



Clinical trial results:

A 24-Week Randomized Double-Blind, Placebo Controlled Withdrawal Trial With a 16-Week Open-Label Lead-In Phase, and 64-Week Open-Label Follow-Up, to Evaluate the Efficacy and Safety of Tocilizumab in Patients with Active Polyarticular Juvenile Idiopathic Arthritis

Summary

EudraCT number	2009-011593-15
Trial protocol	GB DE IT ES BE NL FR
Global end of trial date	28 January 2013

Results information

Result version number	v1 (current)
This version publication date	01 June 2016
First version publication date	01 June 2016

Trial information

Trial identification

Sponsor protocol code	WA19977
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00988221
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland,
Public contact	Roche Trial Information Hotline, Roche Trial Information Hotline, 41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, Roche Trial Information Hotline, 41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000309-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 January 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 January 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This 3-part study evaluated the efficacy and safety of tocilizumab in patients with active polyarticular-course juvenile idiopathic arthritis who have an inadequate response to, or were intolerant of methotrexate. In Part I of the study, all patients received intravenous (iv) infusions of tocilizumab (8 milligrams per kilogram [mg/kg] for patients greater than or equal to ≥ 30 kg, 8 mg/kg or 10 mg/kg for patients less than < 30 kg) every 4 weeks for 16 weeks. In Part II of the study, patients with an adequate response in Part I were randomized to receive either tocilizumab at the same dose as in Part I or placebo every 4 weeks for up to 24 weeks. In Part III of the study, patients received tocilizumab at the same dose as in Part I every 4 weeks for up to another 64 weeks. Standard of care therapy with or without non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate was continued throughout the study.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 October 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Argentina: 19
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Brazil: 18
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Peru: 11
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	United States: 14

Worldwide total number of subjects	188
EEA total number of subjects	73

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	101
Adolescents (12-17 years)	87
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In Part I, patients received either tocilizumab 8 or 10 mg/kg. In Part II, eligible patients were randomized to receive placebo or the same dose of tocilizumab as in Part I of the study. In Part III, patients received the same dose of tocilizumab as in Part I of the study, with adjustments based on weight and change in weight from Baseline.

Period 1

Period 1 title	Part I
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
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Arm title	Tocilizumab 10 mg/kg in Patients Weighing <30 kg
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Arm description:

Patients received tocilizumab 10 mg/kg intravenously every 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	RO4877533
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received tocilizumab intravenously every 4 weeks.

Arm title	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg
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Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

Arm title	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg
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Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

Arm title	Tocilizumab 8 or 10 mg/kg
Arm description: Patients received tocilizumab 8 or 10 mg/kg intravenously every 4 weeks.	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received tocilizumab 8 or 10 mg/kg intravenously every 4 weeks.

Number of subjects in period 1	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg
Started	35	34	119
Completed	31	24	111
Not completed	4	10	8
Insufficient therapeutic response	4	6	5
Adverse event, non-fatal	-	1	2
Refused treatment	-	2	1
Lost to follow-up	-	1	-

Number of subjects in period 1	Tocilizumab 8 or 10 mg/kg
Started	188
Completed	166
Not completed	22
Insufficient therapeutic response	15
Adverse event, non-fatal	3
Refused treatment	3
Lost to follow-up	1

Period 2

Period 2 title	Part II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
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Arm title	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg
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Arm description:

Patients received tocilizumab 10 mg/kg intravenously every 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received tocilizumab 10 mg/kg intravenously every 4 weeks.

Arm title	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg
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Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

Arm title	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg
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Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

Arm title	Placebo
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Arm description:

Patients received placebo to tocilizumab intravenously every 4 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received placebo to tocilizumab intravenously every 4 weeks.

Number of subjects in period 2	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg
Started	16	11	55
Completed	15	11	52
Not completed	1	0	3
Consent withdrawn by subject	-	-	2
Adverse event, non-fatal	1	-	-
Reason not specified	-	-	1

Number of subjects in period 2	Placebo
Started	84
Completed	81
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Reason not specified	-

Period 3

Period 3 title	Part III
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
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Arm title	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg
Arm description: Patients received tocilizumab 10 mg/kg intravenously every 4 weeks.	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: Patients received tocilizumab 10 mg/kg intravenously every 4 weeks.	
Arm title	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg
Arm description: Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.	
Arm title	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg
Arm description: Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.	
Arm title	All Tocilizumab Patients
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: Patients received tocilizumab 8 or 10 mg/kg intravenously every 4 weeks.	

Number of subjects in period 3	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg
Started	30	24	106
Completed	29	23	103
Not completed	1	1	3
Insufficient therapeutic response	-	1	1
Adverse event, non-fatal	1	-	1
Refused treatment	-	-	1

Number of subjects in period 3	All Tocilizumab Patients
Started	160
Completed	160
Not completed	0
Insufficient therapeutic response	-
Adverse event, non-fatal	-
Refused treatment	-

Baseline characteristics

Reporting groups

Reporting group title	Part I
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Reporting group description:

In Part I, patients received either tocilizumab 8 or 10 mg/kg.

Reporting group values	Part I	Total	
Number of subjects	188	188	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	11		
standard deviation	± 4.01	-	
Gender categorical			
Units: Subjects			
Female	144	144	
Male	44	44	

Subject analysis sets

Subject analysis set title	All Tocilizumab Participants
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Subject analysis set type	Full analysis
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Subject analysis set description:

All participants who received 8 or 10 mg/kg of tocilizumab

Subject analysis set title	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Patients weighing < 30 kg at baseline receiving tocilizumab 10 mg/kg whose body weight increased to ≥ 30 kg and ≥ 5 kg over baseline body weight for 3 consecutive visits had the tocilizumab dose reduced to 8 mg/kg.

Reporting group values	All Tocilizumab Participants	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg	
Number of subjects	188	7	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	11		
standard deviation	± 4.01	±	
Gender categorical			
Units: Subjects			
Female	144		
Male	44		

End points

End points reporting groups

Reporting group title	Tocilizumab 10 mg/kg in Patients Weighing <30 kg
Reporting group description: Patients received tocilizumab 10 mg/kg intravenously every 4 weeks.	
Reporting group title	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg
Reporting group description: Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.	
Reporting group title	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg
Reporting group description: Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.	
Reporting group title	Tocilizumab 8 or 10 mg/kg
Reporting group description: Patients received tocilizumab 8 or 10 mg/kg intravenously every 4 weeks.	
Reporting group title	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg
Reporting group description: Patients received tocilizumab 10 mg/kg intravenously every 4 weeks.	
Reporting group title	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg
Reporting group description: Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.	
Reporting group title	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg
Reporting group description: Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.	
Reporting group title	Placebo
Reporting group description: Patients received placebo to tocilizumab intravenously every 4 weeks.	
Reporting group title	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg
Reporting group description: Patients received tocilizumab 10 mg/kg intravenously every 4 weeks.	
Reporting group title	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg
Reporting group description: Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.	
Reporting group title	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg
Reporting group description: Patients received tocilizumab 8 mg/kg intravenously every 4 weeks.	
Reporting group title	All Tocilizumab Patients
Reporting group description: -	
Subject analysis set title	All Tocilizumab Participants
Subject analysis set type	Full analysis
Subject analysis set description: All participants who received 8 or 10 mg/kg of tocilizumab	
Subject analysis set title	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients weighing < 30 kg at baseline receiving tocilizumab 10 mg/kg whose body weight increased to ≥ 30 kg and ≥ 5 kg over baseline body weight for 3 consecutive visits had the tocilizumab dose reduced to 8 mg/kg.	

Primary: Percent of Patients With a Juvenile Idiopathic Arthritis (JIA) American College of Rheumatology 30 (ACR30) Flare in Part II of the Study (Weeks 16-40)

End point title	Percent of Patients With a Juvenile Idiopathic Arthritis (JIA) American College of Rheumatology 30 (ACR30) Flare in Part II of the Study (Weeks 16-40) ^{[1][2]}
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End point description:

JIA ACR30 flare is defined as a $\geq 30\%$ worsening of 3 of 6 variables and no more than 1 of the remaining variables improving $> 30\%$. The 6 variables are physician global assessment of disease activity (worsening of 20 units minimum on a 0-100 visual analog scale [VAS]), parent/patient global assessment of overall well-being (worsening of 20 VAS units minimum), number of joints (minimum of 2 worse) with active arthritis (swelling, or pain and limitation of motion), number of joints (minimum of 2 worse) with limitation of movement, erythrocyte sedimentation rate (ESR), and functional ability assessed using the disability index of the Childhood Health Assessment Questionnaire (CHAQ, 30 questions, 8 domains, 0[best]-3[worst]). Patients who withdrew or who took escape medication are classified as flared. The analysis used the Cochran-Mantel-Haenszel test with the stratification variables background use of methotrexate and oral corticosteroids applied at Week 16.

End point type	Primary
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End point timeframe:

Week 16 through Week 40

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint data were not analyzed for all baseline period arms.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: Percent of patients				
number (confidence interval 95%)	48.1 (37 to 59)	25.6 (16 to 35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Achieving JIA ACR30/50/70/90 Responses in Part I of the Study (Baseline to Week 16)

End point title	Percent of Patients Achieving JIA ACR30/50/70/90 Responses in Part I of the Study (Baseline to Week 16)
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End point description:

A JIA ACR30/50/70/90 response is defined as a $\geq 30/50/70/90\%$ response on 3 of 6 variables and no more than 1 of the remaining variables worsening $> 30\%$. The 6 variables are physician global assessment of disease activity (20 units minimum on a 0-100 VAS), parent/patient global assessment of overall well-being (20 VAS units minimum), number of joints (minimum of 2 worse) with active arthritis (swelling, or pain and limitation of motion), number of joints (minimum of 2 worse) with limitation of movement, erythrocyte sedimentation rate, and functional ability assessed using the CHAQ, 30 questions, 8 domains, 0[best]-3[worst]).

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	119	188
Units: Percent of patients				
number (not applicable)				
ACR30 response	88.6	76.5	93.3	89.4
ACR50 response	80	70.6	87.4	83
ACR70 response	62.9	41.2	68.1	62.2
ACR90 response	31.4	23.5	25.2	26.1

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score Physician Global Assessment of Disease Activity at the End of Part I of the Study (Week 16)

End point title	Percent Change From Baseline in the JIA ACR Component Score Physician Global Assessment of Disease Activity at the End of Part I of the Study (Week 16)
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End point description:

The patient's treating physician provides a rating of the patient's arthritis disease activity on a 0 to 100 mm horizontal scale. The extreme left end of the line represents 'arthritis inactive' (ie, symptom-free and no arthritis symptoms) and the extreme right end represents 'arthritis very active'. A higher score indicates more disease activity. A negative change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	119	188
Units: percent change				
arithmetic mean (standard deviation)	-61.48 (± 48.779)	-65.2 (± 26.17)	-72.61 (± 25.977)	-69.19 (± 31.824)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score Patient/Parent Global Assessment of Overall Well-being at the End of Part I of the Study (Week 16)

End point title	Percent Change From Baseline in the JIA ACR Component Score Patient/Parent Global Assessment of Overall Well-being at the End of Part I of the Study (Week 16)
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End point description:

The patient or parent/guardian, as appropriate, provides a rating of the patient's well-being on a 0 to 100 mm horizontal scale. The extreme left end of the line represents 'very well' (ie, symptom-free and no arthritis disease activity) and the extreme right end represents 'very poor' (ie, maximum arthritis disease activity). A higher score indicates poorer well-being. A negative change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	119	188
Units: Percent change				
arithmetic mean (standard deviation)	-31.65 (± 120.268)	-55.56 (± 42.092)	-53.34 (± 58.686)	-49.46 (± 72.92)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score Number of Joints With Active Arthritis at the End of Part I of the Study (Week 16)

End point title	Percent Change From Baseline in the JIA ACR Component Score Number of Joints With Active Arthritis at the End of Part I of the Study (Week 16)
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End point description:

Joints with active arthritis are defined as joints with swelling present or pain present and limitation of motion. The maximum possible number of joints with active arthritis is 71. The joint assessment is performed by an independent assessor who is not the treating physician and who is blinded to all other aspects of the patient's efficacy and safety data. A negative change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	119	188
Units: Percent change				
arithmetic mean (standard deviation)	-63.36 (± 43.272)	-55.57 (± 44.876)	-72.96 (± 33.915)	-68.15 (± 38.246)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score Number of Joints With Limitation of Movement at the End of Part I of the Study (Week 16)

End point title	Percent Change From Baseline in the JIA ACR Component Score Number of Joints With Limitation of Movement at the End of Part I of the Study (Week 16)
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End point description:

Joints with limitation of movement are defined as joints with limitation of motion. The maximum possible number of joints with limitation of movement is 67. The joint assessment is performed by an independent assessor who is not the treating physician and who is blinded to all other aspects of the patient's efficacy and safety data. A negative change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	119	188
Units: Percent change				
arithmetic mean (standard deviation)	-61.83 (± 34.726)	-49.87 (± 48.091)	-65.96 (± 30.134)	-62.42 (± 34.955)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score ESR at the End of Part I of the Study (Week 16)

End point title	Percent Change From Baseline in the JIA ACR Component Score ESR at the End of Part I of the Study (Week 16)
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End point description:

Erythrocyte sedimentation rate, an acute phase protein, was measured using a kit furnished by the study central laboratory. A negative change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	119	188
Units: Percent change				
arithmetic mean (standard deviation)	-70.98 (± 24.53)	-21.84 (± 159.592)	-70.87 (± 33.4)	-62.54 (± 73.384)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score Functional Ability at the End of Part I of the Study (Week 16)

End point title	Percent Change From Baseline in the JIA ACR Component Score Functional Ability at the End of Part I of the Study (Week 16)
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End point description:

Functional ability is assessed with the Childhood Health Assessment Questionnaire disability index (CHAQ-DI) which consists of 30 questions in 8 domains: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. There are 4 possible responses to each question (0=without any difficulty, 1=with some difficulty, 2=with much difficulty, 3=unable to do). A domain score is the highest score in that domain. If aids and devices listed in the questionnaire or assistance from a person are required to perform a task, a domain score of 0 or 1 is increased to 2; if the domain score is 2 or 3, the domain score is not adjusted. To calculate the overall score, the patient must have a domain score in at least 6 of the 8 domains. The CHAQ-DI score is the sum of the domain scores divided by the number of domains that have a non-missing score and ranges from 0 (best) to 3 (worst). A higher score indicates less ability. A negative change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	119	188
Units: percent change				

arithmetic mean (standard deviation)	-54.48 (\pm 37.214)	-46.16 (\pm 50.961)	-49.07 (\pm 45.048)	-49.62 (\pm 44.573)
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Statistical analyses

No statistical analyses for this end point

Secondary: Juvenile Arthritis Disease Activity Score (JADAS-27) at the End of Part I of the Study (Week 16)

End point title	Juvenile Arthritis Disease Activity Score (JADAS-27) at the End of Part I of the Study (Week 16)
End point description:	
The JADAS-27 is derived from the following components: Physician's global assessment of disease activity on a 0-100 mm visual analog scale (VAS)/10, patient/parent's global assessment of overall well-being on a 0-100 mm VAS/10, normalized erythrocyte sedimentation rate (ESR) (if ESR is \leq 20 then set to 0, if \geq 120 then set to 10, and if $>$ 20 and $<$ 120 then apply formula $[(\text{ESR}-20)/10]$, and number of joints (maximum of 27) with active arthritis (cervical spine, left/right elbow, left/right wrist, left/right metacarpophalangeal (MCP) 1-3, left/right proximal interphalangeal joint (PIP) 1-5, left/right hips, left/right knee and left/right ankle). The scores for the first 3 components range from 0-10; the score for the final component ranges from 0-27. The overall JADAS-27 score ranges from 0-57. A higher score indicates more disease activity.	
End point type	Secondary
End point timeframe:	
Week 16	

End point values	Tocilizumab 10 mg/kg in Patients Weighing $<$ 30 kg	Tocilizumab 8 mg/kg in Patients Weighing $<$ 30 kg	Tocilizumab 8 mg/kg in Patients Weighing \geq 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	119	188
Units: Units on a scale				
arithmetic mean (standard deviation)	9.08 (\pm 8.882)	12.25 (\pm 10.277)	7.83 (\pm 7.122)	8.82 (\pm 8.198)

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Visual Analogue Scale (VAS) Score at the End of Part I of the Study (Week 16)

End point title	Pain Visual Analogue Scale (VAS) Score at the End of Part I of the Study (Week 16)
End point description:	
The patient or parent/guardian, as appropriate, provides a rating of the patient's pain (also called a discomfort index) on a 0 to 100 mm horizontal scale. The extreme left end of the line represents 'no pain' and the extreme right end represents 'very extreme pain'. A higher score indicates more pain.	

End point type	Secondary
End point timeframe:	
Week 16	

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	119	188
Units: mm				
arithmetic mean (standard deviation)	21.9 (± 21.66)	24.1 (± 23.94)	20.3 (± 21.13)	21.2 (± 21.65)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Inactive Disease at the End of Part I of the Study (Week 16)

End point title	Percentage of Patients With Inactive Disease at the End of Part I of the Study (Week 16)
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End point description:

A patient is judged to have inactive disease if all of the following criteria are met: Number of joints with active arthritis = 0; absence of active uveitis, defined by the adverse event preferred terms 'uveitis' and 'intermediate uveitis'; normal erythrocyte sedimentation rate (< 20 mm/hour regardless of age and sex); and physician's global assessment of overall well-being visual analog scale score ≤ 10.

End point type	Secondary
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End point timeframe:

Week 16

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	119	188
Units: Percentage of patients				
number (not applicable)	20	8.8	18.5	17

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With an Elevated C-reactive Protein Concentration at Baseline That Had Normalized at the End of Part I of the Study (Week 16)

End point title	Percentage of Patients With an Elevated C-reactive Protein Concentration at Baseline That Had Normalized at the End of Part I of the Study (Week 16)
End point description: C-reactive protein (CRP), an acute phase protein, was measured in blood samples with a high-sensitivity CRP (hs-CRP) test using laser nephelometry. CRP levels higher than 10 milligrams per deciliter (mg/dL) are considered to be elevated levels.	
End point type	Secondary
End point timeframe: Baseline to Week 16	

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	19	46	78
Units: Percentage of patients				
number (not applicable)	76.9	63.2	87	79.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With an Elevated ESR at Baseline That Had Normalized at the End of Part I of the Study (Week 16)

End point title	Percentage of Patients With an Elevated ESR at Baseline That Had Normalized at the End of Part I of the Study (Week 16)
End point description: Erythrocyte sedimentation rate, an acute phase protein, was measured using a kit furnished by the study central laboratory.	
End point type	Secondary
End point timeframe: Baseline to Week 16	

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	26	73	122
Units: Percent of patients				
number (not applicable)	82.6	57.7	87.7	80.3

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With an Elevated Platelet Count at Baseline That Had Normalized at the End of Part I of the Study (Week 16)

End point title	Percentage of Patients With an Elevated Platelet Count at Baseline That Had Normalized at the End of Part I of the Study (Week 16)
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End point description:

Platelets were measured in blood samples taken from the patients. Platelet counts above 400,00 are considered to be elevated.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	18	43	74
Units: Percentage of patients				
number (not applicable)	84.6	55.6	86	78.4

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With an Elevated White Blood Count at Baseline That Had Normalized at the End of Part I of the Study (Week 16)

End point title	Percentage of Patients With an Elevated White Blood Count at Baseline That Had Normalized at the End of Part I of the Study (Week 16)
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End point description:

White blood cells were measured in blood samples taken from the patients. Counts of more than 10,500 cells per microliter are considered to be elevated levels.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	2	8
Units: Percentage of patients				
number (not applicable)	66.7	66.7	100	75

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Achieving JIA ACR30/50/70/90 Responses at the End of Part II of the Study (Week 40)

End point title	Percent of Patients Achieving JIA ACR30/50/70/90 Responses at the End of Part II of the Study (Week 40) ^[3]
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End point description:

A JIA ACR30/50/70/90 response is defined as a ≥ 30/50/70/90% response on 3 of 6 variables and no more than 1 of the remaining variables worsening > 30%. The 6 variables are physician global assessment of disease activity (20 units minimum on a 0-100 visual analog scale [VAS]), parent/patient global assessment of overall well-being (20 VAS units minimum), number of joints (minimum of 2 worse) with active arthritis (swelling, or pain and limitation of motion), number of joints (minimum of 2 worse) with limitation of movement, erythrocyte sedimentation rate, and functional ability assessed using the disability index of the Childhood Health Assessment Questionnaire (CHAQ, 30 questions, 8 domains, 0[best]-3[worst]). The analysis used the Cochran-Mantel-Haenszel test with the stratification variables background use of methotrexate and oral corticosteroids applied at Week 16.

End point type	Secondary
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End point timeframe:

Week 40

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: Percent of patients				
number (confidence interval 95%)				
ACR30 response	54.3 (43 to 65)	74.4 (65 to 84)		
ACR50 response	51.9 (41 to 63)	73.2 (64 to 83)		
ACR70 response	42 (31 to 53)	64.6 (54 to 75)		
ACR90 response	23.5 (14 to 33)	45.1 (34 to 56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the JIA ACR Component Score Physician Global Assessment of Disease Activity at the End of Part II of the Study (Week 40)

End point title	Change From Baseline in the JIA ACR Component Score Physician Global Assessment of Disease Activity at the End of Part II of the Study (Week 40) ^[4]
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End point description:

The patient's treating physician provides a rating of the patient's arthritis disease activity on a 0 to 100 mm horizontal scale. The extreme left end of the line represents 'arthritis inactive' (ie, symptom-free and no arthritis symptoms) and the extreme right end represents 'arthritis very active'. A higher score indicates more disease activity. A negative change score indicates improvement. Change from baseline was calculated using last observation carried forward imputation for missing values.

End point type	Secondary
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End point timeframe:

Baseline to Week 40

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: Units on a scale				
arithmetic mean (standard deviation)	-38.2 (± 24.77)	-45.6 (± 21.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the JIA ACR Component Score Patient/Parent Global Assessment of Overall Well-being at the End of Part II of the Study (Week 40)

End point title	Change From Baseline in the JIA ACR Component Score Patient/Parent Global Assessment of Overall Well-being at the End of Part II of the Study (Week 40) ^[5]
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End point description:

The patient or parent/guardian, as appropriate, provides a rating of the patient's well-being on a 0 to 100 mm horizontal scale. The extreme left end of the line represents 'very well' (ie, symptom-free and no arthritis disease activity) and the extreme right end represents 'very poor' (ie, maximum arthritis disease activity). A higher score indicates poorer well-being. A negative change score indicates improvement. Change from baseline was calculated using last observation carried forward imputation for missing values.

End point type	Secondary
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End point timeframe:

Baseline to Week 40

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: Units on a scale				
arithmetic mean (standard deviation)	-32.4 (± 28.57)	-31.1 (± 28.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the JIA ACR Component Score Number of Joints With Active Arthritis at the End of Part II of the Study (Week 40)

End point title	Change From Baseline in the JIA ACR Component Score Number of Joints With Active Arthritis at the End of Part II of the Study (Week 40) ^[6]
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End point description:

Joints with active arthritis are defined as joints with swelling present or pain present and limitation of motion. The maximum number of joints with active arthritis is 71. The joint assessment is performed by an independent assessor who is not the treating physician and who is blinded to all other aspects of the patient's efficacy and safety data. A negative change score indicates improvement. Change from baseline was calculated using last observation carried forward imputation for missing values.

End point type	Secondary
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End point timeframe:

Baseline to Week 40

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: Joints				
arithmetic mean (standard deviation)	-11.5 (± 12.77)	-14.5 (± 11.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the JIA ACR Component Score Number of Joints With Limitation of Movement at the End of Part II of the Study (Week 40)

End point title	Change From Baseline in the JIA ACR Component Score Number of Joints With Limitation of Movement at the End of Part II of the Study (Week 40) ^[7]
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End point description:

Joints with limitation of movement are defined as joints with limitation of motion. The maximum number of joints with limitation of movement is 67. The joint assessment is performed by an independent assessor who is not the treating physician and who is blinded to all other aspects of the patient's efficacy

and safety data. A negative change score indicates improvement. Change from baseline was calculated using last observation carried forward imputation for missing values.

End point type	Secondary
End point timeframe:	
Baseline to Week 40	
Notes:	

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: Joints				
arithmetic mean (standard deviation)	-8.1 (± 9.9)	-10.2 (± 8.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the JIA ACR Component Score ESR at the End of Part II of the Study (Week 40)

End point title	Change From Baseline in the JIA ACR Component Score ESR at the End of Part II of the Study (Week 40) ^[8]
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End point description:

Erythrocyte sedimentation rate, an acute phase protein, was measured using a kit furnished by the study central laboratory. A negative change score indicates improvement. Change from baseline was calculated using last observation carried forward imputation for missing values.

End point type	Secondary
End point timeframe:	
Baseline to Week 40	

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: mm/hour				
arithmetic mean (standard deviation)	-14 (± 28.46)	-25.2 (± 21.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the JIA ACR Component Score CHAQ-DI at the

End of Part II of the Study (Week 40)

End point title	Change From Baseline in the JIA ACR Component Score CHAQ-DI at the End of Part II of the Study (Week 40) ^[9]
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End point description:

The Childhood Health Assessment Questionnaire-Disability Index (CHAQ-DI), as a measure of functional ability, consists of 30 questions in 8 domains: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. There are 4 possible responses to each question (0=without any difficulty, 1=with some difficulty, 2=with much difficulty, 3=unable to do). A domain score is the highest score in that domain. To calculate the overall score, the patient must have a domain score in at least 6 of the 8 domains. The CHAQ-DI score is the sum of the domain scores divided by the number of domains that have a non-missing score and ranges from 0 (best) to 3 (worst). A higher score indicates less ability. A negative change score indicates improvement. Change from baseline was calculated using last observation carried forward imputation for missing values.

End point type	Secondary
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End point timeframe:

Baseline to Week 40

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.724 (± 0.6905)	-0.804 (± 0.6534)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Pain VAS Score at the End of Part II of the Study (Week 40)

End point title	Change From Baseline in the Pain VAS Score at the End of Part II of the Study (Week 40) ^[10]
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End point description:

The patient or parent/guardian, as appropriate, provides a rating of the patient's pain (also called a discomfort index) on a 0 to 100 mm horizontal scale. The extreme left end of the line represents 'no pain' and the extreme right end represents 'very extreme pain'. A higher score indicates more pain. A negative change score indicates improvement. Change from baseline was calculated using last observation carried forward (LOCF) imputation for missing values. The analysis was adjusted for the randomization stratification factors background use of methotrexate and background use of oral corticosteroids, and the pain visual analog scale score at Baseline. The adjusted means from the fitted model are presented.

End point type	Secondary
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End point timeframe:

Baseline to Week 40

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: Units on a scale				
arithmetic mean (standard deviation)	-30.2 (± 27.12)	-31.5 (± 31.76)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Tocilizumab 8 or 10 mg/kg
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0076
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-10.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	-2.7

Secondary: Percent of Patients With Inactive Disease at the End of Part II of the Study (Week 40)

End point title	Percent of Patients With Inactive Disease at the End of Part II of the Study (Week 40) ^[11]
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End point description:

A patient is judged to have inactive disease if all of the following criteria are met: Number of joints with active arthritis = 0; absence of active uveitis, defined by the adverse event preferred terms 'uveitis' and 'intermediate uveitis'; normal erythrocyte sedimentation rate (< 20 mm/hour regardless of age and sex); and physician's global assessment of overall well-being visual analog scale score ≤ 10.

The statistical test is not significant due to a break in the hierarchical chain of significance testing.

End point type	Secondary
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End point timeframe:

Week 40

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: Percent of patients				
number (confidence interval 95%)	17.3 (9 to 26)	36.6 (26 to 47)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Tocilizumab 8 or 10 mg/kg v Placebo
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 ^[12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	weighted difference
Point estimate	18
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	32

Notes:

[12] - 1.000 is used here as the test was considered as not significant due to the break in the hierarchical testing chain.

Secondary: Percent of Patients Achieving JIA ACR30/50/70/90 Responses at Weeks 2, 52, and 104

End point title	Percent of Patients Achieving JIA ACR30/50/70/90 Responses at Weeks 2, 52, and 104
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End point description:

A JIA ACR30/50/70/90 response is defined as a $\geq 30/50/70/90\%$ response on 3 of 6 variables and no more than 1 of the remaining variables worsening $> 30\%$. The 6 variables are physician global assessment of disease activity (20 units minimum on a 0-100 visual analog scale [VAS]), parent/patient global assessment of overall well-being (20 VAS units minimum), number of joints (minimum of 2 worse) with active arthritis (swelling, or pain and limitation of motion), number of joints (minimum of 2 worse) with limitation of movement, erythrocyte sedimentation rate, and functional ability assessed using the disability index of the Childhood Health Assessment Questionnaire (CHAQ, 30 questions, 8 domains, 0[best]-3[worst]).

End point type	Secondary
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End point timeframe:

Week 2 to Week 104

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	11	55	82
Units: Percent of patients				
number (not applicable)				
Week 2 - ACR30 Response	55.6	45.5	54.5	52.4
Week 2 - ACR50 Response	33.3	18.2	34.5	32.9
Week 2 - ACR70 Response	11.1	9.1	12.7	11
Week 2 - ACR90 Response	0	0	0	0
Week 52 - ACR30 Response	100	100	96.4	97.6
Week 52 - ACR50 Response	100	90.9	94.5	95.1
Week 52 - ACR70 Response	100	72.7	87.3	86.6
Week 52 - ACR90 Response	88.9	54.5	65.5	65.9
Week 104 - ACR30 Response	100	90.9	94.5	95.1
Week 104 - ACR50 Response	100	90.9	87.3	90.2
Week 104 - ACR70 Response	88.9	90.9	83.6	86.6
Week 104 - ACR90 Response	88.9	72.7	67.3	70.7

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Percent of patients				
number (not applicable)				
Week 2 - ACR30 Response	42.9			
Week 2 - ACR50 Response	42.9			
Week 2 - ACR70 Response	0			
Week 2 - ACR90 Response	0			
Week 52 - ACR30 Response	100			
Week 52 - ACR50 Response	100			
Week 52 - ACR70 Response	85.7			
Week 52 - ACR90 Response	57.1			
Week 104 - ACR30 Response	100			
Week 104 - ACR50 Response	100			
Week 104 - ACR70 Response	100			
Week 104 - ACR90 Response	71.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients With 4 Baseline Disease Characteristics Achieving JIA ACR30/50/70/90 Responses at Week 104

End point title	Percent of Patients With 4 Baseline Disease Characteristics Achieving JIA ACR30/50/70/90 Responses at Week 104
End point description:	
A JIA ACR30/50/70/90 response is defined as a $\geq 30/50/70/90\%$ response on 3 of 6 variables and no more than 1 of the remaining variables worsening $> 30\%$. The 6 variables are physician global assessment of disease activity (20 units minimum on a 0-100 visual analog scale [VAS]), parent/patient global assessment of overall well-being (20 VAS units minimum), number of joints (minimum of 2 worse) with active arthritis (swelling, or pain and limitation of motion), number of joints (minimum of 2 worse) with limitation of movement, erythrocyte sedimentation rate, and functional ability assessed using the disability index of the Childhood Health Assessment Questionnaire (CHAQ, 30 questions, 8 domains, 0[best]-3[worst]).	
End point type	Secondary
End point timeframe:	
Week 2 to Week 104	

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	11	55	82
Units: Percent of patients				
number (not applicable)				
Previous Biologic Use: Yes - ACR30 (n=1,0,25,27,1)	100	0	96	96.3
Previous Biologic Use: Yes - ACR50 (n=1,0,25,27,1)	100	0	80	81.5
Previous Biologic Use: Yes - ACR70 (n=1,0,25,27,1)	0	0	72	70.4
Previous Biologic Use: Yes - ACR90 (n=1,0,25,27,1)	0	0	48	48.1
Previous Biologic Use: No - ACR30 (n=8,11,30,55,6)	100	90.9	93.3	94.5
Previous Biologic Use: No - ACR50 (n=8,11,30,55,6)	100	90.9	93.3	94.5
Previous Biologic Use: No - ACR70 (n=8,11,30,55,6)	100	90.9	93.3	94.5
Previous Biologic Use: No - ACR90 (n=8,11,30,55,6)	100	72.7	83.3	81.8
Methotrexate Use: Yes - ACR30 (n=7,11,42,67,7)	100	90.9	95.2	95.5
Methotrexate Use: Yes - ACR50 (n=7,11,42,67,7)	100	90.9	88.1	91
Methotrexate Use: Yes - ACR70 (n=7,11,42,67,7)	100	90.9	83.3	88.1
Methotrexate Use: Yes - ACR90 (n=7,11,42,67,7)	100	72.7	73.8	76.1
Methotrexate Use: No - ACR30 (n=2,0,13,15,0)	100	0	92.3	93.3
Methotrexate Use: No - ACR50 (n=2,0,13,15,0)	100	0	84.6	86.7
Methotrexate Use: No - ACR70 (n=2,0,13,15,0)	50	0	84.6	80

Methotrexate Use: No - ACR90 (n=2,0,13,15,0)	50	0	46.2	46.7
Oral Corticosteroid Use: Yes - ACR30(n=2,5,23,33,3)	100	80	91.3	90.9
Oral Corticosteroid Use: Yes - ACR50(n=2,5,23,33,3)	100	80	91.3	90.9
Oral Corticosteroid Use: Yes - ACR70(n=2,5,23,33,3)	100	80	82.6	84.8
Oral Corticosteroid Use: Yes - ACR90(n=2,5,23,33,3)	100	80	65.2	69.7
Oral Corticosteroid Use: No - ACR30(n=7,6,32,49,4)	100	100	96.9	98
Oral Corticosteroid Use: No - ACR50(n=7,6,32,49,4)	100	100	84.4	89.8
Oral Corticosteroid Use: No - ACR70(n=7,6,32,49,4)	85.7	100	84.4	87.8
Oral Corticosteroid Use: No - ACR90(n=7,6,32,49,4)	85.7	66.7	68.8	71.4
Rheumatoid Factor: Positive - ACR30(n=0,2,23,27,2)	0	100	95.7	96.3
Rheumatoid Factor: Positive - ACR50(n=0,2,23,27,2)	0	100	91.3	92.6
Rheumatoid Factor: Positive - ACR70(n=0,2,23,27,2)	0	100	91.3	92.6
Rheumatoid Factor: Positive - ACR90(n=0,2,23,27,2)	0	100	78.3	77.8
Rheumatoid Factor: Negative - ACR30(n=9,7,29,50,5)	100	100	93.1	96
Rheumatoid Factor: Negative - ACR50(n=9,7,29,50,5)	100	100	82.8	90
Rheumatoid Factor: Negative - ACR70(n=9,7,29,50,5)	88.9	100	75.9	84
Rheumatoid Factor: Negative - ACR90(n=9,7,29,50,5)	88.9	85.7	58.6	70

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Percent of patients				
number (not applicable)				
Previous Biologic Use: Yes - ACR30 (n=1,0,25,27,1)	100			
Previous Biologic Use: Yes - ACR50 (n=1,0,25,27,1)	100			
Previous Biologic Use: Yes - ACR70 (n=1,0,25,27,1)	100			
Previous Biologic Use: Yes - ACR90 (n=1,0,25,27,1)	100			
Previous Biologic Use: No - ACR30 (n=8,11,30,55,6)	100			
Previous Biologic Use: No - ACR50 (n=8,11,30,55,6)	100			

Previous Biologic Use: No - ACR70 (n=8,11,30,55,6)	100			
Previous Biologic Use: No - ACR90 (n=8,11,30,55,6)	66.7			
Methotrexate Use: Yes - ACR30 (n=7,11,42,67,7)	100			
Methotrexate Use: Yes - ACR50 (n=7,11,42,67,7)	100			
Methotrexate Use: Yes - ACR70 (n=7,11,42,67,7)	100			
Methotrexate Use: Yes - ACR90 (n=7,11,42,67,7)	71.4			
Methotrexate Use: No - ACR30 (n=2,0,13,15,0)	0			
Methotrexate Use: No - ACR50 (n=2,0,13,15,0)	0			
Methotrexate Use: No - ACR70 (n=2,0,13,15,0)	0			
Methotrexate Use: No - ACR90 (n=2,0,13,15,0)	0			
Oral Corticosteroid Use: Yes - ACR30(n=2,5,23,33,3)	100			
Oral Corticosteroid Use: Yes - ACR50(n=2,5,23,33,3)	100			
Oral Corticosteroid Use: Yes - ACR70(n=2,5,23,33,3)	100			
Oral Corticosteroid Use: Yes - ACR90(n=2,5,23,33,3)	66.7			
Oral Corticosteroid Use: No - ACR30(n=7,6,32,49,4)	100			
Oral Corticosteroid Use: No - ACR50(n=7,6,32,49,4)	100			
Oral Corticosteroid Use: No - ACR70(n=7,6,32,49,4)	100			
Oral Corticosteroid Use: No - ACR90(n=7,6,32,49,4)	75			
Rheumatoid Factor: Positive - ACR30(n=0,2,23,27,2)	100			
Rheumatoid Factor: Positive - ACR50(n=0,2,23,27,2)	100			
Rheumatoid Factor: Positive - ACR70(n=0,2,23,27,2)	100			
Rheumatoid Factor: Positive - ACR90(n=0,2,23,27,2)	50			
Rheumatoid Factor: Negative - ACR30(n=9,7,29,50,5)	100			
Rheumatoid Factor: Negative - ACR50(n=9,7,29,50,5)	100			
Rheumatoid Factor: Negative - ACR70(n=9,7,29,50,5)	100			
Rheumatoid Factor: Negative - ACR90(n=9,7,29,50,5)	80			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Juvenile Arthritis Disease Activity Score-71

(JADAS-71) at Week 104

End point title	Change From Baseline in the Juvenile Arthritis Disease Activity Score-71 (JADAS-71) at Week 104
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End point description:

The JADAS-71 is composed of 4 components: Physician global assessment of disease activity on a visual analog scale (VAS) (range = 0-10, left end of the line = arthritis inactive, ie, symptom-free and no arthritis symptoms; right end = arthritis very active), patient/parent global assessment of overall well-being on a VAS (range = 0-10, left end of the line = very well, ie, symptom-free and no arthritis disease activity; right end = very poor, ie, maximum arthritis disease activity), normalized erythrocyte sedimentation rate (ESR) (range = 0-10, If ESR is ≤ 20 mm/h, set to 0. If ≥ 120 mm/h, set to 10 mm/h. If > 20 mm/h and < 120 mm/h, apply formula: $[\text{ESR} - 20 \text{ mm/h}] / 10 \text{ mm/h}$), and a count of active arthritis (swelling present or pain present and limitation of motion) in 71 selected joints (range=0-71). The JADAS-71 is the sum of the 4 component scores and ranges from 0-101. A higher score indicates more arthritis disease activity. A positive change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 104

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	11	51	76
Units: Units on a scale				
arithmetic mean (standard deviation)	-31.4 (± 17.471)	-25.42 (± 13.142)	-25.7 (± 12.2)	-26.05 (± 12.941)

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Units on a scale				
arithmetic mean (standard deviation)	-24.17 (± 14.856)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score Physician Global Assessment of Disease Activity at Week 104

End point title	Percent Change From Baseline in the JIA ACR Component Score Physician Global Assessment of Disease Activity at Week 104
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End point description:

The patient's treating physician provides a rating of the patient's arthritis disease activity on a 0 to 100 mm horizontal scale. The extreme left end of the line represents 'arthritis inactive' (ie, symptom-free and no arthritis symptoms) and the extreme right end represents 'arthritis very active'. A negative change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 104

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	11	51	76
Units: Percent change				
arithmetic mean (standard deviation)	-97.65 (± 2.689)	-90.42 (± 16.306)	-87.58 (± 27.588)	-89.7 (± 23.747)

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Percent change				
arithmetic mean (standard deviation)	-96.01 (± 9.862)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score Patient/Parent Global Assessment of Overall Well-being at Week 104

End point title	Percent Change From Baseline in the JIA ACR Component Score Patient/Parent Global Assessment of Overall Well-being at Week 104
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End point description:

The patient or parent/guardian, as appropriate, provides a rating of the patient's well-being on a 0 to 100 mm horizontal scale. The extreme left end of the line represents 'very well' (ie, symptom-free and no arthritis disease activity) and the extreme right end represents 'very poor' (ie, maximum arthritis disease activity). A negative change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 104

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	11	51	76
Units: Percent change				
arithmetic mean (standard deviation)	-97.01 (± 5.323)	-83.06 (± 25.986)	-75.81 (± 42.143)	-75.35 (± 43.779)

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Percent change				
arithmetic mean (standard deviation)	-38.23 (± 75.749)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline the JIA ACR Component Score Number of Joints With Active Arthritis at Week 104

End point title	Percent Change From Baseline the JIA ACR Component Score Number of Joints With Active Arthritis at Week 104
End point description:	
Joints with active arthritis are defined as joints with swelling present or pain present and limitation of motion. The maximum number of joints with active arthritis is 71. The joint assessment is performed by an independent assessor who is not the treating physician and who is blinded to all other aspects of the patient's efficacy and safety data. A negative change score indicates improvement.	
End point type	Secondary
End point timeframe:	
Baseline to Week 104	

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	11	52	77
Units: Percent change				
arithmetic mean (standard deviation)	-98.57 (± 3.78)	-76.43 (± 44.956)	-88.6 (± 24.043)	-87.73 (± 27.088)

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Percent change				
arithmetic mean (standard deviation)	-88.22 (± 24.908)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score Number of Joints With Limitation of Movement at Week 104

End point title	Percent Change From Baseline in the JIA ACR Component Score Number of Joints With Limitation of Movement at Week 104
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End point description:

Joints with limitation of movement are defined as joints with limitation of motion. The maximum number of joints with limitation of movement is 67. The joint assessment is performed by an independent assessor who is not the treating physician and who is blinded to all other aspects of the patient's efficacy and safety data. A negative change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 104

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	11	52	77
Units: Percent change				
arithmetic mean (standard deviation)	-98.57 (±	-76.66 (±	-79.88 (±	-81.3 (±

3.78)	55.781)	26.831)	31.729)
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End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Percent change				
arithmetic mean (standard deviation)	-81.81 (\pm 32.048)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score ESR at Week 104 [Time Frame: Baseline to Week 104]

End point title	Percent Change From Baseline in the JIA ACR Component Score ESR at Week 104 [Time Frame: Baseline to Week 104]
End point description:	Erythrocyte sedimentation rate, an acute phase protein, was measured using a kit furnished by the study central laboratory. A negative change score indicates improvement.
End point type	Secondary
End point timeframe:	Baseline to Week 104

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing \geq 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	11	52	77
Units: Percent change				
arithmetic mean (standard deviation)	-84.42 (\pm 13.141)	-74.06 (\pm 31.967)	-73.85 (\pm 29.073)	-76.24 (\pm 27.263)

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
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Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Percent change				
arithmetic mean (standard deviation)	-89.21 (\pm 4.682)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the JIA ACR Component Score Functional Ability at Week 104 [Time Frame: Baseline to Week 104]

End point title	Percent Change From Baseline in the JIA ACR Component Score Functional Ability at Week 104 [Time Frame: Baseline to Week 104]
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End point description:

Functional ability is assessed with the Childhood Health Assessment Questionnaire (CHAQ-DI) disability index which consists of 30 questions in 8 domains: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. There are 4 possible responses to each question (0=without any difficulty, 1=with some difficulty, 2=with much difficulty, 3=unable to do). A domain score is the highest score in that domain. If aids and devices listed in the questionnaire or assistance from a person are required to perform a task, a domain score of 0 or 1 is increased to 2; if the domain score is 2 or 3, the domain score is not adjusted. To calculate the overall score, the patient must have a domain score in at least 6 of the 8 domains. The CHAQ-DI score is the sum of the domain scores divided by the number of domains that have a non-missing score and ranges from 0 (best) to 3 (worst). A negative change score indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 104

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing \geq 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	11	52	77
Units: Percent change				
arithmetic mean (standard deviation)	-96.03 (\pm 10.499)	-78.58 (\pm 38.745)	-73.34 (\pm 38.745)	-76.71 (\pm 34.696)

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Percent change				

arithmetic mean (standard deviation)	-79.5 (± 18.622)			
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients With a Minimally Important Improvement in the CHAQ-DI Score at Weeks 16, 40, 52, 80, and 104

End point title	Percent of Patients With a Minimally Important Improvement in the CHAQ-DI Score at Weeks 16, 40, 52, 80, and 104
End point description:	
<p>The CHAQ-DI consists of 30 questions in 8 domains: Dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. There are 4 possible responses to each question (0=without any difficulty, 1=with some difficulty, 2=with much difficulty, 3=unable to do). A domain score is the highest score in that domain. If aids and devices listed in the questionnaire or assistance from a person are required to perform a task, a domain score of 0 or 1 is increased to 2; if the domain score is 2 or 3, the domain score is not adjusted. To calculate the overall score, the patient must have a domain score in at least 6 of the 8 domains. The CHAQ-DI score is the sum of the domain scores divided by the number of domains that have a non-missing score and ranges from 0 (best) to 3 (worst). A minimally important improvement is an improvement ≥ 0.13 over Baseline. Patients who withdrew due to non-safety reasons are classified as non-responders.</p>	
End point type	Secondary
End point timeframe:	
Baseline to Week 104	

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	11	55	82
Units: Percent of patients				
number (not applicable)				
Week 16	77.8	81.8	76.4	78
Week 40	88.9	81.8	78.2	81.7
Week 52	88.9	81.8	80	82.9
Week 80	88.9	90.9	80	84.1
Week 104	88.9	100	80	85.4

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
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Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Percent of patients				
number (not applicable)				
Week 16	85.7			
Week 40	100			
Week 52	100			
Week 80	100			
Week 104	100			

Statistical analyses

No statistical analyses for this end point

Secondary: C-reactive Protein Levels From Baseline to Week 104

End point title	C-reactive Protein Levels From Baseline to Week 104
End point description:	C-reactive protein (CRP), an acute phase protein, was measured in blood samples with a high-sensitivity CRP (hs-CRP) test using laser nephelometry.
End point type	Secondary
End point timeframe:	Baseline to Week 104

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	53	78
Units: mg/L				
arithmetic mean (standard deviation)				
Week 16 (n=9, 7, 53, 75, 6)	1.726 (± 2.7395)	1.077 (± 1.1247)	1.137 (± 3.2472)	1.129 (± 2.9042)
Week 40 (n=7, 11, 51, 76, 7)	3.709 (± 9.0383)	1.591 (± 2.6187)	1.451 (± 5.9168)	1.756 (± 5.8029)
Week 52 (n=8, 10, 52, 77, 7)	3.405 (± 8.6491)	4.584 (± 10.4573)	0.882 (± 2.4335)	1.569 (± 5.0838)
Week 80 (n=8, 10, 51, 76, 7)	2.329 (± 5.9286)	4.867 (± 13.0151)	0.718 (± 1.5474)	1.425 (± 5.225)
Week 104 (n=7, 11, 50, 75, 7)	0.249 (± 0.0949)	1.259 (± 2.8519)	2.032 (± 6.5732)	1.581 (± 5.4965)

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing			
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	<30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: mg/L				
arithmetic mean (standard deviation)				
Week 16 (n=9, 7, 53, 75, 6)	0.22 (± 0.04)			
Week 40 (n=7, 11, 51, 76, 7)	2.286 (± 5.5183)			
Week 52 (n=8, 10, 52, 77, 7)	0.267 (± 0.1325)			
Week 80 (n=8, 10, 51, 76, 7)	0.623 (± 0.6096)			
Week 104 (n=7, 11, 50, 75, 7)	0.2 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Pain VAS Score at Weeks 2, 40, 52, and 104

End point title	Change From Baseline in the Pain VAS Score at Weeks 2, 40, 52, and 104
End point description:	
The patient or parent/guardian, as appropriate, provides a rating of the patient's pain (also called a discomfort index) on a 0 to 100 mm horizontal scale. The extreme left end of the line represents 'no pain' and the extreme right end represents 'very extreme pain'. A higher score indicates more pain. A negative change score indicates improvement.	
End point type	Secondary
End point timeframe:	
Baseline to Week 104	

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	11	55	82
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 2 (n=9, 10, 52, 78, 7)	-11.4 (± 13.16)	-6.1 (± 20.98)	-10.3 (± 21.44)	-9.4 (± 19.8)
Week 40 (n=8, 11, 52, 78, 7)	-44 (± 12.29)	-27.9 (± 35.85)	-33.9 (± 31.64)	-33.3 (± 30.44)
Week 52 (n=8, 1, 52, 78, 7)	-47.8 (± 14.46)	-29.6 (± 28.39)	-35.5 (± 29.07)	-34.9 (± 27.76)
Week 104 (n=7, 11, 51, 76, 7)	-48.9 (± 16.71)	-27.1 (± 39.51)	-34.5 (± 34.59)	-34.4 (± 33.72)

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 2 (n=9, 10, 52, 78, 7)	-4.4 (± 13.13)			
Week 40 (n=8, 11, 52, 78, 7)	-24.7 (± 27.76)			
Week 52 (n=8, 1, 52, 78, 7)	-24 (± 26.59)			
Week 104 (n=7, 11, 51, 76, 7)	-30.7 (± 31.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients With Inactive Disease From Week 16 to Week 104

End point title	Percent of Patients With Inactive Disease From Week 16 to Week 104 ^[13]
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End point description:

A patient is judged to have inactive disease if all of the following criteria are met: Number of joints with active arthritis = 0; absence of active uveitis, defined by the adverse event preferred terms 'uveitis' and 'intermediate uveitis'; normal erythrocyte sedimentation rate (< 20 mm/hour regardless of age and sex); and physician's global assessment of overall well-being visual analog scale score ≤ 10. Patients who withdrew due to non-safety reasons are classified as non-responders.

End point type	Secondary
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End point timeframe:

Week 16 to Week 104

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	11	55	7
Units: Percent of patients				
number (not applicable)				
Week 16	11.1	18.2	20	42.9
Week 40	44.4	45.5	38.2	42.9
Week 52	66.7	45.5	50.9	57.1
Week 80	66.7	54.5	56.4	57.1
Week 104	66.7	54.5	63.6	71.4

End point values	All Tocilizumab Patients			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Percent of patients				
number (not applicable)				
Week 16	20.7			
Week 40	40.2			
Week 52	52.4			
Week 80	57.3			
Week 104	63.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients in Clinical Remission From Week 40 to 104

End point title	Percent of Patients in Clinical Remission From Week 40 to
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End point description:

A patient was in clinical remission if they had inactive disease at all visits in the 6 months prior to and including the visit assessment day. A patient was judged to have inactive disease if all of the following criteria were met: Number of joints with active arthritis = 0; absence of active uveitis, defined by the adverse event preferred terms 'uveitis' and 'intermediate uveitis'; normal erythrocyte sedimentation rate (< 20 mm/hour regardless of age and sex); and physician's global assessment of overall well-being visual analog scale score ≤ 10. Patients who withdrew due to non-safety reasons are classified as non-responders.

End point type	Secondary
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End point timeframe:

Week 40 to Week 104

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	11	55	7
Units: Percent of patients				
number (not applicable)				
Week 40	0	0	7.3	14.3
Week 52	22.2	18.2	18.2	14.3
Week 80	55.6	36.4	25.5	42.9
Week 104	55.6	27.3	34.5	57.1

End point values	All Tocilizumab Patients			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Percent of patients				
number (not applicable)				
Week 40	6.1			
Week 52	18.3			
Week 80	31.7			
Week 104	37.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Patients Achieving JIA ACR30/50/70/90 Responses at Week 104 by Duration of Disease (< 2 Years, ≥ 2 Years)

End point title	Percent of Patients Achieving JIA ACR30/50/70/90 Responses at Week 104 by Duration of Disease (< 2 Years, ≥ 2 Years) ^[15]
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End point description:

A JIA ACR30/50/70/90 response is defined as a ≥ 30/50/70/90% response on 3 of 6 variables and no more than 1 of the remaining variables worsening > 30%. The 6 variables are physician global assessment of disease activity (20 units minimum on a 0-100 visual analog scale [VAS]), parent/patient global assessment of overall well-being (20 VAS units minimum), number of joints (minimum of 2 worse) with active arthritis (swelling, or pain and limitation of motion), number of joints (minimum of 2 worse) with limitation of movement, erythrocyte sedimentation rate, and functional ability assessed using the disability index of the Childhood Health Assessment Questionnaire (CHAQ, 30 questions, 8 domains, 0[best]-3[worst]). Patients who withdrew due to non-safety reasons are classified as non-responders.

End point type	Secondary
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End point timeframe:

Baseline to Week 104

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	11	55	7
Units: Percent of patients				
number (not applicable)				
Disease Duration < 2 Years - ACR30 (n=4,4,17,1,26)	100	100	88.2	100
Disease Duration < 2 Years - ACR50 (n=4,4,17,1,26)	100	100	82.4	100

Disease Duration < 2 Years - ACR70 (n=4,4,17,1,26)	100	100	82.4	100
Disease Duration < 2 Years - ACR90 (n=4,4,17,1,26)	100	100	76.5	100
Disease Duration ≥ 2 Years - ACR30 (n=5,7,38,6,56)	100	85.7	97.4	100
Disease Duration ≥ 2 Years - ACR50 (n=5,7,38,6,56)	100	85.7	89.5	100
Disease Duration ≥ 2 Years - ACR70 (n=5,7,38,6,56)	80	85.7	84.2	100
Disease Duration ≥ 2 Years - ACR90 (n=5,7,38,6,56)	80	57.1	63.2	66.7

End point values	All Tocilizumab Patients			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Percent of patients				
number (not applicable)				
Disease Duration < 2 Years - ACR30 (n=4,4,17,1,26)	92.3			
Disease Duration < 2 Years - ACR50 (n=4,4,17,1,26)	88.5			
Disease Duration < 2 Years - ACR70 (n=4,4,17,1,26)	88.5			
Disease Duration < 2 Years - ACR90 (n=4,4,17,1,26)	84.6			
Disease Duration ≥ 2 Years - ACR30 (n=5,7,38,6,56)	96.4			
Disease Duration ≥ 2 Years - ACR50 (n=5,7,38,6,56)	91.1			
Disease Duration ≥ 2 Years - ACR70 (n=5,7,38,6,56)	85.7			
Disease Duration ≥ 2 Years - ACR90 (n=5,7,38,6,56)	64.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Oral Corticosteroid Dose at Baseline, Week 52, and Week 104

End point title	Oral Corticosteroid Dose at Baseline, Week 52, and Week
End point description: Due to the different types of corticosteroid medications available, the prednisone equivalent was used in the calculation of the oral corticosteroid dose. Values are based on the average daily dose on the study day and if not available the last observation carried forward is used.	
End point type	Secondary
End point timeframe: Baseline to Week 104	

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22	34	119	188
Units: mg/kg/day				
arithmetic mean (standard deviation)				
Baseline (n=22, 34, 119, 188, 13)	0.041 (± 0.0704)	0.079 (± 0.0802)	0.055 (± 0.0708)	0.061 (± 0.0743)
Week 52 (n=17, 24, 105, 159, 13)	0.021 (± 0.0474)	0.037 (± 0.0591)	0.032 (± 0.049)	0.034 (± 0.0518)
Week 104 (n=16, 23, 103, 155, 13)	0.014 (± 0.0418)	0.019 (± 0.0412)	0.02 (± 0.0558)	0.02 (± 0.0518)

End point values	Tocilizumab 10mg/kg to 8 mg/kg in Patients weighing <30kg			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: mg/kg/day				
arithmetic mean (standard deviation)				
Baseline (n=22, 34, 119, 188, 13)	0.095 (± 0.0836)			
Week 52 (n=17, 24, 105, 159, 13)	0.064 (± 0.0599)			
Week 104 (n=16, 23, 103, 155, 13)	0.028 (± 0.0497)			

Statistical analyses

No statistical analyses for this end point

Secondary: Methotrexate Dose at Baseline, Week 52, and Week 104

End point title	Methotrexate Dose at Baseline, Week 52, and Week 104
End point description: Values are based on the average daily dose on the study day and if not available the last observation carried forward is used.	
End point type	Secondary
End point timeframe: Baseline to Week 104	

End point values	Tocilizumab 10 mg/kg in Patients Weighing <30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	Tocilizumab 8 or 10 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	34	119	13
Units: mg/m ² /week				
arithmetic mean (standard deviation)				
Baseline (n=22, 34, 118, 13, 187)	11.304 (± 6.7521)	12.146 (± 5.2822)	8.768 (± 5.5387)	17.562 (± 17.0864)
Week 52 (n=17, 24, 105, 13, 159)	9.247 (± 5.6513)	11.216 (± 4.689)	8.326 (± 4.9825)	15.568 (± 15.2521)
Week 104 (n=16, 23, 103, 13, 155)	8.342 (± 5.2618)	10.05 (± 4.6316)	6.855 (± 5.0401)	11.858 (± 14.3458)

End point values	All Tocilizumab Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	188			
Units: mg/m ² /week				
arithmetic mean (standard deviation)				
Baseline (n=22, 34, 118, 13, 187)	10.292 (± 7.3586)			
Week 52 (n=17, 24, 105, 13, 159)	9.453 (± 6.6963)			
Week 104 (n=16, 23, 103, 13, 155)	7.902 (± 6.4332)			

Statistical analyses

No statistical analyses for this end point

Secondary: Height Standard Deviation Score at Baseline, Week 52, and Week 104

End point title	Height Standard Deviation Score at Baseline, Week 52, and Week 104 ^[17]
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End point description:

The height Standard Deviation Score was calculated using the following formula: (Observed height - median of the reference population)/standard deviation of the reference population. The reference population was defined as that of the same sex and age to the nearest completed year and month using the World Health Organization norms. A negative score indicates less height than the reference population.

End point type	Secondary
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End point timeframe:

Baseline to Week 104

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint data were not analyzed for all baseline period arms.

End point values	Placebo	Tocilizumab 8 or 10 mg/kg	All Tocilizumab Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	84	82	187	
Units: Standard deviation score				
arithmetic mean (standard deviation)				
Baseline	-0.57 (± 1.005)	-0.33 (± 1.29)	-0.51 (± 1.219)	
Week 52	-0.51 (± 1.004)	-0.15 (± 1.216)	-0.33 (± 1.125)	
Week 104	-0.34 (± 0.954)	-0.01 (± 1.15)	-0.18 (± 1.066)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All exposure safety population: All participants randomized into Part I of the study who received at least 1 infusion of tocilizumab and had at least 1 post-baseline safety assessment or event.

Adverse event reporting additional description:

The patients were exposed to weight adjusted doses for the 104 week duration of the study with the exception of those patients randomized in Part II (Weeks 16-40) to receive placebo. Adverse events (AE) are reported for all participants and by the various weight-based dose groups. AEs which occurred in the placebo group in Part II are not included.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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Reporting groups

Reporting group title	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg
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Reporting group description: -

Reporting group title	Tocilizumab 10 mg/kg to 8 mg/kg in Patients Weighing < 30 kg
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Reporting group description: -

Reporting group title	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg
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Reporting group description: -

Reporting group title	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg
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Reporting group description: -

Reporting group title	All Tocilizumab Patients
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Reporting group description: -

Serious adverse events	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 10 mg/kg to 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)	1 / 13 (7.69%)	4 / 34 (11.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Neck injury			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial rupture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Upper limb fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Familial mediterranean fever			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Benign intracranial hypertension			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis sclerosing			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminaemia			

subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychosomatic disease			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scleroderma			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 13 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr Virus Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			

subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 119 (14.29%)	26 / 188 (13.83%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Neck injury			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial rupture			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Familial mediterranean fever			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Benign intracranial hypertension			

subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 119 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis sclerosing			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminaemia			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychosomatic disease			

subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 119 (2.52%)	4 / 188 (2.13%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 119 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 119 (1.68%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Varicella			
subjects affected / exposed	0 / 119 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr Virus Infection			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 119 (0.84%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Tocilizumab 10 mg/kg in Patients Weighing < 30 kg	Tocilizumab 10 mg/kg to 8 mg/kg in Patients Weighing < 30 kg	Tocilizumab 8 mg/kg in Patients Weighing < 30 kg
Total subjects affected by non-serious adverse events subjects affected / exposed	19 / 22 (86.36%)	11 / 13 (84.62%)	25 / 34 (73.53%)
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 2	1 / 34 (2.94%) 1
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	2 / 34 (5.88%) 3
Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	0 / 34 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) Pneumonitis subjects affected / exposed occurrences (all) Nasal obstruction subjects affected / exposed occurrences (all) Productive cough	4 / 22 (18.18%) 4 1 / 22 (4.55%) 1 2 / 22 (9.09%) 3 1 / 22 (4.55%) 1 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0	2 / 13 (15.38%) 3 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 1 / 13 (7.69%) 1 0 / 13 (0.00%) 0 1 / 13 (7.69%) 1 0 / 13 (0.00%) 0	6 / 34 (17.65%) 9 3 / 34 (8.82%) 7 1 / 34 (2.94%) 1 0 / 34 (0.00%) 0 2 / 34 (5.88%) 2 1 / 34 (2.94%) 1

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	0 / 34 (0.00%) 0
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	0 / 34 (0.00%) 0
Sneezing subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	0 / 34 (0.00%) 0
Investigations Transaminases increased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	0 / 34 (0.00%) 0
Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	1 / 13 (7.69%) 1	1 / 34 (2.94%) 1
Arthropod bite subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3	1 / 13 (7.69%) 1	1 / 34 (2.94%) 1
Contusion subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 13 (0.00%) 0	0 / 34 (0.00%) 0
Thermal burn subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 13 (7.69%) 1	2 / 34 (5.88%) 2
Fall subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	1 / 34 (2.94%) 1
Tibia fracture subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	0 / 34 (0.00%) 0
Foot fracture subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	0 / 34 (0.00%) 0
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	3 / 13 (23.08%) 4	5 / 34 (14.71%) 6
Dizziness subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 13 (0.00%) 0	0 / 34 (0.00%) 0
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 3	0 / 34 (0.00%) 0
Eosinophilia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	0 / 34 (0.00%) 0
Hypochromic anaemia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 13 (7.69%) 1	0 / 34 (0.00%) 0
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 13 (0.00%) 0	2 / 34 (5.88%) 2
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 13 (0.00%) 0	1 / 34 (2.94%) 1
Iridocyclitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 13 (0.00%) 0	2 / 34 (5.88%) 2
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 13 (0.00%) 0	2 / 34 (5.88%) 2
Diarrhoea subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 13 (0.00%) 0	2 / 34 (5.88%) 2
Vomiting subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 13 (7.69%) 1	3 / 34 (8.82%) 4

Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 13 (7.69%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Abdominal pain upper			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	5
Mouth ulceration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Aphthous stomatitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Dental caries			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	4
Ingrowing nail			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Alopecia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Erythema			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Prurigo			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 13 (0.00%) 0	2 / 34 (5.88%) 3
Musculoskeletal and connective tissue disorders			
Juvenile arthritis			
subjects affected / exposed	6 / 22 (27.27%)	3 / 13 (23.08%)	6 / 34 (17.65%)
occurrences (all)	6	3	7
Arthralgia			
subjects affected / exposed	3 / 22 (13.64%)	2 / 13 (15.38%)	0 / 34 (0.00%)
occurrences (all)	3	5	0
Muscle disorder			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Polyarthrititis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 22 (31.82%)	1 / 13 (7.69%)	5 / 34 (14.71%)
occurrences (all)	11	1	15
Upper respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)	0 / 13 (0.00%)	4 / 34 (11.76%)
occurrences (all)	6	0	4
Pharyngitis			
subjects affected / exposed	4 / 22 (18.18%)	1 / 13 (7.69%)	3 / 34 (8.82%)
occurrences (all)	7	2	4
Rhinitis			
subjects affected / exposed	1 / 22 (4.55%)	2 / 13 (15.38%)	5 / 34 (14.71%)
occurrences (all)	2	2	8
Ear infection			
subjects affected / exposed	1 / 22 (4.55%)	2 / 13 (15.38%)	2 / 34 (5.88%)
occurrences (all)	1	3	3
Gastroenteritis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	3 / 34 (8.82%)
occurrences (all)	2	0	4
Influenza			

subjects affected / exposed	2 / 22 (9.09%)	1 / 13 (7.69%)	1 / 34 (2.94%)
occurrences (all)	3	1	1
Sinusitis			
subjects affected / exposed	1 / 22 (4.55%)	2 / 13 (15.38%)	2 / 34 (5.88%)
occurrences (all)	1	2	2
Bronchitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	1
Urinary tract infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 13 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Oral herpes			
subjects affected / exposed	2 / 22 (9.09%)	1 / 13 (7.69%)	1 / 34 (2.94%)
occurrences (all)	3	1	1
Pharyngotonsillitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	4
Pneumonia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Laryngitis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 13 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Varicella			
subjects affected / exposed	1 / 22 (4.55%)	2 / 13 (15.38%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Infection parasitic			

subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Mumps			
subjects affected / exposed	0 / 22 (0.00%)	0 / 13 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Abscess			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Skin bacterial infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Abscess limb			
subjects affected / exposed	0 / 22 (0.00%)	1 / 13 (7.69%)	0 / 34 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Tocilizumab 8 mg/kg in Patients Weighing ≥ 30 kg	All Tocilizumab Patients	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 119 (85.71%)	157 / 188 (83.51%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 119 (1.68%)	4 / 188 (2.13%)	
occurrences (all)	2	5	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 119 (3.36%)	7 / 188 (3.72%)	
occurrences (all)	5	9	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	13 / 119 (10.92%)	25 / 188 (13.30%)	
occurrences (all)	16	32	
Oropharyngeal pain			
subjects affected / exposed	15 / 119 (12.61%)	19 / 188 (10.11%)	
occurrences (all)	20	28	
Epistaxis			
subjects affected / exposed	5 / 119 (4.20%)	8 / 188 (4.26%)	
occurrences (all)	5	9	
Rhinorrhoea			
subjects affected / exposed	4 / 119 (3.36%)	6 / 188 (3.19%)	
occurrences (all)	4	6	
Pneumonitis			
subjects affected / exposed	1 / 119 (0.84%)	3 / 188 (1.60%)	
occurrences (all)	1	3	
Nasal obstruction			
subjects affected / exposed	0 / 119 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Productive cough			
subjects affected / exposed	1 / 119 (0.84%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Rhinitis allergic			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Sneezing			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Investigations			
Transaminases increased			
subjects affected / exposed	4 / 119 (3.36%)	5 / 188 (2.66%)	
occurrences (all)	4	5	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	3 / 119 (2.52%)	7 / 188 (3.72%)	
occurrences (all)	4	8	
Arthropod bite			

subjects affected / exposed	2 / 119 (1.68%)	6 / 188 (3.19%)	
occurrences (all)	2	7	
Contusion			
subjects affected / exposed	2 / 119 (1.68%)	4 / 188 (2.13%)	
occurrences (all)	2	4	
Thermal burn			
subjects affected / exposed	0 / 119 (0.00%)	4 / 188 (2.13%)	
occurrences (all)	0	4	
Fall			
subjects affected / exposed	1 / 119 (0.84%)	3 / 188 (1.60%)	
occurrences (all)	1	3	
Tibia fracture			
subjects affected / exposed	2 / 119 (1.68%)	3 / 188 (1.60%)	
occurrences (all)	2	3	
Foot fracture			
subjects affected / exposed	1 / 119 (0.84%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 119 (18.49%)	31 / 188 (16.49%)	
occurrences (all)	41	52	
Dizziness			
subjects affected / exposed	7 / 119 (5.88%)	8 / 188 (4.26%)	
occurrences (all)	11	12	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 119 (0.84%)	2 / 188 (1.06%)	
occurrences (all)	1	4	
Eosinophilia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Hypochromic anaemia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			

Ear pain subjects affected / exposed occurrences (all)	6 / 119 (5.04%) 6	8 / 188 (4.26%) 8	
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	6 / 119 (5.04%) 6	9 / 188 (4.79%) 9	
Iridocyclitis subjects affected / exposed occurrences (all)	0 / 119 (0.00%) 0	2 / 188 (1.06%) 2	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	15 / 119 (12.61%) 26	17 / 188 (9.04%) 28	
Diarrhoea subjects affected / exposed occurrences (all)	14 / 119 (11.76%) 16	17 / 188 (9.04%) 19	
Vomiting subjects affected / exposed occurrences (all)	12 / 119 (10.08%) 14	17 / 188 (9.04%) 20	
Abdominal pain subjects affected / exposed occurrences (all)	12 / 119 (10.08%) 18	16 / 188 (8.51%) 22	
Abdominal pain upper subjects affected / exposed occurrences (all)	8 / 119 (6.72%) 9	10 / 188 (5.32%) 14	
Mouth ulceration subjects affected / exposed occurrences (all)	6 / 119 (5.04%) 11	7 / 188 (3.72%) 12	
Aphthous stomatitis subjects affected / exposed occurrences (all)	3 / 119 (2.52%) 5	5 / 188 (2.66%) 7	
Dental caries subjects affected / exposed occurrences (all)	3 / 119 (2.52%) 3	4 / 188 (2.13%) 4	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	7 / 119 (5.88%)	11 / 188 (5.85%)	
occurrences (all)	8	13	
Ingrowing nail			
subjects affected / exposed	6 / 119 (5.04%)	6 / 188 (3.19%)	
occurrences (all)	7	7	
Urticaria			
subjects affected / exposed	5 / 119 (4.20%)	6 / 188 (3.19%)	
occurrences (all)	7	8	
Eczema			
subjects affected / exposed	3 / 119 (2.52%)	5 / 188 (2.66%)	
occurrences (all)	4	6	
Alopecia			
subjects affected / exposed	1 / 119 (0.84%)	3 / 188 (1.60%)	
occurrences (all)	1	3	
Erythema			
subjects affected / exposed	1 / 119 (0.84%)	3 / 188 (1.60%)	
occurrences (all)	1	3	
Prurigo			
subjects affected / exposed	0 / 119 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Juvenile arthritis			
subjects affected / exposed	37 / 119 (31.09%)	52 / 188 (27.66%)	
occurrences (all)	49	65	
Arthralgia			
subjects affected / exposed	5 / 119 (4.20%)	10 / 188 (5.32%)	
occurrences (all)	7	15	
Muscle disorder			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Polyarthrititis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Infections and infestations			

Nasopharyngitis		
subjects affected / exposed	32 / 119 (26.89%)	45 / 188 (23.94%)
occurrences (all)	57	84
Upper respiratory tract infection		
subjects affected / exposed	17 / 119 (14.29%)	23 / 188 (12.23%)
occurrences (all)	37	47
Pharyngitis		
subjects affected / exposed	18 / 119 (15.13%)	26 / 188 (13.83%)
occurrences (all)	23	36
Rhinitis		
subjects affected / exposed	7 / 119 (5.88%)	15 / 188 (7.98%)
occurrences (all)	7	19
Ear infection		
subjects affected / exposed	10 / 119 (8.40%)	15 / 188 (7.98%)
occurrences (all)	14	21
Gastroenteritis		
subjects affected / exposed	7 / 119 (5.88%)	11 / 188 (5.85%)
occurrences (all)	11	17
Influenza		
subjects affected / exposed	7 / 119 (5.88%)	11 / 188 (5.85%)
occurrences (all)	8	13
Sinusitis		
subjects affected / exposed	5 / 119 (4.20%)	10 / 188 (5.32%)
occurrences (all)	5	10
Bronchitis		
subjects affected / exposed	6 / 119 (5.04%)	8 / 188 (4.26%)
occurrences (all)	8	11
Urinary tract infection		
subjects affected / exposed	6 / 119 (5.04%)	8 / 188 (4.26%)
occurrences (all)	6	8
Oral herpes		
subjects affected / exposed	3 / 119 (2.52%)	7 / 188 (3.72%)
occurrences (all)	3	8
Pharyngotonsillitis		
subjects affected / exposed	6 / 119 (5.04%)	7 / 188 (3.72%)
occurrences (all)	8	9

Otitis media		
subjects affected / exposed	3 / 119 (2.52%)	5 / 188 (2.66%)
occurrences (all)	3	7
Pneumonia		
subjects affected / exposed	3 / 119 (2.52%)	5 / 188 (2.66%)
occurrences (all)	3	5
Respiratory tract infection viral		
subjects affected / exposed	4 / 119 (3.36%)	5 / 188 (2.66%)
occurrences (all)	6	7
Viral infection		
subjects affected / exposed	3 / 119 (2.52%)	4 / 188 (2.13%)
occurrences (all)	3	4
Laryngitis		
subjects affected / exposed	1 / 119 (0.84%)	3 / 188 (1.60%)
occurrences (all)	1	3
Varicella		
subjects affected / exposed	0 / 119 (0.00%)	5 / 188 (2.66%)
occurrences (all)	0	5
Infection parasitic		
subjects affected / exposed	0 / 119 (0.00%)	2 / 188 (1.06%)
occurrences (all)	0	2
Mumps		
subjects affected / exposed	0 / 119 (0.00%)	2 / 188 (1.06%)
occurrences (all)	0	2
Abscess		
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)
occurrences (all)	0	1
Skin bacterial infection		
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)
occurrences (all)	0	1
Respiratory tract infection		
subjects affected / exposed	2 / 119 (1.68%)	4 / 188 (2.13%)
occurrences (all)	2	4
Abscess limb		
subjects affected / exposed	0 / 119 (0.00%)	1 / 188 (0.53%)
occurrences (all)	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported