ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
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A Study of Tocilizumab (RoActemra/Actemra) in Patients With Ankylosing Spondylitis Who Have Had an Inadequate Response to Previous Tumor Necrosis Factor (TNF) Antagonist Therapy

This study has been terminated.
(Clinical development program terminated due to failure to achieve efficacy)

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT01209689

Purpose

This randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of tocilizumab (RoActemra/Actemra) in patients with ankylosing spondylitis (AS) who had an inadequate response to previous tumor necrosis factor (TNF) antagonist therapy. Patients were randomized to receive tocilizumab at a dose of either 8 mg/kg or 4 mg/kg intravenously (iv) or placebo every 4 weeks for 24 weeks. The double-blind treatment period was followed by open-label treatment with tocilizumab 8 mg/kg iv every 4 weeks until Week 104 for all patients.

This study and all further clinical development of tocilizumab AS was halted after a review of 12-week data from Study NA22823, a randomized double-blind, placebo-controlled study in TNF antagonist naïve AS patients, failed to demonstrate efficacy.

Condition	Intervention	Phase
Spondylitis, Ankylosing	Drug: Tocilizumab Drug: Placebo	Phase 3

Study Type: Interventional

Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study
Official Title: A Randomized, Double-blind, Parallel Group Placebo-controlled Study of the Safety and Reduction of Signs and Symptoms During Treatment With Tocilizumab (TCZ) Versus Placebo in Patients With Ankylosing Spondylitis Who Have Had an Inadequate Response to Previous TNF Antagonist Therapy

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Percentage of ASsessment in Ankylosing Spondylitis 20 (ASAS20) Responders at Week 12 [Time Frame: Baseline to Week 12] [Designated as safety issue: No]

  ASAS20 was defined as an improvement of ≥ 20% and an absolute improvement of ≥ 10 units on a 0-100 visual analog scale (VAS) from Baseline to Week 12 in 3 of 4 domains: 1-Patient global assessment (with extremes labelled none and severe), 2-Pain assessment (average total and nocturnal pain scores with extremes labelled no pain and most severe pain), 3-Function (represented by the Bath Ankylosing Spondylitis (BAS) Functional Index [BASFI] average of 10 questions regarding ability to perform specific tasks with extremes labelled easy and impossible), and 4-Inflammation (average of the last 2 questions on the 6-question BAS Disease Activity Index [BASDAI] concerning morning stiffness intensity with extremes labelled none and very severe and duration between 0 and 2 or more hours); and the absence of deterioration (of at least 20% and absolute change of at least 10 units on a 0-100 mm scale) in the remaining domain.

Enrollment: 113
Study Start Date: October 2010
Primary Completion Date: December 2011
Study Completion Date: December 2011

Arms	Assigned Interventions
Experimental: Tocilizumab 4 mg/kg Patients received tocilizumab 4 mg/kg intravenously every 4 weeks for 24 weeks.	Drug: Tocilizumab Other Names: RoActemra Actemra
Experimental: Tocilizumab 8 mg/kg Patients received tocilizumab 8 mg/kg intravenously every 4 weeks for 24 weeks.	Drug: Tocilizumab Other Names: RoActemra Actemra
Placebo Comparator: Placebo Patients received placebo to tocilizumab intravenously every 4 weeks for 24 weeks.	Drug: Placebo

Eligibility

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

Criteria

Inclusion Criteria:

- Adult patients ≥ 18 years of age.
- Ankylosing spondylitis as defined by the modified New York criteria for ≥ 3 months prior to baseline.
- Active disease at screening and baseline (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥ 4.0, spinal pain visual analog scale [VAS] ≥ 40).
- Inadequate response or intolerant to 1 or more previous non-steroidal anti-inflammatory drugs (NSAIDs).
- Inadequate response to treatment with etanercept, infliximab, adalimumab, or golimumab because of inadequate efficacy.
- Tumor necrosis factor (TNF) antagonist therapy must have been discontinued at least 8 weeks prior to baseline (etanercept 4 weeks).
- Traditional disease-modifying anti-rheumatic drugs (DMARDs) must be withdrawn for at least 4 weeks prior to baseline (methotrexate, sulfasalazine, and hydroxychloroquine or chloroquine may be allowed if at stable dose for at least 4 weeks prior to baseline).
- Oral corticosteroids (≥ 10 mg/day prednisone or equivalent) and NSAIDs/cyclooxygenase-2 [COX-2] inhibitors must be at stable dose for at least 4 weeks prior to baseline.

Exclusion Criteria:

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

Contacts and Locations

Locations

United States, California
Huntington Beach, California, United States, 92646
United States, Florida
Aventura, Florida, United States, 33180
Miami, Florida, United States, 33169
Orlando, Florida, United States, 32804
Tampa, Florida, United States, 33609
United States, Georgia
Atlanta, Georgia, United States, 30342
Decatur, Georgia, United States, 30033
Marietta, Georgia, United States, 30060
United States, Idaho
Idaho Falls, Idaho, United States, 83404
United States, Kansas
Wichita, Kansas, United States, 67207
United States, Maryland

Hagerstown, Maryland, United States, 21740
United States, Michigan
St. Claire Shores, Michigan, United States, 48081
United States, New Jersey
Freehold, New Jersey, United States, 07728
United States, North Carolina
Asheville, North Carolina, United States, 28803
Charlotte, North Carolina, United States, 28210
Greensboro, North Carolina, United States, 27408
United States, Pennsylvania
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Austin, Texas, United States, 78731
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Heidelberg, Australia, 3084
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Sydney, Australia, 2050
Woodville, Australia, 5011
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Gent, Belgium, 9000
Kortrijk, Belgium, 8500
Liege, Belgium, 4000
Yvoir, Belgium, 5530
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Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	WA22908 2009-017488-40
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	Because of the early termination of the study and the limited and varying duration of treatment, the 4 mg/kg and 8 mg/kg tocilizumab dose groups were combined in the efficacy and safety analyses and reporting.

Reporting Groups

	Description
Tocilizumab 4 or 8 mg/kg	Patients received tocilizumab 4 or 8 mg/kg intravenously every 4 weeks for 24 weeks.
Placebo	Patients received placebo to tocilizumab intravenously every 4 weeks for 24 weeks.

Overall Study

	Tocilizumab 4 or 8 mg/kg	Placebo
Started	91	22
Completed	0	0
Not Completed	91	22
Insufficient Therapeutic Response	7	2
Refused Treatment	8	3
Adverse Event	4	0
Violation of Selection Criteria at Entry	1	0
Failure to Return	3	0
Sponsor's Decision to Stop the Study	68	17

Baseline Characteristics

Reporting Groups

	Description
Tocilizumab 4 or 8 mg/kg	Patients received tocilizumab 4 or 8 mg/kg intravenously every 4 weeks for 24 weeks.
Placebo	Patients received placebo to tocilizumab intravenously every 4 weeks for 24 weeks.

Baseline Measures

	Tocilizumab 4 or 8 mg/kg	Placebo	Total
Number of Participants	91	22	113
Age, Continuous [units: years] Mean (Standard Deviation)	44.1 (12.08)	45.0 (12.66)	44.3 (12.14)
Gender, Male/Female [units: participants]			
Female	29	8	37

	Tocilizumab 4 or 8 mg/kg	Placebo	Total
Male	62	14	76

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of ASsessment in Ankylosing Spondylitis 20 (ASAS20) Responders at Week 12
Measure Description	ASAS20 was defined as an improvement of ≥ 20% and an absolute improvement of ≥ 10 units on a 0-100 visual analog scale (VAS) from Baseline to Week 12 in 3 of 4 domains: 1-Patient global assessment (with extremes labelled none and severe), 2-Pain assessment (average total and nocturnal pain scores with extremes labelled no pain and most severe pain), 3-Function (represented by the Bath Ankylosing Spondylitis (BAS) Functional Index [BASFI] average of 10 questions regarding ability to perform specific tasks with extremes labelled easy and impossible), and 4-Inflammation (average of the last 2 questions on the 6-question BAS Disease Activity Index [BASDAI] concerning morning stiffness intensity with extremes labelled none and very severe and duration between 0 and 2 or more hours); and the absence of deterioration (of at least 20% and absolute change of at least 10 units on a 0-100 mm scale) in the remaining domain.
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All randomized patients who received at least 1 dose of treatment. The analysis only included assessments while patients were receiving double-blind treatment and that occurred prior to withdrawal or the date when all patients were unblinded (15 Jul 2011). Patients who withdrew or escaped were considered non-responders.

Reporting Groups

	Description
Tocilizumab 4 or 8 mg/kg	Patients received tocilizumab 4 or 8 mg/kg intravenously every 4 weeks for 24 weeks.
Placebo	Patients received placebo to tocilizumab intravenously every 4 weeks for 24 weeks.

Measured Values

	Tocilizumab 4 or 8 mg/kg	Placebo
Number of Participants Analyzed	79	21
Percentage of ASsessment in Ankylosing Spondylitis 20 (ASAS20) Responders at Week 12 [units: Percentage of patients]	12.7	14.3

Reported Adverse Events

Time Frame	For the tocilizumab group, adverse events (AE) were reported from randomization to the end of the study. For the placebo group, AEs were reported from randomization only until participants escaped or switched to tocilizumab.
Additional Description	Safety population: Patients who received at least 1 dose of study medication and had at least 1 post-baseline safety assessment. Patients were assigned to groups as treated; 95 patients in the combined tocilizumab groups, including 4 patients randomized to placebo who received escape therapy of 8 mg/kg tocilizumab at Week 16.

Reporting Groups

	Description
Tocilizumab	Patients randomized to tocilizumab who received intravenous infusions of 4 mg/kg or 8 mg/kg tocilizumab once every 4 weeks for 24 weeks and patients randomized to placebo who switched or escaped to tocilizumab treatment.
Placebo	Patients received placebo to tocilizumab intravenously every 4 weeks for 24 weeks.

Serious Adverse Events

	Tocilizumab	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	6/95 (6.32%)	0/22 (0%)
Immune system disorders		
Anaphylactic reaction [A] †	2/95 (2.11%)	0/22 (0%)
Infections and infestations		
Pasteurella infection [A] †	1/95 (1.05%)	0/22 (0%)
Musculoskeletal and connective tissue disorders		
Ankylosing spondylitis [A] †	1/95 (1.05%)	0/22 (0%)
Sacroiliitis [A] †	1/95 (1.05%)	0/22 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Thyroid cancer [A] †	1/95 (1.05%)	0/22 (0%)

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

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

	Tocilizumab	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	6/95 (6.32%)	1/22 (4.55%)
Nervous system disorders		
Headache [A] †	6/95 (6.32%)	1/22 (4.55%)

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA (14.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

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

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

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

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