, Romania, 011172
- Bucuresti, Romania, 020983

Russian Federation
- Barnaul, Russian Federation, 656024
- Ekaterinburg, Russian Federation, 620102
- Irkutsk, Russian Federation, 664047
- Izhevsk, Russian Federation, 426009
- Kazan, Russian Federation, 420012
- Khanty-Mansiysk, Russian Federation, 628011
- Kursk, Russian Federation, 305007
- Moscow, Russian Federation, 115522
- Novosibirsk, Russian Federation, 630099
- Novosibirsk, Russian Federation, 630117
- St Petersburg, Russian Federation, 191015
- Tjumen, Russian Federation, 625023
- UFA, Russian Federation, 450005
- Ulyanovsk, Russian Federation, 432063
- Vladivostok, Russian Federation, 690105

Serbia
- Belgrade, Serbia, 11000
- Belgrade, Serbia, 11000
- Kragujevac, Serbia, 34000
- Niska Banja, Serbia, 18250
- Nova sad, Serbia, 21000

Spain
- Oviedo, Asturias, Spain, 33006
- Barcelona, Barcelona, Spain, 08003
- La Coruna, La Coruña, Spain, 15006
- Santiago De Compostela, La Coruña, Spain, 15706
- Leganes, Madrid, Spain, 28191
- Madrid, Madrid, Spain, 28046
- Madrid, Madrid, Spain, 28007
- Madrid, Madrid, Spain, 28222
- Madrid, Madrid, Spain, 28041
- Sevilla, Sevilla, Spain, 41009
- Bilbao, Vizcaya, Spain, 48013

Sweden
- Goeteborg, Sweden, 41345
- Umea, Sweden, 90185

Thailand
- Bangkok, Thailand, 10300
- Khon Kaen, Thailand, 40002
- Pathumthani, Thailand, 12120

United Kingdom
- Cannock, United Kingdom, WS11 5XY

Glasgow, United Kingdom, G12 0YN
Leeds, United Kingdom, LS7 4SA
London, United Kingdom, SE5 9RS
Newcastle-upon-Tyne, United Kingdom, NE2 4HH
Norwich, United Kingdom, NR4 7UY

Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Results Publications:

Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, Schett G, Amital H, Navarro-Sarabia F, Hou A, Bernasconi C, Huizinga TW. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis. 2013 Jan;72(1):43-50. doi: 10.1136/annrheumdis-2011-201282. Epub 2012 May 5.

Dougados M, Kissel K, Conaghan PG, Mola EM, Schett G, Gerli R, Hansen MS, Amital H, Xavier RM, Troum O, Bernasconi C, Huizinga TW. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. Ann Rheum Dis. 2014 May;73(5):803-9. doi: 10.1136/annrheumdis-2013-204761. Epub 2014 Jan 28.

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	MA21488 2008-001847-20
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.

	Description
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Overall Study

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Started	279	277
Received Study Drug	277	276
Completed Week 24	259	250
Completed Week 52	243	229
Completed Week 104	222	201
Completed	220	195 [1]
Not Completed	59	82
Adverse Event	24	26
Death	4	6
Withdrew consent	9	12
Insufficient therapeutic response	5	14
Refused treatment/Did not cooperate	7	7
Administrative/Other	5	6
Protocol Violation	2	6
Failure to return	1	4
Did not receive study drug	2	1

[1] Completed=Completed Treatment

Baseline Characteristics

Analysis Population Description

Baseline measures are based on the Safety Population and include all randomized participants who received at least one dose of study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Baseline Measures

	Tocilizumab + Methotrexate	Tocilizumab + Placebo	Total
Number of Participants	277	276	553
Age, Continuous [units: years] Mean (Standard Deviation)	53.0 (13.40)	53.6 (11.91)	53.3 (12.67)
Gender, Male/Female [units: participants]			
Female	227	217	444
Male	50	59	109

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With Disease Activity Score 28 Joints (DAS28) Remission at Week 24
Measure Description	The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. DAS28 Remission is defined as a DAS28 score < 2.6.
Time Frame	Week 24
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg intravenous once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study methotrexate dose for 24 weeks.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants With Disease Activity Score 28 Joints (DAS28) Remission at Week 24 [units: Percentage of participants]	40.4	34.8

Statistical Analysis 1 for Percentage of Participants With Disease Activity Score 28 Joints (DAS28) Remission at Week 24

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2055
	Comments	Cochran-Mantel-Haenszel test stratified by region and baseline DAS28 (≤5.5 and >5.5).
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.260
	Confidence Interval	(2-Sided) 95% 0.882 to 1.799
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Percentage of Participants With Disease Activity Score 28 Joints (DAS28) Remission at Week 24

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1894
	Comments	Logistic regression including treatment , region and baseline DAS28.
	Method	Regression, Logistic
	Comments	Odds ratio is for Tocilizumab + Methotrexate relative to Tocilizumab + Placebo.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.270
	Confidence Interval	(2-Sided) 95% 0.889 to 1.814
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants With American College of Rheumatology (ACR20) Response

Measure Description	ACR20 response is defined as a ≥ 20% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
Time Frame	Baseline, Weeks 24, 52, 104
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants With American College of Rheumatology (ACR20) Response [units: Percentage of participants]		

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Week 24	71.5	70.3
Week 52	70.8	69.2
Week 104	65.7	59.4

Statistical Analysis 1 for Percentage of Participants With American College of Rheumatology (ACR20) Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8742
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

Statistical Analysis 2 for Percentage of Participants With American College of Rheumatology (ACR20) Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6212
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

Statistical Analysis 3 for Percentage of Participants With American College of Rheumatology (ACR20) Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 104
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0963
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

3. Secondary Outcome Measure:

Measure Title	Percentage of Participants With ACR50 Response
Measure Description	ACR50 response is defined as a ≥ 50% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
Time Frame	Baseline, Weeks 24, 52, 104
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants With ACR50 Response [units: Percentage of participants]		
Week 24	45.5	40.2
Week 52	50.2	55.4
Week 104	52.7	46.4

Statistical Analysis 1 for Percentage of Participants With ACR50 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2969
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

Statistical Analysis 2 for Percentage of Participants With ACR50 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2215
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

Statistical Analysis 3 for Percentage of Participants With ACR50 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 104
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1243
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants With ACR70 Response

Measure Description	ACR70 response is defined as a ≥ 70% improvement (reduction) compared with Baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
Time Frame	Baseline, Weeks 24, 52, 104
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants With ACR70 Response [units: Percentage of participants]		

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Week 24	24.5	25.4
Week 52	31.4	31.2
Week 104	34.3	29.3

Statistical Analysis 1 for Percentage of Participants With ACR70 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6775
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

Statistical Analysis 2 for Percentage of Participants With ACR70 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.9976
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

Statistical Analysis 3 for Percentage of Participants With ACR70 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 104
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2168
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

5. Secondary Outcome Measure:

Measure Title	Percentage of Participants With ACR90 Response
Measure Description	ACR90 response is defined as a ≥ 90% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
Time Frame	Baseline, Weeks 24, 52, 104
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants With ACR90 Response [units: Percentage of participants]		
Week 24	5.8	5.1
Week 52	12.6	11.2
Week 104	11.9	9.1

Statistical Analysis 1 for Percentage of Participants With ACR90 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8369
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

Statistical Analysis 2 for Percentage of Participants With ACR90 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6528
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

Statistical Analysis 3 for Percentage of Participants With ACR90 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 104
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2546
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

6. Secondary Outcome Measure:

Measure Title	Time to First ACR20 Response

Measure Description	Time in days from first administration of study drug until ACR20 response. ACR20 response is defined as a ≥ 20% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
Time Frame	104 Weeks
Safety Issue?	No

Analysis Population Description

Intent-to treat population included all randomized participants who received study drug. Censoring occurred at the last assessment for those completing the study or withdrawing early, if a response was not observed. In calculating ACR response, a last observation carried forward approach is used for missing joint count data.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Time to First ACR20 Response [units: Days] Median (95% Confidence Interval)	57.0 (NA to NA) [1]	61.0 (57.0 to 84.0)

[1] The minimum and maximum confidence interval was not estimated; insufficient number of participants with events.

Statistical Analysis 1 for Time to First ACR20 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1018
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Time to First ACR50 Response
Measure Description	Time in days from first administration of study drug until ACR50 response. ACR50 response is defined as a ≥ 50% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate).
Time Frame	104 Weeks
Safety Issue?	No

Analysis Population Description

Intent-to treat population included all randomized participants who received study drug. Censoring occurred at the last assessment for those completing the study or withdrawing early, if a response was not observed. In calculating ACR response, a last observation carried forward approach is used for missing joint count data.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Time to First ACR50 Response [units: Days] Median (95% Confidence Interval)	140.0 (113.0 to 142.0)	143.0 (137.0 to 169.0)

Statistical Analysis 1 for Time to First ACR50 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7176
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

8. Secondary Outcome Measure:

Measure Title	Time to First ACR70 Response
Measure Description	Time in days from first administration of study drug until ACR70 response. ACR70 response is defined as a ≥ 70% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
Time Frame	104 Weeks
Safety Issue?	No

Analysis Population Description

Intent-to treat population included all randomized participants who received study drug. Censoring occurred at the last assessment for those completing the study or withdrawing early, if a response was not observed. In calculating ACR response, a last observation carried forward approach is used for missing joint count data.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.

	Description
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Time to First ACR70 Response [units: Days] Median (95% Confidence Interval)	284.0 (225.0 to 327.0)	307.0 (253.0 to 338.0)

Statistical Analysis 1 for Time to First ACR70 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8526
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

9. Secondary Outcome Measure:

Measure Title	Time to First ACR90 Response

Measure Description	Time in days from first administration of study drug until ACR90 response. ACR90 response is defined as a ≥ 90% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].
Time Frame	104 Weeks
Safety Issue?	No

Analysis Population Description

Intent-to treat population included all randomized participants who received study drug. Censoring occurred at the last assessment for those completing the study or withdrawing early, if a response was not observed. In calculating ACR response, a last observation carried forward approach is used for missing joint count data.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Time to First ACR90 Response [units: Days] Median (95% Confidence Interval)	NA (844.0 to NA) [1]	NA (986.0 to NA) [1]

[1] The median was not reached; the rate was < 50%.

Statistical Analysis 1 for Time to First ACR90 Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2217
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

10. Secondary Outcome Measure:

Measure Title	Area Under Curve (AUC) DAS28
Measure Description	The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. AUC DAS28 was averaged over study days. Analysis of Covariance was adjusted for Baseline DAS28 as a covariate and treatment group and region as fixed factors. Higher calculated AUC values are worse (indicate higher disease activity).
Time Frame	Baseline to Week 24
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population, all randomized participants who received study drug, with data available at Baseline and Week 24.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg intravenous once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study methotrexate dose for 24 weeks.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	255	246
Area Under Curve (AUC) DAS28 [units: Score on a scale*week] Least Squares Mean (Standard Error)	3.97 (0.098)	4.23 (0.092)

Statistical Analysis 1 for Area Under Curve (AUC) DAS28

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0008
	Comments	[Not specified]
	Method	ANCOVA
	Comments	Baseline DAS28 as a covariate.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.26
	Confidence Interval	(2-Sided) 95% -0.41 to -0.11
	Estimation Comments	[Not specified]

11. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Disease Activity Score 28 (DAS28) Remission
Measure Description	The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. DAS28 Remission is defined as a DAS28 score < 2.6.
Time Frame	Week 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants With Disease Activity Score 28 (DAS28) Remission [units: Percentage of participants]	45.5	36.6

Statistical Analysis 1 for Percentage of Participants With Disease Activity Score 28 (DAS28) Remission

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]

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

Statistical Test of Hypothesis	P-Value	0.0245
	Comments	[Not specified]
	Method	Regression, Logistic
	Comments	Logistic regression including treatment, region and baseline DAS28.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.490
	Confidence Interval	(2-Sided) 95% 1.053 to 2.109
	Estimation Comments	Odds ratio is for Tocilizumab + Methotrexate relative to Tocilizumab + Placebo.

Statistical Analysis 2 for Percentage of Participants With Disease Activity Score 28 (DAS28) Remission

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0258
	Comments	Stratified by region and baseline DAS28 (≤ 5.5 and > 5.5).
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.482
	Confidence Interval	(2-Sided) 95% 1.048 to 2.095
	Estimation Comments	[Not specified]

12. Secondary Outcome Measure:

Measure Title	Percentage of Participants With DAS28 Low Disease Activity (LDAS)
Measure Description	The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. LDAS is defined as DAS28 ≤ 3.2.
Time Frame	Weeks 24, 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants With DAS28 Low Disease Activity (LDAS) [units: Percentage of participants]		

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Week 24	61.7	51.4
Week 52	62.5	57.2

Statistical Analysis 1 for Percentage of Participants With DAS28 Low Disease Activity (LDAS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0287
	Comments	[Not specified]
	Method	Other [Wald Chi-square]
	Comments	Asymptotic test; parameter estimate is zero.

Statistical Analysis 2 for Percentage of Participants With DAS28 Low Disease Activity (LDAS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2240
	Comments	[Not specified]
	Method	Other [Wald Chi-square]
	Comments	Asymptotic test; parameter estimate is zero.

13. Secondary Outcome Measure:

Measure Title	Change From Baseline in DAS28 Score

Measure Description	The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A higher value indicated higher disease activity. A negative change from Baseline indicated improvement.
Time Frame	Baseline, Weeks 24, 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in DAS28 Score [units: Score on a scale] Mean (Standard Deviation)		
Week 24	-3.43 (1.326)	-3.21 (1.305)
Week 52	-3.74 (1.406)	-3.67 (1.291)

Statistical Analysis 1 for Change From Baseline in DAS28 Score

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0497
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in DAS28 Score

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3918
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

14. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Good or Moderate European League (EULAR) DAS28 Responses

Measure Description	The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A negative change from Baseline indicated improvement. European League Against Rheumatism (EULAR) Good response: DAS28 ≤ 3.2 or a change from Baseline < -1.2. EULAR Moderate response: DAS28 > 3.2 to ≤ 5.1 or a change from Baseline < -0.6 to ≥ -1.2.
Time Frame	Baseline, 24, 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants With Good or Moderate European League (EULAR) DAS28 Responses [units: Percentage of participants]		

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Week 24	89.5	86.2
Week 52	84.5	78.2

Statistical Analysis 1 for Percentage of Participants With Good or Moderate European League (EULAR) DAS28 Responses

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0019
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

Statistical Analysis 2 for Percentage of Participants With Good or Moderate European League (EULAR) DAS28 Responses

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1181
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Region and baseline DAS28 (≤5.5 and >5.5) included as stratification variables.

15. Secondary Outcome Measure:

Measure Title	Change From Baseline in Swollen Joint Count

Measure Description	66 joints were assessed for swelling and joints are classified as swollen/not swollen giving a total possible swollen joint count score of 0 to 66. A negative change from Baseline indicated improvement.
Time Frame	Baseline, Weeks 24, 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Swollen Joint Count [units: Joint count] Mean (Standard Deviation)		
Week 24 (n=255,246)	-11.33 (8.042)	-11.74 (9.446)
Week 52 (n=237,220)	-12.29 (8.796)	-12.25 (8.949)

Statistical Analysis 1 for Change From Baseline in Swollen Joint Count

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7776
	Comments	P-value is from a 2-sided, Wilcoxon rank-sum test of no difference between the 2 treatment groups in change from baseline.
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in Swollen Joint Count

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8843
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

16. Secondary Outcome Measure:

Measure Title	Change From Baseline in Tender Joint Count
Measure Description	68 joints are assessed for tenderness and joints are classified as tender/not tender giving a total possible tender joint count score of 0 to 68. A negative change from Baseline indicated improvement.
Time Frame	Baseline, Weeks 24, 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Tender Joint Count [units: Joint count] Mean (Standard Deviation)		
Week 24 (n=255,246)	-17.27 (13.358)	-17.00 (13.632)
Week 52 (n=237,220)	-19.45 (13.471)	-18.97 (12.768)

Statistical Analysis 1 for Change From Baseline in Tender Joint Count

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.9095
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in Tender Joint Count

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7179
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

17. Secondary Outcome Measure:

Measure Title	Change From Baseline in Patient Global Assessment of Disease Activity Visual Analog Scale (VAS)
Measure Description	The patients global assessment of disease activity was assessed on a 0 to 100 millimeter (mm) horizontal visual analogue scale (VAS) by the patient. The left-hand extreme of the line equals 0 mm, and was described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme equals 100 mm, as "maximum disease activity" (maximum arthritis disease activity). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Weeks 24, 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Patient Global Assessment of Disease Activity Visual Analog Scale (VAS) [units: mm] Mean (Standard Deviation)		
Week 24 (n=255,246)	-34.31 (25.677)	-32.42 (24.344)
Week 52 (n=239,220)	-38.92 (25.590)	-40.94 (26.211)

Statistical Analysis 1 for Change From Baseline in Patient Global Assessment of Disease Activity Visual Analog Scale (VAS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3113
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in Patient Global Assessment of Disease Activity Visual Analog Scale (VAS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2931
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

18. Secondary Outcome Measure:

Measure Title	Change From Baseline in Physician Global Assessment of Disease Activity Visual Analog Scale (VAS)
Measure Description	The physician global assessment of disease activity was assessed using a 0 to 100 mm horizontal visual analogue scale (VAS) by the physician. The left-hand extreme of the line equals 0 mm, and is described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme equals 100 mm, as "maximum disease activity" (maximum arthritis disease activity). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Weeks 24, 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Physician Global Assessment of Disease Activity Visual Analog Scale (VAS) [units: mm] Mean (Standard Deviation)		
Week 24 (n=249,244)	-40.67 (19.500)	-38.46 (21.654)
Week 52 (n=232,218)	-44.18 (21.092)	-44.68 (21.400)

Statistical Analysis 1 for Change From Baseline in Physician Global Assessment of Disease Activity Visual Analog Scale (VAS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2451
	Comments	P-value is from a 2-sided, Wilcoxon rank-sum test of no difference between the 2 treatment groups in change from baseline.
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in Physician Global Assessment of Disease Activity Visual Analog Scale (VAS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8841
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

19. Secondary Outcome Measure:

Measure Title	Change From Baseline in Patient Global Assessment of Pain (VAS)
Measure Description	The patient assessed their pain using a 0 to 100 millimeter (mm) horizontal visual analogue scale (VAS). The left-hand extreme of the line equals 0 mm, and is described as "no pain" and the right-hand extreme equals 100 mm as "unbearable pain". A negative change from Baseline indicated improvement.
Time Frame	Baseline, Weeks 24, 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Patient Global Assessment of Pain (VAS) [units: mm] Mean (Standard Deviation)		
Week 24 (n=255,246)	-29.34 (26.639)	-29.75 (24.918)
Week 52 (239,220)	-33.09 (26.933)	-38.38 (25.537)

Statistical Analysis 1 for Change From Baseline in Patient Global Assessment of Pain (VAS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.9655
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in Patient Global Assessment of Pain (VAS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0308
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

20. Secondary Outcome Measure:

Measure Title	Change From Baseline in Erythrocyte Sedimentation Rate (ESR)
Measure Description	Blood was collected for Erythrocyte Sedimentation Rate (ESR) (a test that assesses tissue inflammation) and was analyzed at a local laboratory. ESR was measured in millimeters/hour (mm/hr). A reduction in the level is considered an improvement.
Time Frame	Baseline, Weeks 24, 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Erythrocyte Sedimentation Rate (ESR) [units: mm/hr] Mean (Standard Deviation)		
Week 24 (n=255,246)	-30.61 (24.187)	-29.10 (24.518)
Week 52 (n=238,220)	-31.81 (23.025)	-31.18 (24.527)

Statistical Analysis 1 for Change From Baseline in Erythrocyte Sedimentation Rate (ESR)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5186
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in Erythrocyte Sedimentation Rate (ESR)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7706
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

21. Secondary Outcome Measure:

Measure Title	Change From Baseline in C-Reactive Protein (CRP)
Measure Description	Blood was collected for C-Reactive Protein (CRP) (a test for analysis of inflammatory and infectious disorders) and was analyzed at a central laboratory. The serum concentration of CRP was measured in milligrams/deciliter (mg/dL). A reduction in the level is considered an improvement.
Time Frame	Baseline, Weeks 24, 52
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population, all randomized participants who received at least one dose of study drug, with data available for analysis at the given time-point.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in C-Reactive Protein (CRP) [units: mg/dL] Mean (Standard Deviation)		
Week 24 (n=252,241)	-1.37 (2.043)	-1.39 (2.206)
Week 52 (n=236,221)	-1.39 (1.943)	-1.40 (2.216)

Statistical Analysis 1 for Change From Baseline in C-Reactive Protein (CRP)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6067
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in C-Reactive Protein (CRP)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6810
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

22. Secondary Outcome Measure:

Measure Title	Change From Baseline in the Health Assessment Questionnaire Disability Index
Measure Description	The Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) is a patient completed questionnaire specific for rheumatoid arthritis, consisting of 20 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. There are 4 possible responses for each question: 0=without any difficulty, 1=with some difficulty, 2=with much difficulty and 3=unable to do. The score for each of the domains is the highest (worst) score in each domain. A patient must have a domain score for at least 6 of 8 domains to calculate a valid HAQ-DI score which is the sum of domain scores, divided by the number of domains that have a score for a total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Weeks 24, 52
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population, all randomized participants who received study drug, with data available for analysis at the given time-point.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in the Health Assessment Questionnaire Disability Index [units: Score on a scale] Mean (Standard Deviation)		
Week 24 (n=251,241)	-0.56 (0.666)	-0.55 (0.531)
Week 52 (n=235,213)	-0.59 (0.713)	-0.67 (0.630)

Statistical Analysis 1 for Change From Baseline in the Health Assessment Questionnaire Disability Index

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.9323
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in the Health Assessment Questionnaire Disability Index

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1448
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

23. Secondary Outcome Measure:

Measure Title	Change From Baseline in Total Genant Modified Sharp Scores (GSS)
Measure Description	Radiographs were taken of each hand and foot at Baseline, Weeks 24, 52 and104 and were evaluated using the Genant modified method according to Sharp. Erosion Score: A total of 14 locations in each hand and wrist and 6 joints in the foot were evaluated for erosion using an 8-point scale where 0=Normal to 3.5=very severe erosion. Joint Narrowing Score: A total of 13 locations in each hand and wrist and 6 joints in the foot were evaluated for joint narrowing score using a 9-point scale where 0=Normal to 4.0=definite ankylosis (stiffness or fixation of a joint). The maximum total erosion score in the hands is 98 and in the feet 42. The maximum scores for joint space narrowing (JSN) in the hands was104 and in the feet 48. The total score was the sum of scores for erosions and JSN. The maximum total modified GSS was 292. A lower number change from Baseline was better. Analysis of covariance model, with Baseline DAS28 as a covariate and treatment and site as fixed factors.
Time Frame	Baseline, Weeks 24, 52, 104
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population, all randomized participants who received study drug, with data available for analysis at Baseline and the given time point.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Total Genant Modified Sharp Scores (GSS) [units: Score on a scale] Least Squares Mean (Standard Error)		
Week 24 (n= 266,258)	0.18 (0.161)	0.35 (0.152)
Week 52 (n= 269,264)	0.35 (0.370)	0.63 (0.350)
Week 104 (n= 215,202)	0.35 (0.347)	0.95 (0.320)

Statistical Analysis 1 for Change From Baseline in Total Genant Modified Sharp Scores (GSS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2034
	Comments	Baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.17
	Confidence Interval	(2-Sided) 95% -0.43 to 0.09
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in Total Genant Modified Sharp Scores (GSS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3611
	Comments	Baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.28
	Confidence Interval	(2-Sided) 95% -0.88 to 0.32
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Change From Baseline in Total Genant Modified Sharp Scores (GSS)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 104

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

Statistical Test of Hypothesis	P-Value	0.0342
	Comments	Baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.60
	Confidence Interval	(2-Sided) 95% -1.16 to -0.05
	Estimation Comments	[Not specified]

24. Secondary Outcome Measure:

Measure Title	Change From Baseline in Joint Space Narrowing Score
Measure Description	A total of 13 locations in each hand and wrist and 6 joints in the foot were evaluated for joint narrowing score using a 9-point scale where 0=Normal to 4.0=definite ankylosis (stiffness or fixation of a joint). The maximum scores for joint space narrowing (JSN) in the hands was 104 and in the feet 48 for a total possible score of 0 to 152. A lower change from Baseline indicated a better score. Analysis of covariance model included baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
Time Frame	Baseline, Weeks 24, 52, 104
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population, all randomized participants who received study drug, with data available for analysis at Baseline and the given time point.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Joint Space Narrowing Score [units: Score on a scale] Least Squares Mean (Standard Error)		
Week 24 (n= 266, 258)	0.16 (0.121)	0.19 (0.115)
Week 52 (n= 269, 264)	0.45 (0.314)	0.39 (0.297)
Week 104 (n= 215, 202)	0.38 (0.218)	0.70 (0.201)

Statistical Analysis 1 for Change From Baseline in Joint Space Narrowing Score

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7095
	Comments	Baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.04
	Confidence Interval	(2-Sided) 95% -0.23 to 0.16
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in Joint Space Narrowing Score

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8147
	Comments	Baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.06
	Confidence Interval	(2-Sided) 95% -0.45 to 0.57
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Change From Baseline in Joint Space Narrowing Score

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 104

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

Statistical Test of Hypothesis	P-Value	0.0778
	Comments	Baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.32
	Confidence Interval	(2-Sided) 95% -0.67 to 0.04
	Estimation Comments	[Not specified]

25. Secondary Outcome Measure:

Measure Title	Change From Baseline in Erosion Score
Measure Description	A total of 14 locations in each hand and wrist and 6 joints in the foot were evaluated for erosion using an 8-point scale where 0=Normal to 3.5=very severe erosion. The maximum erosion score in the hands was 98 and in the feet 42 for a total possible score of 0 to 140. A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Weeks 24, 52, 104
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population, all randomized participants who received study drug, with data available for analysis at Baseline and the given time point.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Erosion Score [units: Score on a scale] Least Squares Mean (Standard Error)		
Week 24 (n=266,258)	0.03 (0.077)	0.15 (0.072)
Week 52 (n= 269,264)	-0.09 (0.125)	0.25 (0.118)
Week 104 (n= 215,202)	-0.03 (0.169)	0.26 (0.156)

Statistical Analysis 1 for Change From Baseline in Erosion Score

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0441
	Comments	Baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.13
	Confidence Interval	(2-Sided) 95% -0.25 to -0.00
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in Erosion Score

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0012
	Comments	Baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.33
	Confidence Interval	(2-Sided) 95% -0.54 to -0.13
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Change From Baseline in Erosion Score

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 104

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

Statistical Test of Hypothesis	P-Value	0.0372
	Comments	Baseline x-ray and DAS28 as covariates and treatment group and region as fixed effects.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.29
	Confidence Interval	(2-Sided) 95% -0.56 to -0.02
	Estimation Comments	[Not specified]

26. Secondary Outcome Measure:

Measure Title	Percentage of Participants Discontinuing Tocilizumab Due to Remission
Measure Description	The percentage of participants who stopped treatment with tocilizumab due to remission.
Time Frame	Weeks 52, 104
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population (all randomized participants who received study drug) with non-missing DAS28 assessment.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.

	Description
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants Discontinuing Tocilizumab Due to Remission [units: Percentage of participants]		
Week 52 (n=243,231)	28.4	21.6
Week 104 (n=243,229)	53.1	47.6

Statistical Analysis 1 for Percentage of Participants Discontinuing Tocilizumab Due to Remission

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0694
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Stratified by region and categorical baseline DAS28 (≤ 5.5 and > 5.5).
Method of Estimation	Estimation Parameter	Other [Difference]
	Estimated Value	6.75

	Confidence Interval	(2-Sided) 95% -1.02 to 14.52
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Percentage of Participants Discontinuing Tocilizumab Due to Remission

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 104
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1695
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

27. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Withdrew Due to Lack of Sufficient Therapeutic Response
Measure Description	Lack of Sufficient Therapeutic Response was defined as the patient not responding to the drug as expected.
Time Frame	Up to 3 years
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.

	Description
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants Who Withdrew Due to Lack of Sufficient Therapeutic Response [units: Percentage of participants]	1.8	4.7

Statistical Analysis 1 for Percentage of Participants Who Withdrew Due to Lack of Sufficient Therapeutic Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0496
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Stratified by region and categorical baseline DAS28 (≤ 5.5 and > 5.5).

Method of Estimation	Estimation Parameter	Other [Difference]
	Estimated Value	-2.91
	Confidence Interval	(2-Sided) 95% -5.86 to 0.05
	Estimation Comments	[Not specified]

28. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Withdrew Due to Safety Reasons
Measure Description	Safety reasons were defined as adverse events, intercurrent illness or death. An adverse event was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study were reported as adverse events.
Time Frame	Up to 3 years
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Percentage of Participants Who Withdrew Due to Safety Reasons [units: Percentage of participants]	9.7	11.2

Statistical Analysis 1 for Percentage of Participants Who Withdrew Due to Safety Reasons

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5188
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	Stratified by region and categorical baseline DAS28 (≤ 5.5 and > 5.5).

Method of Estimation	Estimation Parameter	Other [Difference]
	Estimated Value	-1.48
	Confidence Interval	(2-Sided) 95% -6.59 to 3.62
	Estimation Comments	[Not specified]

29. Secondary Outcome Measure:

Measure Title	Change From Baseline in Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL)
Measure Description	The RAQoL is a disease specific patient-reported outcome measure that determines the effect rheumatoid arthritis has on a patient's quality of life consisting of 30 questions that are answered either yes=1 or no=0 for a total possible score ranging from 0 (best) to 30 (worst). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Weeks 24, 52, 104
Safety Issue?	No

Analysis Population Description

Participants from the intent-to-treat Population, all participants who received study drug, with data available for analysis at the given time-point. The RAQoL score was administered in a subset of sites for which the questionnaire was available in the local language.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL) [units: Score on a scale] Mean (Standard Deviation)		
Week 24 (n=146,135)	-6.07 (8.005)	-5.19 (7.064)
Week 52 (n=132,111)	-7.28 (8.141)	-6.33 (7.691)
Week 104 (n=87,74)	-6.89 (8.691)	-5.24 (8.899)

Statistical Analysis 1 for Change From Baseline in Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 24
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2652
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	Week 52
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1970
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Statistical Analysis 3 for Change From Baseline in Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL)

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1671
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

30. Secondary Outcome Measure:

Measure Title	Change From Baseline in Academic Medical Center (AMC) Linear Disability Scale (ALDS)

Measure Description	The Academic Medical Center (AMC) Linear Disability Score (ALDS) evaluates the participant's ability to perform activities of daily life consisting of 77 questions answered yes or no . The question difficulty and the patient's ability are arranged on a single hierarchical linear scale. ALDS scores range from 10 to 90 with a higher score representing higher functional status. A positive change from Baseline indicated improvement.
Time Frame	Baseline, Weeks 104
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population, all randomized participants who received study drug, with data available for analysis.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	277	276
Change From Baseline in Academic Medical Center (AMC) Linear Disability Scale (ALDS) [units: Score on a scale] Mean (Standard Deviation)	2.42 (7.773)	0.91 (2.099)

31. Secondary Outcome Measure:

Measure Title	Area Under the Curve (AUC) From Baseline to Week 24 for ACR Response
Measure Description	ACR response was defined as an improvement (reduction) compared with baseline for both total joint count-68 joints and swollen joint count-66 joints, and for three of five variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) where 0=no pain to 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where: 0=no disease activity to 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate]. Area under the curve for ACR response to Week 24 was averaged over study days. Analysis of covariance model includes treatment group, region and baseline DAS28 (≤ 5.5 and > 5.5) as fixed factors.
Time Frame	Baseline to Week 24
Safety Issue?	No

Analysis Population Description

Participants from the intent-to-treat population, all participants who received study drug, with ACR response available for analysis at the time-point. Participants with early withdrawals are not included.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg intravenous once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study methotrexate dose for 24 weeks.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	253	246
Area Under the Curve (AUC) From Baseline to Week 24 for ACR Response [units: Score on a scale*day] Least Squares Mean (Standard Error)	18.95 (4.220)	13.74 (3.979)

Statistical Analysis 1 for Area Under the Curve (AUC) From Baseline to Week 24 for ACR Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]

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

Statistical Test of Hypothesis	P-Value	0.1110
	Comments	[Not specified]
	Method	ANCOVA
	Comments	The analysis of covariance model included treatment group, region and baseline DAS28 (≤ 5.5 and > 5.5) as fixed factors.

Method of Estimation	Estimation Parameter	Other [Adjusted Mean Difference (Wald CI)]
	Estimated Value	5.22
	Confidence Interval	(2-Sided) 95% -1.20 to 11.64
	Estimation Comments	[Not specified]

32. Secondary Outcome Measure:

Measure Title	Area Under the Curve (AUC) From Baseline to Week 52 for ACR Response
Measure Description	ACR response was defined as an improvement (reduction) compared with baseline for both total joint count-68 joints and swollen joint count-66 joints, and for three of five variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) where 0=no pain to 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where: 0=no disease activity to 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].Area under the curve for ACR response to Week 52 averaged over study days. Analysis of covariance model includes treatment group, region and baseline DAS28 (<=5.5 and >5.5) as fixed factors.
Time Frame	Baseline to Week 52
Safety Issue?	No

Analysis Population Description

Participants from the intent-to-treat population, all participants who received study drug, with ACR response available for analysis at the time-point. Participants with early withdrawals are not included.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg intravenous once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study methotrexate dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	236	220
Area Under the Curve (AUC) From Baseline to Week 52 for ACR Response [units: Score on a scale*day] Least Squares Mean (Standard Error)	30.48 (4.901)	32.59 (4.611)

Statistical Analysis 1 for Area Under the Curve (AUC) From Baseline to Week 52 for ACR Response

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6027
	Comments	[Not specified]
	Method	ANCOVA
	Comments	The analysis of covariance model included treatment group, region and baseline DAS28 (≤ 5.5 and > 5.5) as fixed factors.

Method of Estimation	Estimation Parameter	Other [Adjusted Mean Difference (Wald CI)]

	Estimated Value	-2.11
	Confidence Interval	(2-Sided) 95% -10.07 to 5.85
	Estimation Comments	[Not specified]

33. Secondary Outcome Measure:

Measure Title	Time to Tocilizumab Remission
Measure Description	The time in days from initial study drug treatment to tocilizumab remission that occurred when the patient discontinued treatment with tocilizumab.
Time Frame	104 Weeks
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population (all randomized participants who received study drug) with data available for this outcome measure. Participants were censored at the last observed value.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	243	229
Time to Tocilizumab Remission [units: Days] Median (Full Range)	645.0 (360 to 855)	786.0 (351 to 829)

Statistical Analysis 1 for Time to Tocilizumab Remission

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1695
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

34. Secondary Outcome Measure:

Measure Title	Time to Drug-Free Remission
Measure Description	The time in days from initial study drug treatment to drug free remission that occurred when the participant was able to discontinue tocilizumab, methotrexate/placebo and open label disease-modifying antirheumatic drugs (DMARDS).
Time Frame	104 Weeks
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population (all randomized participants who received study drug) with data available for this outcome measure. Participants were censored at the last observed value.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	243	229
Time to Drug-Free Remission [units: Days] Median (Full Range)	NA (366 to 1121) [1]	NA (365 to 1151) [1]

[1] Median was not estimated due to the low number of participants with drug-free remission.

Statistical Analysis 1 for Time to Drug-Free Remission

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0096
	Comments	[Not specified]

	Method	Log Rank
	Comments	[Not specified]

35. Secondary Outcome Measure:

Measure Title	Time to Flare After Tocilizumab Remission
Measure Description	The time in days to a flare (recurrence of disease symptoms) after the patient discontinued treatment with tocilizumab.
Time Frame	104 Weeks
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population (all randomized participants who received study drug) with data available for this outcome measure. Participants were censored at the last observed value.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	129	109
Time to Flare After Tocilizumab Remission [units: Days]	113.0 (25 to 400)	84.0 (1 to 415)

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Median (Full Range)		

Statistical Analysis 1 for Time to Flare After Tocilizumab Remission

Statistical Analysis Overview	Comparison Groups	Tocilizumab + Methotrexate, Tocilizumab + Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0734
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

36. Secondary Outcome Measure:

Measure Title	Time to Restart of Treatment After Discontinuation/Remission
Measure Description	The time in days from treatment discontinuation or remission to the restart of treatment.
Time Frame	104 Weeks
Safety Issue?	No

Analysis Population Description

Participants from the intent-to-treat population, all participants who received study drug, with data available for analysis. Censoring occurred at the last assessment for those completing the study or withdrawing early, if a response had not been observed.

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Measured Values

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
Number of Participants Analyzed	129	109
Time to Restart of Treatment After Discontinuation/ Remission [units: Days] Median (95% Confidence Interval)	113.0 (87.0 to 150.0)	81.0 (58.0 to 91.0)

Reported Adverse Events

Time Frame	[Not specified]
Additional Description	[Not specified]

Reporting Groups

	Description
Tocilizumab + Methotrexate	Tocilizumab 8 mg/kg (up to 800 mg) intravenous (IV) once every 4 weeks + weekly oral methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded methotrexate if a flare occurred.
Tocilizumab + Placebo	Tocilizumab 8 mg/kg (up to 800 mg) IV once every 4 weeks + weekly oral placebo to methotrexate continuing at the patient's pre-study dose for 24 weeks. Patients taking oral corticosteroids remained on their pre-study dose (up to 10 mg/day). Week 24 to Week 52 the dose of tocilizumab and placebo to methotrexate remained the same. Based on DAS28 assessments, corticosteroid dose was adjusted and disease-modifying antirheumatic drug (DMARDS) added. Week 52 to Week 104, based on the DAS28 assessment, treatment was adjusted to one of four protocol specified treatment regimens: Treatment tapering, Continued treatment, Treatment intensification or Maintenance treatment. After Week 100, patients who discontinued tocilizumab because of remission were retreated with the last effective dose of tocilizumab or blinded placebo to methotrexate if a flare occurred.

Serious Adverse Events

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	49/277 (17.69%)	48/276 (17.39%)
Blood and lymphatic system disorders		
Anaemia [A] †	1/277 (0.36%)	1/276 (0.36%)
Leukopenia [A] †	0/277 (0%)	1/276 (0.36%)
Lymphadenitis [A] †	0/277 (0%)	1/276 (0.36%)
Cardiac disorders		
Acute myocardial infarction [A] †	0/277 (0%)	2/276 (0.72%)
Atrial fibrillation [A] †	1/277 (0.36%)	1/276 (0.36%)
Cardiac failure congestive [A] †	2/277 (0.72%)	1/276 (0.36%)
Cardiomyopathy [A] †	0/277 (0%)	1/276 (0.36%)

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Ischaemic cardiomyopathy [A] †	0/277 (0%)	1/276 (0.36%)
Mitral valve incompetence [A] †	0/277 (0%)	1/276 (0.36%)
Myocardial infarction [A] †	1/277 (0.36%)	1/276 (0.36%)
Ear and labyrinth disorders		
Vertigo [A] †	0/277 (0%)	1/276 (0.36%)
Vertigo positional [A] †	1/277 (0.36%)	0/276 (0%)
Eye disorders		
Keratitis [A] †	0/277 (0%)	1/276 (0.36%)
Gastrointestinal disorders		
Gastric ulcer [A] †	0/277 (0%)	1/276 (0.36%)
Gastrointestinal angiodysplasia [A] †	0/277 (0%)	1/276 (0.36%)
Gastrointestinal disorder [A] †	0/277 (0%)	1/276 (0.36%)
Gastrointestinal necrosis [A] †	0/277 (0%)	1/276 (0.36%)
Inguinal hernia [A] †	1/277 (0.36%)	0/276 (0%)
Intestinal perforation [A] †	0/277 (0%)	1/276 (0.36%)
Pancreatitis acute [A] †	1/277 (0.36%)	0/276 (0%)
Rectal haemorrhage [A] †	1/277 (0.36%)	0/276 (0%)
Vomiting [A] †	1/277 (0.36%)	0/276 (0%)
General disorders		
Chest pain [A] †	2/277 (0.72%)	0/276 (0%)
Death [A] †	0/277 (0%)	1/276 (0.36%)
Device breakage [A] †	0/277 (0%)	1/276 (0.36%)
Hyperthermia malignant [A] †	0/277 (0%)	1/276 (0.36%)

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Sudden death [A] †	0/277 (0%)	1/276 (0.36%)
Hepatobiliary disorders		
Cholecystitis acute [A] †	0/277 (0%)	1/276 (0.36%)
Cholelithiasis [A] †	1/277 (0.36%)	0/276 (0%)
Immune system disorders		
Anaphylactic shock [A] †	0/277 (0%)	1/276 (0.36%)
Anaphylactoid reaction [A] †	1/277 (0.36%)	0/276 (0%)
Infections and infestations		
Abdominal abscess [A] †	0/277 (0%)	1/276 (0.36%)
Abscess limb [A] †	0/277 (0%)	1/276 (0.36%)
Anal abscess [A] †	1/277 (0.36%)	0/276 (0%)
Appendicitis [A] †	0/277 (0%)	1/276 (0.36%)
Arthritis bacterial [A] †	1/277 (0.36%)	0/276 (0%)
Bronchopneumonia [A] †	3/277 (1.08%)	0/276 (0%)
Candida endophthalmitis [A] †	0/277 (0%)	1/276 (0.36%)
Cellulitis [A] †	1/277 (0.36%)	0/276 (0%)
Clostridium difficile colitis [A] †	0/277 (0%)	1/276 (0.36%)
Disseminated tuberculosis [A] †	1/277 (0.36%)	0/276 (0%)
Diverticulitis [A] †	0/277 (0%)	1/276 (0.36%)
Erysipelas [A] †	0/277 (0%)	2/276 (0.72%)
Gangrene [A] †	1/277 (0.36%)	0/276 (0%)
Gastroenteritis [A] †	1/277 (0.36%)	0/276 (0%)

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Gastrointestinal candidiasis [A] †	1/277 (0.36%)	0/276 (0%)
Herpes zoster [A] †	1/277 (0.36%)	0/276 (0%)
Infected bunion [A] †	1/277 (0.36%)	0/276 (0%)
Infection [A] †	0/277 (0%)	1/276 (0.36%)
Influenza [A] †	0/277 (0%)	1/276 (0.36%)
Meningitis [A] †	0/277 (0%)	1/276 (0.36%)
Otitis externa [A] †	1/277 (0.36%)	0/276 (0%)
Pelvic abscess [A] †	0/277 (0%)	1/276 (0.36%)
Pneumonia [A] †	0/277 (0%)	3/276 (1.09%)
Postoperative wound infection [A] †	0/277 (0%)	1/276 (0.36%)
Pyelonephritis acute [A] †	0/277 (0%)	1/276 (0.36%)
Renal abscess [A] †	1/277 (0.36%)	0/276 (0%)
Scrotal abscess [A] †	1/277 (0.36%)	0/276 (0%)
Sepsis [A] †	1/277 (0.36%)	0/276 (0%)
Septic shock [A] †	2/277 (0.72%)	0/276 (0%)
Skin infection [A] †	1/277 (0.36%)	0/276 (0%)
Soft tissue infection [A] †	0/277 (0%)	1/276 (0.36%)
Staphylococcal infection [A] †	1/277 (0.36%)	0/276 (0%)
Subcutaneous abscess [A] †	1/277 (0.36%)	0/276 (0%)
Typhoid fever [A] †	0/277 (0%)	1/276 (0.36%)
Injury, poisoning and procedural complications		
Fall [A] †	1/277 (0.36%)	0/276 (0%)

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Femoral neck fracture [A] †	1/277 (0.36%)	2/276 (0.72%)
Hip fracture [A] †	1/277 (0.36%)	0/276 (0%)
Radius fracture [A] †	1/277 (0.36%)	0/276 (0%)
Synovial rupture [A] †	0/277 (0%)	1/276 (0.36%)
Tendon rupture [A] †	0/277 (0%)	2/276 (0.72%)
Ulna fracture [A] †	0/277 (0%)	1/276 (0.36%)
Investigations		
Transaminases increased [A] †	2/277 (0.72%)	2/276 (0.72%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal chest pain [A] †	1/277 (0.36%)	0/276 (0%)
Musculoskeletal discomfort [A] †	1/277 (0.36%)	0/276 (0%)
Myofascial pain syndrome [A] †	1/277 (0.36%)	0/276 (0%)
Osteoarthritis [A] †	0/277 (0%)	1/276 (0.36%)
Spinal osteoarthritis [A] †	1/277 (0.36%)	0/276 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Anal cancer [A] †	0/277 (0%)	1/276 (0.36%)
Basal cell carcinoma [A] †	0/277 (0%)	1/276 (0.36%)
Benign lung neoplasm [A] †	1/277 (0.36%)	0/276 (0%)
Breast cancer [A] †	1/277 (0.36%)	1/276 (0.36%)
Gastrointestinal carcinoma [A] †	1/277 (0.36%)	0/276 (0%)
Glioblastoma [A] †	0/277 (0%)	1/276 (0.36%)
Lung neoplasm malignant [A] †	0/277 (0%)	1/276 (0.36%)
Nervous system disorders		

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Cerebral haemorrhage [A] †	0/277 (0%)	1/276 (0.36%)
Dizziness [A] †	1/277 (0.36%)	0/276 (0%)
Epilepsy [A] †	1/277 (0.36%)	0/276 (0%)
Haemorrhagic stroke [A] †	1/277 (0.36%)	0/276 (0%)
Ischaemic cerebral infarction [A] †	0/277 (0%)	1/276 (0.36%)
Ischaemic stroke [A] †	0/277 (0%)	1/276 (0.36%)
Optic neuritis [A] †	1/277 (0.36%)	0/276 (0%)
Sciatica [A] †	0/277 (0%)	1/276 (0.36%)
Transient ischaemic attack [A] †	1/277 (0.36%)	2/276 (0.72%)
Pregnancy, puerperium and perinatal conditions		
Abortion spontaneous [A] †	1/277 (0.36%)	0/276 (0%)
Psychiatric disorders		
Anxiety [A] †	2/277 (0.72%)	1/276 (0.36%)
Stress [A] †	0/277 (0%)	1/276 (0.36%)
Renal and urinary disorders		
Renal colic [A] †	1/277 (0.36%)	0/276 (0%)
Renal failure acute [A] †	1/277 (0.36%)	0/276 (0%)
Reproductive system and breast disorders		
Colpocele [A] †	0/277 (0%)	1/276 (0.36%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome [A] †	1/277 (0.36%)	0/276 (0%)
Alveolitis [A] †	0/277 (0%)	1/276 (0.36%)
Chronic obstructive pulmonary disease [A] †	1/277 (0.36%)	0/276 (0%)

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Pleurisy [A] †	1/277 (0.36%)	1/276 (0.36%)
Pulmonary oedema [A] †	0/277 (0%)	1/276 (0.36%)
Skin and subcutaneous tissue disorders		
Skin necrosis [A] †	1/277 (0.36%)	0/276 (0%)
Skin ulcer [A] †	0/277 (0%)	1/276 (0.36%)
Vascular disorders		
Aortic stenosis [A] †	0/277 (0%)	1/276 (0.36%)
Hypertension [A] †	1/277 (0.36%)	0/276 (0%)
Intermittent claudication [A] †	0/277 (0%)	1/276 (0.36%)
Peripheral artery stenosis [A] †	0/277 (0%)	1/276 (0.36%)
Phlebitis [A] †	0/277 (0%)	1/276 (0.36%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 15.1

Other Adverse Events

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

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	189/277 (68.23%)	179/276 (64.86%)
Blood and lymphatic system disorders		
Leukopenia [A] †	20/277 (7.22%)	13/276 (4.71%)
Neutropenia [A] †	15/277 (5.42%)	14/276 (5.07%)
Gastrointestinal disorders		
Diarrhoea [A] †	20/277 (7.22%)	21/276 (7.61%)
Nausea [A] †	27/277 (9.75%)	9/276 (3.26%)

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Infections and infestations		
Bronchitis [A] †	17/277 (6.14%)	5/276 (1.81%)
Gastroenteritis [A] †	16/277 (5.78%)	7/276 (2.54%)
Influenza [A] †	18/277 (6.5%)	11/276 (3.99%)
Nasopharyngitis [A] †	43/277 (15.52%)	40/276 (14.49%)
Upper respiratory tract infection [A] †	31/277 (11.19%)	25/276 (9.06%)
Urinary tract infection [A] †	23/277 (8.3%)	18/276 (6.52%)
Investigations		
Alanine aminotransferase increased [A] †	33/277 (11.91%)	15/276 (5.43%)
Blood cholesterol increased [A] †	12/277 (4.33%)	15/276 (5.43%)
Transaminases increase [A] †	30/277 (10.83%)	15/276 (5.43%)
Metabolism and nutrition disorders		
Hypercholesterolemia [A] †	34/277 (12.27%)	33/276 (11.96%)
Musculoskeletal and connective tissue disorders		
Back pain [A] †	29/277 (10.47%)	21/276 (7.61%)
Rheumatoid arthritis [A] †	14/277 (5.05%)	15/276 (5.43%)
Nervous system disorders		
Headache [A] †	18/277 (6.5%)	21/276 (7.61%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	21/277 (7.58%)	16/276 (5.8%)
Skin and subcutaneous tissue disorders		
Rash [A] †	15/277 (5.42%)	7/276 (2.54%)
Vascular disorders		

	Tocilizumab + Methotrexate	Tocilizumab + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Hypertension [A] †	13/277 (4.69%)	19/276 (6.88%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 15.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

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

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

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

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