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A Study to Assess the Effect of Tocilizumab + Methotrexate on Prevention of Structural Joint Damage in Patients With Moderate to Severe Active Rheumatoid Arthritis (RA)

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT00106535

Purpose

This 3 arm study will compare the safety and efficacy, with respect to a reduction in signs and symptoms and prevention of joint damage, of tocilizumab versus placebo, both in combination with methotrexate (MTX) in patients with moderate to severe active rheumatoid arthritis. Patients will be randomized to receive tocilizumab 4 mg/kg IV, tocilizumab 8 mg/kg IV or placebo IV, every 4 weeks. All patients will also receive methotrexate, 10-25 mg/week. The anticipated time on study treatment is 1-2 years and the target sample size is 500+ individuals. After completion of the 2 year study participants could participate in the optional 3 year open label extension phase (year 3 to 5).

Condition	Intervention	Phase
Rheumatoid Arthritis	Drug: tocilizumab [RoActemra/Actemra] Drug: Placebo Drug: Methotrexate	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study

Official Title: A Randomized, Double-blind Study of Safety and Prevention of Structural Joint Damage During Treatment With Tocilizumab Versus Placebo, in Combination With Methotrexate, in Patients With Moderate to Severe Rheumatoid Arthritis

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Percentage of Participants With American College of Rheumatology-ACR20 Response [Time Frame: Baseline, Week 24] [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.
- Change From Baseline in Modified Total Sharp-Genant Score at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  Radiographs were taken of each hand and foot at Baseline and Week 52 and evaluated at a central reading service by two independent radiologists 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 100 (normalized from 98) and in the feet 42, the maximum scores for joint space narrowing in the hands is 100 (normalized from 104) and in the feet 48. The maximum modified Sharp score achievable is 290. A lower number change from Baseline indicated a better score.
- Change in Physical Function as Measured by the Area Under the Curve (AUC) for the Change From Baseline in the Health Assessment Questionnaire (HAQ) Disability Index at Week 52 [Time Frame: Baseline to Week 52] [Designated as safety issue: No]
  HAQ-DI consisted of 20 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities rated on a 4-point scale where 0=without any difficulty to 3=unable to do. The sum of scores was divided by the number of domains with a score for a total possible score of 0 (best) to 3 (worst). Functional disability was determined as a cumulative measure of HAQ-DI over 1 year by using the AUC of the change from baseline in HAQ-DI score through week 52. Decreases in AUC of change from baseline in HAQ-DI indicate a greater average improvement in physical function over time and represent a decrease in sustained impairment. For patients with missing week 52 HAQ-DI score, the AUC of the change from baseline was standardized to 52 weeks using the latest timepoint available for calculation of the AUC. The mean was adjusted for region. A negative change from baseline indicated improvement.
- Change From Baseline in the Modified Total Sharp-Genant Score at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]
  Radiographs of each hand and foot were taken at Baseline and Week 104 and evaluated at a central reading service by two independent radiologists 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 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 100 and in the feet 42, the maximum scores for joint space narrowing in the hands is 100 and in the feet 48. The maximum modified Sharp score achievable is 290. A lower number change from Baseline indicated a better score.
- Change in Physical Function as Measured by the Area Under the Curve for the Change From Baseline in the Health Assessment Questionnaire- Disability Index (HAQ-DI) at Week 104 [Time Frame: Baseline to Week 104] [Designated as safety issue: No]
  HAQ-DI consisted of 20 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities rated on a 4-point scale where 0=without any difficulty to 3=unable to do. The sum of scores was divided by the number of domains with a score for a total possible score of 0 (best) to 3 (worst). Functional disability was determined as a cumulative measure of HAQ-DI over 2 years by using the AUC of the change from baseline in HAQ-DI score through week 104. Decreases in AUC of change from baseline in HAQ-DI indicated a gr eater average improvement in physical function over time and represent a decrease in sustained impairment. For patients with missing week 104 HAQ-DI score, the AUC of the

change from baseline was standardized to 104 weeks using the latest timepoint available for calculation of the AUC. A negative change from baseline indicated improvement.

Secondary Outcome Measures:

- Percentage of Participants With ACR50 Response [Time Frame: Baseline, Week 24] [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,Week 24] [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].
- Swollen Joint Count (66 Joint Count): Mean Change From Baseline at Week 24 [Time Frame: Baseline, Week 24] [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.
- Tender Joint Count (68 Joint Count): Mean Change From Baseline at Week 24 [Time Frame: Baseline, Week 24] [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.
- Patient's Global Visual Analog Scale (VAS): Mean Change From Baseline at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  The patient's global assessment of disease activity is assessed on a 0 to 100 mm horizontal visual analogue scale (VAS) by the patient. 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.
- Physician's Global VAS: Mean Change From Baseline at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  The physician's global assessment of disease activity is assessed on 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).
- Patient's Pain VAS: Mean Change From Baseline at Week 24 [Time Frame: Baseline and Week 24] [Designated as safety issue: No]
  The patient assessed their pain on 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 indicated improvement.
- C-Reactive Protein (CRP): Mean Change From Baseline at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  The serum concentration of C-Reactive Protein (CRP) is measured in mg/dL. A reduction in the level is considered an improvement.
- Erythrocyte Sedimentation Rate: Mean Change From Baseline at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  The Erythrocyte Sedimentation Rate (ESR) was measured in mm/hr. A reduction in the level is considered an improvement.
- Health Assessment Questionnaire Disability Index (HAQ-DI): Mean Change From Baseline at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  HAQ-DI is a self-completed patient questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. Calculate HAQ-DI the patient must have a domain score

for at least 6 of 8 domains. The HAQ-DI is the sum of the scores, divided by the number of domains that have a score (in range 6-8) for a total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from baseline indicated improvement.

- Percentage of Participants With American College of Rheumatology (ACR20) Response at Week 52 [Time Frame: Baseline, Week 52] [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 ACR20 Response at Week 104 [Time Frame: Baseline, Week 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 at Week 52 [Time Frame: Baseline, Week 52] [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 ACR50 Response at Week 104 [Time Frame: Baseline, Week 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 at Week 52 [Time Frame: Baseline, Week 52] [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 ACR70 Response at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

ACR50 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 ACR70 Response Maintained for 6 Consecutive Months [Time Frame: 104 Weeks] [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.
- Change From Baseline in Swollen Joint Count at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  66 joints were assessed at Baseline and Week 52 for swelling and joints are classified as swollen/not swollen for a total possible swollen joint count of 0 (best) to 66 (worst). A negative change from Baseline indicated improvement.
- Change From Baseline in Tender Joint Count at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  68 joints were assessed at Baseline and Week 52 for tenderness and joints were classified as tender/not tender for a total possible tender joint count of 0 (best) to 68 (worst). A negative change from Baseline indicated improvement.
- Change From Baseline in Patient's Global Assessment of Disease Activity at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  The patient's global assessment of disease activity is assessed at Baseline and Week 52 using a 0 to 100 mm horizontal visual analogue scale (VAS) by the patient. 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 Physicians Global Assessment of Disease Activity at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  The physician's 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 the Patient's Pain VAS at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  The patient assessed their pain at Baseline and Week 52 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 C-Reactive Protein (CRP) at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  Blood was collected for C-Reactive Protein (CRP) at Baseline and Week 52 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 Erythrocyte Sedimentation Rate (ESR) at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  Blood was collected for Erythrocyte Sedimentation Rate (ESR) at Baseline and Week 52 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 Swollen Joint Count at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]
  66 joints were assessed at Baseline and Week 104 for swelling and joints were classified as swollen/not swollen for a total possible swollen joint count of 0 (best) to 66 (worst). A negative change from Baseline indicated improvement.
- Change From Baseline in Tender Joint Count at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

68 joints were assessed for tenderness and joints were classified as tender/not tender for a total possible tender joint count of 0 (best) to 68 (worst). A negative change from Baseline indicated improvement.

- Change From Baseline in Patient's Global Assessment of Disease Activity at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

  The patient's global assessment of disease activity was assessed at Baseline and Week 104 using a 0 to 100 mm horizontal visual analogue scale (VAS) by the patient. 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 Physicians Global Assessment of Disease Activity at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

  The physician's global assessment of disease activity was assessed at Baseline and Week 104 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 the Patient's Pain VAS at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

  The patient assessed their pain at Baseline and Week 104 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 C-Reactive Protein (CRP) at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

  Blood was collected for C-Reactive Protein (CRP) at Baseline and Week 104 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 Erythrocyte Sedimentation Rate (ESR) at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

  Blood was collected for Erythrocyte Sedimentation Rate (ESR) at Baseline and Week 104 and was analyzed at a local laboratory. ESR was measured in millimeters/hour (mm/hr). A reduction in the level is considered an improvement.
- Percentage of Participants Who Achieve an Improvement of at Least 0.3 Units From Baseline in the HAQ Disability Index at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]

  The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a patient completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0 (without any difficulty) to 3 (unable to do). HAQ-DI=sum of worst scores in each domain divided by the number of domains answered for a total possible score of 0 (best) to 3 (worst).
- Percentage of Participants Who Achieve an Improvement of at Least 0.3 Units From Baseline in the HAQ Disability Index at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

  The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a patient completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0 (without any difficulty) to 3 (unable to do).HAQ-DI=sum of worst scores in each domain divided by the number of domains answered for a total possible score of 0 (best) to 3 (worst). .
- Area Under Curve (AUC) of the ACRn to Week 24 [Time Frame: 24 Weeks] [Designated as safety issue: No]

  The ACRn is defined as each patient's lowest percent improvement from Baseline of 3 measures: tender joint count (68 joints), swollen joint count (66 joints), and the improved score achieved in at least 3 of the 5 remaining ACR core components (physician global assessment, patient global assessment, pain, HAQ, and C-reactive protein or ESR, respectively). AUC of ACRn, a continuous variable, was calculated from Baseline to Week 24. A positive score change from Baseline indicated an improvement. The higher the ACRn score the better.
- Area Under Curve (AUC) of the ACRn to Week 52 [Time Frame: 52 Weeks] [Designated as safety issue: No]

  The ACRn is defined as each patient's lowest percent improvement from Baseline of 3 measures: tender joint count (68 joints), swollen joint count (66 joints), and the improved score achieved in at least 3 of the 5 remaining ACR core components (physician global assessment, patient global

assessment, pain, HAQ, and C-reactive protein or ESR, respectively). AUC of ACRn, a continuous variable, was calculated from Baseline to Week 52. A positive score change from Baseline indicated an improvement. The higher the ACRn score the better.

- Area Under Curve (AUC) of the ACRn Score at Week 104 [Time Frame: 104 Weeks] [Designated as safety issue: No]
  The ACRn is defined as each patient's lowest percent improvement from Baseline of 3 measures: tender joint count (68 joints), swollen joint count (66 joints), and the improved score achieved in at least 3 of the 5 remaining ACR core components (physician global assessment, patient global assessment, pain, HAQ, and C-reactive protein or ESR, respectively). AUC of ACRn, a continuous variable, was calculated from Baseline to Week 104. A positive score change from Baseline indicated an improvement. The higher the ACRn score the better.
- Change From Baseline in Disease Activity Score (DAS28) at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity], and ESR. DAS28 total scores range from 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.
- Change From Baseline in Disease Activity Score (DAS28) at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity], and ESR. DAS28 total scores range from 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.
- Change From Baseline in Disease Activity Score (DAS28) at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]
  The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity], and ESR. DAS28 total scores range from 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.
- Percentage of Participants With DAS28 Good or Moderate EULAR Response at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] , and ESR. DAS28 total scores range from 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 and 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.
- Percentage of Participants With DAS28 Good or Moderate EULAR Response at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity (mm) [visual analog scale: 0=no disease activity to 100=maximum disease activity] , and ESR. DAS28 total scores range from 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 and 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.
- Percentage of Participants With DAS28 Good or Moderate EULAR Response at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]
  The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity (mm) [visual analog scale: 0=no disease activity to 100=maximum disease activity] , and ESR. DAS28 total scores range from 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 and 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.
- Percentage of Participants With DAS28 Remission at Week 24 [Time Frame: Week 24] [Designated as safety issue: Yes]

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). DAS28 total scores range from 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 Remission at Week 52 [Time Frame: Week 52] [Designated as safety issue: Yes]
  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). DAS28 total scores range from 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 Remission at Week 104 [Time Frame: Week 104] [Designated as safety issue: Yes]
  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). DAS28 total scores range from 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.
- Area Under Curve (AUC) of Disease Activity Score (DAS28) at Week 24 [Time Frame: 24 Weeks] [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). DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. Higher calculated AUC values are worse (indicate higher disease activity).
- Area Under Curve (AUC) of Disease Activity Score (DAS28) at Week 52 [Time Frame: 52 Weeks] [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). DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. Higher calculated AUC values are worse (indicate higher disease activity).
- Area Under Curve (AUC) of Disease Activity Score (DAS28) at Week 104 [Time Frame: 104 Weeks] [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). DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. Higher calculated AUC values are worse (indicate higher disease activity).
- Change From Baseline in Modified Total Sharp-Genant Score at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  Radiographs were taken of each hand and foot at Baseline and Week 24 and evaluated at a central reading service by two independent radiologists 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 100 and in the feet 42, the maximum scores for joint space narrowing in the hands is 100 and in the feet 48. The maximum modified Sharp score achievable is 290. A lower number change from Baseline indicated a better score.
- Change From Baseline in Modified Total Sharp-Genant Score at Week 80 [Time Frame: Baseline, Week 80] [Designated as safety issue: No]
  Radiographs were taken of each hand and foot at Baseline and Week 80 and evaluated at a central reading service by two independent radiologists 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 100 and in the feet 42, the maximum scores for joint space narrowing in the hands is 100 and in the feet 48. The maximum modified Sharp score achievable is 290. A lower number change from Baseline indicated a better score.
- Change From Baseline in Erosion Score at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]

Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). A lower number change from Baseline indicated a better score.

- Change From Baseline in Erosion Score at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). A lower number change from Baseline indicated a better score.
- Change From Baseline in Erosion Score at Week 80 [Time Frame: Baseline, Week 80] [Designated as safety issue: No]
  Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). A lower number change from Baseline indicated a better score.
- Change From Baseline in Erosion Score at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]
  Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). A lower number change from Baseline indicated a better score.
- Change From Baseline in Joint Space Narrowing Score at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). A lower change from Baseline indicated a better score.
- Change From Baseline in Joint Space Narrowing Score at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). A lower number change from Baseline indicated a better score.
- Change From Baseline in Joint Space Narrowing Score at Week 80 [Time Frame: Baseline, Week 80] [Designated as safety issue: No]
  Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). A lower number change from Baseline indicated a better score.
- Change From Baseline in Joint Space Narrowing Score at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]
  Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). A lower number change from Baseline indicated a better score.
- Percentage of Participants With no Progression of Erosion at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). No progression of Erosion score was defined as a change from Baseline of less than or equal to zero.
- Percentage of Participants With no Progression of Erosion at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). No progression of Erosion score was defined as a change from Baseline of less than or equal to zero.
- Percentage of Participants With no Progression of Erosion at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]
  Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). No progression of Erosion score was defined as a change from Baseline of less than or equal to zero.
- Percentage of Participants With no Progression of Joint Space Narrowing at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). No progression of Joint Space Narrowing score was defined as a change from Baseline of less than or equal to zero.
- Percentage of Participants With no Progression of Joint Space Narrowing at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]

Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). No progression of Joint Space Narrowing score is defined as a change from Baseline of less than or equal to zero.

- Percentage of Participants With no Progression of Joint Space Narrowing at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

  Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). No progression of Joint Space Narrowing score is defined as a change from Baseline of less than or equal to zero.
- Change From Baseline in HAQ Disability Index (HAQ-DI) at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]

  HAQ-DI is a self-completed questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. To Calculate HAQ-DI the patient must have a domain score for at least 6 of 8 domains. The HAQ-DI is the sum of the scores, divided by the number of domains that have a score (in range 6-8) for a total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from baseline indicated improvement.
- Change From Baseline in HAQ Disability Index at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

  HAQ-DI is a self-completed questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. To Calculate HAQ-DI the patient must have a domain score for at least 6 of 8 domains. The HAQ-DI is the sum of the scores, divided by the number of domains that have a score (in range 6-8). Total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from Baseline indicated improvement.
- Change From Baseline in Quality Life Short Form-36 (SF-36) Score at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]

  The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement.
- Change From Baseline in SF-36 Score at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]

  The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from Baseline indicates improvement.
- Change From Baseline in SF-36 Score at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]

  The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from Baseline indicated improvement.
- Change From Baseline in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) Score at Week 24 [Time Frame: Baseline, Week 24] [Designated as safety issue: No]

  FACIT-F is a 13-item questionnaire. Patients scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the patient's response to the questions (with the exception of 2 negatively stated), the greater the patient's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the patient's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). A higher score reflects an improvement in the patient's health status.
- Change From Baseline in FACIT-F Score at Week 52 [Time Frame: Baseline, Week 52] [Designated as safety issue: No]

  FACIT-F is a 13-item questionnaire. Patients scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the patient's response to the questions (with the exception of 2 negatively stated), the greater the patient's fatigue. For all questions, except for the 2 negatively stated ones, the

code was reversed and a new score was calculated as (4 minus the patient's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). A higher score reflects an improvement in the patient's health status.

- Change From Baseline in FACIT-F Score at Week 104 [Time Frame: Baseline, Week 104] [Designated as safety issue: No]
  FACIT-F is a 13-item questionnaire. Patients scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the patient's response to the questions (with the exception of 2 negatively stated), the greater the patient's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the patient's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). A higher score reflects an improvement in the patient's health status.
- Change From Baseline in Rheumatoid Factor (RF) at Week 24 in Those Patients With Positive RF [Time Frame: Baseline, Week 24] [Designated as safety issue: No]
  Blood was collected for Rheumatoid Factor (RF) at Baseline and Week 24 and was analyzed at a central laboratory. RF level was reported in international units/milliliter (IU/mL). A positive RF= >15 IU/mL. A lower number change from Baseline indicated a better result.
- Change From Baseline in Rheumatoid Factor (RF) at Week 52 in Those Patients With Positive RF [Time Frame: Baseline, Week 52] [Designated as safety issue: No]
  Blood was collected for Rheumatoid Factor (RF) at Baseline and Week 52 and was analyzed at a central laboratory. RF level was reported in international units/milliliter (IU/mL). A positive RF= >15 IU/mL. A lower number change from Baseline indicated a better result.
- Change From Baseline in Rheumatoid Factor (RF) at Week 104 in Those Patients With Positive RF [Time Frame: Baseline, Week 104] [Designated as safety issue: No]
  Blood was collected for Rheumatoid Factor (RF) at Baseline and Week 104 and was analyzed at a central laboratory. RF level was reported in international units/milliliter (IU/mL). A positive RF= >15 IU/mL. A lower number change from Baseline indicated a better result.
- Time to Onset of ACR20 by Treatment Group [Time Frame: 6 months] [Designated as safety issue: No]
  Time in days until ACR20 response. ACR20 response was 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 Onset of ACR50 by Treatment Group [Time Frame: 6 months] [Designated as safety issue: No]
  Time in days until ACR50 response. ACR50 response was 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 Onset of ACR70 by Treatment Group [Time Frame: 6 months] [Designated as safety issue: No]
  Time in days 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.
- Percentage of Participants Who Withdraw Due to Lack of Sufficient Therapeutic Response [Time Frame: 104 Weeks] [Designated as safety issue: No]

Insufficient therapeutic response (patient not responding to the drug as assessed by the physician) was selected by the investigator as a reason that the patient withdrew from the study.

- Percentage of Participants in Each Treatment Group Who Receive Escape Therapy [Time Frame: 104 Weeks] [Designated as safety issue: No]
  In Escape 1, participants in the Tocilizumab 4 mg/kg + Methotrexate and Tocilizumab 8 mg/kg + Methotrexate groups received tocilizumab 8 mg/kg as escape therapy. Participants in the Placebo + Methotrexate group received tocilizumab 4 mg/kg as escape therapy. In Escape 2, all participants received tocilizumab 8 mg/kg.
- Percentage of Participants Who Achieved Remission According to the ACR Remission Criteria by Week 24 [Time Frame: 24 Weeks] [Designated as safety issue: No]
  The percentage of participants, who achieved ACR remission at any study visit up to Week 24. ACR remission required that all five of the following criteria were met for at least two consecutive months: morning stiffness < 15 minutes, no fatigue, no joint pain, no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths, and ESR < 30 mm/hr for a female or 20 mm/hr for a male.
- Percentage of Participants Who Achieved Remission According to the ACR Remission Criteria by Week 52 [Time Frame: 52 Weeks] [Designated as safety issue: No]
  The percentage of participants, who achieved ACR remission at any study visit up to Week 52. ACR remission required that all five of the following criteria were met for at least two consecutive months: morning stiffness < 15 minutes, no fatigue, no joint pain, no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths, and ESR < 30 mm/hr for a female or 20 mm/hr for a male.
- Percentage of Participants Who Achieved Remission According to the ACR Remission Criteria by Week 104 [Time Frame: 104 Weeks] [Designated as safety issue: No]
  The percentage of participants who achieved ACR remission at any study visit up to Week 104. ACR remission required that all five of the following criteria were met for at least two consecutive months: morning stiffness < 15 minutes, no fatigue, no joint pain, no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths, and ESR < 30 mm/hr for a female or 20 mm/hr for a male.
- Percentage of Participants Who Achieved Complete Clinical Response at Week 52 [Time Frame: 52 Weeks] [Designated as safety issue: No]
  Complete clinical response is defined as a continuous 6-month period of remission by ACR criteria [defined as five of the following criteria are met for at least two consecutive months: morning stiffness < 15 minutes, no fatigue, no joint pain, no joint tenderness or swelling, and ESR < 30 mm/hr for a female or 20 mm/hr for a male] and no radiographic progression [defined as change from baseline ≤ 0 in the total Sharp-Genant score, erosion score, and JSN score]. Patients who achieve a complete clinical response at any time in the study are counted as responders, even if the response is not maintained.
- Percentage of Participants Who Achieved Complete Clinical Response at Week 104 [Time Frame: 104 Weeks] [Designated as safety issue: No]
  Complete clinical response is defined as a continuous 6-month period of remission by ACR criteria [defined as five of the following criteria are met for at least two consecutive months: morning stiffness < 15 minutes, no fatigue, no joint pain, no joint tenderness or swelling, and ESR < 30 mm/hr for a female or 20 mm/hr for a male] and no radiographic progression [defined as change from baseline ≤ 0 in the total Sharp-Genant score, erosion score, and JSN score].
- End of Study: Percentage of Participants With ACR Response at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  ACR20/50/70/90 response is defined as a ≥ 20/50/70/90% 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.
- End of Study: Percentage of Participants With DAS28 Remission at Week 260 [Time Frame: Week 260] [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). DAS28 total scores range from 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.

- End of Study: Percentage of Participants With DAS28 Low Disease Activity (LDA) at Week 260 [Time Frame: Week 260] [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). DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. LDA is defined as DAS28 ≤3.2.
- End of Study: Percentage of Participants With DAS28 European League Against Rheumatism (EULAR) Good or Moderate Response at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity (mm), and ESR. DAS28 total scores range from 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. EULAR Good response: DAS28 ≤ 3.2 and 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.
- End of Study: Change From Baseline in Swollen Joint Count at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  66 joints were assessed at Baseline and Week 260 for swelling and joints are classified as swollen/not swollen for a total possible swollen joint count of 0 (best) to 66 (worst). A negative change from Baseline indicated improvement.
- End of Study: Change From Baseline in Tender Joint Count at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  68 joints were assessed at Baseline and Week 260 for tenderness and joints are classified as tender/not tender for a total possible swollen joint count of 0 (best) to 68 (worst). A negative change from Baseline indicated improvement.
- End of Study: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  HAQ-DI is a self-completed questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. To Calculate HAQ-DI the patient must have a domain score for at least 6 of 8 domains. The HAQ-DI is the sum of the scores, divided by the number of domains that have a score (in range 6-8) for a total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from Baseline indicated improvement.
- End of Study: Change From Baseline in the Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS) at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  The patient's global assessment of disease activity was assessed at Baseline and Week 104 using a 0 to 100 mm horizontal visual analogue scale (VAS) by the patient. 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.
- End of Study: Change From Baseline in the Physician's Global Assessment of Disease Activity VAS at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  The physician's 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.
- End of Study: Change From Baseline in the Patient's Pain VAS at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  The patient assessed their pain at Baseline and Week 260 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.
- End of Study: Percentage of Participants With Clinical Improvement in the FACIT-Fatigue Score at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  FACIT-F is a 13-item questionnaire. Patients scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the patient's response to the questions (with the exception of 2 negatively stated), the greater the patient's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the patient's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). Clinically relevant improvement is defined as a ≥5 change from Baseline.

- End of Study: Percentage of Participants With Clinical Relevant Improvement in the SF-36 Score at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. Clinically relevant improvement is defined as a ≥5 change from Baseline.
- End of Study: Change From Baseline in Total Sharp-Genant Score at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  Radiographs were taken of each hand and foot at Baseline and Week 260 and evaluated at a central reading service by two independent radiologists 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 100 and in the feet 42, the maximum scores for joint space narrowing in the hands is 100 and in the feet 48. The maximum modified Sharp score achievable is 290. A lower number change from Baseline indicated a better score. The results were reported based on the treatment the patient was originally randomized to.
- End of Study: Change From Baseline in Erosion Score at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  Radiographs were taken of a total of 14 locations in each hand and wrist and 6 joints in the foot and were evaluated for erosion using an 8-point scale where 0=Normal to 3.5=very severe erosion for a total possible score of 0 (best) to 142 (worst). A lower number change from Baseline indicated a better score.
- End of Study: Change From Baseline in Joint Space Narrowing Score at Week 260 [Time Frame: Baseline, Week 260] [Designated as safety issue: No]
  Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). A lower number change from Baseline indicated a better score.

Enrollment: 1196
Study Start Date: January 2005
Primary Completion Date: May 2007
Study Completion Date: July 2012

Arms	Assigned Interventions
Experimental: Tocilizumab 4 mg/kg + Methotrexate Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly for 52 weeks. From Week 16 participants with < 20% improvement in swollen and tender joints counts were eligible for escape therapy with tocilizumab. After Week 52 participants were able to switch to open label treatment with tocilizumab 8 mg/kg every 4 weeks for 12 months in year 2 (except patients who had a >70% improvement in both swollen and tender joint counts who remained on blinded treatment).	Drug: tocilizumab [RoActemra/Actemra] 4 mg/kg or 8 mg/kg IV/month every 4 weeks. Other Names: RoActemra Actemra Drug: Methotrexate 10-25 mg/week

Arms	Assigned Interventions
Participants who completed year 2 of the study were eligible to enter an optional open-label long-term extension period (Year 3 to 5) and received Tocilizumab 8 mg/kg every 4 weeks.	
Experimental: Tocilizumab 8 mg/kg + Methotrexate Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly for 52 weeks. From Week 16 participants with < 20% improvement in swollen and tender joints counts were eligible for escape therapy with tocilizumab. After Week 52 participants were able to switch to open label treatment with tocilizumab 8 mg/kg every 4 weeks for 12 months in year 2 (except patients who had a >70% improvement in both swollen and tender joint counts who remained on blinded treatment). Participants who completed year 2 of the study were eligible to enter an optional open-label long-term extension period (Year 3 to 5) and received Tocilizumab 8 mg/kg every 4 weeks.	Drug: tocilizumab [RoActemra/Actemra] 4 mg/kg or 8 mg/kg IV/month every 4 weeks. Other Names: RoActemra Actemra Drug: Methotrexate 10-25 mg/week
Placebo Comparator: Placebo + Methotrexate Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly for 52 weeks. From Week 16 participants with < 20% improvement in swollen and tender joints counts were eligible for escape therapy with tocilizumab. After Week 52 participants were able to switch to open label treatment with tocilizumab 8 mg/kg every 4 weeks for 12 months in year 2 (except patients who had a >70% improvement in both swollen and tender joint counts who remained on blinded treatment). Participants who completed year 2 of the study were eligible to enter an optional open-label	Drug: Placebo IV/month Drug: Methotrexate 10-25 mg/week

Arms	Assigned Interventions
long-term extension period (Year 3 to 5) and received Tocilizumab 8 mg/kg every 4 weeks.	

Eligibility

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

Criteria

Inclusion Criteria:

- adult patients at least 18 years of age with moderate to severe active RA for at least 6 months;
- inadequate response to a stable dose of MTX;
- patients of reproductive potential must be using reliable methods of contraception.

Exclusion Criteria:

- major surgery (including joint surgery) within 8 weeks before entering study, or planned surgery within 6 months after entering study;
- prior treatment failure with an anti-tumor necrosis factor agent;
- women who are pregnant or breast-feeding.

Contacts and Locations

Locations

United States, Alabama
Birmingham, Alabama, United States, 35233-7333
Huntsville, Alabama, United States, 35801
United States, Arizona
Scottsdale, Arizona, United States, 85251
Tucson, Arizona, United States, 85724
United States, California
Anaheim, California, United States, 92801
Long Beach, California, United States, 90806
Los Angeles, California, United States, 90095
San Diego, California, United States, 92108
San Francisco, California, United States, 94118
Santa Maria, California, United States, 93454
Torrance, California, United States, 90505
United States, Colorado
Boulder, Colorado, United States, 80304
Colorado Springs, Colorado, United States, 80910

Denver, Colorado, United States, 80230
United States, Florida
Aventura, Florida, United States, 33180
Fort Lauderdale, Florida, United States, 33334
Tampa, Florida, United States, 33614
West Palm Beach, Florida, United States, 33407
United States, Idaho
Boise, Idaho, United States, 83702
Coeur D'alene, Idaho, United States, 83814
Idaho Falls, Idaho, United States, 83404
Meridan, Idaho, United States, 83642
United States, Illinois
Chicago, Illinois, United States, 60612-3824
Rockford, Illinois, United States, 61103
United States, Indiana
Indianapolis, Indiana, United States, 46202-5100
United States, Kentucky
Lexington, Kentucky, United States, 40515
United States, Maryland
Frederick, Maryland, United States, 21702
Hagerstown, Maryland, United States, 21740
Wheaton, Maryland, United States, 20902
United States, Missouri
Saint Louis, Missouri, United States, 63131
St Louis, Missouri, United States, 63141
United States, Montana
Billings, Montana, United States, 59101
Missoula, Montana, United States, 59802
United States, Nevada
Reno, Nevada, United States, 89502
United States, New Hampshire
Dover, New Hampshire, United States, 03820
United States, New Jersey
Medford, New Jersey, United States, 08055
Voorhees, New Jersey, United States, 08043
United States, New York
Albany, New York, United States, 12206
Brooklyn, New York, United States, 11201
Lake Success, New York, United States, 11042
New York, New York, United States, 10016
Stony Brook, New York, United States, 11794-8161
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Asheville, North Carolina, United States, 28801
Charlotte, North Carolina, United States, 28211
Raleigh, North Carolina, United States, 27609

Wilmington, North Carolina, United States, 28401
United States, Ohio
Canton, Ohio, United States, 44718
United States, Oklahoma
Oklahoma City, Oklahoma, United States, 73109
Tulsa, Oklahoma, United States, 74135
United States, Oregon
Eugene, Oregon, United States, 97401
United States, Pennsylvania
Bethlehem, Pennsylvania, United States, 18015
Duncansville, Pennsylvania, United States, 16635
Philadelphia, Pennsylvania, United States, 19140
Wyomissing, Pennsylvania, United States, 19610
Wyomissing, Pennsylvania, United States, 19610
United States, Puerto Rico
Ponce, Puerto Rico, United States, 00716
San Juan, Puerto Rico, United States, 00936-5067
United States, South Carolina
Columbia, South Carolina, United States, 29204
United States, Tennessee
Nashville, Tennessee, United States, 37203
United States, Texas
Dallas, Texas, United States, 75231
San Antonio, Texas, United States, 78217
United States, Washington
Olympia, Washington, United States, 98502
Seattle, Washington, United States, 98104
United States, Wisconsin
Glendale, Wisconsin, United States, 53217
Australia
Adelaide, Australia, 5011
Malvern, Australia, 3144
Melbourne, Australia, 3168
New Lambton, Australia, 2305
Shenton Park, Australia, 6008
St. Leonards, Australia, 2139
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Porto Alegre, Brazil, 91350-200
Rio de Janeiro, Brazil, 20551-030
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Sao Paulo, Brazil, 04026-000
Sao Paulo, Brazil, 5403900
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Helsinki, Finland, 00290
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Bobigny, France, 93009
Bois Guillaume, France, 76233
Bordeaux, France, 33076
Le Kremlin Bicetre, France, 94270
Lille, France, 59037
Nice, France, 06202
Orleans, France, 45000
Paris, France, 75651
Paris, France, 75877
Strasbourg, France, 67098
Toulouse, France, 31059
Vandoeuvre-les-nancy, France, 54511

Greece
Athens, Greece, 15121
Athens, Greece, 15127
Athens, Greece, 11527
Heraklion, Greece, 71110

Italy
Brescia, Italy, 25123
Coppito, Italy, 67100
Firenze, Italy, 50139
Genova, Italy, 16132
Milano, Italy, 20157
Milano, Italy, 20122
Napoli, Italy, 80131
Padova, Italy, 35128
Pavia, Italy, 27100
Pisa, Italy, 56100
Reggio Emilia, Italy, 42100
Roma, Italy, 00161
Torino, Italy, 10128
Udine, Italy, 33100

Valeggio Sul Mincio, Italy, 37067
Varese, Italy, 21100
Verona, Italy, 37134

Mexico

Chihuahua, Mexico, 31000
Mexico City, Mexico, 06726
Mexico City, Mexico, 03100
Mexico City, Mexico, 07360
Mexico City, Mexico, 06700
Monterrey, Mexico, 64460
Obregon, Mexico, 85000

Norway

Haugesund, Norway, 5528
Lillehammer, Norway, 2609
Tromsø, Norway, 9038

Poland

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Dzialdowo, Poland, 13-200
Elblag, Poland, 82-300
Kalisz, Poland, 62-800
Krakow, Poland, 30-119
Krakow, Poland, 30-510
Poznan, Poland, 60-218
Szczecin, Poland, 71-252
Ustron, Poland, 43-450
Warszawa, Poland, 00-909
Warszawa, Poland, 02-637
Warszawa, Poland, 02-637

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Cape Town, South Africa, 7500
Cape Town, South Africa, 4001
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Spain

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Cádiz, Spain, 11009
Merida, Spain, 97500
Sabadell, Spain, 08208
Santander, Spain, 39008
Sevilla, Spain, 41009

Switzerland

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St. Gallen, Switzerland, 9007

Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party: Hoffmann-La Roche
Study ID Numbers: WA17823
Health Authority: United States: Food and Drug Administration

Study Results

Participant Flow

Pre-Assignment Details	This study was divided into two phases: a 2-year core placebo controlled treatment phase and an optional 3-year extension phase.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly for 52 weeks. From Week 16 participants with < 20% improvement in swollen and tender joints counts were eligible for escape therapy with tocilizumab. After Week 52 participants were able to switch to open label treatment with tocilizumab 8 mg/kg every 4 weeks for 12 months in year 2 (except patients who had a >70% improvement in both swollen and tender joint counts who remained on blinded treatment). Participants who completed year 2 of the study were eligible to enter an optional open-label long-term extension period (Year 3 to 5) and received Tocilizumab 8 mg/kg every 4 weeks.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab (TCZ) 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly for 52 weeks. From Week 16 participants with < 20% improvement in swollen and tender joints counts were eligible for escape therapy with tocilizumab. After Week 52 participants were able to switch to open label treatment with tocilizumab 8 mg/kg every 4 weeks for 12 months in year 2 (except patients who had a >70% improvement in both swollen and tender joint counts who remained on blinded treatment). Participants who completed year 2 of the study were eligible to enter an optional open-label long-term extension (LTE) period (Year 3 to 5) and received Tocilizumab 8 mg/kg every 4 weeks.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly for 52 weeks. From Week 16 participants with < 20% improvement in swollen and tender joints counts were eligible for escape therapy with tocilizumab. After Week 52 participants were able to switch to open label treatment with tocilizumab 8 mg/kg every 4 weeks for 12 months in year 2 (except patients who had a >70% improvement in both swollen and tender joint counts who remained on blinded treatment). Participants who completed year 2 of the study were eligible to enter an optional open-label long-term extension period (Year 3 to 5) and received Tocilizumab 8 mg/kg every 4 weeks.

	Description
All Tocilizumab Exposure + MTX	All tocilizumab (TCZ) exposure + methotrexate (MTX) group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either Placebo, Tocilizumab 4 mg/kg or Tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received 8 mg/kg IV every 4 weeks.

2-year Placebo Controlled Period

	Placebo + Methotrexate	Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 8 mg/kg + Methotrexate	All Tocilizumab Exposure + MTX
Started	394	401	401	0
Intent-to-treat: Received Study Drug	393	399	398	0
Safety: Actual Treatment Received	392	399	399	0
Completed Week 24	356	373	366	0
Completed Week 52	326	342	338	0
Completed	287 [1]	309 [2]	310 [3]	0
Not Completed	107	92	91	0

[1] Completed Week 104 (Year 2). 284 participants randomized to the Placebo arm entered the LTE period.
[2] Completed Week 104. 304 participants randomized to the TCZ 4 mg/kg arm entered the LTE period.
[3] Completed Week 104. 306 participants randomized to the TCZ 8 mg/kg arm entered the LTE period.

Long-term Extension Period (Year 3 to 5)

	Placebo + Methotrexate	Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 8 mg/kg + Methotrexate	All Tocilizumab Exposure + MTX
Started	0	0	0	894 [1]
Completed	0	0	0	704 [2]
Not Completed	0	0	0	190

[1] Entered the Long-term Extension.
[2] Completed the study.

Baseline Characteristics

Analysis Population Description

Baseline measures are based on the Intent-to-treat population that included all randomized participants who received study drug.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Baseline Measures

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate	Total
Number of Participants	393	399	398	1190
Age, Continuous [units: years] Mean (Standard Deviation)	51.3 (12.41)	51.4 (12.59)	53.4 (11.72)	52.0 (12.24)
Gender, Male/Female [units: participants]				
Female	328	336	325	989
Male	65	63	73	201

Outcome Measures

1. Primary 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, Week 24

Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 8 mg/kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With American College of Rheumatology-ACR20 Response [units: Percentage of participants]	27.0	50.6	56.3

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

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 4 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

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

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 8 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

2. Primary Outcome Measure:

Measure Title	Change From Baseline in Modified Total Sharp-Genant Score at Week 52
Measure Description	Radiographs were taken of each hand and foot at Baseline and Week 52 and evaluated at a central reading service by two independent radiologists 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 100 (normalized from 98) and in the feet 42, the maximum scores for joint space narrowing in the hands is 100 (normalized from 104) and in the feet 48. The maximum modified Sharp score achievable is 290. A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 52
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat (ITT) population, all randomized participants who received at least one dose of study drug, with Baseline and post-Baseline radiographic data available for this outcome measure. Linear extrapolation was used to impute missing week 52 data. Data collected after withdrawal or on escape therapy is excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	290	339	348
Change From Baseline in Modified Total Sharp-Genant Score at Week 52 [units: Score on a scale] Mean (Standard Deviation)	1.13 (2.962)	0.34 (1.451)	0.29 (1.282)

Statistical Analysis 1 for Change From Baseline in Modified Total Sharp-Genant Score at Week 52

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 4 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Van Elteren's test]
	Comments	Stratified by region.

Statistical Analysis 2 for Change From Baseline in Modified Total Sharp-Genant Score at Week 52

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 8 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Van Elteren's test]
	Comments	Stratified by region.

3. Primary Outcome Measure:

Measure Title	Change in Physical Function as Measured by the Area Under the Curve (AUC) for the Change From Baseline in the Health Assessment Questionnaire (HAQ) Disability Index at Week 52
Measure Description	HAQ-DI consisted of 20 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities rated on a 4-point scale where 0=without any difficulty to 3=unable to do. The sum of scores was divided by the number of domains with a score for a total possible score of 0 (best) to 3 (worst). Functional disability was determined as a cumulative measure of HAQ-DI over 1 year by using the AUC of the change from baseline in HAQ-DI score through week 52. Decreases in AUC of change from baseline in HAQ-DI indicate a greater average improvement in physical function over time and represent a decrease in sustained impairment. For patients with missing week 52 HAQ-DI score, the AUC of the change from baseline was standardized to 52 weeks using the latest timepoint available for calculation of the AUC. The mean was adjusted for region. A negative change from baseline indicated improvement.
Time Frame	Baseline to Week 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. No imputation was used for missing HAQ scores. All assessments were set to missing after a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	366	376	374
Change in Physical Function as Measured by the Area Under the Curve (AUC) for the Change From Baseline in the Health Assessment Questionnaire (HAQ) Disability Index at Week 52 [units: Score on a scale*week] Least Squares Mean (Full Range)	-58.11 (-699.8 to 401.0)	-128.37 (-1059.6 to 266.8)	-144.06 (-895.7 to 323.7)

Statistical Analysis 1 for Change in Physical Function as Measured by the Area Under the Curve (AUC) for the Change From Baseline in the Health Assessment Questionnaire (HAQ) Disability Index at Week 52

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 4 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	Adjusted for region and original treatment group.
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-70.26
	Confidence Interval	(2-Sided) 95% -96.96 to -43.56
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change in Physical Function as Measured by the Area Under the Curve (AUC) for the Change From Baseline in the Health Assessment Questionnaire (HAQ) Disability Index at Week 52

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 8 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	Adjusted for region and original treatment group.
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-85.95

	Confidence Interval	(2-Sided) 95% -112.69 to -59.22
	Estimation Comments	[Not specified]

4. Primary Outcome Measure:

Measure Title	Change From Baseline in the Modified Total Sharp-Genant Score at Week 104
Measure Description	Radiographs of each hand and foot were taken at Baseline and Week 104 and evaluated at a central reading service by two independent radiologists 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 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 100 and in the feet 42, the maximum scores for joint space narrowing in the hands is 100 and in the feet 48. The maximum modified Sharp score achievable is 290. A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 104
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 Baseline and post-Baseline radiographic data available for this outcome measure. Data collected after withdrawal or for patients on escape therapy the data is excluded. Missing data was imputed using linear extrapolation.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	294	343	353
Change From Baseline in the Modified Total Sharp-Genant Score at Week 104 [units: Score on a scale] Mean (Standard Deviation)	1.96 (5.956)	0.58 (2.357)	0.37 (1.547)

5. Primary Outcome Measure:

Measure Title	Change in Physical Function as Measured by the Area Under the Curve for the Change From Baseline in the Health Assessment Questionnaire- Disability Index (HAQ-DI) at Week 104
Measure Description	HAQ-DI consisted of 20 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities rated on a 4-point scale where 0=without any difficulty to 3=unable to do. The sum of scores was divided by the number of domains with a score for a total possible score of 0 (best) to 3 (worst). Functional disability was determined as a cumulative measure of HAQ-DI over 2 years by using the AUC of the change from baseline in HAQ-DI score through week 104. Decreases in AUC of change from baseline in HAQ-DI indicated a gr eater average improvement in physical function over time and represent a decrease in sustained impairment. For patients with missing week 104 HAQ-DI score, the AUC of the change from baseline was standardized to 104 weeks using the latest timepoint available for calculation of the AUC. A negative change from baseline indicated improvement.
Time Frame	Baseline to Week 104
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. No imputation was used for missing HAQ scores. For patients who received escape therapy, the HAQ-DI was set to missing from the time they entered escape.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	366	376	374
Change in Physical Function as Measured by the Area Under the Curve for the Change From Baseline in the Health Assessment Questionnaire- Disability Index (HAQ-DI) at Week 104 [units: Score on a scale*week] Least Squares Mean (Full Range)	-139.40 (-1503.9 to 801.9)	-287.50 (-2145.6 to 630.8)	-320.80 (-1776.6 to 677.2)

Statistical Analysis 1 for Change in Physical Function as Measured by the Area Under the Curve for the Change From Baseline in the Health Assessment Questionnaire- Disability Index (HAQ-DI) at Week 104

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 4 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	Adjusted for region.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-148.10
	Confidence Interval	(2-Sided) 95% -205.22 to -90.98
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change in Physical Function as Measured by the Area Under the Curve for the Change From Baseline in the Health Assessment Questionnaire- Disability Index (HAQ-DI) at Week 104

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 8 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	Adjusted for region.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-181.40
	Confidence Interval	(2-Sided) 95% -238.60 to -124.21
	Estimation Comments	[Not specified]

6. 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, Week 24
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With ACR50 Response [units: Percentage of participants]	9.7	25.1	32.2

Statistical Analysis 1 for Percentage of Participants With ACR50 Response

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 4 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Statistical Analysis 2 for Percentage of Participants With ACR50 Response

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 8 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

7. 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,Week 24
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With ACR70 Response [units: Percentage of participants]	2.0	11.0	12.6

Statistical Analysis 1 for Percentage of Participants With ACR70 Response

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 4 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Statistical Analysis 2 for Percentage of Participants With ACR70 Response

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 8 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

8. Secondary Outcome Measure:

Measure Title	Swollen Joint Count (66 Joint Count): Mean Change From Baseline at Week 24
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.
Time Frame	Baseline, 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 for analysis. LOCF was used for swollen joint counts. All assessments were set to missing from the time a patient received escape therapy and only pre-escape therapy joint count assessments were carried forward.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

	Description
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Swollen Joint Count (66 Joint Count): Mean Change From Baseline at Week 24 [units: joint count] Mean (Standard Deviation)			
Baseline Swollen Joint Count (SJC)	16.6 (9.23)	17.0 (9.78)	17.3 (9.48)
Change from Baseline at Week 24 (n=391,399, 397)	-2.9 (10.37)	-7.9 (9.31)	-9.0 (9.76)

9. Secondary Outcome Measure:

Measure Title	Tender Joint Count (68 Joint Count): Mean Change From Baseline at Week 24
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.
Time Frame	Baseline, 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 for analysis. LOCF was used for swollen joint counts. All assessments were set to missing from the time a patient received escape therapy and only pre-escape therapy joint count assessments were carried forward.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Tender Joint Count (68 Joint Count): Mean Change From Baseline at Week 24 [units: joint count] Mean (Standard Deviation)			
Baseline Tender Joint Count (TJC)	27.9 (14.80)	27.9 (14.15)	29.3 (15.22)
Change from Baseline at Week 24 (n=391,399, 397)	-4.8 (14.61)	-12.2 (14.94)	-14.2 (14.58)

10. Secondary Outcome Measure:

Measure Title	Patient's Global Visual Analog Scale (VAS): Mean Change From Baseline at Week 24
Measure Description	The patient’s global assessment of disease activity is assessed on a 0 to 100 mm horizontal visual analogue scale (VAS) by the patient. 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, 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 for analysis. No imputation was used for missing VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Patient's Global Visual Analog Scale (VAS): Mean Change From Baseline at Week 24 [units: millimeters (mm)] Mean (Standard Deviation)			
Baseline Patient Visual Analog Scale (VAS)	63.1 (23.36)	61.0 (23.25)	62.7 (22.49)
Change from Baseline at Week 24 (n=213,308,316)	-17.5 (26.60)	-25.2 (27.09)	-25.2 (24.95)

11. Secondary Outcome Measure:

Measure Title	Physician's Global VAS: Mean Change From Baseline at Week 24
Measure Description	The physician’s global assessment of disease activity is assessed on 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).
Time Frame	Baseline, 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 for analysis. No imputation was used for missing VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Physician's Global VAS: Mean Change From Baseline at Week 24 [units: mm] Mean (Standard Deviation)			
Baseline Physician's Visual Analog Scale (VAS)	63.1 (17.34)	62.3 (16.8)	62.7 (16.90)
Change from Baseline at Week 24 (n=214,307,320)	-29.0 (24.35)	-36.1 (24.31)	-39.8 (21.82)

12. Secondary Outcome Measure:

Measure Title	Patient's Pain VAS: Mean Change From Baseline at Week 24
Measure Description	The patient assessed their pain on 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 indicated improvement.
Time Frame	Baseline and 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 for analysis. No imputation used for missing VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Patient's Pain VAS: Mean Change From Baseline at Week 24 [units: mm]			

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Mean (Standard Deviation)			
Baseline Patient Pain Visual Analog Scale (VAS)	55.3 (22.07)	53.3 (21.97)	55.7 (22.34)
Change from Baseline at Week 24 (n=213,308,317)	-12.5 (24.92)	-19.5 (25.24)	-21.8 (25.93)

13. Secondary Outcome Measure:

Measure Title	C-Reactive Protein (CRP): Mean Change From Baseline at Week 24
Measure Description	The serum concentration of C-Reactive Protein (CRP) is measured in mg/dL. A reduction in the level is considered an improvement.
Time Frame	Baseline, 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 for analysis. No imputation was used for missing CRP. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
C-Reactive Protein (CRP): Mean Change From Baseline at Week 24 [units: milligrams/deciliter (mg/dL)] Mean (Standard Deviation)			
Baseline C-Reactive Protein (CRP)	2.235 (2.5068)	2.076 (2.3892)	2.337 (2.6065)
Change from Baseline at Week 24 (n=214,308,321)	-0.3560 (2.12778)	-0.9558 (2.35222)	-2.0699 (2.50035)

14. Secondary Outcome Measure:

Measure Title	Erythrocyte Sedimentation Rate: Mean Change From Baseline at Week 24
Measure Description	The Erythrocyte Sedimentation Rate (ESR) was measured in mm/hr. A reduction in the level is considered an improvement.
Time Frame	Baseline, 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 for analysis. No imputation was used for missing ESR. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Erythrocyte Sedimentation Rate: Mean Change From Baseline at Week 24 [units: millimeters/hour (mm/hr)] Mean (Standard Deviation)			
Baseline Erythrocyte Sedimentation Rate (ESR)	46.5 (24.69)	45.9 (25.12)	46.4 (24.8)
Change from Baseline at Week 24 (n=211,304,318)	-9.5 (24.01)	-21.8 (23.71)	-36.8 (24.12)

15. Secondary Outcome Measure:

Measure Title	Health Assessment Questionnaire Disability Index (HAQ-DI): Mean Change From Baseline at Week 24

Measure Description	HAQ-DI is a self-completed patient questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. Calculate HAQ-DI the patient must have a domain score for at least 6 of 8 domains. The HAQ-DI is the sum of the scores, divided by the number of domains that have a score (in range 6-8) for a total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from baseline indicated improvement.
Time Frame	Baseline, 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 for analysis. No imputation was used for missing HAQ-DI. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Health Assessment Questionnaire Disability Index (HAQ-DI): Mean Change From Baseline at Week 24 [units: Scores on a scale] Mean (Standard Deviation)			
Baseline HAQ-DI	1.5 (0.62)	1.5 (0.64)	1.5 (0.60)
Change from Baseline at Week 24 (n=197,292,301)	-0.32 (0.516)	-0.45 (0.531)	-0.51 (0.580)

16. Secondary Outcome Measure:

Measure Title	Percentage of Participants With American College of Rheumatology (ACR20) Response at Week 52

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, Week 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With American College of Rheumatology (ACR20) Response at Week 52 [units: Percentage of participants]	24.7	47.9	55.8

17. Secondary Outcome Measure:

Measure Title	Percentage of Participants With ACR20 Response at Week 104

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, Week 104
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With ACR20 Response at Week 104 [units: Percentage of participants]	29.3	49.1	54.5

18. Secondary Outcome Measure:

Measure Title	Percentage of Participants With ACR50 Response at Week 52

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, Week 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With ACR50 Response at Week 52 [units: Percentage of participants]	10.2	30.3	36.4

19. Secondary Outcome Measure:

Measure Title	Percentage of Participants With ACR50 Response at Week 104

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, Week 104
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With ACR50 Response at Week 104 [units: Percentage of participants]	19.8	37.6	38.9

20. Secondary Outcome Measure:

Measure Title	Percentage of Participants With ACR70 Response at Week 52

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, Week 52
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With ACR70 Response at Week 52 [units: Percentage of participants]	3.8	16.5	20.1

21. Secondary Outcome Measure:

Measure Title	Percentage of Participants With ACR70 Response at Week 104

Measure Description	ACR50 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, Week 104
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With ACR70 Response at Week 104 [units: Percentage of participants]	12.2	24.3	22.4

22. Secondary Outcome Measure:

Measure Title	Percentage of Participants With ACR70 Response Maintained for 6 Consecutive Months

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	104 Weeks
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew prematurely or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With ACR70 Response Maintained for 6 Consecutive Months [units: Percentage of participants]	5.6	11.5	14.3

23. Secondary Outcome Measure:

Measure Title	Change From Baseline in Swollen Joint Count at Week 52
Measure Description	66 joints were assessed at Baseline and Week 52 for swelling and joints are classified as swollen/not swollen for a total possible swollen joint count of 0 (best) to 66 (worst). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Week 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. LOCF was used for swollen joint counts. All assessments were set to missing from the time a patient received escape therapy and only pre-escape therapy joint count assessments were carried forward.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	391	399	397
Change From Baseline in Swollen Joint Count at Week 52 [units: Joint count] Mean (Standard Deviation)	-2.5 (11.07)	-8.0 (9.95)	-10.2 (10.65)

24. Secondary Outcome Measure:

Measure Title	Change From Baseline in Tender Joint Count at Week 52
Measure Description	68 joints were assessed at Baseline and Week 52 for tenderness and joints were classified as tender/not tender for a total possible tender joint count of 0 (best) to 68 (worst). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Week 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. LOCF was used for missing tender joint data. All assessments were set to missing from the time a patient received escape therapy and only pre-escape therapy joint count assessments were carried forward.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	391	399	397
Change From Baseline in Tender Joint Count at Week 52 [units: Joint count] Mean (Standard Deviation)	-4.1 (15.53)	-12.3 (15.74)	-15.6 (16.04)

25. Secondary Outcome Measure:

Measure Title	Change From Baseline in Patient's Global Assessment of Disease Activity at Week 52
Measure Description	The patient’s global assessment of disease activity is assessed at Baseline and Week 52 using a 0 to 100 mm horizontal visual analogue scale (VAS) by the patient. 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, Week 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. No imputation was used for missing VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	156	248	281
Change From Baseline in Patient's Global Assessment of Disease Activity at Week 52 [units: Score on a scale] Mean (Standard Deviation)	-21.1 (26.22)	-27.2 (28.83)	-29.8 (25.61)

26. Secondary Outcome Measure:

Measure Title	Change From Baseline in Physicians Global Assessment of Disease Activity at Week 52
Measure Description	The physician's 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, Week 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. No imputation was used for missing VAS assessments. All assessments were set to missing after the patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	155	246	279
Change From Baseline in Physicians Global Assessment of Disease Activity at Week 52	-35.2 (25.13)	-42.2 (23.57)	-45.4 (22.22)

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
[units: Score on a scale] Mean (Standard Deviation)			

27. Secondary Outcome Measure:

Measure Title	Change From Baseline in the Patient's Pain VAS at Week 52
Measure Description	The patient assessed their pain at Baseline and Week 52 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, Week 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. No imputation was used for missing VAS assessments. Data was set to missing for patients who received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	156	248	282
Change From Baseline in the Patient's Pain VAS at Week 52 [units: Score on a scale] Mean (Standard Deviation)	-15.0 (25.10)	-22.9 (25.70)	-26.1 (25.51)

28. Secondary Outcome Measure:

Measure Title	Change From Baseline in C-Reactive Protein (CRP) at Week 52
Measure Description	Blood was collected for C-Reactive Protein (CRP) at Baseline and Week 52 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, Week 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. No imputation was made for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	157	247	282
Change From Baseline in C-Reactive Protein (CRP) at Week 52 [units: mg/dL] Mean (Standard Deviation)	-0.3800 (2.50681)	-1.0615 (2.39897)	-2.2584 (2.71950)

29. Secondary Outcome Measure:

Measure Title	Change From Baseline in Erythrocyte Sedimentation Rate (ESR) at Week 52
Measure Description	Blood was collected for Erythrocyte Sedimentation Rate (ESR) at Baseline and Week 52 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, Week 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. No imputation was used for missing data. Data was set to missing for patients who received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	149	235	274
Change From Baseline in Erythrocyte Sedimentation Rate (ESR) at Week 52 [units: mm/hr] Mean (Standard Deviation)	-10.9 (24.27)	-25.6 (24.68)	-38.5 (24.31)

30. Secondary Outcome Measure:

Measure Title	Change From Baseline in Swollen Joint Count at Week 104
Measure Description	66 joints were assessed at Baseline and Week 104 for swelling and joints were classified as swollen/not swollen for a total possible swollen joint count of 0 (best) to 66 (worst). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Week 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. LOCF was used for swollen joint counts. All assessments were set to missing from the time a patient received escape therapy and only pre-escape therapy joint count assessments were carried forward.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

	Description
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	391	399	397
Change From Baseline in Swollen Joint Count at Week 104 [units: Joint count] Mean (Standard Deviation)	-3.5 (11.65)	-9.0 (10.76)	-11.3 (11.31)

31. Secondary Outcome Measure:

Measure Title	Change From Baseline in Tender Joint Count at Week 104
Measure Description	68 joints were assessed for tenderness and joints were classified as tender/not tender for a total possible tender joint count of 0 (best) to 68 (worst). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Week 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. LOCF was used for tender joint counts. All assessments were set to missing from the time a patient received escape therapy and only pre-escape therapy joint count assessments were carried forward.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	391	399	397

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Change From Baseline in Tender Joint Count at Week 104 [units: Joint count] Mean (Standard Deviation)	-5.9 (17.07)	-13.6 (16.53)	-17.7 (16.73)

32. Secondary Outcome Measure:

Measure Title	Change From Baseline in Patient's Global Assessment of Disease Activity at Week 104
Measure Description	The patient's global assessment of disease activity was assessed at Baseline and Week 104 using a 0 to 100 mm horizontal visual analogue scale (VAS) by the patient. 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, Week 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. No imputation was used for missing VAS assessments. All assessments were set to missing from the time a patient received escape therapy

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	137	228	248
Change From Baseline in Patient's Global Assessment of Disease Activity at Week 104 [units: Score on a scale] Mean (Standard Deviation)	-33.2 (26.35)	-31.6 (27.05)	-33.9 (26.60)

33. Secondary Outcome Measure:

Measure Title	Change From Baseline in Physicians Global Assessment of Disease Activity at Week 104
Measure Description	The physician's global assessment of disease activity was assessed at Baseline and Week 104 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, Week 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. No imputation was used for missing VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	139	229	250
Change From Baseline in Physicians Global Assessment of Disease Activity at Week 104 [units: Score on a scale] Mean (Standard Deviation)	-43.9 (21.55)	-49.1 (20.33)	-48.7 (22.20)

34. Secondary Outcome Measure:

Measure Title	Change From Baseline in the Patient's Pain VAS at Week 104

Measure Description	The patient assessed their pain at Baseline and Week 104 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, Week 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. No imputation was used for missing VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	137	228	248
Change From Baseline in the Patient's Pain VAS at Week 104 [units: Score on a scale] Mean (Standard Deviation)	-25.6 (24.44)	-26.6 (25.39)	-28.9 (25.47)

35. Secondary Outcome Measure:

Measure Title	Change From Baseline in C-Reactive Protein (CRP) at Week 104
Measure Description	Blood was collected for C-Reactive Protein (CRP) at Baseline and Week 104 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, Week 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. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	139	231	251
Change From Baseline in C-Reactive Protein (CRP) at Week 104 [units: mg/dL] Mean (Standard Deviation)	-1.6346 (2.28001)	-1.6863 (2.20965)	-2.3068 (2.65256)

36. Secondary Outcome Measure:

Measure Title	Change From Baseline in Erythrocyte Sedimentation Rate (ESR) at Week 104
Measure Description	Blood was collected for Erythrocyte Sedimentation Rate (ESR) at Baseline and Week 104 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, Week 104
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. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

	Description
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	139	231	247
Change From Baseline in Erythrocyte Sedimentation Rate (ESR) at Week 104 [units: mm/hr] Mean (Standard Deviation)	-30.7 (22.26)	-35.4 (25.07)	-36.9 (23.39)

37. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Achieve an Improvement of at Least 0.3 Units From Baseline in the HAQ Disability Index at Week 52
Measure Description	The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a patient completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0 (without any difficulty) to 3 (unable to do). HAQ-DI=sum of worst scores in each domain divided by the number of domains answered for a total possible score of 0 (best) to 3 (worst).
Time Frame	Baseline, Week 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. No imputation was used for missing data. All assessments were set to missing for patients who received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	146	235	263
Percentage of Participants Who Achieve an Improvement of at Least 0.3 Units From Baseline in the HAQ Disability Index at Week 52 [units: Percentage of participants]	52.7	59.6	62.7

38. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Achieve an Improvement of at Least 0.3 Units From Baseline in the HAQ Disability Index at Week 104
Measure Description	The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a patient completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0 (without any difficulty) to 3 (unable to do).HAQ-DI=sum of worst scores in each domain divided by the number of domains answered for a total possible score of 0 (best) to 3 (worst). .
Time Frame	Baseline, Week 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. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	127	218	231
Percentage of Participants Who Achieve an Improvement of at Least 0.3 Units From Baseline in the HAQ Disability Index at Week 104 [units: Percentage of participants]	58.3	63.3	62.3

39. Secondary Outcome Measure:

Measure Title	Area Under Curve (AUC) of the ACRn to Week 24
Measure Description	The ACRn is defined as each patient's lowest percent improvement from Baseline of 3 measures: tender joint count (68 joints), swollen joint count (66 joints), and the improved score achieved in at least 3 of the 5 remaining ACR core components (physician global assessment, patient global assessment, pain, HAQ, and C-reactive protein or ESR, respectively). AUC of ACRn, a continuous variable, was calculated from Baseline to Week 24. A positive score change from Baseline indicated an improvement. The higher the ACRn score the better.
Time Frame	24 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 analysis. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ score, CRP, ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	216	308	320
Area Under Curve (AUC) of the ACRn to Week 24	609.11 (5551.669)	2791.49 (5479.514)	3528.89 (5812.582)

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
[units: Score on a scale*week] Mean (Standard Deviation)			

40. Secondary Outcome Measure:

Measure Title	Area Under Curve (AUC) of the ACRn to Week 52
Measure Description	The ACRn is defined as each patient's lowest percent improvement from Baseline of 3 measures: tender joint count (68 joints), swollen joint count (66 joints), and the improved score achieved in at least 3 of the 5 remaining ACR core components (physician global assessment, patient global assessment, pain, HAQ, and C-reactive protein or ESR, respectively). AUC of ACRn, a continuous variable, was calculated from Baseline to Week 52. A positive score change from Baseline indicated an improvement. The higher the ACRn score the better.
Time Frame	52 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 analysis. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ score, CRP, ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	156	247	279
Area Under Curve (AUC) of the ACRn to Week 52 [units: Score on a scale*week] Least Squares Mean (Full Range)	5551.25 (-49420.8 to 25818.8)	10763.54 (-74637.5 to 33589.0)	12644.01 (-13773.8 to 31246.7)

Statistical Analysis 1 for Area Under Curve (AUC) of the ACRn to Week 52

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 4 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	ANOVA
	Comments	Adjusted for region.
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	5212.28
	Confidence Interval	(2-Sided) 95% 3139.40 to 7285.16
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Area Under Curve (AUC) of the ACRn to Week 52

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 8 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Adjusted for region.
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	7092.76
	Confidence Interval	(2-Sided) 95% 5066.16 to 9119.36

	Estimation Comments	[Not specified]

41. Secondary Outcome Measure:

Measure Title	Area Under Curve (AUC) of the ACRn Score at Week 104
Measure Description	The ACRn is defined as each patient's lowest percent improvement from Baseline of 3 measures: tender joint count (68 joints), swollen joint count (66 joints), and the improved score achieved in at least 3 of the 5 remaining ACR core components (physician global assessment, patient global assessment, pain, HAQ, and C-reactive protein or ESR, respectively). AUC of ACRn, a continuous variable, was calculated from Baseline to Week 104. A positive score change from Baseline indicated an improvement. The higher the ACRn score the better.
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 analysis. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ score, CRP, ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	138	228	249
Area Under Curve (AUC) of the ACRn Score at Week 104 [units: Score on a scale*week] Mean (Standard Deviation)	21094.97 (22341.489)	27141.08 (24296.659)	30876.59 (18177.420)

42. Secondary Outcome Measure:

Measure Title	Change From Baseline in Disease Activity Score (DAS28) at Week 24

Measure Description	The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity], and ESR. DAS28 total scores range from 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.
Time Frame	Baseline, 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 for analysis. LOCF was used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	208	301	311
Change From Baseline in Disease Activity Score (DAS28) at Week 24 [units: Score on a scale] Mean (Standard Deviation)	-1.49 (1.257)	-2.45 (1.401)	-3.28 (1.383)

43. Secondary Outcome Measure:

Measure Title	Change From Baseline in Disease Activity Score (DAS28) at Week 52
Measure Description	The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity], and ESR. DAS28 total scores range from 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.

Time Frame	Baseline, Week 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. LOCF was used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	153	247	273
Change From Baseline in Disease Activity Score (DAS28) at Week 52 [units: Score on a scale] Mean (Standard Deviation)	-1.88 (1.319)	-2.97 (1.391)	-3.80 (1.263)

44. Secondary Outcome Measure:

Measure Title	Change From Baseline in Disease Activity Score (DAS28) at Week 104
Measure Description	The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity], and ESR. DAS28 total scores range from 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.
Time Frame	Baseline, Week 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. LOCF used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	134	223	238
Change From Baseline in Disease Activity Score (DAS28) at Week 104 [units: Score on a scale] Mean (Standard Deviation)	-3.70 (1.416)	-3.82 (1.306)	-4.14 (1.344)

45. Secondary Outcome Measure:

Measure Title	Percentage of Participants With DAS28 Good or Moderate EULAR Response at Week 24
Measure Description	The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] , and ESR. DAS28 total scores range from 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 and 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, Week 24
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. For patients who received escape therapy, withdrew prematurely or where the DAS28 score was missing the response was set to 'No response'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 8 mg/kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With DAS28 Good or Moderate EULAR Response at Week 24 [units: Percentage of participants]			
Good EULAR Response	5.9	24.6	40.7
Moderate EULAR Response	28.8	39.6	33.7

46. Secondary Outcome Measure:

Measure Title	Percentage of Participants With DAS28 Good or Moderate EULAR Response at Week 52
Measure Description	The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity (mm) [visual analog scale: 0=no disease activity to 100=maximum disease activity] , and ESR. DAS28 total scores range from 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 and 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, Week 52
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. For patients who received escape therapy, withdrew prematurely or where the DAS28 score was missing the response was set to 'No response'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 8 mg/kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With DAS28 Good or Moderate EULAR Response at Week 52 [units: Percentage of participants]			
Good Response	7.1	27.6	44.0
Moderate Response	22.1	30.3	24.1

47. Secondary Outcome Measure:

Measure Title	Percentage of Participants With DAS28 Good or Moderate EULAR Response at Week 104
Measure Description	The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity (mm) [visual analog scale: 0=no disease activity to 100=maximum disease activity] , and ESR. DAS28 total scores range from 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 and 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, Week 104
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation was used for missing ESR and VAS assessments. For patients who received escape therapy, withdrew prematurely or where the DAS28 score was missing the response was set to 'No response'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants With DAS28 Good or Moderate EULAR Response at Week 104 [units: Percentage of participants]			
Good Response	23.4	39.6	45.7
Moderate Response	9.7	15.8	13.1

48. Secondary Outcome Measure:

Measure Title	Percentage of Participants With 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). DAS28 total scores range from 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?	Yes

Analysis Population Description

Participants from the Intent-to-treat population (all randomized participants who received study drug) with data available for analysis. LOCF was used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	212	304	315
Percentage of Participants With DAS28 Remission at Week 24 [units: Percentage of participants]	3.8	17.8	33.3

49. Secondary Outcome Measure:

Measure Title	Percentage of Participants With DAS28 Remission at Week 52
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). DAS28 total scores range from 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?	Yes

Analysis Population Description

Participants from the Intent-to-treat population (all randomized participants who received study drug) with data available for analysis. LOCF was used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

	Description
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	156	249	275
Percentage of Participants With DAS28 Remission at Week 52 [units: Percentage of participants]	7.7	30.5	48.0

50. Secondary Outcome Measure:

Measure Title	Percentage of Participants With DAS28 Remission at Week 104
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). DAS28 total scores range from 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 104
Safety Issue?	Yes

Analysis Population Description

Participants from the Intent-to-treat population (all randomized participants who received study drug) with data available for analysis. LOCF was used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	136	224	241
Percentage of Participants With DAS28 Remission at Week 104 [units: Percentage of participants]	52.9	55.4	64.7

51. Secondary Outcome Measure:

Measure Title	Area Under Curve (AUC) of Disease Activity Score (DAS28) 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). DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. Higher calculated AUC values are worse (indicate higher disease activity).
Time Frame	24 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 analysis. LOCF used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	208	301	311
Area Under Curve (AUC) of Disease Activity Score (DAS28) at Week 24	895.85 (179.465)	767.02 (208.462)	670.45 (193.506)

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
[units: Score on a scale*week] Mean (Standard Deviation)			

52. Secondary Outcome Measure:

Measure Title	Area Under Curve (AUC) of Disease Activity Score (DAS28) at Week 52
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). DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. Higher calculated AUC values are worse (indicate higher disease activity).
Time Frame	52 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 analysis. LOCF was used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	146	230	265
Area Under Curve (AUC) of Disease Activity Score (DAS28) at Week 52 [units: Score on a scale*week] Mean (Standard Deviation)	1755.25 (353.653)	1423.12 (415.188)	1235.80 (412.134)

53. Secondary Outcome Measure:

Measure Title	Area Under Curve (AUC) of Disease Activity Score (DAS28) at Week 104
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). DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. Higher calculated AUC values are worse (indicate higher disease activity).
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 analysis. LOCF was used for tender and swollen joint counts, no imputation used for missing ESR and VAS assessments. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	134	223	238
Area Under Curve (AUC) of Disease Activity Score (DAS28) at Week 104 [units: Score on a scale*week] Mean (Standard Deviation)	2793.01 (675.840)	2426.11 (743.882)	2094.71 (749.148)

54. Secondary Outcome Measure:

Measure Title	Change From Baseline in Modified Total Sharp-Genant Score at Week 24

Measure Description	Radiographs were taken of each hand and foot at Baseline and Week 24 and evaluated at a central reading service by two independent radiologists 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 100 and in the feet 42, the maximum scores for joint space narrowing in the hands is 100 and in the feet 48. The maximum modified Sharp score achievable is 290. A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 24
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 Baseline and post-Baseline radiographic data available for this outcome measure. Data collected after withdraw or on escape therapy is excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	283	327	334
Change From Baseline in Modified Total Sharp-Genant Score at Week 24 [units: Score on a scale] Mean (Standard Deviation)	0.51 (1.336)	0.22 (0.843)	0.19 (0.985)

55. Secondary Outcome Measure:

Measure Title	Change From Baseline in Modified Total Sharp-Genant Score at Week 80

Measure Description	Radiographs were taken of each hand and foot at Baseline and Week 80 and evaluated at a central reading service by two independent radiologists 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 100 and in the feet 42, the maximum scores for joint space narrowing in the hands is 100 and in the feet 48. The maximum modified Sharp score achievable is 290. A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 80
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 Baseline and post-Baseline radiographic data available for this outcome measure. Linear extrapolation was used to impute missing data. Data collected after withdraw or on escape therapy is excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	294	343	353
Change From Baseline in Modified Total Sharp-Genant Score at Week 80 [units: Score on a scale] Mean (Standard Deviation)	1.60 (4.658)	0.46 (1.845)	0.31 (1.273)

56. Secondary Outcome Measure:

Measure Title	Change From Baseline in Erosion Score at Week 24
Measure Description	Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). A lower number change from Baseline indicated a better score.

Time Frame	Baseline, Week 24
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 Baseline and post-Baseline radiographic data available for this outcome measure. Data was set to missing for patients who withdrew or received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	283	327	334
Change From Baseline in Erosion Score at Week 24 [units: Score on a scale] Mean (Standard Deviation)	0.36 (0.928)	0.15 (0.563)	0.11 (0.625)

Statistical Analysis 1 for Change From Baseline in Erosion Score at Week 24

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 4 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0023
	Comments	[Not specified]
	Method	Other [Van Elteren's test]
	Comments	Stratified by region.

Statistical Analysis 2 for Change From Baseline in Erosion Score at Week 24

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 8 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Van Elteren's test]
	Comments	[Not specified]

57. Secondary Outcome Measure:

Measure Title	Change From Baseline in Erosion Score at Week 52
Measure Description	Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 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 Baseline and post-Baseline radiographic data for this outcome measure. Missing Week 52 data was imputed using Linear extrapolation. Data was set to missing for patients who withdrew or received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	290	339	348
Change From Baseline in Erosion Score at Week 52 [units: Score on a scale] Mean (Standard Deviation)	0.71 (1.892)	0.21 (0.920)	0.17 (0.860)

Statistical Analysis 1 for Change From Baseline in Erosion Score at Week 52

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 4 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0001
	Comments	[Not specified]
	Method	Other [Van Elteren's test]
	Comments	Stratified by region.

Statistical Analysis 2 for Change From Baseline in Erosion Score at Week 52

Statistical Analysis Overview	Comparison Groups	Placebo + Methotrexate, Tocilizumab 8 mg/kg + Methotrexate
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Van Elteren's test]
	Comments	Stratified by region.

58. Secondary Outcome Measure:

Measure Title	Change From Baseline in Erosion Score at Week 80
Measure Description	Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 80
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 Baseline and post-Baseline radiographic data available for this outcome measure. Linear extrapolation was used to impute missing data. Data collected after withdraw or on escape therapy is excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	294	343	353
Change From Baseline in Erosion Score at Week 80 [units: Score on a scale] Mean (Standard Deviation)	1.01 (3.101)	0.27 (1.101)	0.18 (1.060)

59. Secondary Outcome Measure:

Measure Title	Change From Baseline in Erosion Score at Week 104
Measure Description	Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 104
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 Baseline and post-Baseline radiographic data available for this outcome measure. Linear extrapolation was used to impute missing data. Data collected after withdraw or on escape therapy is excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	294	343	353
Change From Baseline in Erosion Score at Week 104 [units: Score on a scale] Mean (Standard Deviation)	1.24 (3.947)	0.34 (1.337)	0.22 (1.301)

60. Secondary Outcome Measure:

Measure Title	Change From Baseline in Joint Space Narrowing Score at Week 24
Measure Description	Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). A lower change from Baseline indicated a better score.
Time Frame	Baseline, Week 24
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 Baseline and post-Baseline radiographic data available for this outcome measure. Data was set to missing for patients who withdrew or received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.

	Description
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	283	327	334
Change From Baseline in Joint Space Narrowing Score at Week 24 [units: Score on a scale] Mean (Standard Deviation)	0.15 (0.659)	0.07 (0.416)	0.08 (0.468)

61. Secondary Outcome Measure:

Measure Title	Change From Baseline in Joint Space Narrowing Score at Week 52
Measure Description	Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 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 Baseline and post-Baseline radiographic data available for this outcome measure. Missing data was imputed using linear extrapolation. Data collected after withdraw or on escape therapy was excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	290	339	348
Change From Baseline in Joint Space Narrowing Score at Week 52 [units: Score on a scale] Mean (Standard Deviation)	0.42 (1.695)	0.13 (0.739)	0.12 (0.640)

62. Secondary Outcome Measure:

Measure Title	Change From Baseline in Joint Space Narrowing Score at Week 80
Measure Description	Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 80
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 Baseline and post-Baseline radiographic data available for this outcome measure. Missing data was imputed using linear extrapolation. Data collected after withdraw or on escape therapy was excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	294	343	353
Change From Baseline in Joint Space Narrowing Score at Week 80 [units: Score on a scale]	0.59 (2.589)	0.19 (1.035)	0.13 (0.626)

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Mean (Standard Deviation)			

63. Secondary Outcome Measure:

Measure Title	Change From Baseline in Joint Space Narrowing Score at Week 104
Measure Description	Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 104
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 Baseline and post-Baseline radiographic data available for this outcome measure. Missing data was imputed using linear extrapolation. Data collected after withdraw or on escape therapy was excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	294	343	353
Change From Baseline in Joint Space Narrowing Score at Week 104 [units: Score on a scale] Mean (Standard Deviation)	0.72 (3.321)	0.24 (1.368)	0.15 (0.772)

64. Secondary Outcome Measure:

Measure Title	Percentage of Participants With no Progression of Erosion at Week 24
Measure Description	Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). No progression of Erosion score was defined as a change from Baseline of less than or equal to zero.
Time Frame	Baseline, Week 24
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 Baseline and post-Baseline radiographic data available for this outcome measure. Data collected after withdraw or on escape therapy was excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	283	327	334
Percentage of Participants With no Progression of Erosion at Week 24 [units: Percentage of participants]	73.9	83.8	88.3

65. Secondary Outcome Measure:

Measure Title	Percentage of Participants With no Progression of Erosion at Week 52
Measure Description	Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). No progression of Erosion score was defined as a change from Baseline of less than or equal to zero.
Time Frame	Baseline, Week 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 Baseline and post-Baseline radiographic data available for this outcome measure. Missing data was imputed using linear extrapolation. Data collected after withdraw or on escape therapy was excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	290	339	348
Percentage of Participants With no Progression of Erosion at Week 52 [units: Percentage of participants]	70.0	82.6	86.8

66. Secondary Outcome Measure:

Measure Title	Percentage of Participants With no Progression of Erosion at Week 104
Measure Description	Radiographs were taken of 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 for a total possible score of 0 (best) to 142 (worst). No progression of Erosion score was defined as a change from Baseline of less than or equal to zero.
Time Frame	Baseline, Week 104
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 Baseline and post-Baseline radiographic data available for this outcome measure. Missing data was imputed using linear extrapolation. Data collected after withdrawal or on escape therapy was excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.

	Description
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	294	343	353
Percentage of Participants With no Progression of Erosion at Week 104 [units: Percentage of participants]	71.1	78.4	85.6

67. Secondary Outcome Measure:

Measure Title	Percentage of Participants With no Progression of Joint Space Narrowing at Week 24
Measure Description	Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). No progression of Joint Space Narrowing score was defined as a change from Baseline of less than or equal to zero.
Time Frame	Baseline, Week 24
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 Baseline and post-Baseline radiographic data available for this outcome measure. Data collected after withdrawal or on escape therapy was excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	283	327	334
Percentage of Participants With no Progression of Joint Space Narrowing at Week 24 [units: Percentage of participants]	88.3	91.4	91.9

68. Secondary Outcome Measure:

Measure Title	Percentage of Participants With no Progression of Joint Space Narrowing at Week 52
Measure Description	Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). No progression of Joint Space Narrowing score is defined as a change from Baseline of less than or equal to zero.
Time Frame	Baseline, Week 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 Baseline and post-Baseline radiographic data available for this outcome measure. Missing data was imputed using linear extrapolation. Data collected after withdrawal or on escape therapy was excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	290	339	348
Percentage of Participants With no Progression of Joint Space Narrowing at Week 52 [units: Percentage of participants]	84.5	90.6	90.5

69. Secondary Outcome Measure:

Measure Title	Percentage of Participants With no Progression of Joint Space Narrowing at Week 104
Measure Description	Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). No progression of Joint Space Narrowing score is defined as a change from Baseline of less than or equal to zero.
Time Frame	Baseline, Week 104
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 Baseline and post-Baseline radiographic data available for this outcome measure. Missing data was imputed using linear extrapolation. Data collected after withdrawal or on escape therapy was excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	294	343	353
Percentage of Participants With no Progression of Joint Space Narrowing at Week 104 [units: Percentage of participants]	80.3	86.0	91.2

70. Secondary Outcome Measure:

Measure Title	Change From Baseline in HAQ Disability Index (HAQ-DI) at Week 52

Measure Description	HAQ-DI is a self-completed questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/ grooming, arising, eating, walking, hygiene, reach, grip; common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. To Calculate HAQ-DI the patient must have a domain score for at least 6 of 8 domains. The HAQ-DI is the sum of the scores, divided by the number of domains that have a score (in range 6-8) for a total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from baseline indicated improvement.
Time Frame	Baseline, Week 52
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population (all participants who received at least one dose of study drug) with data available for analysis. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	146	235	263
Change From Baseline in HAQ Disability Index (HAQ-DI) at Week 52 [units: Score on a scale] Mean (Standard Deviation)	-0.39 (0.570)	-0.52 (0.607)	-0.58 (0.583)

71. Secondary Outcome Measure:

Measure Title	Change From Baseline in HAQ Disability Index at Week 104
Measure Description	HAQ-DI is a self-completed questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/ grooming, arising, eating, walking, hygiene, reach, grip; common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. To Calculate HAQ-DI the patient must have a domain score for at least 6 of 8 domains. The HAQ-DI is the sum of the scores, divided by the number of domains that have a score (in range 6-8). Total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from Baseline indicated improvement.

Time Frame	Baseline, Week 104
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population (all participants who received at least one dose of study drug) with data available for analysis. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	127	218	231
Change From Baseline in HAQ Disability Index at Week 104 [units: Score on a scale] Mean (Standard Deviation)	-0.50 (0.612)	-0.58 (0.608)	-0.61 (0.661)

72. Secondary Outcome Measure:

Measure Title	Change From Baseline in Quality Life Short Form-36 (SF-36) Score at Week 24
Measure Description	The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement.
Time Frame	Baseline, Week 24
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population (all participants who received at least one dose of study drug) with data available for analysis. No imputation was used for missing data. . Data was set to missing for patients who received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	203	283	294
Change From Baseline in Quality Life Short Form-36 (SF-36) Score at Week 24 [units: Score on a scale] Mean (Standard Deviation)			
Physical component score	5.54 (8.459)	8.15 (8.135)	8.46 (8.520)
Mental component score	3.27 (11.092)	4.63 (11.702)	5.17 (10.869)

73. Secondary Outcome Measure:

Measure Title	Change From Baseline in SF-36 Score at Week 52
Measure Description	The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from Baseline indicates improvement.
Time Frame	Baseline, Week 52
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population (all participants who received at least one dose of study drug) with data available for analysis. No imputation was used for missing data. Data was set to missing for patients who received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	144	230	261
Change From Baseline in SF-36 Score at Week 52 [units: Score on a scale] Mean (Standard Deviation)			
Physical component summary score	5.6 (8.42)	9.2 (8.29)	10.0 (9.13)
Mental component summary score	3.7 (10.67)	5.6 (11.94)	5.5 (11.49)

74. Secondary Outcome Measure:

Measure Title	Change From Baseline in SF-36 Score at Week 104
Measure Description	The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from Baseline indicated improvement.
Time Frame	Baseline, Week 104
Safety Issue?	No

Analysis Population Description

Participants from the Intent-to-treat population (all participants who received at least one dose of study drug) with data available for analysis. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.

	Description
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	130	211	228
Change From Baseline in SF-36 Score at Week 104 [units: Score on a scale] Mean (Standard Deviation)			
Physical component score	8.7 (9.53)	10.1 (9.50)	9.8 (9.66)
Mental component score	5.2 (10.27)	5.7 (11.22)	6.2 (11.55)

75. Secondary Outcome Measure:

Measure Title	Change From Baseline in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) Score at Week 24
Measure Description	FACIT-F is a 13-item questionnaire. Patients scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the patient's response to the questions (with the exception of 2 negatively stated), the greater the patient's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the patient's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). A higher score reflects an improvement in the patient's health status.
Time Frame	Baseline, Week 24
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. No imputation was used for missing FACIT-Fatigue scores. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

	Description
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	214	307	313
Change From Baseline in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) Score at Week 24 [units: Score on a scale] Mean (Standard Deviation)	5.32 (10.133)	7.14 (10.145)	6.91 (8.877)

76. Secondary Outcome Measure:

Measure Title	Change From Baseline in FACIT-F Score at Week 52
Measure Description	FACIT-F is a 13-item questionnaire. Patients scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the patient's response to the questions (with the exception of 2 negatively stated), the greater the patient's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the patient's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). A higher score reflects an improvement in the patient's health status.
Time Frame	Baseline, Week 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. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	157	250	276
Change From Baseline in FACIT-F Score at Week 52 [units: Score on a scale] Mean (Standard Deviation)	5.57 (10.087)	8.14 (10.880)	8.27 (9.387)

77. Secondary Outcome Measure:

Measure Title	Change From Baseline in FACIT-F Score at Week 104
Measure Description	FACIT-F is a 13-item questionnaire. Patients scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the patient's response to the questions (with the exception of 2 negatively stated), the greater the patient's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the patient's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). A higher score reflects an improvement in the patient's health status.
Time Frame	Baseline, Week 104
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. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	138	224	244
Change From Baseline in FACIT-F Score at Week 104	6.62 (9.544)	7.85 (10.578)	8.63 (9.737)

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
[units: Score on a scale] Mean (Standard Deviation)			

78. Secondary Outcome Measure:

Measure Title	Change From Baseline in Rheumatoid Factor (RF) at Week 24 in Those Patients With Positive RF
Measure Description	Blood was collected for Rheumatoid Factor (RF) at Baseline and Week 24 and was analyzed at a central laboratory. RF level was reported in international units/milliliter (IU/mL). A positive RF= >15 IU/mL. A lower number change from Baseline indicated a better result.
Time Frame	Baseline, Week 24
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 positive RF at Baseline. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	179	252	268
Change From Baseline in Rheumatoid Factor (RF) at Week 24 in Those Patients With Positive RF [units: IU/mL] Mean (Standard Deviation)	-44.7 (273.71)	-79.3 (315.06)	-75.6 (205.76)

79. Secondary Outcome Measure:

Measure Title	Change From Baseline in Rheumatoid Factor (RF) at Week 52 in Those Patients With Positive RF
Measure Description	Blood was collected for Rheumatoid Factor (RF) at Baseline and Week 52 and was analyzed at a central laboratory. RF level was reported in international units/milliliter (IU/mL). A positive RF= >15 IU/mL. A lower number change from Baseline indicated a better result.
Time Frame	Baseline, Week 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 positive RF at Baseline. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	132	208	232
Change From Baseline in Rheumatoid Factor (RF) at Week 52 in Those Patients With Positive RF [units: IU/mL] Mean (Standard Deviation)	-21.5 (444.37)	8.6 (575.02)	-71.6 (213.45)

80. Secondary Outcome Measure:

Measure Title	Change From Baseline in Rheumatoid Factor (RF) at Week 104 in Those Patients With Positive RF
Measure Description	Blood was collected for Rheumatoid Factor (RF) at Baseline and Week 104 and was analyzed at a central laboratory. RF level was reported in international units/milliliter (IU/mL). A positive RF= >15 IU/mL. A lower number change from Baseline indicated a better result.
Time Frame	Baseline, Week 104
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 positive RF at Baseline. No imputation was used for missing data. All assessments were set to missing from the time a patient received escape therapy.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	115	191	206
Change From Baseline in Rheumatoid Factor (RF) at Week 104 in Those Patients With Positive RF [units: IU/mL] Mean (Standard Deviation)	-29.0 (304.46)	-25.1 (431.29)	-39.2 (253.29)

81. Secondary Outcome Measure:

Measure Title	Time to Onset of ACR20 by Treatment Group
Measure Description	Time in days until ACR20 response. ACR20 response was 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	6 months
Safety Issue?	No

Analysis Population Description

Participants from the ITT population [N=393,399,398] (all randomized participants who received study drug) with ACR20 response. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who withdrew, received escape therapy or who did not achieve a response were censored.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	209	299	328
Time to Onset of ACR20 by Treatment Group [units: Days] Median (95% Confidence Interval)	116.0 (113.0 to 141.0)	57.0 (57.0 to 82.0)	57.0 (56.0 to 57.0)

82. Secondary Outcome Measure:

Measure Title	Time to Onset of ACR50 by Treatment Group
Measure Description	Time in days until ACR50 response. ACR50 response was 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	6 months
Safety Issue?	No

Analysis Population Description

Participants from the ITT population [N=393,399,398] (all randomized participants who received study drug) with ACR50 response. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who withdrew, received escape therapy or who did not achieve a response were censored.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	76	178	205
Time to Onset of ACR50 by Treatment Group [units: Days] Median (95% Confidence Interval)	NA (173.0 to NA) [1]	170.0 (169.0 to NA) [1]	141.0 (139.0 to 169.0)

[1] Value not calculable due to insufficient events.

83. Secondary Outcome Measure:

Measure Title	Time to Onset of ACR70 by Treatment Group
Measure Description	Time in days 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	6 months
Safety Issue?	No

Analysis Population Description

Participants from the ITT population [N=393,399,398] (all randomized participants who received study drug) with ACR70 response. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who withdrew, received escape therapy or who did not achieve a response were censored.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	23	89	95
Time to Onset of ACR70 by Treatment Group [units: Days] Median (95% Confidence Interval)	NA (NA to NA) [1]	NA (176.0 to NA) [1]	NA (NA to NA) [1]

[1] Value not calculable due to insufficient events.

84. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Withdraw Due to Lack of Sufficient Therapeutic Response
Measure Description	Insufficient therapeutic response (patient not responding to the drug as assessed by the physician) was selected by the investigator as a reason that the patient withdrew from the study.
Time Frame	104 Weeks
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received at least 1 dose of study drug. Data on escape therapy is excluded.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

	Description
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants Who Withdraw Due to Lack of Sufficient Therapeutic Response [units: Percentage of participants]	3.1	0.3	0.5

85. Secondary Outcome Measure:

Measure Title	Percentage of Participants in Each Treatment Group Who Receive Escape Therapy
Measure Description	In Escape 1, participants in the Tocilizumab 4 mg/kg + Methotrexate and Tocilizumab 8 mg/kg + Methotrexate groups received tocilizumab 8 mg/kg as escape therapy. Participants in the Placebo + Methotrexate group received tocilizumab 4 mg/kg as escape therapy. In Escape 2, all participants received tocilizumab 8 mg/kg.
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 analysis.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	392	399	398

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Percentage of Participants in Each Treatment Group Who Receive Escape Therapy [units: Percentage of participants]			
Escape 1 Therapy	50	24	15
Escape 2 Therapy	8	2	3

86. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Achieved Remission According to the ACR Remission Criteria by Week 24
Measure Description	The percentage of participants, who achieved ACR remission at any study visit up to Week 24. ACR remission required that all five of the following criteria were met for at least two consecutive months: morning stiffness < 15 minutes, no fatigue, no joint pain, no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths, and ESR < 30 mm/hr for a female or 20 mm/hr for a male.
Time Frame	24 Weeks
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for morning stiffness, FACIT-Fatigue score, ESR and VAS assessment. Patients with missing data, early withdrawal or who received escape therapy were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants Who Achieved Remission According to the ACR Remission Criteria by Week 24	0.0	0.3	0.0

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
[units: Percentage of participants]			

87. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Achieved Remission According to the ACR Remission Criteria by Week 52
Measure Description	The percentage of participants, who achieved ACR remission at any study visit up to Week 52. ACR remission required that all five of the following criteria were met for at least two consecutive months: morning stiffness < 15 minutes, no fatigue, no joint pain, no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths, and ESR < 30 mm/hr for a female or 20 mm/hr for a male.
Time Frame	52 Weeks
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for morning stiffness, FACIT-Fatigue score, ESR and VAS assessment. Patients with missing data, early withdrawal or who received escape therapy were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants Who Achieved Remission According to the ACR Remission Criteria by Week 52 [units: Percentage of participants]	0.0	1.8	1.5

88. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Achieved Remission According to the ACR Remission Criteria by Week 104
Measure Description	The percentage of participants who achieved ACR remission at any study visit up to Week 104. ACR remission required that all five of the following criteria were met for at least two consecutive months: morning stiffness < 15 minutes, no fatigue, no joint pain, no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths, and ESR < 30 mm/hr for a female or 20 mm/hr for a male.
Time Frame	104 Weeks
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received study drug. LOCF was used for tender and swollen joint counts, no imputation used for morning stiffness, FACIT-Fatigue score, ESR and VAS assessment. Patients with missing data, early withdrawal or who received escape therapy were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 8 mg/kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants Who Achieved Remission According to the ACR Remission Criteria by Week 104 [units: Percentage of participants]	0.0	2.0	2.5

89. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Achieved Complete Clinical Response at Week 52

Measure Description	Complete clinical response is defined as a continuous 6-month period of remission by ACR criteria [defined as five of the following criteria are met for at least two consecutive months: morning stiffness < 15 minutes, no fatigue, no joint pain, no joint tenderness or swelling, and ESR < 30 mm/hr for a female or 20 mm/hr for a male] and no radiographic progression [defined as change from baseline ≤ 0 in the total Sharp-Genant score, erosion score, and JSN score]. Patients who achieve a complete clinical response at any time in the study are counted as responders, even if the response is not maintained.
Time Frame	52 Weeks
Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received at least 1 dose of study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants Who Achieved Complete Clinical Response at Week 52 [units: Percentage of participants]	0.0	0.3	0.5

90. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Achieved Complete Clinical Response at Week 104
Measure Description	Complete clinical response is defined as a continuous 6-month period of remission by ACR criteria [defined as five of the following criteria are met for at least two consecutive months: morning stiffness < 15 minutes, no fatigue, no joint pain, no joint tenderness or swelling, and ESR < 30 mm/hr for a female or 20 mm/hr for a male] and no radiographic progression [defined as change from baseline ≤ 0 in the total Sharp-Genant score, erosion score, and JSN score].
Time Frame	104 Weeks

Safety Issue?	No

Analysis Population Description

Intent-to-treat population included all randomized participants who received at least 1 dose of study drug. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. Patients who received escape therapy, withdrew or where an ACR could not be calculated, were set to 'Non Responder'.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly.
Tocilizumab 4 mg/kg + Methotrexate	Tocilizumab 4 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.
Tocilizumab 8 mg/kg + Methotrexate	Tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly.

Measured Values

	Placebo + Methotrexate	Tocilizumab 4 mg/ kg + Methotrexate	Tocilizumab 8 mg/ kg + Methotrexate
Number of Participants Analyzed	393	399	398
Percentage of Participants Who Achieved Complete Clinical Response at Week 104 [units: Percentage of participants]	0	0.3	1.0

91. Secondary Outcome Measure:

Measure Title	End of Study: Percentage of Participants With ACR Response at Week 260
Measure Description	ACR20/50/70/90 response is defined as a ≥ 20/50/70/90% 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, Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treatment population, all exposure group, with data available at Baseline and Week 260. LOCF was used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	473
End of Study: Percentage of Participants With ACR Response at Week 260 [units: Percentage of participants]	
ACR 20 Response	82.9
ACR 50 Response	64.9
ACR 70 Response	42.1
ACR 90 Response	16.7

92. Secondary Outcome Measure:

Measure Title	End of Study: Percentage of Participants With DAS28 Remission at Week 260
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). DAS28 total scores range from 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 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treatment population, all exposure group, with data available at Week 260. Last observation carried forward was used for tender and swollen joint counts. No imputation used for ESR and Patients Global Assessment of Disease Activity VAS.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	458
End of Study: Percentage of Participants With DAS28 Remission at Week 260 [units: Percentage of participants]	59.4

93. Secondary Outcome Measure:

Measure Title	End of Study: Percentage of Participants With DAS28 Low Disease Activity (LDA) at Week 260
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). DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. LDA is defined as DAS28 ≤3.2.
Time Frame	Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treatment population, all exposure group, with data available at Week 260. Last observation carried forward was used for tender and swollen joint counts. No imputation used for ESR and Patients Global Assessment of Disease Activity VAS.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	458
End of Study: Percentage of Participants With DAS28 Low Disease Activity (LDA) at Week 260 [units: Percentage of participants]	73.8

94. Secondary Outcome Measure:

Measure Title	End of Study: Percentage of Participants With DAS28 European League Against Rheumatism (EULAR) Good or Moderate Response at Week 260
Measure Description	The DAS28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity (mm), and ESR. DAS28 total scores range from 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. EULAR Good response: DAS28 ≤ 3.2 and 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, Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treatment population, all exposure group, with data available at Week 260. Last observation carried forward was used for tender and swollen joint counts. No imputation used for ESR and Patients Global Assessment of Disease Activity VAS.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	455
End of Study: Percentage of Participants With DAS28 European League Against Rheumatism (EULAR) Good or Moderate Response at Week 260 [units: Percentage of participants]	
Good Response	74.1
Moderate Response	24.0

95. Secondary Outcome Measure:

Measure Title	End of Study: Change From Baseline in Swollen Joint Count at Week 260
Measure Description	66 joints were assessed at Baseline and Week 260 for swelling and joints are classified as swollen/not swollen for a total possible swollen joint count of 0 (best) to 66 (worst). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treat population, All Tocilizumab Exposure group, with data available at Baseline and Week 260. Last observation carried forward was used for missing joint counts.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	480
End of Study: Change From Baseline in Swollen Joint Count at Week 260 [units: Joint Count] Mean (Standard Deviation)	-14.2 (10.34)

96. Secondary Outcome Measure:

Measure Title	End of Study: Change From Baseline in Tender Joint Count at Week 260
Measure Description	68 joints were assessed at Baseline and Week 260 for tenderness and joints are classified as tender/not tender for a total possible swollen joint count of 0 (best) to 68 (worst). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treat population, All Tocilizumab Exposure group, with data available at Baseline and Week 260. Last observation carried forward was used for missing joint counts.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	480
End of Study: Change From Baseline in Tender Joint Count at Week 260 [units: Joint Count] Mean (Standard Deviation)	-23.6 (14.20)

97. Secondary Outcome Measure:

Measure Title	End of Study: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 260
Measure Description	HAQ-DI is a self-completed questionnaire specific for RA. It consists of 20 questions referring to 8 domains: dressing/ grooming, arising, eating, walking, hygiene, reach, grip; common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. To Calculate HAQ-DI the patient must have a domain score for at least 6 of 8 domains. The HAQ-DI is the sum of the scores, divided by the number of domains that have a score (in range 6-8) for a total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from Baseline indicated improvement.
Time Frame	Baseline, Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treat population, All Tocilizumab Exposure group, with data available at Baseline and Week 260. No imputation was used for missing HAQ score.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/ kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	444

	All Tocilizumab Exposure + MTX
End of Study: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 260 [units: Score on a scale] Mean (Standard Deviation)	-0.58 (0.657)

98. Secondary Outcome Measure:

Measure Title	End of Study: Change From Baseline in the Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS) at Week 260
Measure Description	The patient's global assessment of disease activity was assessed at Baseline and Week 104 using a 0 to 100 mm horizontal visual analogue scale (VAS) by the patient. 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, Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treat population, all tocilizumab exposure group, with data available at Baseline and Week 260. No imputation was used for missing VAS assessments.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	471
End of Study: Change From Baseline in the Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS) at Week 260 [units: mm]	-33.7 (27.22)

	All Tocilizumab Exposure + MTX
Mean (Standard Deviation)	

99. Secondary Outcome Measure:

Measure Title	End of Study: Change From Baseline in the Physician's Global Assessment of Disease Activity VAS at Week 260
Measure Description	The physician’s 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, Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treat population, all tocilizumab exposure group, with data available at Baseline and Week 260. No imputation was used for missing VAS assessments.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	469
End of Study: Change From Baseline in the Physician's Global Assessment of Disease Activity VAS at Week 260 [units: mm] Mean (Standard Deviation)	-48.7 (21.70)

100. Secondary Outcome Measure:

Measure Title	End of Study: Change From Baseline in the Patient's Pain VAS at Week 260
Measure Description	The patient assessed their pain at Baseline and Week 260 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, Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treat population, all tocilizumab exposure group, with data available at Baseline and Week 260. No imputation was used for missing VAS assessments.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	471
End of Study: Change From Baseline in the Patient's Pain VAS at Week 260 [units: mm] Mean (Standard Deviation)	-28.2 (26.78)

101. Secondary Outcome Measure:

Measure Title	End of Study: Percentage of Participants With Clinical Improvement in the FACIT-Fatigue Score at Week 260
Measure Description	FACIT-F is a 13-item questionnaire. Patients scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the patient's response to the questions (with the exception of 2 negatively stated), the greater the patient's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the patient's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). Clinically relevant improvement is defined as a ≥5 change from Baseline.

Time Frame	Baseline, Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treat population, All Tocilizumab Exposure group, with data available for analysis at Baseline and Week 260.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	473
End of Study: Percentage of Participants With Clinical Improvement in the FACIT-Fatigue Score at Week 260 [units: Percentage of participants]	64.1

102. Secondary Outcome Measure:

Measure Title	End of Study: Percentage of Participants With Clinical Relevant Improvement in the SF-36 Score at Week 260
Measure Description	The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. Clinically relevant improvement is defined as a ≥5 change from Baseline.
Time Frame	Baseline, Week 260
Safety Issue?	No

Analysis Population Description

Participants from the Modified Intent-to-treat population, All Tocilizumab Exposure group, with data available for analysis at Baseline and Week 260.

Reporting Groups

	Description
All Tocilizumab Exposure + MTX	All tocilizumab exposure group included all participants who received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	All Tocilizumab Exposure + MTX
Number of Participants Analyzed	442
End of Study: Percentage of Participants With Clinical Relevant Improvement in the SF-36 Score at Week 260 [units: Percentage of participants]	
Mental Components Summary	43.7
Physical Components summary	69.9

103. Secondary Outcome Measure:

Measure Title	End of Study: Change From Baseline in Total Sharp-Genant Score at Week 260
Measure Description	Radiographs were taken of each hand and foot at Baseline and Week 260 and evaluated at a central reading service by two independent radiologists 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 100 and in the feet 42, the maximum scores for joint space narrowing in the hands is 100 and in the feet 48. The maximum modified Sharp score achievable is 290. A lower number change from Baseline indicated a better score. The results were reported based on the treatment the patient was originally randomized to.
Time Frame	Baseline, Week 260
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 Baseline, Week 104 and post-Week 104 radiographic data available for this outcome measure. Linear extrapolation was used to impute missing data.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.
Tocilizumab + Methotrexate	All participants received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	Placebo + Methotrexate	Tocilizumab + Methotrexate
Number of Participants Analyzed	258	545
End of Study: Change From Baseline in Total Sharp-Genant Score at Week 260 [units: Score on a scale] Mean (Standard Deviation)	3.30 (6.093)	1.54 (4.272)

104. Secondary Outcome Measure:

Measure Title	End of Study: Change From Baseline in Erosion Score at Week 260
Measure Description	Radiographs were taken of a total of 14 locations in each hand and wrist and 6 joints in the foot and were evaluated for erosion using an 8-point scale where 0=Normal to 3.5=very severe erosion for a total possible score of 0 (best) to 142 (worst). A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 260
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 Baseline, Week 104 and post-Week 104 radiographic data available for this outcome measure. Linear extrapolation was used to impute missing data.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

	Description
Tocilizumab + Methotrexate	All participants received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	Placebo + Methotrexate	Tocilizumab + Methotrexate
Number of Participants Analyzed	258	545
End of Study: Change From Baseline in Erosion Score at Week 260 [units: Score on a scale] Mean (Standard Deviation)	1.95 (3.640)	0.83 (2.657)

105. Secondary Outcome Measure:

Measure Title	End of Study: Change From Baseline in Joint Space Narrowing Score at Week 260
Measure Description	Radiographs were taken of 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) for a total possible score of 0 (best) to 148 (worst). A lower number change from Baseline indicated a better score.
Time Frame	Baseline, Week 260
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 Baseline, Week 104 and post-Week 104 radiographic data available for this outcome measure. Missing data was imputed using linear extrapolation.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.
Tocilizumab + Methotrexate	All participants received at least one dose of tocilizumab during the placebo controlled core study or the long term extension period plus MTX 10-25 mg (oral or parenteral) weekly. Participants received either: placebo, tocilizumab 4 mg/kg or tocilizumab 8 mg/kg in the 2 year placebo controlled core treatment phase. In the extension 3 to 5 year period, all participants received tocilizumab 8 mg/kg IV every 4 weeks.

Measured Values

	Placebo + Methotrexate	Tocilizumab + Methotrexate
Number of Participants Analyzed	258	545
End of Study: Change From Baseline in Joint Space Narrowing Score at Week 260 [units: Score on a scale] Mean (Standard Deviation)	1.35 (3.134)	0.71 (2.222)

Reported Adverse Events

Time Frame	Day 1 thru the End of the Study (Up to 6.0 years).
Additional Description	Safety population included all participants who received study treatment based on the treatment actually received. The number of participants at risk is the number of participants in each arm with an adverse event recorded while receiving that treatment. Participants may be counted in more than one arm.

Reporting Groups

	Description
Placebo + Methotrexate	Placebo intravenously (IV) every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly. Total Exposure Placebo + MTX = 282.36 patient-years (PY).
All Tocilizumab 4 mg/kg + Methotrexate	All participants who received tocilizumab (TCZ) 4 mg/kg IV every 4 weeks plus methotrexate (MTX) 10-25 mg (oral or parenteral) weekly during the study. Total exposure TCZ 4mg + MTX = 580.99 PY.
All Tocilizumab 8 mg/kg + Methotrexate	All participants who received tocilizumab 8 mg/kg IV every 4 weeks plus MTX 10-25 mg (oral or parenteral) weekly during the study. Total exposure TCZ 8mg + MTX = 3797.94 PY.

Serious Adverse Events

	Placebo + Methotrexate	All Tocilizumab 4 mg/kg + Methotrexate	All Tocilizumab 8 mg/kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	26/392 (6.63%)	58/599 (9.68%)	267/1054 (25.33%)
Blood and lymphatic system disorders			

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Anemia [A] †	1/392 (0.26%)	0/599 (0%)	3/1054 (0.28%)
Bicytopenia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Bone marrow failure [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Hilar lymphadenopathy [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Iron deficiency anaemia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Leukopenia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Microcytic anaemia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Neutropenia [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Pancytopenia [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Thrombocytopenia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Cardiac disorders			
Acute myocardial infarction [A] †	0/392 (0%)	2/599 (0.33%)	1/1054 (0.09%)
Angina pectoris [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Atrial fibrillation [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Cardiac failure [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Cardiac failure congestive [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Cardio-respiratory arrest [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Cardiomyopathy [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Coronary artery disease [A] †	0/392 (0%)	1/599 (0.17%)	5/1054 (0.47%)
Coronary artery stenosis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Mitral valve incompetence [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Myocardial infarction [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Palpitations [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pericarditis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Sinus tachycardia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Supraventricular tachycardia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Ventricular fibrillation [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Ventricular hypokinesia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Endocrine disorders			
Goitre [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Hyperthyroidism [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Hypothyroidism [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Eye disorders			
Corneal perforation [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Retinal detachment [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Ulcerative keratitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Gastrointestinal disorders			
Abdominal adhesions [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Abdominal pain [A] †	0/392 (0%)	0/599 (0%)	4/1054 (0.38%)
Abdominal pain lower [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Diverticular perforation [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Diverticulum intestinal [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Dysphagia [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Enteritis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Gastric ulcer [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Gastritis [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Gastrointestinal telangiectasia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Haemorrhoidal haemorrhage [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Haemorrhoids [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Hiatus hernia [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Ileus paralytic [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Inflammatory bowel disease [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Inguinal hernia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Intestinal polyp [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Irritable bowel syndrome [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Large intestinal ulcer [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Mouth ulceration [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Pancreatic pseudocyst [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pancreatitis [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Pancreatitis necrotising [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Rectal haemorrhage [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Sigmoiditis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Umbilical hernia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
General disorders			

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Chest pain [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Death [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Device dislocation [A] †	0/392 (0%)	0/599 (0%)	4/1054 (0.38%)
Influenza like illness [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Infusion site reaction [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Non-cardiac chest pain [A] †	0/392 (0%)	0/599 (0%)	4/1054 (0.38%)
Hepatobiliary disorders			
Acute hepatic failure [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Autoimmune hepatitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Bile duct stone [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Biliary tract disorder [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Cholecystitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Cholecystitis acute [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Cholelithiasis [A] †	1/392 (0.26%)	0/599 (0%)	4/1054 (0.38%)
Hepatic cirrhosis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Hepatic vein thrombosis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Hepatitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Portal vein thrombosis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Immune system disorders			
Anaphylactic reaction [A] †	0/392 (0%)	2/599 (0.33%)	1/1054 (0.09%)
Anaphylactic shock [A] †	0/392 (0%)	2/599 (0.33%)	0/1054 (0%)
Drug hypersensitivity [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/kg + Methotrexate	All Tocilizumab 8 mg/kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Infections and infestations			
Abdominal abscess [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Abdominal wall abscess [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Abscess soft tissue [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Appendiceal abscess [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Appendicitis [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Appendicitis perforated [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Arthritis bacterial [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Breast abscess [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Bronchitis [A] †	0/392 (0%)	0/599 (0%)	5/1054 (0.47%)
Bronchopneumonia [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Bursitis infective [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Candida osteomyelitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Cellulitis [A] †	0/392 (0%)	1/599 (0.17%)	10/1054 (0.95%)
Cholecystitis infective [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Clostridial infection [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Coccidioidomycosis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Cystitis [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Dengue fever [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Diverticulitis [A] †	0/392 (0%)	0/599 (0%)	4/1054 (0.38%)
Empyema [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Endocarditis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Epiglottitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Erysipelas [A] †	0/392 (0%)	0/599 (0%)	4/1054 (0.38%)
External ear cellulitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Gallbladder empyema [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Gastroenteritis [A] †	2/392 (0.51%)	2/599 (0.33%)	3/1054 (0.28%)
Gastroenteritis viral [A] †	0/392 (0%)	2/599 (0.33%)	0/1054 (0%)
Groin abscess [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Hepatitis C [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Herpes zoster [A] †	1/392 (0.26%)	0/599 (0%)	1/1054 (0.09%)
Infection [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Infectious pleural effusion [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Localised infection [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Lower respiratory tract infection [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Lung infection [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Meningitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Mycobacterium chelonae infection [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Osteomyelitis [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Otitis media [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pharyngitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pneumonia [A] †	2/392 (0.51%)	3/599 (0.5%)	16/1054 (1.52%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Pneumonia bacterial [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pneumonia cryptococcal [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pneumonia legionella [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Post procedural infection [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Prostate infection [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pseudomonas infection [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Pyelonephritis [A] †	0/392 (0%)	1/599 (0.17%)	3/1054 (0.28%)
Respiratory tract infection [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Respiratory tract infection viral [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Salpingitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Sepsis [A] †	0/392 (0%)	1/599 (0.17%)	2/1054 (0.19%)
Septic shock [A] †	0/392 (0%)	1/599 (0.17%)	2/1054 (0.19%)
Staphylococcal abscess [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Staphylococcal bacteraemia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Staphylococcal device related infection [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Staphylococcal infection [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Staphylococcal sepsis [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Systemic candida [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Tuberculous pleurisy [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Tubo-ovarian abscess [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Upper respiratory tract infection [A] †	0/392 (0%)	1/599 (0.17%)	2/1054 (0.19%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Urinary tract infection [A] †	1/392 (0.26%)	0/599 (0%)	5/1054 (0.47%)
Varicella [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Injury, poisoning and procedural complications			
Accident [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Alcohol poisoning [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Ankle fracture [A] †	1/392 (0.26%)	0/599 (0%)	1/1054 (0.09%)
Dislocation of vertebra [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Femur fracture [A] †	0/392 (0%)	0/599 (0%)	7/1054 (0.66%)
Hip fracture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Humerus fracture [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Injury [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Joint injury [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Ligament rupture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Lower limb fracture [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Multiple fractures [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Muscle rupture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Patella fracture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pelvic fracture [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Periprosthetic fracture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Post procedural haemorrhage [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Post procedural stroke [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/kg + Methotrexate	All Tocilizumab 8 mg/kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Procedural complication [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pubis fracture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Radius fracture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Rib fracture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Spinal compression fracture [A] †	1/392 (0.26%)	0/599 (0%)	3/1054 (0.28%)
Splenic rupture [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Subdural haematoma [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Synovial rupture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Tendon rupture [A] †	0/392 (0%)	1/599 (0.17%)	2/1054 (0.19%)
Tibia fracture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Vascular pseudoaneurysm [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Wound dehiscence [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Wrist fracture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Investigations			
Blood pressure decreased [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Transaminases increased [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Metabolism and nutrition disorders			
Dehydration [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Diabetes mellitus [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Diabetes mellitus inadequate control [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Hypoglycaemia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Malnutrition [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Musculoskeletal and connective tissue disorders			
Foot deformity [A] †	0/392 (0%)	0/599 (0%)	4/1054 (0.38%)
Intervertebral disc degeneration [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Intervertebral disc disorder [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Intervertebral disc protrusion [A] †	1/392 (0.26%)	0/599 (0%)	2/1054 (0.19%)
Jaw cyst [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Lumbar spinal stenosis [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Metatarsalgia [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Muscle disorder [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Osteoarthritis [A] †	0/392 (0%)	2/599 (0.33%)	8/1054 (0.76%)
Osteonecrosis [A] †	1/392 (0.26%)	0/599 (0%)	1/1054 (0.09%)
Osteoporotic fracture [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Rheumatoid arthritis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Spinal column stenosis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Spinal osteoarthritis [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Spondylolisthesis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal cancer [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Basal cell carcinoma [A] †	0/392 (0%)	2/599 (0.33%)	1/1054 (0.09%)
Benign lung neoplasm [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Bowen's disease [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Breast cancer [A] †	1/392 (0.26%)	1/599 (0.17%)	1/1054 (0.09%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/kg + Methotrexate	All Tocilizumab 8 mg/kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Breast cancer stage II [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Cardiac myxoma [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Cervix carcinoma stage 0 [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Cervix carcinoma stage III [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Endometrial cancer [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Endometrial cancer metastatic [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Extranodal marginal zone B-cell lymphoma (malt type) [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Gastrooesophageal cancer [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Large cell carcinoma of the respiratory tract stage unspecified [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Lung adenocarcinoma metastatic [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Lung adenocarcinoma stage I [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Lung squamous cell carcinoma stage III [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Malignant melanoma [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Metastatic malignant melanoma [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Neuroendocrine carcinoma [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Non-small cell lung cancer [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Non-small cell lung cancer metastatic [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Ovarian cancer metastatic [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Parathyroid tumour benign [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Prostate cancer [A] †	0/392 (0%)	2/599 (0.33%)	2/1054 (0.19%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Renal cell carcinoma [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Renal cell carcinoma stage I [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Small cell lung cancer metastatic [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Squamous cell carcinoma of skin [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Thyroid cancer [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Tongue cancer metastatic [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Transitional cell carcinoma [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Uterine leiomyoma [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Nervous system disorders			
Carotid artery occlusion [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Carotid artery stenosis [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Carpal tunnel syndrome [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Cerebral atrophy [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Cerebral ischaemia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Cerebrovascular accident [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Convulsion [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Demyelination [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Encephalitis [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Haemorrhagic stroke [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Headache [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Hypoglycaemic unconsciousness [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/kg + Methotrexate	All Tocilizumab 8 mg/kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Lumbar radiculopathy [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Myasthenia gravis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Optic neuritis [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Presyncope [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Radiculopathy [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Sciatica [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Subarachnoid haemorrhage [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Syncope [A] †	0/392 (0%)	1/599 (0.17%)	2/1054 (0.19%)
Transient ischaemic attack [A] †	1/392 (0.26%)	0/599 (0%)	3/1054 (0.28%)
Vasculitis cerebral [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous [A] †	1/392 (0.26%)	0/599 (0%)	1/1054 (0.09%)
Pregnancy [A] †	0/392 (0%)	0/599 (0%)	3/1054 (0.28%)
Psychiatric disorders			
Anxiety [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Confusional state [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Depression [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Major depression [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Renal and urinary disorders			
Calculus ureteric [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Calculus urinary [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Nephrolithiasis [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Renal colic [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Renal failure [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Renal failure chronic [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Scleroderma renal crisis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Urinary bladder polyp [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Reproductive system and breast disorders			
Cervical dysplasia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Endometriosis [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Metrorrhagia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Ovarian cyst [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Rectocele [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Uterine polyp [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Vaginal haemorrhage [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Respiratory, thoracic and mediastinal disorders			
Acute interstitial pneumonitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Acute pulmonary oedema [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Asthma [A] †	0/392 (0%)	1/599 (0.17%)	2/1054 (0.19%)
Atelectasis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Chronic obstructive pulmonary disease [A] †	0/392 (0%)	0/599 (0%)	2/1054 (0.19%)
Dyspnoea [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Haemoptysis [A] †	1/392 (0.26%)	0/599 (0%)	1/1054 (0.09%)
Haemothorax [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/kg + Methotrexate	All Tocilizumab 8 mg/kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Interstitial lung disease [A] †	0/392 (0%)	1/599 (0.17%)	1/1054 (0.09%)
Organising pneumonia [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pleural fibrosis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pneumothorax [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Pulmonary embolism [A] †	0/392 (0%)	1/599 (0.17%)	4/1054 (0.38%)
Pulmonary haemorrhage [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Respiratory failure [A] †	1/392 (0.26%)	0/599 (0%)	2/1054 (0.19%)
Rheumatoid lung [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Skin and subcutaneous tissue disorders			
Angioedema [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Dermatitis allergic [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Digital ulcer [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Generalised erythema [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Ingrowing nail [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Leukocytoclastic vasculitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Palpable purpura [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Skin ulcer [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Urticaria [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Vascular disorders			
Aortic aneurysm [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Arterial insufficiency [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Deep vein thrombosis [A] †	1/392 (0.26%)	0/599 (0%)	4/1054 (0.38%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Diffuse vasculitis [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Femoral artery occlusion [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Hypertension [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Hypertensive crisis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Hypotension [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)
Thrombophlebitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Varicophlebitis [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Vasculitis [A] †	0/392 (0%)	1/599 (0.17%)	0/1054 (0%)
Venous insufficiency [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Venous thrombosis limb [A] †	0/392 (0%)	0/599 (0%)	1/1054 (0.09%)
Wegener's granulomatosis [A] †	1/392 (0.26%)	0/599 (0%)	0/1054 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 15.0

Other Adverse Events

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

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	169/392 (43.11%)	303/599 (50.58%)	835/1054 (79.22%)
Gastrointestinal disorders			
Abdominal pain upper [A] †	8/392 (2.04%)	17/599 (2.84%)	53/1054 (5.03%)
Diarrhoea [A] †	10/392 (2.55%)	23/599 (3.84%)	85/1054 (8.06%)
Gastritis [A] †	5/392 (1.28%)	18/599 (3.01%)	73/1054 (6.93%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/kg + Methotrexate	All Tocilizumab 8 mg/kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Nausea [A] †	18/392 (4.59%)	19/599 (3.17%)	69/1054 (6.55%)
General disorders			
Oedema peripheral [A] †	8/392 (2.04%)	10/599 (1.67%)	64/1054 (6.07%)
Infections and infestations			
Bronchitis [A] †	21/392 (5.36%)	32/599 (5.34%)	135/1054 (12.81%)
Gastroenteritis [A] †	9/392 (2.3%)	19/599 (3.17%)	82/1054 (7.78%)
Influenza [A] †	16/392 (4.08%)	19/599 (3.17%)	100/1054 (9.49%)
Nasopharyngitis [A] †	18/392 (4.59%)	30/599 (5.01%)	123/1054 (11.67%)
Pharyngitis [A] †	10/392 (2.55%)	23/599 (3.84%)	103/1054 (9.77%)
Sinusitis [A] †	10/392 (2.55%)	30/599 (5.01%)	111/1054 (10.53%)
Upper respiratory tract infection [A] †	29/392 (7.4%)	55/599 (9.18%)	256/1054 (24.29%)
Urinary tract infection [A] †	20/392 (5.1%)	34/599 (5.68%)	170/1054 (16.13%)
Injury, poisoning and procedural complications			
Contusion [A] †	6/392 (1.53%)	9/599 (1.5%)	55/1054 (5.22%)
Investigations			
Alanine aminotransferase increased [A] †	5/392 (1.28%)	10/599 (1.67%)	66/1054 (6.26%)
Transaminases increased [A] †	6/392 (1.53%)	29/599 (4.84%)	97/1054 (9.2%)
Metabolism and nutrition disorders			
Hypercholesterolaemia [A] †	3/392 (0.77%)	5/599 (0.83%)	58/1054 (5.5%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] †	8/392 (2.04%)	10/599 (1.67%)	56/1054 (5.31%)
Back pain [A] †	9/392 (2.3%)	14/599 (2.34%)	105/1054 (9.96%)

	Placebo + Methotrexate	All Tocilizumab 4 mg/ kg + Methotrexate	All Tocilizumab 8 mg/ kg + Methotrexate
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Osteoarthritis [A] †	4/392 (1.02%)	4/599 (0.67%)	55/1054 (5.22%)
Rheumatoid arthritis [A] †	16/392 (4.08%)	19/599 (3.17%)	99/1054 (9.39%)
Nervous system disorders			
Headache [A] †	8/392 (2.04%)	25/599 (4.17%)	88/1054 (8.35%)
Psychiatric disorders			
Depression [A] †	11/392 (2.81%)	12/599 (2%)	60/1054 (5.69%)
Respiratory, thoracic and mediastinal disorders			
Cough [A] †	12/392 (3.06%)	16/599 (2.67%)	53/1054 (5.03%)
Vascular disorders			
Hypertension [A] †	12/392 (3.06%)	34/599 (5.68%)	141/1054 (13.38%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 15.0

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

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

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

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

Results Point of Contact:

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