ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 11/11/2014

ClinicalTrials.gov ID: NCT01195272

Study Identification

Unique Protocol ID:	ML25243
Brief Title:	A Study of the Effects of RoActemra/Actemra (Tocilizumab) on Neutrophils in Patients With Active Rheumatoid Arthritis Who Have an Inadequate Response to Biologic and/or Non-biologic DMARDs.
Official Title:	A 52 Week, Single Center, Open-label Study to Evaluate Neutrophil Function and Survival Effects of Tocilizumab (TCZ) in Patients With Active Rheumatoid Arthritis (RA) on Background Non-biologic DMARDs Who Have an Inadequate Response to Current Non-biologic DMARD and/or Anti-TNF Therapy
Secondary IDs:	2010-018331-18

Study Status

Record Verification:	November 2014
Overall Status:	Completed
Study Start:	August 2010
Primary Completion:	March 2012 [Actual]
Study Completion:	March 2012 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? No Delayed Posting?
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 10/H0904/14 Board Name: Sunderland Research Ethics Committte Board Affiliation: National Research Ethics Service Phone: 0191 4283545 Email: bill.hackett@suntpct.nhs.uk
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	United Kingdom: Medicines and Healthcare Products Regulatory Agency

Study Description

Brief Summary:	This open-label, single arm study will assess the effect of RoActemra/Actemra (tocilizumab) on neutrophils and monitor safety and benefit-risk of RoActemra/Actemra treatment in patients with active rheumatoid arthritis who have an inadequate response to current biologic or non-biologic disease-modifying antirheumatic drugs (DMARDs). Patients will receive RoActemra/Actemra at a dose of 8 mg/kg intravenously every 4 weeks, either as monotherapy or in combination with their current non-biologic DMARD. Anticipated time on study treatment is 52 weeks.
Detailed Description:	

Conditions

Conditions:	Rheumatoid Arthritis
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 4

Intervention Model:	Single Group Assignment
Number of Arms:	1
Masking:	Open Label
Allocation:	Non-Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	21 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Single Arm	Drug: tocilizumab [RoActemra/Actemra] 8 mg/kg iv every 4 weeks, 52 weeks

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Gender:	Both
Accepts Healthy Volunteers?:	No

Criteria: Inclusion Criteria:

- Adult patients, >/= 18 years of age
- Moderate to severe active rheumatoid arthritis of >/= 6 months duration
- DAS28 >/= 3.2 at screening and baseline
- Inadequate response to biologic or non-biologic DMARDs
- Biologic DMARDs must be withdrawn (approximately 5 half-lives for the agent) before first dose of study drug
- If continuing on a non-biologic DMARD, dose should be stable for at least 8 weeks
- Oral corticosteroids must have been at stable dose for at least 25 out of 28 days prior to baseline

Exclusion Criteria:

- Major surgery (including joint surgery) within 8 weeks prior to screening or not recovered from prior surgery
- Rheumatic autoimmune disease other then RA
- Functional class IV as defined by the American College of Rheumatology (ACR) classification
- Prior history of or current inflammatory joint disease other than RA

- Previous treatment with any cell-depleting therapies
- Intraarticular or parenteral corticosteroids within 4 weeks prior to baseline
- Active infection or history of recurrent infection
- Positive for HIV or hepatitis B or C
- History of or current primary or secondary immunodeficiency

Contacts/Locations

Study Officials: Clinical Trials
Study Director
Hoffmann-La Roche

Locations: United Kingdom
Liverpool, United Kingdom, L9 7AL

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Tocilizumab 8 Milligrams Per Kilogram (mg/kg)	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) intravenously (IV), once every 4 weeks up to 52 weeks (total of 13 infusions).

Overall Study

	Tocilizumab 8 Milligrams Per Kilogram (mg/kg)
Started	21
Completed	17
Not Completed	4

	Tocilizumab 8 Milligrams Per Kilogram (mg/kg)
Adverse Event	1
Lack of Efficacy	3

Baseline Characteristics

Analysis Population Description

Safety Population: all participants who received at least 1 dose of tocilizumab treatment and had at least 1 post-baseline safety assessment.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Baseline Measures

	Tocilizumab 8 mg/kg
Number of Participants	21
Age, Continuous [units: Years] Mean (Standard Deviation)	49.2 (11.2)
Gender, Male/Female [units: participants]	
Female	18
Male	3

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis
Measure Description	Aging neutrophils translocate phosphatidylserine from the inner leaflet of the plasma membrane to the outer leaflet during the early stages of apoptosis. This translocation can be measured due to the affinity of fluorescein isothiocyanate (FITC)-labeled annexin V to bind exposed phosphatidylserine. Cells that stain positive to Annexin V binding are apoptotic. At 4 hours (hrs) and 20 hrs stimulated and control samples were analyzed for levels of apoptosis.
Time Frame	Visits 2, 3, 5, and 8 (Baseline and Weeks 4, 12 and 24)
Safety Issue?	No

Analysis Population Description

Intent-to-treat (ITT) Population: all participants in the Safety Population who provided follow-up data for neutrophils or at least 1 efficacy variable. n (number) equals (=) number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19
Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis [units: percentage of cells staining positive] Mean (Standard Deviation)	
Visit 2, 4 hrs (n=19)	8.95 (5.46)
Visit 3, 4 hrs (n=19)	7.36 (4.18)
Visit 5, 4 hrs (n=19)	8.45 (4.64)
Visit 8, 4 hrs (n=15)	12.43 (6.34)
Visit 2, 20 hrs (n=19)	53.97 (8.97)
Visit 3, 20 hrs (n=19)	50.32 (10.64)
Visit 5, 20 hrs (n=19)	50.50 (15.51)
Visit 8, 20 hrs (n=15)	48.24 (10.37)

Statistical Analysis 1 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.308
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 2 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.415
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 3 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.335
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 4 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 8 versus Visit 2

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

Statistical Test of Hypothesis	P-Value	0.120
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 5 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 8 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.061
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 6 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 8 versus Visit 5
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.031
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 7 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.131
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 8 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.202
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 9 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.484
	Comments	[Not specified]

	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 10 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 8 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.047
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 11 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 8 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.285
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 12 for Mean Percentage of Cells Staining Positive for Annexin V Binding in Apoptosis

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 8 versus Visit 5
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.315
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

2. Primary Outcome Measure:

Measure Title	Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)
Measure Description	Aging neutrophils translocate phosphatidylserine from the inner leaflet of the plasma membrane to the outer leaflet during the early stages of apoptosis. This translocation can be measured due to the affinity of FITC-labeled annexin V to bind exposed phosphatidylserine. Cells that stain positive to Annexin V binding are apoptotic. At 4 hrs and 20 hrs stimulated and control samples were analyzed for levels of apoptosis. GM-CSF is an agent that delays apoptosis. Percentage of cells that stained positive for Annexin V binding in the presence or absence of GM-CSF (GM-CSF delayed or constitutive) were determined by flow cytometry.
Time Frame	Visits 2, 3, 5, and 8 (Baseline and Weeks 4, 12 and 24)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19
Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) [units: percentage of cells staining positive] Mean (Standard Deviation)	
Visit 2, 4 hrs (n=19)	5.46 (6.73)
Visit 3, 4 hrs (n=19)	4.18 (7.13)

	Tocilizumab 8 mg/kg
Visit 5, 4 hrs (n=19)	4.64 (3.18)
Visit 8, 4 hrs (n=15)	6.34 (2.58)
Visit 2, 20 hrs (n=19)	27.00 (11.16)
Visit 3, 20 hrs (n=19)	28.35 (10.95)
Visit 5, 20 hrs (n=19)	29.68 (14.78)
Visit 8, 20 hrs (n=15)	27.79 (12.01)

Statistical Analysis 1 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.288
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 2 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.318
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 3 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.400
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 4 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 8 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.317
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 5 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 8 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.137
	Comments	[Not specified]

	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 6 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	4 hrs: Visit 8 versus Visit 5
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.052
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 7 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.354
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 8 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.266
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 9 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.378
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 10 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 8 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.422
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 11 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 8 versus Visit 3

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

Statistical Test of Hypothesis	P-Value	0.444
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Statistical Analysis 12 for Mean Percentage of Cells Staining Positive for Annexin V Binding With Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	20 hrs: Visit 8 versus Visit 5
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.345
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

3. Primary Outcome Measure:

Measure Title	Mean Fluorescence Intensity of CD11b on Neutrophil Surface
Measure Description	Neutrophils were incubated with labeled antibodies against CD11b. Flow cytometry was used to determine the mean fluorescence intensity. Greater fluorescence correlates with greater adhesion, migration, and ingestion of complement-opsonized particles.
Time Frame	Visits 2, 3, and 5 (Baseline and Weeks 4 and 12)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19
Mean Fluorescence Intensity of CD11b on Neutrophil Surface [units: fluorescence intensity unit] Mean (Standard Deviation)	
Visit 2 (n=19)	286.40 (105.86)
Visit 3 (n=17)	275.33 (127.37)
Visit 5 (n=16)	240.93 (77.50)

Statistical Analysis 1 for Mean Fluorescence Intensity of CD11b on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.39
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 2 for Mean Fluorescence Intensity of CD11b on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.08
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 3 for Mean Fluorescence Intensity of CD11b on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.18
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

4. Primary Outcome Measure:

Measure Title	Mean Fluorescence Intensity of CD18 on Neutrophil Surface
Measure Description	Neutrophils were incubated with labeled antibodies against CD18. Flow cytometry was used to determine the mean fluorescence intensity. Greater fluorescence correlates with greater adhesion, migration, and ingestion of complement-opsonized particles.
Time Frame	Visits 2, 3, and 5 (Baseline and Weeks 4 and 12)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed at each visit

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19
Mean Fluorescence Intensity of CD18 on Neutrophil Surface [units: fluorescence intensity unit] Mean (Standard Deviation)	
Visit 2 (n=19)	20.33 (8.30)
Visit 3 (n=17)	20.47 (12.31)
Visit 5 (n=16)	22.47 (15.42)

Statistical Analysis 1 for Mean Fluorescence Intensity of CD18 on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.48
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 2 for Mean Fluorescence Intensity of CD18 on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.30
	Comments	[Not specified]

	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 3 for Mean Fluorescence Intensity of CD18 on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.34
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

5. Primary Outcome Measure:

Measure Title	Mean Fluorescence Intensity of CD62L (L Selectin) on Neutrophil Surface
Measure Description	Neutrophils were incubated with labeled antibody against CD62L (L selectin). Flow cytometry was used to determine the mean fluorescence intensity. Greater fluorescence correlates with greater adhesion of neutrophils to vessel walls.
Time Frame	Visits 2, 3 and 5 (Baseline and Weeks 4 and 12)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19

	Tocilizumab 8 mg/kg
Mean Fluorescence Intensity of CD62L (L Selectin) on Neutrophil Surface [units: fluorescence intensity unit] Mean (Standard Deviation)	
Visit 2 (n=19)	20.56 (10.05)
Visit 3 (n=17)	23.40 (11.55)
Visit 5 (n=16)	19.93 (15.32)

Statistical Analysis 1 for Mean Fluorescence Intensity of CD62L (L Selectin) on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.22
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 2 for Mean Fluorescence Intensity of CD62L (L Selectin) on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.44
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 3 for Mean Fluorescence Intensity of CD62L (L Selectin) on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.23
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

6. Primary Outcome Measure:

Measure Title	Mean Fluorescence Intensity of CD63 on Neutrophil Surface
Measure Description	Neutrophils were incubated with labeled antibody against CD63b. Flow cytometry was used to determine the mean fluorescence intensity. Greater fluorescence correlates with greater azurophilic degranulation, an indicator of greater microbe killing.
Time Frame	Visits 2, 3, and 5 (Baseline and Weeks 4 and 12)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19
Mean Fluorescence Intensity of CD63 on Neutrophil Surface [units: fluorescence intensity unit] Mean (Standard Deviation)	

	Tocilizumab 8 mg/kg
Visit 2 (n=19)	31.00 (20.68)
Visit 3 (n=17)	26.34 (14.55)
Visit 5 (n=16)	30.28 (16.53)

Statistical Analysis 1 for Mean Fluorescence Intensity of CD63 on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.22
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 2 for Mean Fluorescence Intensity of CD63 on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.46
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 3 for Mean Fluorescence Intensity of CD63 on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.24
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

7. Primary Outcome Measure:

Measure Title	Mean Fluorescence Intensity of Interleukin-6 Receptor (Il-6R) on Neutrophil Surface
Measure Description	Neutrophils were incubated with labeled antibody against IL-6R. Flow cytometry was used to determine the mean fluorescence intensity. Greater fluorescence correlates with greater density of membrane bound IL-6 receptor.
Time Frame	Visits 2, 3, and 5 (Baseline and Weeks 4 and 12)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19
Mean Fluorescence Intensity of Interleukin-6 Receptor (Il-6R) on Neutrophil Surface [units: fluorescence intensity unit] Mean (Standard Deviation)	
Visit 2 (n=19)	2.72 (1.50)

	Tocilizumab 8 mg/kg
Visit 3 (n=17)	3.69 (1.97)
Visit 5 (n=16)	4.42 (2.55)

Statistical Analysis 1 for Mean Fluorescence Intensity of Interleukin-6 Receptor (Il-6R) on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.05
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 2 for Mean Fluorescence Intensity of Interleukin-6 Receptor (Il-6R) on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.01
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 3 for Mean Fluorescence Intensity of Interleukin-6 Receptor (Il-6R) on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3

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

Statistical Test of Hypothesis	P-Value	0.18
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

8. Primary Outcome Measure:

Measure Title	Mean Fluorescence Intensity of Membrane Bound Tumor Necrosis Factor Alpha (mTNFα) on Neutrophil Surface
Measure Description	Neutrophils were incubated with labeled antibody against mTNF. Flow cytometry was used to determine the mean fluorescence intensity. Greater fluorescence correlates to a greater density of membrane bound TNF.
Time Frame	Visits 2, 3, and 5 (Baseline and Weeks 4 and 12)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19
Mean Fluorescence Intensity of Membrane Bound Tumor Necrosis Factor Alpha (mTNFα) on Neutrophil Surface [units: fluorescence intensity unit] Mean (Standard Deviation)	
Visit 2 (n=19)	3.49 (3.32)
Visit 3 (n=17)	3.55 (3.29)
Visit 5 (n=16)	3.75 (4.85)

Statistical Analysis 1 for Mean Fluorescence Intensity of Membrane Bound Tumor Necrosis Factor Alpha (mTNFα) on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.48
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 2 for Mean Fluorescence Intensity of Membrane Bound Tumor Necrosis Factor Alpha (mTNFα) on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.43
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 3 for Mean Fluorescence Intensity of Membrane Bound Tumor Necrosis Factor Alpha (mTNFα) on Neutrophil Surface

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.44
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

9. Primary Outcome Measure:

Measure Title	Mean Chemiluminescence (Area Under the Concentration-time Curve [AUC]) of Neutrophil Reactive Species Production Using Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) Stimulation
Measure Description	Using luminol as a substrate for reactive oxidants, a chemical reaction is produced resulting in photon emission (chemiluminescence). fMLP stimulation is mediated through the fMLP receptor on the cell surface. The fMLP response is only observed in primed neutrophils and response is a measure of in vivo priming. Measurements of reactive oxygen species are calculated as total chemiluminescence or the AUC.
Time Frame	Visit 2, 3, 5, and 8 (Baseline and predose at Weeks 4, 12 and 24)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19
Mean Chemiluminescence (Area Under the Concentration-time Curve [AUC]) of Neutrophil Reactive Species Production Using Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) Stimulation [units: chemiluminescence units*hours] Mean (Standard Deviation)	
Visit 2 (n=19)	8671 (4597.18)
Visit 3 (n=18)	9971 (7139.36)
Visit 5 (n=17)	32361 (72947.87)

	Tocilizumab 8 mg/kg
Visit 8 (n=14)	10573 (5537.06)

Statistical Analysis 1 for Mean Chemiluminescence (Area Under the Concentration-time Curve [AUC]) of Neutrophil Reactive Species Production Using Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.313
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 2 for Mean Chemiluminescence (Area Under the Concentration-time Curve [AUC]) of Neutrophil Reactive Species Production Using Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.083
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 3 for Mean Chemiluminescence (Area Under the Concentration-time Curve [AUC]) of Neutrophil Reactive Species Production Using Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3

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

Statistical Test of Hypothesis	P-Value	0.092
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 4 for Mean Chemiluminescence (Area Under the Concentration-time Curve [AUC]) of Neutrophil Reactive Species Production Using Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.145
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 5 for Mean Chemiluminescence (Area Under the Concentration-time Curve [AUC]) of Neutrophil Reactive Species Production Using Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.398
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 6 for Mean Chemiluminescence (Area Under the Concentration-time Curve [AUC]) of Neutrophil Reactive Species Production Using Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 5
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.138
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

10. Primary Outcome Measure:

Measure Title	Mean Chemiluminescence (AUC) of Neutrophil Reactive Species Production Using Phorbol 12-Myristate 13-Acetate (PMA) Stimulation
Measure Description	Using luminol as a substrate for reactive oxidants, a chemical reaction is produced resulting in photon emission (chemiluminescence). PMA is a receptor-independent stimulator of the respiratory burst and the PMA response measures the total capacity of neutrophils to generate reactive oxidants. Measurements of reactive oxygen species are calculated as total chemiluminescence or the AUC.
Time Frame	Visit 2, 3, 5, and 8 (Baseline and predose at Weeks 4, 12 and 24)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19

	Tocilizumab 8 mg/kg
Mean Chemiluminescence (AUC) of Neutrophil Reactive Species Production Using Phorbol 12-Myristate 13-Acetate (PMA) Stimulation [units: chemiluminescence units * hours] Mean (Standard Deviation)	
Visit 2 (n=19)	141039 (72621.95)
Visit 3 (n=18)	145304 (48836.93)
Visit 5 (n=17)	157028 (73054.72)
Visit 8 (n=14)	116968 (51291.31)

Statistical Analysis 1 for Mean Chemiluminescence (AUC) of Neutrophil Reactive Species Production Using Phorbol 12-Myristate 13-Acetate (PMA) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.467
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 2 for Mean Chemiluminescence (AUC) of Neutrophil Reactive Species Production Using Phorbol 12-Myristate 13-Acetate (PMA) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.250
	Comments	[Not specified]

	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 3 for Mean Chemiluminescence (AUC) of Neutrophil Reactive Species Production Using Phorbol 12-Myristate 13-Acetate (PMA) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.060
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 4 for Mean Chemiluminescence (AUC) of Neutrophil Reactive Species Production Using Phorbol 12-Myristate 13-Acetate (PMA) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.149
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 5 for Mean Chemiluminescence (AUC) of Neutrophil Reactive Species Production Using Phorbol 12-Myristate 13-Acetate (PMA) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.061
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 6 for Mean Chemiluminescence (AUC) of Neutrophil Reactive Species Production Using Phorbol 12-Myristate 13-Acetate (PMA) Stimulation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 5
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.047
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

11. Primary Outcome Measure:

Measure Title	Percentage of Neutrophils Positive for Propidium Iodide (PI)-Labeled Staphylococcus Aureus (S. Aureus) Uptake
Measure Description	S. aureus were heat killed then labeled with PI and opsonized with AB serum (SAPI). S. aureus was then incubated with the neutrophils for 30 minutes at 37 degrees Celsius. The neutrophils were washed, then the percentage of cells positive for the labeled S. aureus (that is, phagocytosed) was calculated via flow cytometry. A higher percentage represented more active phagocytosis.
Time Frame	Visit 2, 3, 5, and 8 (Baseline and Weeks 4, 12 and 24)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19
Percentage of Neutrophils Positive for Propidium Iodide (PI)-Labeled Staphylococcus Aureus (S. Aureus) Uptake [units: percentage of positive neutrophils] Mean (Standard Deviation)	
Visit 2 (n=19)	96.59 (3.01)
Visit 3 (n=19)	97.47 (2.56)
Visit 5 (n=17)	97.53 (2.68)
Visit 8 (n=15)	97.25 (2.27)

Statistical Analysis 1 for Percentage of Neutrophils Positive for Propidium Iodide (PI)-Labeled Staphylococcus Aureus (S. Aureus) Uptake

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.169
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 2 for Percentage of Neutrophils Positive for Propidium Iodide (PI)-Labeled Staphylococcus Aureus (S. Aureus) Uptake

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.165
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 3 for Percentage of Neutrophils Positive for Propidium Iodide (PI)-Labeled Staphylococcus Aureus (S. Aureus) Uptake

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.471
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 4 for Percentage of Neutrophils Positive for Propidium Iodide (PI)-Labeled Staphylococcus Aureus (S. Aureus) Uptake

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.243
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 5 for Percentage of Neutrophils Positive for Propidium Iodide (PI)-Labeled Staphylococcus Aureus (S. Aureus) Uptake

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 3

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

Statistical Test of Hypothesis	P-Value	0.396
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 6 for Percentage of Neutrophils Positive for Propidium Iodide (PI)-Labeled Staphylococcus Aureus (S. Aureus) Uptake

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 5
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.375
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

12. Primary Outcome Measure:

Measure Title	Percentage of Neutrophils Positive for Dihydrorhodamine-123 (DHR) Oxidation
Measure Description	Phagocytosis can be measured by incubating neutrophils with PI-labeled heat killed S. aureus following incubation for 30 minutes. Neutrophils are co-incubated with DHR, which becomes oxidized by the products of the respiratory burst generated during phagocytosis. Fluorescence can then be measured by flow cytometry.
Time Frame	Visit 2, 3, 5, and 8 (Baseline and Weeks 4, 12 and 24)
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	19
Percentage of Neutrophils Positive for Dihydrorhodamine-123 (DHR) Oxidation [units: percentage of positive neutrophils] Mean (Standard Deviation)	
Visit 2 (n=19)	99.21 (2.43)
Visit 3 (n=19)	99.20 (1.93)
Visit 5 (n=17)	99.91 (0.18)
Visit 8 (n=15)	99.92 (0.22)

Statistical Analysis 1 for Percentage of Neutrophils Positive for Dihydrorhodamine-123 (DHR) Oxidation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 3 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.496
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 2 for Percentage of Neutrophils Positive for Dihydrorhodamine-123 (DHR) Oxidation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 2

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

Statistical Test of Hypothesis	P-Value	0.122
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 3 for Percentage of Neutrophils Positive for Dihydrorhodamine-123 (DHR) Oxidation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 5 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.070
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 4 for Percentage of Neutrophils Positive for Dihydrorhodamine-123 (DHR) Oxidation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 2
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.135
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 5 for Percentage of Neutrophils Positive for Dihydrorhodamine-123 (DHR) Oxidation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 3
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.082
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Statistical Analysis 6 for Percentage of Neutrophils Positive for Dihydrorhodamine-123 (DHR) Oxidation

Statistical Analysis Overview	Comparison Groups	Tocilizumab 8 mg/kg
	Comments	Visit 8 versus Visit 5
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.461
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

13. Secondary Outcome Measure:

Measure Title	Disease Activity Score Based on 28-Joint Count (DAS28)
Measure Description	The DAS28 is a combined index for measuring disease activity in rheumatoid arthritis. The index includes swollen and tender joint counts, acute phase response (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]), and general health status. The DAS28, which uses a 28 joint count, is derived from the original DAS, which includes a 44 swollen joint count. The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity.
Time Frame	Screening, Baseline, and Weeks 4, 8, 12, 16, 20, 24, 36, 48, and 52
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	21
Disease Activity Score Based on 28-Joint Count (DAS28) [units: score on a scale] Mean (Standard Deviation)	
Screening (n=21)	5.67 (1.22)
Baseline (n=21)	6.15 (1.26)
Week 4 (n=21)	4.90 (1.40)
Week 8 (n=20)	4.31 (1.64)
Week 12 (n=20)	3.83 (1.45)
Week 16 (n=20)	3.81 (1.69)
Week 20 (n=20)	3.92 (1.45)
Week 24 (n=16)	3.26 (1.49)
Week 36 (n=12)	3.27 (1.33)
Week 48 (n=11)	3.59 (1.62)
Week 52 (n=18)	3.58 (1.51)

14. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Acceptable and Not Acceptable Benefit-Risk Assessments
Measure Description	Benefit:Risk was defined at the participant level. It was considered acceptable if the DAS28 improvement represented at least a moderate European League Against Rheumatism (EULAR) response. The risks were based on the known adverse event (AE) profile of tocilizumab rather than on the actual AEs experienced by each participant

Time Frame	Weeks 12, 24, and 36
Safety Issue?	No

Analysis Population Description

ITT Population; n=number of participants analyzed for the specified parameter at a given visit.

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Measured Values

	Tocilizumab 8 mg/kg
Number of Participants Analyzed	20
Percentage of Participants With Acceptable and Not Acceptable Benefit-Risk Assessments [units: percentage of participants]	
Acceptable, Week 12	100
Not Acceptable, Week 12	0
Acceptable, Week 24	94
Not Acceptable, Week 24	6
Acceptable, Week 36	92
Not Acceptable, Week 36	8

Reported Adverse Events

Time Frame	Adverse events were recorded from the date of Screening until the End of Study which was the follow up visit after 48 Weeks of extension treatment period.
Additional Description	[Not specified]

Reporting Groups

	Description
Tocilizumab 8 mg/kg	Participants received tocilizumab 8 mg/kg (maximum dose 800 mg) IV, once every 4 weeks up to 52 weeks (total of 13 infusions).

Serious Adverse Events

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Total	4/21 (19.05%)
Blood and lymphatic system disorders	
Neutropenia A [1] *	1/21 (4.76%)
Infections and infestations	
Pneumonia Viral A *	1/21 (4.76%)
Injury, poisoning and procedural complications	
Hip Fracture A *	1/21 (4.76%)
Respiratory, thoracic and mediastinal disorders	
Pulmonary Embolism A *	1/21 (4.76%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (14.0)

[1] After the third Tocilizumab administration was given patient had a neutrophil count of 0.39 x 109/L. No infection was reported. when the neutrophil count reached back to 2.16 x 109/L, the event was considered to have resolved without intervention.

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Total	21/21 (100%)
Blood and lymphatic system disorders	
Neutropenia A *	2/21 (9.52%)
Cardiac disorders	

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Palpitations [A] *	1/21 (4.76%)
Endocrine disorders	
Cushingoid [A] *	1/21 (4.76%)
Gastrointestinal disorders	
Abdominal pain [A] *	1/21 (4.76%)
Abdominal tenderness [A] *	1/21 (4.76%)
Constipation [A] *	4/21 (19.05%)
Diarrhea [A] *	7/21 (33.33%)
Dry mouth [A] *	4/21 (19.05%)
Dyspepsia [A] *	4/21 (19.05%)
Gastric ulcer [A] *	1/21 (4.76%)
Gastroesophageal reflux disease [A] *	1/21 (4.76%)
Gastrointestinal haemorrhage [A] *	1/21 (4.76%)
Mouth ulceration [A] *	3/21 (14.29%)
Nausea [A] *	3/21 (14.29%)
General disorders	
Chest pain [A] *	1/21 (4.76%)
Fatigue [A] *	4/21 (19.05%)
Malaise [A] *	3/21 (14.29%)
Infections and infestations	
Candidiasis [A] *	1/21 (4.76%)
Cystitis [A] *	1/21 (4.76%)
Ear infection [A] *	3/21 (14.29%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Eye infection [A] *	1/21 (4.76%)
Herpes simplex [A] *	1/21 (4.76%)
Herpes zoster [A] *	1/21 (4.76%)
Lower respiratory tract infection [A] *	9/21 (42.86%)
Nasopharyngitis [A] *	8/21 (38.1%)
Pneumonia [A] *	1/21 (4.76%)
Sinusitis [A] *	1/21 (4.76%)
Tooth abscess [A] *	1/21 (4.76%)
Urinary tract infection [A] *	3/21 (14.29%)
Injury, poisoning and procedural complications	
Arthropod bite [A] *	1/21 (4.76%)
Fall [A] *	1/21 (4.76%)
Infusion related reaction [A] *	1/21 (4.76%)
Investigations	
Blood cholesterol increased [A] *	1/21 (4.76%)
Neutrophil count decreased [A] *	2/21 (9.52%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] *	4/21 (19.05%)
Axillary mass [A] *	1/21 (4.76%)
Back pain [A] *	4/21 (19.05%)
Joint lock [A] *	2/21 (9.52%)
Joint stiffness [A] *	1/21 (4.76%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Joint swelling [A] *	4/21 (19.05%)
Musculoskeletal discomfort [A] *	2/21 (9.52%)
Musculoskeletal stiffness [A] *	1/21 (4.76%)
Myalgia [A] *	1/21 (4.76%)
Neck pain [A] *	1/21 (4.76%)
Pain in extremity [A] *	3/21 (14.29%)
Rheumatoid arthritis [A] *	10/21 (47.62%)
Nervous system disorders	
Dizziness [A] *	1/21 (4.76%)
Dysgeusia [A] *	1/21 (4.76%)
Headache [A] *	4/21 (19.05%)
Sciatica [A] *	1/21 (4.76%)
Psychiatric disorders	
Anxiety [A] *	1/21 (4.76%)
Depression [A] *	1/21 (4.76%)
Insomnia [A] *	1/21 (4.76%)
Renal and urinary disorders	
Dysuria [A] *	1/21 (4.76%)
Reproductive system and breast disorders	
Dysmenorrhea [A] *	1/21 (4.76%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] *	3/21 (14.29%)
Oropharyngeal pain [A] *	4/21 (19.05%)

	Tocilizumab 8 mg/kg
	Affected/At Risk (%)
Productive cough [A] *	1/21 (4.76%)
Pulmonary fibrosis [A] *	2/21 (9.52%)
Skin and subcutaneous tissue disorders	
Alopecia [A] *	1/21 (4.76%)
Heat rash [A] *	1/21 (4.76%)
Night sweats [A] *	1/21 (4.76%)
Pruritus allergic [A] *	1/21 (4.76%)
Pruritus generalised [A] *	1/21 (4.76%)
Psoriasis [A] *	1/21 (4.76%)
Rash [A] *	3/21 (14.29%)
Rash pruritic [A] *	1/21 (4.76%)
Seborrhoeic dermatitis [A] *	1/21 (4.76%)
Vascular disorders	
Hot flush [A] *	1/21 (4.76%)
Hypertension [A] *	2/21 (9.52%)
Peripheral coldness [A] *	2/21 (9.52%)
Vasculitis [A] *	1/21 (4.76%)

* Indicates events were collected by non-systematic methods.
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.

Results Point of Contact:

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