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A Study of RoActemra/Actemra (Tocilizumab) in Patients With Ankylosing Spondylitis Who Have Failed Treatment With NSAIDs

This study has been terminated.
(Recruitment halted: Failed to achieve efficacy)

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT01209702

Purpose

This randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of RoActemra/Actemra (tocilizumab) in patients with ankylosing spondylitis (AS) who have failed treatment with non-steroidal anti-inflammatory drugs and are naïve to tumor necrsos factor (TNF) antagonist therapy. In Part 1 of the study, patients will be randomized to receive either RoActemra/Actemra 8 mg/kg intravenously (IV) or placebo every 4 weeks for 12 weeks. In Part 2, patients will be randomized to receive RoActemra at either 8 mg/kg or 4 mg/kg IV or placebo every 4 weeks for 24 weeks. The double-blind treatment period will be followed by open-label treatment with RoActemra/Actemra 8 mg/kg iv every 4 weeks until Week 208 for all patients. Anticipated time on study treatment is 208 weeks.

Condition	Intervention	Phase
Spondylitis, Ankylosing	Biological/Vaccine: tocilizumab Drug: Placebo	Phase 3

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

Official Title: A Ph II/III Seamless, Multi-center, Randomized, Double-blind, Placebo-controlled Study of the Reduction in Signs and Symptoms and Inhibition of Structural Damage During Treatment With Tocilizumab Versus Placebo in Patients With Ankylosing Spondylitis Who Have Failed Non-steroidal Anti-inflammatory Drugs and Are naïve to TNF Antagonist Therapy NSAIDs

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Part 1: Percentage of Participants Achieving a 20% Improvement in Assessment in Ankylosing Spondylitis (ASAS20) at Week 12 [Time Frame: Baseline and Week 12] [Designated as safety issue: No]

  ASAS is composed of four domains. To achieve an ASAS20 response required improvement of ≥20% and ≥ 1 unit (10 mm) in at least 3 domains and no worsening of ≥ 20 % and ≥ 1 unit (10 mm) in the remaining domain. -The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). -The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. -The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values. -The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Part 2: Percentage of Participants Achieving a 20% Improvement in Assessment in Ankylosing Spondylitis (ASAS20) at Week 12 [Time Frame: Baseline and Week 12] [Designated as safety issue: No]

  ASAS is composed of four domains. To achieve an ASAS20 response required improvement of ≥20% and ≥ 1 unit (10 mm) in at least 3 domains and no worsening of ≥ 20 % and ≥ 1 unit (10 mm) in the remaining domain. -The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). -The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. -The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values. -The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Secondary Outcome Measures:

- Part 2: Percentage of Participants Achieving a 20% Improvement in Assessment in Ankylosing Spondylitis (ASAS20) at Week 24 [Time Frame: Baseline and Week 24] [Designated as safety issue: No]

  ASAS is composed of four domains. To achieve an ASAS20 response required improvement of ≥20% and ≥ 1 unit (10 mm) in at least 3 domains and no worsening of ≥ 20 % and ≥ 1 unit (10 mm) in the remaining domain. -The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). -The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. -The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values. -The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Percentage of Participants Who Achieved a Value <2 in Each of the 4 ASAS Parameters at Week 12 [Time Frame: Week 12] [Designated as safety issue: No]

  Assessment in Ankylosing Spondylitis (ASAS) is composed of four domains. • The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). • The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. • The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI), the mean of 10 self-assessment questions on a 100 mm VAS. • The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Each of the above 4 domains are measured on a scale from 0-100 mm, but reported on a 0-10 cm scale. A score of less than 2 units (20 mm) in each domain is defined as partial remission.

- Percentage of Participants Achieving a 40% Improvement in Assessment in Ankylosing Spondylitis (ASAS40) at Week 12 [Time Frame: Baseline and Week 12] [Designated as safety issue: No]
  ASAS is composed of four domains. To achieve an ASAS40 response required improvement of ≥40% and ≥ 2 units (20 mm) in at least 3 domains and no worsening at all in the remaining domain. • The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). • The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. • The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values. • The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Part 2: Percentage of Participants Achieving a 40% Improvement in Assessment in Ankylosing Spondylitis (ASAS40) at Week 24 [Time Frame: Baseline and Week 24] [Designated as safety issue: No]
  ASAS is composed of four domains. To achieve an ASAS40 response required improvement of ≥40% and ≥ 2 units (20 mm) in at least 3 domains and no worsening at all in the remaining domain. • The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). • The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. • The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values. • The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Change From Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [Time Frame: Baseline and Week 12] [Designated as safety issue: No]
  The BASDAI is a patient-administered assessment of 6 parameters specific to AS. The following parameters were assessed on a 100-mm horizontal visual analogue: fatigue, spinal pain, peripheral arthritis, enthesitis, intensity of morning stiffness, and duration of morning stiffness. For questions 1 to 5, the left-hand extreme of the line (0) represents "none" (symptom-free) and the right-hand extreme (100) represents "very severe" (maximum severity). For question 6, a time axis was used, with the left-hand extreme of the line representing "0 hours" and the right-hand extreme representing "2 or more hours". The BASDAI score was calculated as follows: BASDAI = [Q1 + Q2 + Q3 + Q4 + (Q5 + Q6)/2]/5. The total score is tabulated on a scale from 0 (best) to 10 cm (worst).
- Change From Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) [Time Frame: Baseline and Week 12] [Designated as safety issue: No]
  The Bath Ankylosing Spondylitis Functional Index (BASFI) is an assessment of function in AS patients. The participant provides their assessment of their ability to perform 10 activities on a 100 mm horizontal visual analog scale (VAS) ranging from 0 (easy) to 100 (impossible). The BASFI score is the mean of these values and is tabulated on a 0 (best) to 10 (worst) cm scale.
- Change From Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) [Time Frame: Baseline and Week 12] [Designated as safety issue: No]
  The Bath Ankylosing Spondylitis Metrology Index linear function is a combined index of 5 clinical measurements (performed by the Joint Assessor) which reflect axial mobility in the AS patient. The measurements to assess mobility are: 1. Tragus-to-wall; 2. Modified Schober (lumbar flexion); 3. Cervical rotation; 4. Lateral spinal flexion; 5. Intermalleolar distance. The BASMI linear result is the average of the 5 assessments and ranges from 0 to 10. The higher the BASMI score the more severe the patient's limitation of movement due to their AS.
- Change From Baseline in C-Reactive Protein [Time Frame: Baseline and Week 12] [Designated as safety issue: No]
  Levels of C-reactive protein (CRP) were measured from blood samples taken at Baseline and at Week 12.
- Part 2: Area Under the Plasma Concentration Versus Time Curve of Tocilizumab [Time Frame: Week 12, pre-dose and at the end of infusion, on the 2nd and 7th day of Week 12, 14 days post-dose (Week 14) and 28 days post-dose (pre-dose of Week 16 infusion).] [Designated as safety issue: No]
  Area under the plasma concentration versus time curve (AUC) of tocilizumab at steady state after 12 weeks of treatment.
- Part 2: Peak Plasma Concentration of Tocilizumab [Time Frame: Week 12, pre-dose and at the end of infusion, on the 2nd and 7th day of Week 12, 14 days post-dose (Week 14) and 28 days post-dose (pre-dose of Week 16 infusion).] [Designated as safety issue: No]
  The peak plasma concentration (Cmax) of tocilizumab at steady state after 12 weeks of treatment.
- Part 2: Elimination Half-life of Tocilizumab [Time Frame: Week 12, pre-dose and at the end of infusion, on the 2nd and 7th day of Week 12, 14 days post-dose (Week 14) and 28 days post-dose (pre-dose of Week 16 infusion).] [Designated as safety issue: No]

Elimination half-life of tocilizumab at steady state after 12 weeks of treatment.

- Part 2: Clearance of Tocilizumab [Time Frame: Week 12, pre-dose and at the end of infusion, on the 2nd and 7th day of Week 12, 14 days post-dose (Week 14) and 28 days post-dose (pre-dose of Week 16 infusion).] [Designated as safety issue: No]
  Clearance of tocilizumab at steady state after 12 weeks of treatment.
- Part 2: Volume of Distribution of Tocilizumab [Time Frame: Week 12, pre-dose and at the end of infusion, on the 2nd and 7th day of Week 12, 14 days post-dose (Week 14) and 28 days post-dose (pre-dose of Week 16 infusion).] [Designated as safety issue: No]
  Volume of distribution of tocilizumab at steady state after 12 weeks of treatment.
- Change From Baseline in the Level of Interleukin-6 [Time Frame: Baseline and Week 12] [Designated as safety issue: No]
  Interleukin-6 levels were measured from blood samples taken pre-dose at Baseline and after 12 weeks of treatment. The analysis was not performed for participants in Part 2 due to premature study termination.
- Change From Baseline in Level of Soluble Interleukin-6 Receptor [Time Frame: Baseline and Week 12] [Designated as safety issue: No]
  Soluble Interleukin-6 receptor levels were measured from blood samples taken pre-dose at Baseline and after 12 weeks of treatment. The analysis was not performed for participants in Part 2 due to premature study termination.
- Number of Participants With Anti-tocilizumab Antibodies [Time Frame: From Baseline until end of study (a maximum treatment duration of 40 weeks).] [Designated as safety issue: No]
  A positive anti-tocilizumab antibody result was defined as a negative assay result at Baseline and a positive post-baseline screening assay with positive confirmation or neutralizing assay at the same visit.
- Part 2: Radiographic Change According to the Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [Time Frame: Baseline and Week 104] [Designated as safety issue: No]
  Radiographs were to be assessed using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). The mSASSS is a four-point scoring system for lateral radiographs of the lumbar and cervical spine and has been shown to reliably track disease progression over time, where: *0 = No abnormality; *1 = Erosion, sclerosis, or squaring; *2 = Syndesmophyte; *3 = Total bony bridging at each site.
- Part 2: Percentage of Participants With a Reduction of Magnetic Resonance Imaging (MRI) Proven Spinal Inflammation [Time Frame: Baseline and Week 24] [Designated as safety issue: No]
  Magentic resonance imaging of the axial skeleton was to be performed at Baseline and Week 24. MRI scans will be evaluated using the ankylosing spondylitis spinal MRI activity (ASspiMRI-a) score, grading activity (0-6) per vertebral unit in 23 units.
- Part 1: The Number of Participants With Adverse Events [Time Frame: Up to 40 weeks] [Designated as safety issue: No]
  A serious adverse event (AE) is any event that is fatal, life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant or requires intervention to prevent one or other of the outcomes listed above. The intensity of each AE was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.02. A severe AE was any event of Grade 4 (life-threatening consequences; urgent intervention indicated) or 5 (death related to AE).

Enrollment: 306
Study Start Date: September 2010
Primary Completion Date: May 2011
Study Completion Date: December 2011

Arms	Assigned Interventions
Placebo Comparator: Part 1: Placebo Participants received intravenous infusions of placebo once every 4 weeks until Week 12. Following the Week 12 visit, participants who completed Part 1	Drug: Placebo Placebo to tocilizumab administered intravenously every 4 weeks

Arms	Assigned Interventions
of the study received open-label 8 mg/kg tocilizumab through Week 208.	
Experimental: Part 1: Tocilizumab Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants who completed Part 1 of the study received open-label 8 mg/kg tocilizumab through Week 208.	Biological/Vaccine: tocilizumab Administered intravenously (iv) every 4 weeks Other Names: RoActemra/Actemra
Placebo Comparator: Part 2: Placebo Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were, at the investigator's discretion, eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase, however the study was terminated prior to any participants reaching this stage.	Drug: Placebo Placebo to tocilizumab administered intravenously every 4 weeks
Experimental: Part 2: Tocilizumab 4 mg/kg Participants received intravenous infusions of 4 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were, at the investigator's discretion, eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive	Biological/Vaccine: tocilizumab Administered intravenously (iv) every 4 weeks Other Names: RoActemra/Actemra

Arms	Assigned Interventions
tocilizumab 8 mg/kg in the common open-label extension phase, however the study was terminated prior to any participants reaching this stage.	
Experimental: Part 2: Tocilizumab 8 mg/kg Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were, at the investigator's discretion, eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase, however the study was terminated prior to any participants reaching this stage.	Biological/Vaccine: tocilizumab Administered intravenously (iv) every 4 weeks Other Names: RoActemra/Actemra

Detailed Description:

This study was planned as a Phase II/III seamless, multicenter, randomized, double-blind, placebo-controlled study in patients with AS who were naïve to TNF antagonist therapy. The study consisted of 2 parts, each preceded by a screening visit and followed by a common open-label extension phase. Recruitment into Part 2 commenced after completion of enrollment for Part 1.

Part 1 was designed as a Phase II study exploring the efficacy and safety of tocilizumab therapy versus placebo. Part 1 was intended to determine whether Part 2 of the study would continue, based on a Week 12 analysis.

Part 2 was designed to provide pivotal Phase III efficacy and safety data for tocilizumab in patients with AS. Approximately 400 patients were to be enrolled. Once randomization into Part 1 was complete, randomization into Part 2 of the study was to be initiated.

Based on the results of the Week 12 Part 1 analyses of the primary endpoint (ASAS20) and secondary endpoints, and in consideration of all available safety data, a benefit/risk assessment was made and it was decided to halt the study because of lack of overall efficacy. Most patients did not complete the 24-week double-blind treatment period in Part 2.

Eligibility

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

Criteria

Inclusion Criteria

- Adult patients, ≥ 18 years of age
- Ankylosing Spondylitis as defined by the modified New York criteria for ≥ 3 months prior to baseline
- Active disease at screening and baseline (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥4.0, spinal pain visual analog scale [VAS] ≥40)
- Inadequate response or intolerant to 1 or more previous non-steroidal anti-inflammatory drugs (NSAIDs)
- Traditional disease-modifying anti-rheumatic drugs (DMARDs) must be withdrawn for at least 4 weeks prior to baseline (methotrexate, sulfasalazine and hydroxychloroquine or chloroquine may be allowed if at stable dose for at least 4 weeks prior to baseline)
- Oral corticosteroids (≥ 10 mg/day prednisone or equivalent) and NSAIDs/COX-2 inhibitors must be at stable dose for at least 4 weeks prior to baseline

Exclusion Criteria:

- Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months after randomization
- Total ankylosis of spine (as determined by investigator)
- Inflammatory rheumatic disease other than ankylosing spondylitis
- Active, acute uveitis at baseline
- Treatment with tumor necrosis factor (TNF) antagonist therapy at any time prior to baseline
- Intra-articular or tendon injections or parenteral corticosteroids within 4 weeks prior to screening
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- Active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infection
- History of or currently active primary or secondary immunodeficiency
- Body weight > 150 kg

Contacts and Locations

Locations

United States, California
Huntington Beach, California, United States, 92646
United States, Florida
Aventura, Florida, United States, 33180
Orlando, Florida, United States, 32804
United States, Georgia
Atlanta, Georgia, United States, 30342
Decatur, Georgia, United States, 30033
Marietta, Georgia, United States, 30060
United States, Idaho
Idaho Falls, Idaho, United States, 83404
United States, Kansas
Wichita, Kansas, United States, 67207
United States, Maryland
Cumberland, Maryland, United States, 21502
United States, Michigan
St. Claire Shores, Michigan, United States, 48081
United States, North Carolina

Charlotte, North Carolina, United States, 28210
Greensboro, North Carolina, United States, 27408
United States, Pennsylvania
Duncansville, Pennsylvania, United States, 16635
United States, South Carolina
Hickory, South Carolina, United States, 28602
United States, Texas
Houston, Texas, United States, 77004
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Heidelberg, Australia, 3084
Hobart, Australia, 7000
Malvern East, Australia, 3145
Maroochydore, Australia, 4558
Sydney, Australia, 2050
Woodville, Australia, 5011
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Bruxelles, Belgium, 1200
Kortrijk, Belgium, 8500
Liege, Belgium, 4000
Yvoir, Belgium, 5530
Brazil
Cuiabá, Brazil, 78025-000
Goiania, Brazil, 74110-120
Sao Paulo, Brazil, 04026-000
Sao Paulo, Brazil, 04039-000
São Paulo, Brazil, 04266-010
Bulgaria
Plovdiv, Bulgaria, 4002
Plovdiv, Bulgaria, 4003
Ruse, Bulgaria, 7002
Sevlievo, Bulgaria, 5400
Sofia, Bulgaria, 1606
Sofia, Bulgaria, 1612
Sofia, Bulgaria, 1233
Sofia, Bulgaria, 1709
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Calgary, Alberta, Canada, T2N 2T9
Canada, Manitoba
Winnipeg, Manitoba, Canada, R3A 1M3
Canada, Newfoundland and Labrador
St John's, Newfoundland and Labrador, Canada, A1C 5B8
Canada, Ontario
Kitchener, Ontario, Canada, N2M 5N6
Mississauga, Ontario, Canada, L5M 2V8

St. Catharines, Ontario, Canada, L2N 7E4
Toronto, Ontario, Canada, M9W 6V1

Canada, Quebec

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Krakow, Poland, 30-119
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Lublin, Poland, 20-607
Poznan, Poland, 60-218
Torun, Poland, 87-100
Warszawa, Poland, 00-909
Warszawa, Poland, 02-256
Warszawa, Poland, 00-235
Wroclaw, Poland, 51-124

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Cape Town, South Africa, 8001
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Pretoria, South Africa, 0184
Pretoria, South Africa, 0002
Pretoria, South Africa, 0084
Stellenbosch, South Africa, 7600

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Córdoba, Spain, 14004
La Coruna, Spain, 15006
Lugo, Spain, 27004
Madrid, Spain, 28009
Madrid, Spain, 28046
Madrid, Spain, 28222
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Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	NA22823 2009-017443-34
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Pre-Assignment Details	In Part 1, patients were randomized in a 1:1 ratio to placebo or tocilizumab (TCZ) 8 mg/kg. In Part 2, patients were randomized in a 2:1:1 ratio to TCZ 8 mg/kg, TCZ 4 mg/kg, or placebo, respectively. Due to the early stopping of the study and limitations in available data the TCZ dose groups in Part 2 were combined.

Reporting Groups

	Description
Part 1: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Overall Study

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	Part 2: Tocilizumab
Started	51	51	51	153
Treated	51	51	51	152
Escape or Switched to Tocilizumab	51	0	6	0
Completed 12 Weeks Treatment	50	48	12	59
Completed 24 Weeks Treatment	19	28	3	10
Completed	0	0	0	0
Not Completed	51	51	51	153

Baseline Characteristics

Reporting Groups

	Description
Combined Placebo	Participants in Part 1 and Part 2 who received intravenous infusions of placebo once every 4 weeks.

	Description
Combined Tocilizumab	Participants randomized in Part 1 and Part 2 to receive intravenous infusions of 4 mg/kg (in Part 2 only) or 8 mg/kg tocilizumab once every 4 weeks.

Baseline Measures

	Combined Placebo	Combined Tocilizumab	Total
Number of Participants	102	203	305
Age, Continuous [1] [units: years] Mean (Standard Deviation)	41.2 (11.33)	40.4 (11.42)	40.7 (11.38)
Gender, Male/Female [units: participants]			
Female	29	53	82
Male	73	150	223
Age - Part 1 population [2] [units: years] Mean (Standard Deviation)	42.7 (12.64)	41.6 (11.22)	42.1 (11.91)
Gender - Part 1 Population [2] [units: participants]			
Female	11	15	26
Male	40	36	76

[1] Demographic data are provided for all participants who received at least one tocilizumab/placebo infusion.

[2] Demographic data for the Part 1 population: Placebo = 51 participants, Tocilizumab = 51 participants, total = 102 participants.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Part 1: Percentage of Participants Achieving a 20% Improvement in Assessment in Ankylosing Spondylitis (ASAS20) at Week 12

Measure Description	ASAS is composed of four domains. To achieve an ASAS20 response required improvement of ≥20% and ≥ 1 unit (10 mm) in at least 3 domains and no worsening of ≥ 20 % and ≥ 1 unit (10 mm) in the remaining domain. • The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). • The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. • The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values. • The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
Time Frame	Baseline and Week 12
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) population included all patients who were randomized into the study and received at least one tocilizumab/placebo infusion.

If the response at the 12-week visit could not be determined due to early withdrawal or missing data then the patient was considered a non-responder.

Reporting Groups

	Description
Part 1: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 12.
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12.

Measured Values

	Part 1: Placebo	Part 1: Tocilizumab
Number of Participants Analyzed	51	51
Part 1: Percentage of Participants Achieving a 20% Improvement in Assessment in Ankylosing Spondylitis (ASAS20) at Week 12 [units: percentage of participants]	27.5	37.3

2. Primary Outcome Measure:

Measure Title	Part 2: Percentage of Participants Achieving a 20% Improvement in Assessment in Ankylosing Spondylitis (ASAS20) at Week 12

Measure Description	ASAS is composed of four domains. To achieve an ASAS20 response required improvement of ≥20% and ≥ 1 unit (10 mm) in at least 3 domains and no worsening of ≥ 20 % and ≥ 1 unit (10 mm) in the remaining domain. • The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). • The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. • The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values. • The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
Time Frame	Baseline and Week 12
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) population. The analysis only includes assessments while the patient was receiving double blind medication, and occurred prior to both withdrawal and the 15 July 2011 (date at which all patients were unblinded). Patients who withdrew or escaped are considered as non-responders until week 24.

Reporting Groups

	Description
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks.

Measured Values

	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	51	119
Part 2: Percentage of Participants Achieving a 20% Improvement in Assessment in Ankylosing Spondylitis (ASAS20) at Week 12 [units: percentage of participants]	7.8	9.2

3. Secondary Outcome Measure:

Measure Title	Part 2: Percentage of Participants Achieving a 20% Improvement in Assessment in Ankylosing Spondylitis (ASAS20) at Week 24

Measure Description	ASAS is composed of four domains. To achieve an ASAS20 response required improvement of ≥20% and ≥ 1 unit (10 mm) in at least 3 domains and no worsening of ≥ 20 % and ≥ 1 unit (10 mm) in the remaining domain. • The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). • The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. • The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values. • The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
Time Frame	Baseline and Week 24
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) population. The analysis only includes assessments while the patient was receiving double blind medication, and occurred prior to both withdrawal and the 15 July 2011 (date at which all patients were unblinded). Patients who withdrew or escaped are considered as non-responders until week 24.

Reporting Groups

	Description
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks.

Measured Values

	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	49	101
Part 2: Percentage of Participants Achieving a 20% Improvement in Assessment in Ankylosing Spondylitis (ASAS20) at Week 24 [units: percentage of participants]	0.0	0.0

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Achieved a Value <2 in Each of the 4 ASAS Parameters at Week 12

Measure Description	Assessment in Ankylosing Spondylitis (ASAS) is composed of four domains. • The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). • The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. • The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI), the mean of 10 self-assessment questions on a 100 mm VAS. • The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Each of the above 4 domains are measured on a scale from 0-100 mm, but reported on a 0-10 cm scale. A score of less than 2 units (20 mm) in each domain is defined as partial remission.
Time Frame	Week 12
Safety Issue?	No

Analysis Population Description

Intent-to-treat. If the response at the Week 12 visit could not be determined due to early withdrawal or missing data then the patient is considered a non-responder. The analysis was not performed for participants in Part 2 due to premature study termination.

Reporting Groups

	Description
Part 1: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	51	51	0	0
Percentage of Participants Who Achieved a Value <2 in Each of the 4 ASAS Parameters at Week 12 [units: percentage of participants]	2.0	0.0		

5. Secondary Outcome Measure:

Measure Title	Percentage of Participants Achieving a 40% Improvement in Assessment in Ankylosing Spondylitis (ASAS40) at Week 12
Measure Description	ASAS is composed of four domains. To achieve an ASAS40 response required improvement of ≥40% and ≥ 2 units (20 mm) in at least 3 domains and no worsening at all in the remaining domain. • The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). • The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. • The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values. • The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
Time Frame	Baseline and Week 12
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) population. If the response at the Week 12 visit could not be determined due to early withdrawal or missing data then the patient is considered a non-responder. The analysis was not performed for participants in Part 2 due to premature study termination.

Reporting Groups

	Description
Part 1: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.

	Description
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	51	51	0	0
Percentage of Participants Achieving a 40% Improvement in Assessment in Ankylosing Spondylitis (ASAS40) at Week 12 [units: percentage of participants]	19.6	11.8		

6. Secondary Outcome Measure:

Measure Title	Part 2: Percentage of Participants Achieving a 40% Improvement in Assessment in Ankylosing Spondylitis (ASAS40) at Week 24
Measure Description	ASAS is composed of four domains. To achieve an ASAS40 response required improvement of ≥40% and ≥ 2 units (20 mm) in at least 3 domains and no worsening at all in the remaining domain. • The patient's global assessment of current disease status, measured on a 100 mm visual analog scale (VAS), from symptom-free / no AS symptoms (0) to maximum AS disease severity (100). • The patient's overall assessment of the severity of spinal pain based on responses to 2 questions assessed on a 100 mm VAS, from no pain (0) to most severe pain (100). The spinal pain score is the mean of these 2 questions. • The function component was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values. • The inflammation component of the ASAS was determined by the mean of questions 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
Time Frame	Baseline and Week 24
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT), Part 2 study population. This analysis was not performed due to premature study termination.

Reporting Groups

	Description
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

7. Secondary Outcome Measure:

Measure Title	Change From Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
Measure Description	The BASDAI is a patient-administered assessment of 6 parameters specific to AS. The following parameters were assessed on a 100-mm horizontal visual analogue: fatigue, spinal pain, peripheral arthritis, enthesitis, intensity of morning stiffness, and duration of morning stiffness. For questions 1 to 5, the left-hand extreme of the line (0) represents "none" (symptom-free) and the right-hand extreme (100) represents "very severe" (maximum severity). For question 6, a time axis was used, with the left-hand extreme of the line representing "0 hours" and the right-hand extreme representing "2 or more hours". The BASDAI score was calculated as follows: BASDAI = [Q1 + Q2 + Q3 + Q4 + (Q5 + Q6)/2]/5. The total score is tabulated on a scale from 0 (best) to 10 cm (worst).
Time Frame	Baseline and Week 12
Safety Issue?	No

Analysis Population Description

Intent-to-treat population where data were available.

Reporting Groups

	Description
Part 1: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	51	51	51	152
Change From Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [units: cm] Mean (Standard Deviation)				
Baseline [N=51, 51, 51, 152]	6.77 (1.322)	6.62 (1.327)	6.86 (1.506)	6.41 (1.527)
Week 12 [N=51, 48, 20, 53]	5.65 (2.042)	5.64 (1.833)	6.20 (1.900)	5.39 (2.183)
Change from Baseline [N=51, 48, 20, 53]	-1.12 (1.991)	-1.02 (1.813)	-0.53 (1.637)	-1.17 (1.919)

8. Secondary Outcome Measure:

Measure Title	Change From Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI)

Measure Description	The Bath Ankylosing Spondylitis Functional Index (BASFI) is an assessment of function in AS patients. The participant provides their assessment of their ability to perform 10 activities on a 100 mm horizontal visual analog scale (VAS) ranging from 0 (easy) to 100 (impossible). The BASFI score is the mean of these values and is tabulated on a 0 (best) to 10 (worst) cm scale.
Time Frame	Baseline and Week 12
Safety Issue?	No

Analysis Population Description

Intent-to-treat population for whom data were available. The analysis was not performed for participants in Part 2.

Reporting Groups

	Description
Part 1: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	51	51	0	0
Change From Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) [units: cm] Mean (Standard Deviation)				
Baseline [N=51,51]	5.60 (2.071)	6.24 (2.069)		
Week 12 [N=51, 48]	4.84 (2.257)	5.55 (2.004)		

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	Part 2: Tocilizumab
Change from Baseline [N=51, 48]	-0.76 (1.660)	-0.73 (1.736)		

9. Secondary Outcome Measure:

Measure Title	Change From Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI)
Measure Description	The Bath Ankylosing Spondylitis Metrology Index linear function is a combined index of 5 clinical measurements (performed by the Joint Assessor) which reflect axial mobility in the AS patient. The measurements to assess mobility are: 1. Tragus-to-wall; 2. Modified Schober (lumbar flexion); 3. Cervical rotation; 4. Lateral spinal flexion; 5. Intermalleolar distance. The BASMI linear result is the average of the 5 assessments and ranges from 0 to 10. The higher the BASMI score the more severe the patient's limitation of movement due to their AS.
Time Frame	Baseline and Week 12
Safety Issue?	No

Analysis Population Description

Intent-to-treat population where data were available. The analysis was not performed for participants in Part 2 due to premature study termination.

Reporting Groups

	Description
Part 1: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

	Description
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	51	51	0	0
Change From Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) [units: scores on a scale] Mean (Standard Deviation)				
Baseline [N=50, 47]	4.35 (1.604)	4.58 (1.772)		
Week 12 [N=50, 47]	4.29 (1.682)	4.40 (1.943)		
Change from Baseline [N=50, 46]	-0.06 (0.832)	-0.21 (1.197)		

10. Secondary Outcome Measure:

Measure Title	Change From Baseline in C-Reactive Protein
Measure Description	Levels of C-reactive protein (CRP) were measured from blood samples taken at Baseline and at Week 12.
Time Frame	Baseline and Week 12
Safety Issue?	No

Analysis Population Description

Intent-to-treat population where data were available. The analysis was not performed for participants in Part 2 due to premature study termination.

Reporting Groups

	Description
Part 1: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.

	Description
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	51	51	0	0
Change From Baseline in C-Reactive Protein [units: mg/dL] Mean (Standard Deviation)				
Baseline [N=51, 51]	1.75 (1.850)	1.62 (2.248)		
Week 12 [N=50, 48]	1.58 (1.733)	0.36 (1.008)		
Change from Baseline [N=50, 48]	-0.17 (1.005)	-1.34 (2.442)		

11. Secondary Outcome Measure:

Measure Title	Part 2: Area Under the Plasma Concentration Versus Time Curve of Tocilizumab
Measure Description	Area under the plasma concentration versus time curve (AUC) of tocilizumab at steady state after 12 weeks of treatment.
Time Frame	Week 12, pre-dose and at the end of infusion, on the 2nd and 7th day of Week 12, 14 days post-dose (Week 14) and 28 days post-dose (pre-dose of Week 16 infusion).
Safety Issue?	No

Analysis Population Description

Due to premature study termination pharmacokinetic parameters were not analyzed.

Reporting Groups

	Description
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 2: Tocilizumab
Number of Participants Analyzed	0

No data displayed because Outcome Measure has zero total participants analyzed.

12. Secondary Outcome Measure:

Measure Title	Part 2: Peak Plasma Concentration of Tocilizumab
Measure Description	The peak plasma concentration (Cmax) of tocilizumab at steady state after 12 weeks of treatment.
Time Frame	Week 12, pre-dose and at the end of infusion, on the 2nd and 7th day of Week 12, 14 days post-dose (Week 14) and 28 days post-dose (pre-dose of Week 16 infusion).
Safety Issue?	No

Analysis Population Description

Due to premature study termination pharmacokinetic parameters were not analyzed.

Reporting Groups

	Description
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 2: Tocilizumab
Number of Participants Analyzed	0

No data displayed because Outcome Measure has zero total participants analyzed.

13. Secondary Outcome Measure:

Measure Title	Part 2: Elimination Half-life of Tocilizumab
Measure Description	Elimination half-life of tocilizumab at steady state after 12 weeks of treatment.
Time Frame	Week 12, pre-dose and at the end of infusion, on the 2nd and 7th day of Week 12, 14 days post-dose (Week 14) and 28 days post-dose (pre-dose of Week 16 infusion).
Safety Issue?	No

Analysis Population Description

Due to premature study termination pharmacokinetic parameters were not analyzed.

Reporting Groups

	Description
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 2: Tocilizumab
Number of Participants Analyzed	0

No data displayed because Outcome Measure has zero total participants analyzed.

14. Secondary Outcome Measure:

Measure Title	Part 2: Clearance of Tocilizumab
Measure Description	Clearance of tocilizumab at steady state after 12 weeks of treatment.
Time Frame	Week 12, pre-dose and at the end of infusion, on the 2nd and 7th day of Week 12, 14 days post-dose (Week 14) and 28 days post-dose (pre-dose of Week 16 infusion).
Safety Issue?	No

Analysis Population Description

Due to premature study termination pharmacokinetic parameters were not analyzed.

Reporting Groups

	Description
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 2: Tocilizumab
Number of Participants Analyzed	0

No data displayed because Outcome Measure has zero total participants analyzed.

15. Secondary Outcome Measure:

Measure Title	Part 2: Volume of Distribution of Tocilizumab
Measure Description	Volume of distribution of tocilizumab at steady state after 12 weeks of treatment.
Time Frame	Week 12, pre-dose and at the end of infusion, on the 2nd and 7th day of Week 12, 14 days post-dose (Week 14) and 28 days post-dose (pre-dose of Week 16 infusion).
Safety Issue?	No

Analysis Population Description

Due to premature study termination pharmacokinetic parameters were not analyzed.

Reporting Groups

	Description
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 2: Tocilizumab
Number of Participants Analyzed	0

No data displayed because Outcome Measure has zero total participants analyzed.

16. Secondary Outcome Measure:

Measure Title	Change From Baseline in the Level of Interleukin-6
Measure Description	Interleukin-6 levels were measured from blood samples taken pre-dose at Baseline and after 12 weeks of treatment. The analysis was not performed for participants in Part 2 due to premature study termination.
Time Frame	Baseline and Week 12
Safety Issue?	No

Analysis Population Description

Pharmacokinetic (PK) Population: All patients who received at least one tocilizumab infusion and had at least one PK and pharmacodynamic sample. Only patients with available data at each time point are included (indicated by N). Patients who did not receive their Week 8 dose were excluded.

Reporting Groups

	Description
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 1: Tocilizumab	Part 2: Tocilizumab
Number of Participants Analyzed	44	0
Change From Baseline in the Level of Interleukin-6 [units: pg/mL] Mean (Standard Deviation)		
Baseline [N=41]	10 (11.8)	
Week 12 [N=40]	78 (61.5)	
Change from Baseline [N=37]	67 (58.3)	

17. Secondary Outcome Measure:

Measure Title	Change From Baseline in Level of Soluble Interleukin-6 Receptor
Measure Description	Soluble Interleukin-6 receptor levels were measured from blood samples taken pre-dose at Baseline and after 12 weeks of treatment. The analysis was not performed for participants in Part 2 due to premature study termination.
Time Frame	Baseline and Week 12
Safety Issue?	No

Analysis Population Description

Pharmacokinetic Population: All patients who received at least one tocilizumab infusion and had at least one pharmacokinetic and pharmacodynamic sample. Only those patients with available data at each time point are included in the analysis (indicated by N). Patients who did not receive their week 8 dose were excluded.

Reporting Groups

	Description
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 1: Tocilizumab	Part 2: Tocilizumab
Number of Participants Analyzed	44	0
Change From Baseline in Level of Soluble Interleukin-6 Receptor [units: ng/mL] Mean (Standard Deviation)		
Baseline [N=41]	42 (11.5)	
Week 12 [N=40]	536 (173.1)	
Change from Baseline [N=37]	496 (173.9)	

18. Secondary Outcome Measure:

Measure Title	Number of Participants With Anti-tocilizumab Antibodies
Measure Description	A positive anti-tocilizumab antibody result was defined as a negative assay result at Baseline and a positive post-baseline screening assay with positive confirmation or neutralizing assay at the same visit.
Time Frame	From Baseline until end of study (a maximum treatment duration of 40 weeks).
Safety Issue?	No

Analysis Population Description

All patients treated with tocilizumab and screened for anti-tocilizumab antibodies at any timepoint.

Reporting Groups

	Description
All Tocilizumab	Participants who received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks in either Part 1 or Part 2, including participants randomized to placebo who switched or escaped to tocilizumab treatment.

Measured Values

	All Tocilizumab
Number of Participants Analyzed	257
Number of Participants With Anti-tocilizumab Antibodies [units: participants]	4

19. Secondary Outcome Measure:

Measure Title	Part 2: Radiographic Change According to the Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS)
Measure Description	Radiographs were to be assessed using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). The mSASSS is a four-point scoring system for lateral radiographs of the lumbar and cervical spine and has been shown to reliably track disease progression over time, where: • 0 = No abnormality; • 1 = Erosion, sclerosis, or squaring; • 2 = Syndesmophyte; • 3 = Total bony bridging at each site.
Time Frame	Baseline and Week 104
Safety Issue?	No

Analysis Population Description

This outcome measure was not analyzed due to premature study termination.

Reporting Groups

	Description
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

20. Secondary Outcome Measure:

Measure Title	Part 2: Percentage of Participants With a Reduction of Magnetic Resonance Imaging (MRI) Proven Spinal Inflammation
Measure Description	Magentic resonance imaging of the axial skeleton was to be performed at Baseline and Week 24. MRI scans will be evaluated using the ankylosing spondylitis spinal MRI activity (ASspiMRI-a) score, grading activity (0-6) per vertebral unit in 23 units.
Time Frame	Baseline and Week 24
Safety Issue?	No

Analysis Population Description

Due to premature study termination this outcome measure was not analyzed.

Reporting Groups

	Description
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 24. Participants who did not attain an ASsessment in Ankylosing Spondylitis-20 (ASAS20) response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.
Part 2: Tocilizumab	Participants received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks until Week 24. Participants who did not attain an ASAS20 response at Week 16 were eligible to receive open-label escape therapy consisting of 8 mg/kg tocilizumab. After Week 24, participants were to receive open-label treatment with 8 mg/kg tocilizumab every 4 weeks until Week 104. At the completion of Week 104, all Part 2 participants were to receive tocilizumab 8 mg/kg in the common open-label extension phase.

Measured Values

	Part 2: Placebo	Part 2: Tocilizumab
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

21. Secondary Outcome Measure:

Measure Title	Part 1: The Number of Participants With Adverse Events
Measure Description	A serious adverse event (AE) is any event that is fatal, life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/ birth defect or is medically significant or requires intervention to prevent one or other of the outcomes listed above. The intensity of each AE was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.02. A severe AE was any event of Grade 4 (life-threatening consequences; urgent intervention indicated) or 5 (death related to AE).
Time Frame	Up to 40 weeks
Safety Issue?	No

Analysis Population Description

The safety analysis population included all patients who received at least one tocilizumab/placebo infusion and had at least one postdose safety assessment. Patients were assigned to treatment groups as treated for analysis.

Reporting Groups

	Description
Part 1: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.

Measured Values

	Part 1: Placebo	Part 1: Tocilizumab
Number of Participants Analyzed	51	51
Part 1: The Number of Participants With Adverse Events [units: participants]		
Any adverse event	27	30
Serious adverse event	0	2
Death	0	0
Withdrawals due to AE	0	0
Severe AE	0	0

Reported Adverse Events

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

Reporting Groups

	Description
Part 1: Placebo	Participants received intravenous infusions of placebo once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.

	Description
Part 1: Tocilizumab	Participants received intravenous infusions of 8 mg/kg tocilizumab once every 4 weeks until Week 12. Following the Week 12 visit, participants were to receive open-label 8 mg/kg tocilizumab through Week 208 in the common open-label extension phase.
Part 2: Placebo	Participants received intravenous infusions of placebo once every 4 weeks. AEs reported only until participants escaped or switched to tocilizumab.
All Tocilizumab	Participants who received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks in either Part 1 or Part 2. This group includes participants randomized to placebo who switched or escaped to tocilizumab treatment for whom adverse events are reported after the start of treatment with tocilizumab.

Serious Adverse Events

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	All Tocilizumab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	0/51 (0%)	2/51 (3.92%)	0/51 (0%)	11/260 (4.23%)
Eye disorders				
Iridocyclitis [A] †	0/51 (0%)	1/51 (1.96%)	0/51 (0%)	1/260 (0.38%)
Gastrointestinal disorders				
Duodenal ulcer perforation [A] †	0/51 (0%)	0/51 (0%)	0/51 (0%)	1/260 (0.38%)
Intestinal obstruction [A] †	0/51 (0%)	0/51 (0%)	0/51 (0%)	1/260 (0.38%)
Hepatobiliary disorders				
Cholecystitis [A] †	0/51 (0%)	1/51 (1.96%)	0/51 (0%)	1/260 (0.38%)
Immune system disorders				
Anaphylactic reaction [A] †	0/51 (0%)	0/51 (0%)	0/51 (0%)	2/260 (0.77%)
Hypersensitivity [A] †	0/51 (0%)	0/51 (0%)	0/51 (0%)	1/260 (0.38%)
Infections and infestations				
Bursitis infective staphylococcal [A] †	0/51 (0%)	0/51 (0%)	0/51 (0%)	1/260 (0.38%)
Musculoskeletal and connective tissue disorders				
Ankylosing spondylitis [A] †	0/51 (0%)	0/51 (0%)	0/51 (0%)	1/260 (0.38%)
Osteoarthritis [A] †	0/51 (0%)	0/51 (0%)	0/51 (0%)	1/260 (0.38%)

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	All Tocilizumab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Renal and urinary disorders				
Nephrolithiasis [A] †	0/51 (0%)	0/51 (0%)	0/51 (0%)	1/260 (0.38%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 14.0

Other Adverse Events

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

	Part 1: Placebo	Part 1: Tocilizumab	Part 2: Placebo	All Tocilizumab
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	1/51 (1.96%)	3/51 (5.88%)	1/51 (1.96%)	8/260 (3.08%)
Vascular disorders				
Hypertension [A] †	1/51 (1.96%)	3/51 (5.88%)	1/51 (1.96%)	8/260 (3.08%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 14.0

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

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

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

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

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