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A Long-term Extension Study of Tocilizumab (Myeloma Receptor Antibody [MRA]) in Patients With Rheumatoid Arthritis

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT00721123

Purpose

This open-label, international multi-center extension study WA18695 was designed to assess the long term safety of tocilizumab in patients who had moderate to severe active rheumatoid arthritis (RA). Patients enrolled in the WA18695 study had previously received treatment in the 24-week, placebo-controlled, Phase III Study WA17822. Eligible patients were assigned to treatment with 8 mg/kg tocilizumab every 4 weeks for a maximum of 5 years.

Condition	Intervention	Phase
Rheumatoid Arthritis	Drug: Tocilizumab	Phase 3

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, N/A, Safety/Efficacy Study
Official Title: Long-term Extension Study of Safety During Treatment With Tocilizumab (MRA) in Patients Completing Treatment in WA17822

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Adverse Event (AE) Summary Over Time [Time Frame: through 264 Weeks] [Designated as safety issue: No]

The number of participants experiencing at least one adverse event (AE) is recorded for each 12-month time period, with multiple occurrences in a single individual counted. Because months were calculated as 28 days, the periods actually equate to 48 weeks.

- Summary Adverse Event Rates Over Time [Time Frame: through 264 Weeks] [Designated as safety issue: No]
  Patient year (PY) refers to duration in study, calculated from first active drug intake to last safety assessment available + 1. Patient year rates with confidence interval were calculated for adverse events of interest in evaluating the long-term safety of the product being studied. Abbreviations include the following: adverse event (AE), adverse event of special interest (AESI), gastrointestinal (GI), serious adverse event (SAE), and investigational product (IP). Hypersensitivity events were defined as AEs that occurred during or within 24 hours of IP infusion and were not deemed "unrelated" to trial treatment by the investigator. This definition includes all types of AEs, regardless of whether or not they were consistent with hypersensitivity. Medical confirmation of the AESI "GI perforation" was based on medical adjudication of events captured by the GI Perforation Standardised MedDRA Queries (SMQs).
- Overall Death Rate Over Time [Time Frame: through 264 Weeks] [Designated as safety issue: No]
  Patient year (PY) refers to duration in study, calculated from first active drug intake to last safety assessment available + 1. To calculate the death rate, the total cumulative number of years that all participants were exposed to the drug, from first active drug intake to last safety assessment available + 1, was calculated as 2461.94. Since 10 participants died during that time, the death rate per year was not informative (0.00). Therefore, the overall death rate was calculated with the confidence interval based on events per 100 patient years exposure.

Secondary Outcome Measures:

- Participants Showing Improvement in Rheumatoid Arthritis Symptoms Over Time, Through 264 Weeks [Time Frame: through 264 Weeks] [Designated as safety issue: No]
  The American College of Rheumatology (ACR) established certain criteria to measure improvement in rheumatoid arthritis symptoms that include tender or swollen joint counts and five other criteria, including acute phase reactant, patient assessment, physician assessment, pain scale, and disability/ functional questionnaire. Clinical trials use the ACR Score, based on those criteria, as a standard for reporting different degrees of improvement in rheumatoid arthritis symptoms. Scores on the ACR scale may be up to ACR100 because the number after "ACR" is the percent of improvement in tender or swollen joint counts as well as in three of the other five criteria. Clinical trials determine the percentage of participants who achieve that score - that percentage of improvement.
- Percentage of Participants Classified as Responders by Disease Activity Scores Over Time, Through 264 Weeks [Time Frame: through 264 Weeks] [Designated as safety issue: No]
  The disease activity score 28 (DAS28) is a combined index for measuring disease activity in rheumatic arthritis (RA) that includes swollen and tender joint counts, erythrocyte sedimentation rate (ESR), and general health (GH) status. The DAS28 scale ranges from 0 to 10, where lower scores represent less disease activity. Participants with DAS28 scores less than 2.6 were categorized as responders with remission and those with DAS 28 scores of 3.2 or less were categorized as responders with low disease activity (LDA). The percentage of participants classified as responders in each category was recorded over time.
- Percentage of Participants Classified as Responders by EULAR Response Over Time, Through 264 Weeks [Time Frame: through 264 Weeks] [Designated as safety issue: No]
  Participants were classified as responders based on a European League Against Rheumatism (EULAR) response of Good or Moderate. Comparing the DAS28 from one patient on two different time points, it is possible to define improvement or response. The EULAR response criteria take into consideration both the first score and the change in score in order to classify them as good response, moderate response or no response. The percentage of participants who were classified as responders was recorded, as posted below.
- Change From Baseline in Scores for Swollen and Tender Joint Counts Over Time, Through 264 Weeks [Time Frame: through 264 Weeks] [Designated as safety issue: No]
  Swollen joint count (SJC) includes an assessment of 66 joints, and tender joint count (TJC) include an assessment of 68 joints. Joint prosthesis, arthrodesis or fused joints were not considered. Joints were assessed and classified as swollen/not swollen, and tender/not tender, by pressure and joint manipulation on physical examination. Change from Baseline in the SJC and TJC were calculated at given time points, and a negative change indicates improvement. A small proportion of participants in the all-exposure population reduced or stopped their oral corticosteroid use due to sustained efficacy (defined as at least a 50% improvement in both swollen joint count (SJC) and tender joint count (TJC).

- Change From Baseline in Scores for Health Assessment Questionnaire − Disability Index Over Time, Through 264 Weeks [Time Frame: through 264 Weeks] [Designated as safety issue: No]

  The Stanford Health Assessment Questionnaire - Disability Index (HAQ-DI) is a questionnaire specific for rheumatoid arthritis with 8 component sets (domains): dressing/grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Each domain has 2-3 questions (for a total of 20) that participants answer with categorical answers enumerated as a scale of 0-3, where 0=without any difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. To calculate the HAQ-DI the patient must have a domain score for at least 6 of the eight domains. The HAQ-DI is the sum of the domain scores, divided by the number of domains that have a score (in range 6-8). The resulting HAQ-DI scores are on a scale that ranges from 0 to 3, where 0=lowest level of difficulty and 3=highest level of difficulty. A negative change from baseline indicates improvement.
- Change From Baseline in Scores for Patient's Global Assessment of Disease Activity Over Time, Through 264 Weeks [Time Frame: through 264 Weeks] [Designated as safety issue: No]

  Patient's global assessment of disease activity is the patient's overall assessment of their disease activity during specified time periods on a 100 mm horizontal visual analogue scale (VAS). The left-hand extreme of the line was described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme as "maximum disease activity" (maximum arthritis disease activity). Change from baseline was calculated for given periods, and a negative change indicates improvement.
- Change From Baseline in Scores for Physician's Global Assessment of Disease Activity Over Time, Through 264 Weeks [Time Frame: through 264 Weeks] [Designated as safety issue: No]

  Physician's global assessment of disease activity is the treating physician's assessment of the patient's current disease activity on a 100 mm horizontal visual analogue scale (VAS). The extreme left end of the line was described as "no disease activity" (symptom-free and no arthritis symptoms) and the extreme right end as "maximum disease activity". Change from baseline was calculated for given periods, and a negative change indicates improvement.
- Change From Baseline in Scores for Patient's Level of Pain Over Time, Through 264 Weeks [Time Frame: through 264 Weeks] [Designated as safety issue: No]

  The patient's assessment of the patient's current level of pain on a 100 mm horizontal VAS was recorded. The extreme left end of the line was described as "no pain" and the extreme right end as "unbearable pain". Change from baseline was calculated for given periods, and a negative change indicates improvement.
- Percentage of Participants With at Least a 5-point Improvement From Baseline in Quality of Life Measure for Fatigue Over Time, Through 264 Weeks [Time Frame: through 264 Weeks] [Designated as safety issue: No]

  Quality of life is measured using the sub-scale for Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F). The assessment was originally developed for chronic illnesses and is now widely used for patients with rheumatoid arthritis. FACIT-F is a 13-item questionnaire. Participants score each item on a 5-point scale: 0 (Not at all) to 4 (Very much), for a highest possible score of 52. The responses are transformed into a FACIT-F score, where a higher score reflects an improvement. The percentage of participants with at least a 5-point improvement from baseline in the Facit-F score is shown at categorical time points.
- Percentage of Participants With at Least a 5-point Improvement From Baseline in Quality of Life Using the 36-Item Short-Form Health Survey (SF-36) Over Time, Through 264 Weeks [Time Frame: through 264 Weeks] [Designated as safety issue: No]

  The SF-36 Health Survey is a standardized questionnaire consisting of 36 questions that measures patient-reported symptoms on 8 dimensions; it is used to assess health-related quality of life (HRQoL). The Physical Component Summary (PCS) score summarizes the subscales Physical Functioning, Role-Physical, Bodily Pain, and General Health. The Mental Component Summary (MCS) score summarizes the subscales Vitality, Social Functioning, Role-Emotional, and Mental Health. Each score was scaled from 0 to 100. A positive change score indicates better HRQoL. The percentage of participants with at least a 5-point improvement from baseline is presented for each subscale.

Enrollment: 538
Study Start Date: August 2005
Primary Completion Date: May 2012
Study Completion Date: May 2012

Arms	Assigned Interventions
Experimental: Tocilizumab 8 mg/kg All participants received tocilizumab 8 mg/kg to a maximum of 800 mg, administered by intravenous (IV) infusion over one hour, every 4 weeks. Concomitant therapies were limited to dosage and administration constraints detailed in the protocol.	Drug: Tocilizumab Tocilizumab (myeloma receptor antibody [MRA]) was supplied in sterile solution of 20 mg TCZ/mL for aseptic preparation of infusion bags for IV administration. Other Names: RoActemra Actemra Tocilizumab (MRA) TCZ

Detailed Description:

The primary objective of this extension study was to assess the long-term safety of 8 mg/kg tocilizumab with regard to adverse events (AEs) and laboratory result abnormalities.

The secondary objectives were as follows:

- To explore the possibility of reducing concomitant steroid treatment
- To determine the long-term efficacy of 8 mg/kg tocilizumab with regard to reduction in signs and symptoms
- To better understand and predict tocilizumab efficacy, response, safety, and progression of rheumatoid arthritis (RA) and associated diseases with regard to its effect on biomarkers

No viable biomarkers for TCZ treatment effects were identified from the controlled studies. There were, therefore, no biomarkers that warranted further investigation in long-term studies, so no biomarker data are reported.

The extension study WA18695 was an open-label, international multi-center study in patients with moderate to severe active rheumatoid arthritis (RA) who had completed treatment in the 24 weeks placebo-controlled Phase III study WA17822. Patients entering WA17822 had an inadequate response to methotrexate (MTX), and, during WA17822, patients had received treatment with intravenous infusions of tocilizumab 4 mg/kg, 8 mg/kg, or placebo every 4 weeks with background MTX therapy.

All patients who completed the planned course of treatment or escape therapy in the WA17822 study were eligible to enter the WA18695 long-term extension study, where they were assigned to treatment with 8 mg/kg RoActemra/Actemra plus MTX. The dose of RA medications such as MTX and nonsteroidal anti-inflammatory drugs (NSAIDs), but excluding corticosteroids, was to be kept stable for the first 48 weeks of the WA18695 study. During this time dose reductions in these treatments were only allowed as clinically required for safety reasons. After week 48, the administration of disease-modifying antirheumatic drugs (DMARDs) and NSAIDs could be changed, according to the investigator's practice and as tolerated by the patient.

Eligibility

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

Criteria

Inclusion Criteria:

- Patients who have completed participation in the Phase III study WA17822 (NCT00106548) in adult rheumatoid arthritis.

Exclusion Criteria:

- Treatment with any investigational agent since the last administration of study drug in WA17822.
- Treatment with intravenous (IV) gammaglobulin, plasmapheresis, or Prosorba column since the last administration of study drug in WA17822.
- Treatment with an anti-tumor necrosis factor or anti-interleukin-1 agent, or a T cell costimulation modulator since the last administration of study drug in WA17822.
- Previous treatment with any cell-depleting therapies.
- Parenteral, intramuscular, or intra-articular corticosteroids within 6 weeks prior to baseline.

Contacts and Locations

Locations

Argentina
- Buenos Aires, Argentina, C1015ABO
- Buenos Aires, Argentina, C1428DQG
- Buenos Aires, Argentina, 1405

Australia
- Adelaide, Australia, 5041
- Maroochydore, Australia, 4558
- Shenton Park, Australia, 6008

Austria
- Wien, Austria, 1130
- Wien, Austria, 1090
- Wien, Austria, 1160

Brazil
- Porto Alegre, Brazil, 91350-200
- Sao Paulo, Brazil, 04027-000

Bulgaria
- Sofia, Bulgaria, 1784
- Sofia, Bulgaria, 1606
- Varna, Bulgaria, 9010

Canada, Alberta
- Calgary, Alberta, Canada, T2N 2T9

Canada, British Columbia
- Victoria, British Columbia, Canada, V8V 3P9

Canada, Manitoba
- Winnipeg, Manitoba, Canada, R3A 1M3

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

Canada, Ontario

Burlington, Ontario, Canada, L7R 1E2
Newmarket, Ontario, Canada, L3Y 3R7
Ottawa, Ontario, Canada, K1H 1A2
Toronto, Ontario, Canada, M4N 3M5

Canada, Quebec

Montreal, Quebec, Canada, H2L 1S6
Montreal, Quebec, Canada, H1T 2M4
Sainte-foy, Quebec, Canada, G1W 4R4

France

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Creteil, France, 94010
Le Mans, France, 72000
Paris, France, 75679
Paris, France, 75475
Paris, France, 75679
Paris, France, 75571

Germany

Bad Bramstedt, Germany, 24576
Bad Nauheim, Germany, 61231
Baden-baden, Germany, 76530
Berlin, Germany, 14059
Erlangen, Germany, 91056
Heidelberg, Germany, 69120
Heidelberg, Germany, 69120
Koeln, Germany, 50924
Tübingen, Germany, 72076

Hong Kong

Hong Kong, Hong Kong, 852
Hong Kong, Hong Kong
Tuen Mun, Hong Kong, 852

Hungary

Budapest, Hungary, 1023
Debrecen, Hungary, 4032
Pécs, Hungary, 7632

Israel

Beer Sheva, Israel, 84101
Haifa, Israel, 31096
Haifa, Israel, 31048
Jerusalem, Israel, 91120
Petach Tikva, Israel, 49100
Tel Aviv, Israel, 64239

Italy

Cona (ferrara), Italy, 44124
Gazzi, Italy, 98125
Palermo, Italy, 90127

Siena, Italy, 53100
Udine, Italy, 33100

Mexico
Chihuahua, Mexico, 31000
Guadalajara, Mexico, 44690
Mexico, Mexico, 44620
Mexico City, Mexico, 14080
Mexico City, Mexico, 07760
San Luis Potosi, Mexico, 78240

Singapore
Singapore, Singapore, 119074
Singapore, Singapore, 258499

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Piestany, Slovakia, 921 01

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Bern, Switzerland, 3010
Lausanne, Switzerland, 1011

Thailand
Bangkok, Thailand, 10400
Bangkok, Thailand, 10700
Bangkok, Thailand, 10400
Chiang Mai, Thailand, 50200

Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	WA18695
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Patients received tocilizumab (TCZ) 8 mg/kg intravenously every 4 weeks.

Overall Study

	Tocilizumab 8 mg/kg
Started	538
Completed	355
Not Completed	183
Adverse Event	96
Death	10
Insufficient Therapeutic Response	21
Protocol Violation	1
Refused Treatment	41
Failure to Return	9
Withdrawal by Subject	5

Baseline Characteristics

Analysis Population Description

All-exposure population: All patients who entered the study and received at least one dose of tocilizumab at any time. Baseline was defined as the first dose of study drug, whether that occurred in the WA17822 study or the WA18695 study.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.

Baseline Measures

	Tocilizumab 8 mg/kg
Number of Participants	538
Age, Continuous [units: years] Mean (Standard Deviation)	50.8 (12.03)
Gender, Male/Female [units: participants]	
Female	443
Male	95

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Adverse Event (AE) Summary Over Time
Measure Description	The number of participants experiencing at least one adverse event (AE) is recorded for each 12-month time period, with multiple occurrences in a single individual counted. Because months were calculated as 28 days, the periods actually equate to 48 weeks.
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time.

Reporting Groups

	Description
Months 0 - 12	Participants with scores during Months 0-12, which equates to baseline through Week 48.
Months 13 − 24	Participants with scores during Months 13 − 24, which equates to Weeks 49-96.
Months 25 - 36	Participants with scores during Months 25 - 36, which equates to Weeks 97-144.
Months 37 − 48	Participants with scores during Months 37 − 48, which equates to Weeks 145-192.
Months Greater Than 48	Participants with scores during Months greater than 48, which equates to Weeks 193-264.

Measured Values

	Months 0 - 12	Months 13 − 24	Months 25 - 36	Months 37 − 48	Months Greater Than 48
Number of Participants Analyzed	538	509	463	434	414
Adverse Event (AE) Summary Over Time [units: Participants]					
Experienced an adverse event	433	390	333	294	329
Experienced a serious adverse event	55	55	55	35	74
Experienced AE leading to withdrawal	24	17	22	8	32

2. Primary Outcome Measure:

Measure Title	Summary Adverse Event Rates Over Time
Measure Description	Patient year (PY) refers to duration in study, calculated from first active drug intake to last safety assessment available + 1. Patient year rates with confidence interval were calculated for adverse events of interest in evaluating the long-term safety of the product being studied. Abbreviations include the following: adverse event (AE), adverse event of special interest (AESI), gastrointestinal (GI), serious adverse event (SAE), and investigational product (IP). Hypersensitivity events were defined as AEs that occurred during or within 24 hours of IP infusion and were not deemed “unrelated” to trial treatment by the investigator. This definition includes all types of AEs, regardless of whether or not they were consistent with hypersensitivity. Medical confirmation of the AESI "GI perforation" was based on medical adjudication of events captured by the GI Perforation Standardised MedDRA Queries (SMQs).
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time.

Reporting Groups

	Description
Months 0 - 12	Participants with scores during Months 0-12, which equates to baseline through Week 48 (Total PY=486.34).
Months 13 − 24	Participants with scores during Months 13 − 24, which equates to Weeks 49-96 (Total PY=444.49).
Months 25 - 36	Participants with scores during Months 25 - 36, which equates to Weeks 97-144 (Total PY=410.93).
Months 37 − 48	Participants with scores during Months 37 − 48, which equates to Weeks 145-192 (Total PY=388.25).
Months Greater Than 48	Participants with scores during Months greater than 48, which equates to Weeks 193-264 (Total PY=731.93).

Measured Values

	Months 0 - 12	Months 13 − 24	Months 25 - 36	Months 37 − 48	Months Greater Than 48
Number of Participants Analyzed	538	509	463	434	414
Summary Adverse Event Rates Over Time [units: Adverse Events per 100 Patient Years] Number (95% Confidence Interval)					
Total AE rate	393.76 (376.32 to 411.80)	286.17 (270.66 to 302.34)	260.14 (244.78 to 276.22)	249.84 (234.36 to 266.07)	212.04 (201.62 to 222.86)
Total SAE rate	12.54 (9.59 to 16.11)	13.05 (9.91 to 16.87)	18.74 (14.79 to 23.42)	12.62 (9.34 to 16.69)	13.12 (10.62 to 16.02)

	Months 0 - 12	Months 13 − 24	Months 25 - 36	Months 37 − 48	Months Greater Than 48
Rate for AEs leading to withdrawal	5.14 (3.33 to 7.59)	3.82 (2.23 to 6.12)	5.35 (3.36 to 8.11)	2.06 (0.89 to 4.06)	4.37 (2.99 to 6.17)
AESI All Infections	92.94 (84.57 to 101.92)	87.52 (79.03 to 96.66)	87.36 (78.56 to 96.88)	87.32 (78.27 to 97.12)	72.82 (66.77 to 79.27)
AESI Serious Infections	3.29 (1.88 to 5.34)	2.47 (1.24 to 4.43)	5.60 (3.55 to 8.40)	3.35 (1.78 to 5.73)	3.55 (2.32 to 5.20)
AESI Opportunistic infections	0 (NA to NA) [1]	0.22 (0.01 to 1.25)	0 (NA to NA) [1]	0.52 (0.06 to 1.86)	0.27 (0.03 to 0.99)
AESI Hypersensitivity events	27.35 (22.90 to 32.41)	9.90 (7.19 to 13.29)	5.35 (3.36 to 8.11)	3.86 (2.16 to 6.37)	4.10 (2.77 to 5.85)
AESI Hepatic events	0.41 (0.05 to 1.49)	0.90 (0.25 to 2.30)	0.49 (0.06 to 1.76)	1.03 (0.28 to 2.64)	0.68 (0.22 to 1.59)
AESI Myocardial infarction	0.62 (0.13 to 1.80)	0 (NA to NA) [2]	0.24 (0.01 to 1.36)	0.77 (0.16 to 2.26)	0.27 (0.03 to 0.99)
AESI Stroke, ischemic or hemorrhagic	0.21 (0.01 to 1.15)	0.22 (0.01 to 1.25)	0.73 (0.15 to 2.13)	0.26 (0.01 to 1.44)	0.41 (0.08 to 1.20)
AESI GI perforation	0 (NA to NA) [3]	0 (NA to NA) [3]	0.49 (0.06 to 1.76)	0.26 (0.01 to 1.44)	0 (NA to NA) [3]
AESI Malignancy	1.23 (0.45 to 2.69)	1.80 (0.78 to 3.55)	0.97 (0.27 to 2.49)	0.77 (0.16 to 2.26)	1.50 (0.75 to 2.69)
AESI Demyelinating disorders	0.21 (0.01 to 1.15)	0 (NA to NA) [4]	0 (NA to NA) [4]	0 (NA to NA) [4]	0 (NA to NA) [4]
AESI Serious bleeding disorders	0.62 (0.13 to 1.80)	0.45 (0.05 to 1.63)	0.49 (0.06 to 1.76)	0.26 (0.01 to 1.44)	0.68 (0.22 to 1.59)

[1] There were no opportunistic infections in this period.
[2] There were no myocardial infarctions in this period.
[3] There were no medically confirmed GI perforations in this period.
[4] There were no demyelinating disorders in this period.

3. Primary Outcome Measure:

Measure Title	Overall Death Rate Over Time

Measure Description	Patient year (PY) refers to duration in study, calculated from first active drug intake to last safety assessment available + 1. To calculate the death rate, the total cumulative number of years that all participants were exposed to the drug, from first active drug intake to last safety assessment available + 1, was calculated as 2461.94. Since 10 participants died during that time, the death rate per year was not informative (0.00). Therefore, the overall death rate was calculated with the confidence interval based on events per 100 patient years exposure.
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which included all participants who entered the study and received at least one dose of tocilizumab at any time.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Patients received tocilizumab (TCZ) 8 mg/kg intravenously every 4 weeks.

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	538
Overall Death Rate Over Time [units: Deaths per 100 PY] Number (95% Confidence Interval)	0.41 (0.19 to 0.75)

4. Secondary Outcome Measure:

Measure Title	Participants Showing Improvement in Rheumatoid Arthritis Symptoms Over Time, Through 264 Weeks
Measure Description	The American College of Rheumatology (ACR) established certain criteria to measure improvement in rheumatoid arthritis symptoms that include tender or swollen joint counts and five other criteria, including acute phase reactant, patient assessment, physician assessment, pain scale, and disability/functional questionnaire. Clinical trials use the ACR Score, based on those criteria, as a standard for reporting different degrees of improvement in rheumatoid arthritis symptoms. Scores on the ACR scale may be up to ACR100 because the number after “ACR” is the percent of improvement in tender or swollen joint counts as well as in three of the other five criteria. Clinical trials determine the percentage of participants who achieve that score – that percentage of improvement.
Time Frame	through 264 Weeks

Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab, with a score at the given time point.

Reporting Groups

	Description
Week 24	Participants with scores at 24 weeks post-baseline.
Week 48	Participants with scores at 48 weeks post-baseline.
Week 108	Participants with scores at 108 weeks post-baseline.
Week 156	Participants with scores at 156 weeks post-baseline.
Week 204	Participants with scores at 204 weeks post-baseline.
Week 264	Participants with scores at 264 weeks post-baseline.

Measured Values

	Week 24	Week 48	Week 108	Week 156	Week 204	Week 264
Number of Participants Analyzed	522	480	422	413	387	367
Participants Showing Improvement in Rheumatoid Arthritis Symptoms Over Time, Through 264 Weeks [units: Percentage of Participants]						
ACR20	63.2	76.0	81.2	83.3	82.2	83.9
ACR50	41.2	50.6	58.1	59.6	62.5	67.8
ACR70	17.4	27.1	38.2	41.9	42.1	45.8
ACR90	4.8	5.2	11.3	15.3	16.8	19.3

5. Secondary Outcome Measure:

Measure Title	Percentage of Participants Classified as Responders by Disease Activity Scores Over Time, Through 264 Weeks

Measure Description	The disease activity score 28 (DAS28) is a combined index for measuring disease activity in rheumatic arthritis (RA) that includes swollen and tender joint counts, erythrocyte sedimentation rate (ESR), and general health (GH) status. The DAS28 scale ranges from 0 to 10, where lower scores represent less disease activity. Participants with DAS28 scores less than 2.6 were categorized as responders with remission and those with DAS 28 scores of 3.2 or less were categorized as responders with low disease activity (LDA). The percentage of participants classified as responders in each category was recorded over time.
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time.

Reporting Groups

	Description
Week 24	Participants with scores at 24 weeks post-baseline.
Week 48	Participants with scores at 48 weeks post-baseline.
Week 108	Participants with scores at 108 weeks post-baseline.
Week 156	Participants with scores at 156 weeks post-baseline.
Week 204	Participants with scores at 204 weeks post-baseline.
Week 264	Participants with scores at 264 weeks post-baseline.

Measured Values

	Week 24	Week 48	Week 108	Week 156	Week 204	Week 264
Number of Participants Analyzed	516	470	430	410	381	363
Percentage of Participants Classified as Responders by Disease Activity Scores Over Time, Through 264 Weeks [units: Percentage of Participants]						
Responders with Remission (DAS<2.6)	24.6	43.0	53.7	54.9	57.2	60.6
Responders with Low Disease Activity (DAS</= 3.2)	41.7	57.7	67.0	71.2	70.6	72.2

6. Secondary Outcome Measure:

Measure Title	Percentage of Participants Classified as Responders by EULAR Response Over Time, Through 264 Weeks

Measure Description	Participants were classified as responders based on a European League Against Rheumatism (EULAR) response of Good or Moderate. Comparing the DAS28 from one patient on two different time points, it is possible to define improvement or response. The EULAR response criteria take into consideration both the first score and the change in score in order to classify them as good response, moderate response or no response. The percentage of participants who were classified as responders was recorded, as posted below.
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time.

Reporting Groups

	Description
Week 24	Participants with scores at 24 weeks post-baseline.
Week 48	Participants with scores at 48 weeks post-baseline.
Week 108	Participants with scores at 108 weeks post-baseline.
Week 156	Participants with scores at 156 weeks post-baseline.
Week 204	Participants with scores at 204 weeks post-baseline.
Week 264	Participants with scores at 264 weeks post-baseline.

Measured Values

	Week 24	Week 48	Week 108	Week 156	Week 204	Week 264
Number of Participants Analyzed	514	468	429	409	380	362
Percentage of Participants Classified as Responders by EULAR Response Over Time, Through 264 Weeks [units: Percentage of Participants]						
EULAR Good Response	41.2	56.6	65.5	70.9	69.5	71.0
EULAR Moderate Response	48.1	39.1	29.8	25.9	26.8	25.1

7. Secondary Outcome Measure:

Measure Title	Change From Baseline in Scores for Swollen and Tender Joint Counts Over Time, Through 264 Weeks

Measure Description	Swollen joint count (SJC) includes an assessment of 66 joints, and tender joint count (TJC) include an assessment of 68 joints. Joint prosthesis, arthrodesis or fused joints were not considered. Joints were assessed and classified as swollen/not swollen, and tender/not tender, by pressure and joint manipulation on physical examination. Change from Baseline in the SJC and TJC were calculated at given time points, and a negative change indicates improvement. A small proportion of participants in the all-exposure population reduced or stopped their oral corticosteroid use due to sustained efficacy (defined as at least a 50% improvement in both swollen joint count (SJC) and tender joint count (TJC).
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time, with a score at the given time point.

Reporting Groups

	Description
Week 24	Participants with scores at 24 weeks post-baseline.
Week 48	Participants with scores at 48 weeks post-baseline.
Week 108	Participants with scores at 108 weeks post-baseline.
Week 156	Participants with scores at 156 weeks post-baseline.
Week 204	Participants with scores at 204 weeks post-baseline.
Week 264	Participants with scores at 264 weeks post-baseline.

Measured Values

	Week 24	Week 48	Week 108	Week 156	Week 204	Week 264
Number of Participants Analyzed	532	506	454	422	405	371
Change From Baseline in Scores for Swollen and Tender Joint Counts Over Time, Through 264 Weeks [units: Joints] Mean (Standard Deviation)						
Swollen Joint Count (SJC)	-11.7 (11.50)	-13.6 (11.04)	-15.6 (11.51)	-16.2 (11.46)	-16.2 (11.48)	-16.5 (11.26)
Tender Joint Count (TJC)	-17.4 (14.82)	-20.3 (15.12)	-23.1 (15.82)	-23.8 (16.14)	-23.8 (15.89)	-24.8 (16.37)

8. Secondary Outcome Measure:

Measure Title	Change From Baseline in Scores for Health Assessment Questionnaire − Disability Index Over Time, Through 264 Weeks
Measure Description	The Stanford Health Assessment Questionnaire - Disability Index (HAQ-DI) is a questionnaire specific for rheumatoid arthritis with 8 component sets (domains): dressing/grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Each domain has 2-3 questions (for a total of 20) that participants answer with categorical answers enumerated as a scale of 0-3, where 0=without any difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. To calculate the HAQ-DI the patient must have a domain score for at least 6 of the eight domains. The HAQ-DI is the sum of the domain scores, divided by the number of domains that have a score (in range 6-8). The resulting HAQ-DI scores are on a scale that ranges from 0 to 3, where 0=lowest level of difficulty and 3=highest level of difficulty. A negative change from baseline indicates improvement.
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time, with a score at the given time point.

Reporting Groups

	Description
Week 24	Participants with scores at 24 weeks post-baseline.
Week 48	Participants with scores at 48 weeks post-baseline.
Week 108	Participants with scores at 108 weeks post-baseline.
Week 156	Participants with scores at 156 weeks post-baseline.
Week 204	Participants with scores at 204 weeks post-baseline.
Week 264	Participants with scores at 264 weeks post-baseline.

Measured Values

	Week 24	Week 48	Week 108	Week 156	Week 204	Week 264
Number of Participants Analyzed	445	408	376	349	332	316
Change From Baseline in Scores for Health Assessment Questionnaire − Disability Index Over Time, Through 264 Weeks [units: Units on a Scale] Mean (Standard Deviation)	-0.49 (0.582)	-0.53 (0.614)	-0.59 (0.636)	-0.61 (0.655)	-0.65 (0.661)	-0.62 (0.693)

9. Secondary Outcome Measure:

Measure Title	Change From Baseline in Scores for Patient's Global Assessment of Disease Activity Over Time, Through 264 Weeks
Measure Description	Patient’s global assessment of disease activity is the patient’s overall assessment of their disease activity during specified time periods on a 100 mm horizontal visual analogue scale (VAS). The left-hand extreme of the line was described as “no disease activity” (symptom-free and no arthritis symptoms) and the right-hand extreme as “maximum disease activity” (maximum arthritis disease activity). Change from baseline was calculated for given periods, and a negative change indicates improvement.
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time, with a score at the given time point.

Reporting Groups

	Description
Week 24	Participants with scores at 24 weeks post-baseline.
Week 48	Participants with scores at 48 weeks post-baseline.
Week 108	Participants with scores at 108 weeks post-baseline.
Week 156	Participants with scores at 156 weeks post-baseline.
Week 204	Participants with scores at 204 weeks post-baseline.
Week 264	Participants with scores at 264 weeks post-baseline.

Measured Values

	Week 24	Week 48	Week 108	Week 156	Week 204	Week 264
Number of Participants Analyzed	521	479	442	414	387	367
Change From Baseline in Scores for Patient's Global Assessment of Disease Activity Over Time, Through 264 Weeks [units: Units on a Scale] Mean (Standard Deviation)	-26.6 (26.87)	-30.3 (27.71)	-31.1 (27.65)	-31.6 (26.74)	-33.0 (26.83)	-32.9 (27.58)

10. Secondary Outcome Measure:

Measure Title	Change From Baseline in Scores for Physician's Global Assessment of Disease Activity Over Time, Through 264 Weeks
Measure Description	Physician’s global assessment of disease activity is the treating physician’s assessment of the patient’s current disease activity on a 100 mm horizontal visual analogue scale (VAS). The extreme left end of the line was described as “no disease activity” (symptom-free and no arthritis symptoms) and the extreme right end as “maximum disease activity”. Change from baseline was calculated for given periods, and a negative change indicates improvement.
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time, with a score at the given time point.

Reporting Groups

	Description
Week 24	Participants with scores at 24 weeks post-baseline.
Week 48	Participants with scores at 48 weeks post-baseline.
Week 108	Participants with scores at 108 weeks post-baseline.
Week 156	Participants with scores at 156 weeks post-baseline.
Week 204	Participants with scores at 204 weeks post-baseline.
Week 264	Participants with scores at 264 weeks post-baseline.

Measured Values

	Week 24	Week 48	Week 108	Week 156	Week 204	Week 264
Number of Participants Analyzed	521	479	439	416	389	369
Change From Baseline in Scores for Physician's Global Assessment of Disease Activity Over Time, Through 264 Weeks [units: Units on a Scale] Mean (Standard Deviation)	-33.8 (23.33)	-38.1 (23.77)	-41.1 (23.79)	-43.2 (23.26)	-44.8 (22.66)	-44.4 (23.64)

11. Secondary Outcome Measure:

Measure Title	Change From Baseline in Scores for Patient's Level of Pain Over Time, Through 264 Weeks

Measure Description	The patient’s assessment of the patient's current level of pain on a 100 mm horizontal VAS was recorded. The extreme left end of the line was described as “no pain” and the extreme right end as “unbearable pain”. Change from baseline was calculated for given periods, and a negative change indicates improvement.
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time, with a score at the given time point.

Reporting Groups

	Description
Week 24	Participants with scores at 24 weeks post-baseline.
Week 48	Participants with scores at 48 weeks post-baseline.
Week 108	Participants with scores at 108 weeks post-baseline.
Week 156	Participants with scores at 156 weeks post-baseline.
Week 204	Participants with scores at 204 weeks post-baseline.
Week 264	Participants with scores at 264 weeks post-baseline.

Measured Values

	Week 24	Week 48	Week 108	Week 156	Week 204	Week 264
Number of Participants Analyzed	521	479	442	414	388	367
Change From Baseline in Scores for Patient's Level of Pain Over Time, Through 264 Weeks [units: Units on a Scale] Mean (Standard Deviation)	-23.7 (26.38)	-26.7 (27.27)	-28.0 (26.33)	-28.1 (25.99)	-29.5 (26.98)	-29.2 (26.84)

12. Secondary Outcome Measure:

Measure Title	Percentage of Participants With at Least a 5-point Improvement From Baseline in Quality of Life Measure for Fatigue Over Time, Through 264 Weeks

Measure Description	Quality of life is measured using the sub-scale for Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F). The assessment was originally developed for chronic illnesses and is now widely used for patients with rheumatoid arthritis. FACIT-F is a 13-item questionnaire. Participants score each item on a 5-point scale: 0 (Not at all) to 4 (Very much), for a highest possible score of 52. The responses are transformed into a FACIT-F score, where a higher score reflects an improvement. The percentage of participants with at least a 5-point improvement from baseline in the Facit-F score is shown at categorical time points.
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time, with a score at the given time point.

Reporting Groups

	Description
Week 24	Participants with scores at 24 weeks post-baseline.
Week 48	Participants with scores at 48 weeks post-baseline.
Week 108	Participants with scores at 108 weeks post-baseline.
Week 156	Participants with scores at 156 weeks post-baseline.
Week 204	Participants with scores at 204 weeks post-baseline.
Week 264	Participants with scores at 264 weeks post-baseline.

Measured Values

	Week 24	Week 48	Week 108	Week 156	Week 204	Week 264
Number of Participants Analyzed	523	482	444	414	390	370
Percentage of Participants With at Least a 5-point Improvement From Baseline in Quality of Life Measure for Fatigue Over Time, Through 264 Weeks [units: Percentage of Participants]	66.0	58.7	61.5	62.3	60.0	62.2

13. Secondary Outcome Measure:

Measure Title	Percentage of Participants With at Least a 5-point Improvement From Baseline in Quality of Life Using the 36-Item Short-Form Health Survey (SF-36) Over Time, Through 264 Weeks

Measure Description	The SF-36 Health Survey is a standardized questionnaire consisting of 36 questions that measures patient-reported symptoms on 8 dimensions; it is used to assess health-related quality of life (HRQoL). The Physical Component Summary (PCS) score summarizes the subscales Physical Functioning, Role-Physical, Bodily Pain, and General Health. The Mental Component Summary (MCS) score summarizes the subscales Vitality, Social Functioning, Role-Emotional, and Mental Health. Each score was scaled from 0 to 100. A positive change score indicates better HRQoL. The percentage of participants with at least a 5-point improvement from baseline is presented for each subscale.
Time Frame	through 264 Weeks
Safety Issue?	No

Analysis Population Description

All exposure population, which includes all participants who entered the study and received at least one dose of tocilizumab at any time, with a score at the given time point.

Reporting Groups

	Description
Week 24	Participants with scores at 24 weeks post-baseline.
Week 48	Participants with scores at 48 weeks post-baseline.
Week 108	Participants with scores at 108 weeks post-baseline.
Week 156	Participants with scores at 156 weeks post-baseline.
Week 204	Participants with scores at 204 weeks post-baseline.
Week 264	Participants with scores at 264 weeks post-baseline.

Measured Values

	Week 24	Week 48	Week 108	Week 156	Week 204	Week 264
Number of Participants Analyzed	423	424	395	373	344	334
Percentage of Participants With at Least a 5-point Improvement From Baseline in Quality of Life Using the 36-Item Short-Form Health Survey (SF-36) Over Time, Through 264 Weeks [units: Percentage of Participants]						
SF-36 MCS	48.2	46.2	48.6	49.9	49.7	49.1
SF-36 PCS	63.8	69.1	71.1	71.3	73.3	71.3

Reported Adverse Events

Time Frame	[Not specified]
Additional Description	All-exposure population: All patients who entered the study and received at least 1 dose of tocilizumab at any time.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.

Serious Adverse Events

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Total	199/538 (36.99%)
Blood and lymphatic system disorders	
Anaemia [A] †	2/538 (0.37%)
Anaemia of chronic disease [A] †	1/538 (0.19%)
Iron deficiency anaemia [A] †	1/538 (0.19%)
Cardiac disorders	
Acute coronary syndrome [A] †	2/538 (0.37%)
Acute myocardial infarction [A] †	3/538 (0.56%)
Angina unstable [A] †	2/538 (0.37%)
Arteriosclerosis coronary artery [A] †	1/538 (0.19%)
Atrial fibrillation [A] †	3/538 (0.56%)
Atrioventricular block complete [A] †	1/538 (0.19%)
Cardiac failure [A] †	1/538 (0.19%)
Cardiac failure congestive [A] †	1/538 (0.19%)
Cardio-respiratory arrest [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Coronary artery disease [A] †	2/538 (0.37%)
Dressler's syndrome [A] †	1/538 (0.19%)
Myocardial infarction [A] †	2/538 (0.37%)
Supraventricular extrasystoles [A] †	1/538 (0.19%)
Supraventricular tachycardia [A] †	2/538 (0.37%)
Tachyarrhythmia [A] †	1/538 (0.19%)
Ear and labyrinth disorders	
Sudden hearing loss [A] †	1/538 (0.19%)
Vertigo [A] †	1/538 (0.19%)
Endocrine disorders	
Goitre [A] †	1/538 (0.19%)
Eye disorders	
Cataract [A] †	2/538 (0.37%)
Ulcerative keratitis [A] †	1/538 (0.19%)
Gastrointestinal disorders	
Abdominal pain [A] †	1/538 (0.19%)
Abdominal pain upper [A] †	1/538 (0.19%)
Anal fistula [A] †	1/538 (0.19%)
Constipation [A] †	1/538 (0.19%)
Crohn's disease [A] †	1/538 (0.19%)
Diarrhoea [A] †	2/538 (0.37%)
Diverticular perforation [A] †	2/538 (0.37%)
Flatulence [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Gastritis [A] †	3/538 (0.56%)
Gastrointestinal haemorrhage [A] †	1/538 (0.19%)
Gastrooesophageal reflux disease [A] †	1/538 (0.19%)
Glossitis [A] †	1/538 (0.19%)
Haemorrhoidal haemorrhage [A] †	1/538 (0.19%)
Inguinal hernia [A] †	4/538 (0.74%)
Large intestinal ulcer [A] †	1/538 (0.19%)
Melaena [A] †	1/538 (0.19%)
Oesophageal perforation [A] †	1/538 (0.19%)
Pancreatitis [A] †	2/538 (0.37%)
Pancreatitis acute [A] †	1/538 (0.19%)
Rectal haemorrhage [A] †	1/538 (0.19%)
Umbilical hernia [A] †	1/538 (0.19%)
General disorders	
Chest pain [A] †	1/538 (0.19%)
Device breakage [A] †	2/538 (0.37%)
Device dislocation [A] †	2/538 (0.37%)
Non-cardiac chest pain [A] †	2/538 (0.37%)
Hepatobiliary disorders	
Cholecystitis [A] †	4/538 (0.74%)
Cholecystitis acute [A] †	2/538 (0.37%)
Cholecystitis chronic [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Cholelithiasis [A] †	4/538 (0.74%)
Perforation bile duct [A] †	1/538 (0.19%)
Immune system disorders	
Allergy to arthropod bite [A] †	1/538 (0.19%)
Anaphylactic reaction [A] †	1/538 (0.19%)
Sarcoidosis [A] †	1/538 (0.19%)
Infections and infestations	
Abscess limb [A] †	3/538 (0.56%)
Abscess neck [A] †	1/538 (0.19%)
Appendicitis [A] †	1/538 (0.19%)
Arthritis bacterial [A] †	1/538 (0.19%)
Bronchitis [A] †	1/538 (0.19%)
Bronchopneumonia [A] †	3/538 (0.56%)
Bursitis infective staphylococcal [A] †	1/538 (0.19%)
Cellulitis [A] †	4/538 (0.74%)
Cellulitis staphylococcal [A] †	2/538 (0.37%)
Diverticulitis [A] †	5/538 (0.93%)
Douglas' abscess [A] †	1/538 (0.19%)
Endocarditis staphylococcal [A] †	1/538 (0.19%)
Erysipelas [A] †	4/538 (0.74%)
Gastroenteritis [A] †	4/538 (0.74%)
Gastrointestinal infection [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Helicobacter gastritis [A] †	1/538 (0.19%)
Herpes zoster [A] †	2/538 (0.37%)
Intervertebral discitis [A] †	1/538 (0.19%)
Lobar pneumonia [A] †	1/538 (0.19%)
Lung Abscess [A] †	1/538 (0.19%)
Mediastinitis [A] †	1/538 (0.19%)
Osteomyelitis [A] †	1/538 (0.19%)
Peritonitis [A] †	1/538 (0.19%)
Peritonsillar abscess [A] †	1/538 (0.19%)
Pneumonia [A] †	12/538 (2.23%)
Pneumonia pneumococcal [A] †	2/538 (0.37%)
Post procedural infection [A] †	1/538 (0.19%)
Postoperative wound infection [A] †	2/538 (0.37%)
Proteus infection [A] †	1/538 (0.19%)
Pulmonary sepsis [A] †	1/538 (0.19%)
Pulmonary tuberculosis [A] †	2/538 (0.37%)
Pyelonephritis acute [A] †	1/538 (0.19%)
Respiratory tract infection [A] †	2/538 (0.37%)
Sepsis [A] †	3/538 (0.56%)
Septic arthritis [A] †	1/538 (0.19%)
Sinusitis [A] †	2/538 (0.37%)
Soft tissue infection [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Staphylococcal septic shock [A] †	1/538 (0.19%)
Subcutaneous abscess [A] †	2/538 (0.37%)
Tuberculosis [A] †	1/538 (0.19%)
Tuberculous pleurisy [A] †	1/538 (0.19%)
Upper respiratory tract infection [A] †	1/538 (0.19%)
Urinary tract infection [A] †	3/538 (0.56%)
Varicella [A] †	2/538 (0.37%)
Wound infection [A] †	1/538 (0.19%)
Injury, poisoning and procedural complications	
Ankle fracture [A] †	1/538 (0.19%)
Carbon monoxide poisoning [A] †	1/538 (0.19%)
Contusion [A] †	1/538 (0.19%)
Dislocation of vertebra [A] †	1/538 (0.19%)
Femoral neck fracture [A] †	2/538 (0.37%)
Femur fracture [A] †	2/538 (0.37%)
Fractured ischium [A] †	1/538 (0.19%)
Gas poisoning [A] †	1/538 (0.19%)
Hand fracture [A] †	1/538 (0.19%)
Hip fracture [A] †	1/538 (0.19%)
Incision site haematoma [A] †	1/538 (0.19%)
Joint injury [A] †	1/538 (0.19%)
Laceration [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Lower limb fracture [A] †	1/538 (0.19%)
Meniscus lesion [A] †	1/538 (0.19%)
Overdose [A] †	1/538 (0.19%)
Periprosthetic fracture [A] †	1/538 (0.19%)
Post procedural complication [A] †	1/538 (0.19%)
Post procedural haemorrhage [A] †	2/538 (0.37%)
Postoperative fever [A] †	1/538 (0.19%)
Radius fracture [A] †	1/538 (0.19%)
Tendon rupture [A] †	1/538 (0.19%)
Tibia fracture [A] †	1/538 (0.19%)
Upper limb fracture [A] †	1/538 (0.19%)
Vascular bypass dysfunction [A] †	1/538 (0.19%)
Wound dehiscence [A] †	1/538 (0.19%)
Wrist fracture [A] †	1/538 (0.19%)
Metabolism and nutrition disorders	
Hypokalaemia [A] †	1/538 (0.19%)
Musculoskeletal and connective tissue disorders	
Back pain [A] †	3/538 (0.56%)
Foot deformity [A] †	1/538 (0.19%)
Haemarthrosis [A] †	1/538 (0.19%)
Intervertebral disc protrusion [A] †	3/538 (0.56%)
Lumbar spinal stenosis [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Lupus-like syndrome [A] †	1/538 (0.19%)
Muscle necrosis [A] †	1/538 (0.19%)
Muscular weakness [A] †	1/538 (0.19%)
Musculoskeletal chest pain [A] †	1/538 (0.19%)
Osteoarthritis [A] †	6/538 (1.12%)
Osteonecrosis [A] †	1/538 (0.19%)
Osteoporotic fracture [A] †	2/538 (0.37%)
Pain in extremity [A] †	1/538 (0.19%)
Rheumatoid arthritis [A] †	1/538 (0.19%)
Spinal osteoarthritis [A] †	1/538 (0.19%)
Spondylolisthesis [A] †	1/538 (0.19%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Basal cell carcinoma [A] †	1/538 (0.19%)
Breast cancer [A] †	3/538 (0.56%)
Breast cancer in situ [A] †	2/538 (0.37%)
Breast cancer stage II [A] †	1/538 (0.19%)
Breast cancer stage III [A] †	1/538 (0.19%)
Colon cancer metastatic [A] †	1/538 (0.19%)
Colon cancer stage II [A] †	1/538 (0.19%)
Diffuse large B-cell lymphoma stage III [A] †	1/538 (0.19%)
Endometrial cancer [A] †	1/538 (0.19%)
Haemangioma [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Hepatic neoplasm malignant [A] †	1/538 (0.19%)
Laryngeal cancer metastatic [A] †	1/538 (0.19%)
Lipoma [A] †	1/538 (0.19%)
Lung adenocarcinoma [A] †	1/538 (0.19%)
Lung adenocarcinoma stage III [A] †	1/538 (0.19%)
Malignant pleural effusion [A] †	1/538 (0.19%)
Metastatic gastric cancer [A] †	1/538 (0.19%)
Metastatic squamous cell carcinoma [A] †	1/538 (0.19%)
Ovarian cancer metastatic [A] †	1/538 (0.19%)
Ovarian epithelial cancer [A] †	1/538 (0.19%)
Prostate cancer stage I [A] †	1/538 (0.19%)
Rectal cancer stage III [A] †	1/538 (0.19%)
Skin papilloma [A] †	1/538 (0.19%)
Small cell lung cancer state unspecified [A] †	1/538 (0.19%)
Squamous cell carcinoma of the cervix [A] †	3/538 (0.56%)
Thyroid adenoma [A] †	1/538 (0.19%)
Uterine leiomyoma [A] †	1/538 (0.19%)
Nervous system disorders	
Carpal tunnel syndrome [A] †	1/538 (0.19%)
Cerebral ischaemia [A] †	1/538 (0.19%)
Dyskinesia [A] †	1/538 (0.19%)
Essential tremor [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Haemorrhagic stroke [A] †	1/538 (0.19%)
Headache [A] †	1/538 (0.19%)
Hypertensive encephalopathy [A] †	1/538 (0.19%)
Hypoaesthesia [A] †	1/538 (0.19%)
Migraine [A] †	1/538 (0.19%)
Nerve root compression [A] †	1/538 (0.19%)
Presyncope [A] †	1/538 (0.19%)
Sciatica [A] †	3/538 (0.56%)
Syncope [A] †	1/538 (0.19%)
Thrombotic cerebral infarction [A] †	1/538 (0.19%)
Tremor [A] †	1/538 (0.19%)
Pregnancy, puerperium and perinatal conditions	
Abortion spontaneous [A] †	3/538 (0.56%)
Pregnancy [A] †	3/538 (0.56%)
Psychiatric disorders	
Adjustment disorder [A] †	1/538 (0.19%)
Anxiety [A] †	1/538 (0.19%)
Confusional state [A] †	2/538 (0.37%)
Delirium [A] †	1/538 (0.19%)
Major depression [A] †	1/538 (0.19%)
Schizophrenia [A] †	1/538 (0.19%)
Suicide attempt [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Renal and urinary disorders	
Calculus urinary [A] †	1/538 (0.19%)
Nephrolithiasis [A] †	1/538 (0.19%)
Renal colic [A] †	1/538 (0.19%)
Urinary incontinence [A] †	1/538 (0.19%)
Reproductive system and breast disorders	
Endometriosis [A] †	1/538 (0.19%)
Female genital tract fistula [A] †	1/538 (0.19%)
Ovarian cyst [A] †	2/538 (0.37%)
Uterine haemorrhage [A] †	2/538 (0.37%)
Uterine polyp [A] †	1/538 (0.19%)
Uterine prolapse [A] †	1/538 (0.19%)
Respiratory, thoracic and mediastinal disorders	
Acute respiratory failure [A] †	1/538 (0.19%)
Emphysema [A] †	1/538 (0.19%)
Interstitial lung disease [A] †	2/538 (0.37%)
Mediastinal haemorrhage [A] †	1/538 (0.19%)
Pleural effusion [A] †	1/538 (0.19%)
Pneumonitis [A] †	1/538 (0.19%)
Pulmonary embolism [A] †	2/538 (0.37%)
Rheumatoid lung [A] †	1/538 (0.19%)
Skin and subcutaneous tissue disorders	
Actinic keratosis [A] †	1/538 (0.19%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Angioedema [A] †	1/538 (0.19%)
Cutaneous vasculitis [A] †	1/538 (0.19%)
Erythema [A] †	1/538 (0.19%)
Hyperkeratosis [A] †	1/538 (0.19%)
Vascular disorders	
Deep vein thrombosis [A] †	1/538 (0.19%)
Hypertension [A] †	3/538 (0.56%)
Hypertensive crisis [A] †	1/538 (0.19%)
Iliac artery occlusion [A] †	1/538 (0.19%)
Orthostatic hypotension [A] †	1/538 (0.19%)
Peripheral arterial occlusive disease [A] †	1/538 (0.19%)
Vasculitis necrotising [A] †	1/538 (0.19%)
Vericose vein [A] †	2/538 (0.37%)

† 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%

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Total	475/538 (88.29%)
Blood and lymphatic system disorders	
Leukopenia [A] †	31/538 (5.76%)
Ear and labyrinth disorders	
Vertigo [A] †	27/538 (5.02%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Eye disorders	
Conjunctivitis [A] †	27/538 (5.02%)
Gastrointestinal disorders	
Abdominal pain [A] †	32/538 (5.95%)
Abdominal pain upper [A] †	32/538 (5.95%)
Diarrhoea [A] †	85/538 (15.8%)
Dyspepsia [A] †	85/538 (15.8%)
Gastritis [A] †	35/538 (6.51%)
Gastrooesophageal reflux disease [A] †	28/538 (5.2%)
Mouth ulceration [A] †	29/538 (5.39%)
Nausea [A] †	50/538 (9.29%)
Infections and infestations	
Bronchitis [A] †	83/538 (15.43%)
Gastroenteritis [A] †	69/538 (12.83%)
Influenza [A] †	43/538 (7.99%)
Nasopharyngitis [A] †	133/538 (24.72%)
Oral herpes [A] †	37/538 (6.88%)
Pharyngitis [A] †	60/538 (11.15%)
Rhinitis [A] †	31/538 (5.76%)
Sinusitis [A] †	32/538 (5.95%)
Upper respiratory tract infection [A] †	136/538 (25.28%)
Urinary tract infection [A] †	93/538 (17.29%)
Investigations	

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Alanine aminotransferase increased [A] †	59/538 (10.97%)
Transaminases increased [A] †	51/538 (9.48%)
Metabolism and nutrition disorders	
Hypercholesterolaemia [A] †	33/538 (6.13%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] †	37/538 (6.88%)
Back pain [A] †	64/538 (11.9%)
Rheumatoid arthritis [A] †	64/538 (11.9%)
Nervous system disorders	
Dizziness [A] †	35/538 (6.51%)
Headache [A] †	89/538 (16.54%)
Psychiatric disorders	
Depression [A] †	43/538 (7.99%)
Insomnia [A] †	30/538 (5.58%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] †	46/538 (8.55%)
Oropharyngeal pain [A] †	32/538 (5.95%)
Skin and subcutaneous tissue disorders	
Rash [A] †	30/538 (5.58%)
Vascular disorders	
Hypertension [A] †	107/538 (19.89%)

† 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.

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