



Clinical trial results:

A PHASE Ib, OPEN-LABEL, MULTICENTER STUDY TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF TOCILIZUMAB FOLLOWING SUBCUTANEOUS ADMINISTRATION TO PATIENTS WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

Summary

EudraCT number	2012-003490-26
Trial protocol	DE IT GB ES Outside EU/EEA
Global end of trial date	13 June 2017

Results information

Result version number	v1 (current)
This version publication date	24 December 2017
First version publication date	24 December 2017

Trial information

Trial identification

Sponsor protocol code	WA28118
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01904292
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 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?	
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	13 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2017
Global end of trial reached?	Yes
Global end of trial date	13 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics, pharmacodynamics, and safety of subcutaneously administered tocilizumab in participants with Systemic Juvenile Idiopathic Arthritis (sJIA)

Protection of trial subjects:

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	51
EEA total number of subjects	25

Notes:

Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	3
Children (2-11 years)	28
Adolescents (12-17 years)	20
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were assigned to one of two dosing regimens based on the following BW criteria: patients weighing < 30 kg received 162 mg of TCZ SC Q10D or TCZ SC Q2W for 52 weeks. Patients weighing > 30 kg received 162 mg of TCZ SC QW for 52 weeks.

Pre-assignment

Screening details:

Screening tests and evaluations were performed within 21 days prior to baseline.

All screening evaluations had to be completed and reviewed to confirm that patients met all eligibility criteria before enrollment. Patients who initially failed screening could be re-screened on one occasion only at the discretion of the investigator.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tocilizumab 162 mg - Q10D or Q2W

Arm description:

Participants with body weight < 30 kg received 162 milligrams (mg) of tocilizumab either Q10D or Q2W for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	Actemra, RoActemra
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received Sub-cutaneous Tocilizumab (SC TCZ) based on Body Weight; patients weighing < 30 kg received 162 mg of TCZ either Q10D (every ten days) or Q2W (every two weeks) for 52 weeks

Arm title	Tocilizumab 162 mg - QW
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Arm description:

Participants with body weight \geq 30 kg received 162 mg of tocilizumab QW, for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	Actemra, RoActemra
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received Sub-cutaneous Tocilizumab (SC TCZ) based on Body Weight; patients weighing \geq 30 kg received 162 mg of TCZ QW (every week) for 52 weeks

Number of subjects in period 1	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW
Started	25	26
Completed	21	23
Not completed	4	3
Adverse event, serious fatal	2	-
Physician decision	-	1
Lack of efficacy	2	2

Baseline characteristics

Reporting groups

Reporting group title	Tocilizumab 162 mg - Q10D or Q2W
Reporting group description: Participants with body weight<30 kg received 162 milligrams (mg) of tocilizumab either Q10D or Q2W for 52 weeks.	
Reporting group title	Tocilizumab 162 mg - QW
Reporting group description: Participants with body weight =>30 kg received 162 mg of tocilizumab QW, for 52 weeks.	

Reporting group values	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW	Total
Number of subjects	25	26	51
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	5.1	13.3	
standard deviation	± 3.2	± 3.2	-
Gender categorical Units: Subjects			
Female	13	16	29
Male	12	10	22

End points

End points reporting groups

Reporting group title	Tocilizumab 162 mg - Q10D or Q2W
Reporting group description: Participants with body weight<30 kg received 162 milligrams (mg) of tocilizumab either Q10D or Q2W for 52 weeks.	
Reporting group title	Tocilizumab 162 mg - QW
Reporting group description: Participants with body weight =>30 kg received 162 mg of tocilizumab QW, for 52 weeks.	
Subject analysis set title	Tocilizumab 162 mg - Q2W
Subject analysis set type	Sub-group analysis
Subject analysis set description: This analysis set includes all the patients with BW<30kg. The steady-state Cmin, Cmax and AUC parameters for those patients who received TCZ Q10D were computed as if they received the Q2W dosage regimen.	

Primary: Minimum Serum Concentration (Cmin) of Tocilizumab

End point title	Minimum Serum Concentration (Cmin) of Tocilizumab ^{[1][2]}
End point description: The Pharmacokinetic profile of Tocilizumab is evaluated in terms of Model Computed Steady-State Cmin.	
End point type	Primary
End point timeframe: Samples taken at visits: - w 0,2,6,10,12,14,26,38,52 -BW<30 kg and <2years old(YO); - w 0,2,6,8,10,12,14,26,38,52-BW<30 kg and >=2YO; - w 0,1,2,4,8,13,14,26,38,52- BW>=30 kg;	

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: Descriptive statistics only were planned for this endpoint.

[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: The missing reporting group has been replaced by the ad hoc analysis set for this endpoint.

End point values	Tocilizumab 162 mg - QW	Tocilizumab 162 mg - Q2W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26	25		
Units: mcg/mL				
median (full range (min-max))	72.37 (19.52 to 157.8)	64.15 (16.61 to 135.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-Time Curve (AUC) of Tocilizumab

End point title	Area Under the Concentration-Time Curve (AUC) of
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End point description:

The Pharmacokinetic (PK) profile of TCZ is evaluated in terms of Model Computed Steady-State AUC.

End point type	Primary
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End point timeframe:

Samples taken at visits:

- w 0,2,6,10,12,14,26,38,52 -BW<30 kg and <2years old(YO);
- w 0,2,6,8,10,12,14,26,38,52-BW<30 kg and >=2YO;
- w 0,1,2,4,8,13,14,26,38,52- BW>=30 kg;

Notes:

[3] - 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: Descriptive statistics only were planned for this endpoint.

[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: The missing reporting group has been replaced by the ad hoc analysis set for this endpoint.

End point values	Tocilizumab 162 mg - QW	Tocilizumab 162 mg - Q2W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26	25		
Units: mcg*day/mL				
median (full range (min-max))	1154 (334 to 2370)	1298 (539 to 2792)		

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Serum Concentration (Cmax) of Tocilizumab

End point title	Maximum Serum Concentration (Cmax) of Tocilizumab ^{[5][6]}
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End point description:

The Pharmacokinetic profile of Tocilizumab is evaluated in terms of Model Computed Steady-State Cmax.

End point type	Primary
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End point timeframe:

Samples taken at visits:

- w 0,2,6,10,12,14,26,38,52 -BW<30 kg and <2years old(YO);
- w 0,2,6,8,10,12,14,26,38,52-BW<30 kg and >=2YO;
- w 0,1,2,4,8,13,14,26,38,52- BW>=30 kg;

Notes:

[5] - 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: Descriptive statistics only were planned for this endpoint.

[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: The missing reporting group has been replaced by the ad hoc analysis set for this endpoint.

End point values	Tocilizumab 162 mg - QW	Tocilizumab 162 mg - Q2W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26	25		
Units: mcg/mL				
median (full range (min-max))	89.8 (26.37 to 190.2)	126.6 (51.67 to 265.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Interleukin-6 (IL6) Levels

End point title	Serum Interleukin-6 (IL6) Levels
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End point description:

The Pharmacodynamic profile of TCZ is evaluated in terms of IL-6 serum concentration. 99999 indicates that the value was not estimated at that week for that reporting group.

End point type	Secondary
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End point timeframe:

Samples taken at visits:

- w 0,2,6,10,12,14,26,38,52 -BW<30 kg and <2years old(YO);
- w 0,2,6,8,10,12,14,26,38,52-BW<30 kg and >=2YO;
- w 0,1,2,4,8,13,14,26,38,52- BW>=30 kg;

End point values	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[7]	26 ^[8]		
Units: pg/ml				
median (full range (min-max))				
Baseline (N=18, 21)	28.350 (1.46 to 208.00)	19.800 (3.12 to 153.00)		
Week 1 (N= 0, 22)	99999 (99999 to 99999)	36.300 (11.20 to 1160.00)		
Week 2 (N=23, 20)	35.200 (3.12 to 935.00)	22.200 (11.10 to 395.00)		
Week 4 (N= 6, 24)	73.300 (11.40 to 816.00)	27.000 (10.80 to 2530.00)		
Week 6 (N=15, 0)	30.300 (12.10 to 618.00)	99999 (99999 to 99999)		
Week 8 (N=16, 24)	80.400 (3.12 to 625.00)	33.650 (11.90 to 1130.00)		
Week 10 (N= 22, 0)	39.600 (3.12 to 4690.00)	99999 (99999 to 99999)		
Week 12 (N=18, 0)	45.500 (12.00 to 482.00)	99999 (99999 to 99999)		
Week 13 (N= 0, 13)	99999 (99999 to 99999)	23.600 (10.10 to 168.00)		
Week 14 (N=23, 19)	74.600 (12.60 to 2190.00)	28.200 (9.46 to 416.00)		
Week 26 (N=19, 22)	50.200 (11.30 to 337.00)	25.800 (8.40 to 906.00)		
Week 38 (N= 17, 23)	27.200 (6.55 to 771.00)	22.500 (7.98 to 354.00)		

Week 52 (N= 17, 20)	40.800 (13.70 to 297.00)	25.200 (8.43 to 182.00)		
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Notes:

[7] - The number of participants analysed per every single week is reported below (N=)

[8] - The number of participants analysed per every single week is reported below (N=)

Statistical analyses

No statistical analyses for this end point

Secondary: Soluble IL-6 Receptor (sIL-6R) Levels

End point title	Soluble IL-6 Receptor (sIL-6R) Levels
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End point description:

The pharmacodynamic profile of TCZ is evaluated in terms of sIL-6R serum concentration. 99999 indicates that the value was not estimated at that week for that reporting group.

End point type	Secondary
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End point timeframe:

Samples taken at visits:

- w 0,2,6,10,12,14,26,38,52 -BW<30 kg and <2years old(YO);
- w 0,2,6,8,10,12,14,26,38,52-BW<30 kg and >=2YO;
- w 0,1,2,4,8,13,14,26,38,52- BW>=30 kg;

End point values	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[9]	26 ^[10]		
Units: ng/ml				
median (full range (min-max))				
Baseline (N=19, 22)	57.50 (21.0 to 1240.0)	419.50 (27.1 to 1170.0)		
Week 1 (N=0, 25)	99999 (99999 to 99999)	447.00 (234.0 to 1020.0)		
Week 2 (N=25, 22)	575.00 (44.3 to 1260.0)	456.50 (149.0 to 1030.0)		
Week 4 (N=8, 25)	705.00 (521.0 to 1060.0)	575.00 (194.0 to 1010.0)		
Week 6 (N=15, 0)	751.00 (43.7 to 1170.0)	99999 (99999 to 99999)		
Week 8 (N=19, 24)	716.00 (67.7 to 1270.0)	738.00 (418.0 to 1090.0)		
Week 10 (N=22, 0)	714.00 (114.0 to 1480.0)	99999 (99999 to 99999)		
Week 12 (N=18, 0)	716.50 (488.0 to 1190.0)	99999 (99999 to 99999)		
Week 13 (N=0, 14)	99999 (99999 to 99999)	664.00 (395.0 to 1050.0)		
Week 14 (N=23, 20)	736.00 (503.0 to 1830.0)	710.00 (428.0 to 1070.0)		
Week 26 (N=21, 22)	775.00 (500.0 to 1910.0)	645.50 (346.0 to 1060.0)		
Week 38 (N=20, 23)	782.00 (301.0 to 1420.0)	583.00 (262.0 to 1230.0)		

Week 52 (N=18, 20)	737.00 (270.0 to 1490.0)	598.00 (199.0 to 1070.0)		
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Notes:

[9] - The number of participants analysed per every single week is reported below (N=)

[10] - The number of participants analysed per every single week is reported below (N=)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum C-Reactive Protein (CRP) Levels

End point title	Serum C-Reactive Protein (CRP) Levels
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End point description:

The pharmacodynamic profile of TCZ is evaluated in terms of CRP serum concentration. 99999 indicates that the value was not estimated at that week for that reporting group.

End point type	Secondary
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End point timeframe:

Samples for this analysis were taken at:

W-3,0,1,2,3,4,6,8,10,12,13,14,18,22,26,30,34,38,42,46,50,52 - BW \geq 30kg

W-3,0,2,4,6,10,14,18,22,26,30,34,38,42,46,50,52-BW<30kg - \geq 2YO

W-3,0,2,4,6,10,12,14,18,22,26,30,34,38,42,46,50,52 -BW<30kg - <2YO

End point values	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[11]	26 ^[12]		
Units: mg/L				
median (full range (min-max))				
Baseline (N=25, 26)	3.270 (0.20 to 186.00)	0.305 (0.20 to 117.00)		
Week 1 (N=0, 26)	99999 (99999 to 99999)	0.200 (0.20 to 9.00)		
Week 2 (N=25, 23)	0.200 (0.20 to 139.00)	0.200 (0.20 to 1.58)		
Week 3 (N=8, 25)	0.200 (0.20 to 0.43)	0.200 (0.20 to 2.06)		
Week 4 (N=23, 24)	0.200 (0.20 to 150.00)	0.200 (0.20 to 1.27)		
Week 6 (N=16, 25)	0.200 (0.20 to 27.70)	0.200 (0.20 to 1.06)		
Week 8 (N=7, 24)	0.200 (0.20 to 0.83)	0.200 (0.20 to 1.25)		
Week 10 (N=23, 24)	0.200 (0.20 to 22.60)	0.200 (0.20 to 3.65)		
Week 12 (N=7, 24)	0.200 (0.20 to 0.38)	0.200 (0.20 to 2.55)		
Week 13 (N=0, 21)	99999 (99999 to 99999)	0.200 (0.20 to 2.23)		
Week 14 (N=23, 23)	0.200 (0.20 to 0.48)	0.200 (0.20 to 1.36)		
Week 18 (N=23, 23)	0.200 (0.20 to 3.50)	0.200 (0.20 to 2.61)		

Week 22 (N=23, 23)	0.200 (0.20 to 0.36)	0.200 (0.20 to 1.82)		
Week 26 (N=22, 23)	0.200 (0.20 to 3.46)	0.200 (0.20 to 1.89)		
Week 30 (N=22, 22)	0.200 (0.20 to 0.85)	0.200 (0.20 to 1.67)		
Week 34 (N=22, 23)	0.200 (0.20 to 0.91)	0.200 (0.20 to 1.95)		
Week 38 (N=21, 23)	0.200 (0.20 to 11.90)	0.200 (0.20 to 1.39)		
Week 42 (N=15, 23)	0.200 (0.20 to 3.92)	0.200 (0.20 to 1.43)		
Week 46 (N=20, 23)	0.200 (0.20 to 0.36)	0.200 (0.20 to 2.11)		
Week 50 (N=20, 23)	0.200 (0.20 to 1.01)	0.200 (0.20 to 5.00)		
Week 52 (N=17, 18)	0.200 (0.20 to 1.23)	0.200 (0.20 to 2.45)		

Notes:

[11] - The number of participants analysed per every single week is reported below (N=)

[12] - The number of participants analysed per every single week is reported below (N=)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Erythrocyte Sedimentation Rate (ESR)

End point title	Serum Erythrocyte Sedimentation Rate (ESR)
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End point description:

The pharmacodynamic profile of TCZ is evaluated in terms of ESR.

99999 indicates that the value was not estimated at that week for that reporting group.

End point type	Secondary
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End point timeframe:

Samples for this analysis were taken at:

W-3,0,1,2,3,4,6,8,10,12,13,14,18,22,26,30,34,38,42,46,50,52 - BW ≥ 30kg

W-3,0,2,4,6,10,14,18,22,26,30,34,38,42,46,50,52 - BW < 30kg - ≥ 2YO

W-3,0,2,4,6,10,12,14,18,22,26,30,34,38,42,46,50,52 - BW < 30kg - < 2YO

End point values	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[13]	26 ^[14]		
Units: mm/h				
median (full range (min-max))				
Baseline (N=25, 26)	10.00 (0.0 to 120.0)	5.00 (0.0 to 90.0)		
Week 1 (N=0, 26)	99999 (99999 to 99999)	5.00 (1.0 to 50.0)		
Week 2 (N=22, 23)	5.00 (0.0 to 40.0)	4.00 (0.0 to 28.0)		
Week 3 (N=8, 25)	3.50 (2.0 to 8.0)	3.00 (1.0 to 12.0)		
Week 4 (N=23, 25)	3.00 (0.0 to 65.0)	4.00 (0.0 to 20.0)		

Week 6 (N=15, 25)	3.00 (0.0 to 10.0)	3.00 (0.0 to 9.0)		
Week 8 (N=8, 24)	3.50 (2.0 to 9.0)	3.00 (0.0 to 12.0)		
Week 10 (N=23, 24)	3.00 (0.0 to 9.0)	3.00 (0.0 to 20.0)		
Week 12 (N=7, 23)	3.00 (2.0 to 6.0)	3.00 (0.0 to 18.0)		
Week 13 (N=0, 21)	99999 (99999 to 99999)	4.00 (1.0 to 16.0)		
Week 14 (N=22, 22)	2.00 (0.0 to 8.0)	3.00 (1.0 to 11.0)		
Week 18 (N=22, 23)	2.00 (0.0 to 9.0)	4.00 (0.0 to 15.0)		
Week 22 (N=23, 23)	3.00 (0.0 to 9.0)	3.48 (0.0 to 20.0)		
Week 26 (N=22, 23)	2.00 (0.0 to 9.0)	3.00 (0.0 to 16.0)		
Week 30 (N=21, 23)	2.00 (0.0 to 6.0)	3.00 (0.0 to 18.0)		
Week 34 (N=22, 23)	2.00 (0.0 to 10.0)	3.00 (0.0 to 16.0)		
Week 38 (N=19, 23)	2.00 (0.0 to 15.0)	3.00 (0.0 to 25.0)		
Week 42 (N=15, 21)	3.00 (0.0 to 12.0)	3.00 (0.0 to 18.0)		
Week 46 (N=20, 22)	2.00 (0.0 to 8.0)	3.00 (0.0 to 15.0)		
Week 50 (N=21, 23)	2.00 (0.0 to 10.0)	2.00 (0.0 to 17.0)		
Week 52 (N=19, 23)	2.00 (0.0 to 5.0)	2.00 (1.0 to 24.0)		

Notes:

[13] - The number of participants analysed per every single week is reported below (N=)

[14] - The number of participants analysed per every single week is reported below (N=)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-TCZ Antibodies

End point title	Number of Participants with Anti-TCZ Antibodies
End point description: The pharmacodynamic profile of TCZ is evaluated in terms of number of Participants with treatment-induced Anti-Tocilizumab Antibodies.	
End point type	Secondary
End point timeframe: Anti-TCZ antibodies were measured at approximately 3 month intervals during the study and at the last study visit or at the time of early withdrawal from the study.	

End point values	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: Number of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with At Least 1 Adverse Event (AE)

End point title	Number of Participants with At Least 1 Adverse Event (AE)
End point description: The safety profile of TCZ is evaluated in terms of number of participants with at least one AE and one SAE.	
End point type	Secondary
End point timeframe: All AEs, are reported after initiation of study drug until 3 months after the last dose of study drug. After this period, any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with study drug are reported.	

End point values	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: Number of participants				
Any AE	25	25		
SAE	5	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants reporting adverse events of special interest (AESI)

End point title	Number of participants reporting adverse events of special interest (AESI)
End point description: The safety profile of TCZ is evaluated in terms of number of participants reporting AESI. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term. Severity refers to the intensity of an AE according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) i.e. from grade 1 (mild) up to grade 5 (Death related to adverse event).	
End point type	Secondary

End point timeframe:

All AEs, are reported after initiation of study drug until 3 months after the last dose of study drug. After this period, any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with study drug are reported.

End point values	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: Number of participants				
Sepsis - grade 5	1	0		
Oral Candidiasis - grade 2	1	0		
Pneumonia - grade 3	1	0		
Pneumonia - grade 4	1	0		
Abscess soft tissue - grade 3	1	0		
Injection Site Reactions - grade 1	5	12		
Injection Site Reactions - grade 2	0	3		
Injection Site Reactions - grade 3	1	1		
Hypersensitivity - grade 1	1	0		
Platelet Count Decreased - grade 2	1	0		
Pyrexia - grade 1	0	1		
Pruritus - grade 1	1	0		
Pulmonary Haemorrhage - grade 5	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients reporting clinical laboratory abnormalities

End point title	Number of patients reporting clinical laboratory abnormalities
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End point description:

The safety profile of TCZ is evaluated in terms of number of patients with clinical laboratory abnormalities. Severity refers to the intensity of an AE according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) i.e. from grade 1 (mild) up to grade 5 (Death related to adverse event).

For a patient with multiple post-baseline lab abnormalities, the highest (worst) grade of these abnormalities for the given lab test is reported.

End point type	Secondary
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End point timeframe:

All AEs, are reported after initiation of study drug until 3 months after the last dose of study drug. After this period, any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with study drug are reported.

End point values	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: Number of participants				
Hemoglobin Low - grade 1	3	2		
Hemoglobin Low - grade 2	1	0		
Hemoglobin Low - grade 3	1	0		
Hemoglobin High - grade 1	5	0		
Lymphocytes Abs Low - grade 1	6	10		
Lymphocytes Abs Low - grade 2	1	0		
Lymphocytes Abs Low - grade 3	0	1		
Lymphocytes Abs High - grade 2	4	3		
Neutrophils, Total, Abs Low - grade 1	0	3		
Neutrophils, Total, Abs Low - grade 2	8	5		
Neutrophils, Total, Abs Low - grade 3	4	8		
Platelet Low - grade 1	10	2		
White Blood Cell Count Low - grade 1	12	10		
White Blood Cell Count Low - grade 2	2	5		
White Blood Cell Count Low - grade 3	1	0		
Alkaline Phosphatase High - grade 1	3	3		
Alkaline Phosphatase High - grade 2	1	0		
Bilirubin High - grade 1	1	3		
Bilirubin High - grade 2	0	2		
Blood Glucose (fasting) Low - grade 1	12	2		
Blood Glucose (fasting) Low - grade 2	2	0		
Blood Glucose (fasting) High - grade 1	5	7		
Calcium Low - grade 1	1	0		
Calcium Low - grade 2	0	1		
Calcium Low - grade 4	0	1		
Calcium High - grade 1	9	5		
Creatinine High - grade 1	12	24		
Creatinine High - grade 2	9	1		
Glucose Low - grade 1	3	2		
Phosphorus Low - grade 1	0	1		
Potassium Low - grade 2	1	1		
Potassium High - grade 1	1	0		
Potassium High - grade 2	0	1		
Potassium High - grade 3	0	1		
Potassium High - grade 4	0	1		
SGOT/AST High - grade 1	3	7		
SGOT/AST High - grade 2	1	0		
SGOT/AST High - grade 3	1	0		
SGPT/ALT High - grade 1	6	6		
SGPT/ALT High - grade 2	1	2		
SGPT/ALT High - grade 3	1	0		
SGPT/ALT High - grade 4	1	0		
Uric Acid High - grade 3	8	5		
Cholesterol High - grade 1	2	1		
Triglycerides High - grade 1	3	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs, are reported after initiation of study drug until 3 months after the last dose of study drug. After this period, any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with study drug are reported.

Adverse event reporting additional description:

The safety analyses will include all enrolled patients who received at least one dose of study drug, with patients grouped according to the treatment received (safety population). The safety analysis population will include all patients who received at least one dose of study drug and who have at least one post-dose assessment.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Tocilizumab 162 mg - Q10D or Q2W
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Reporting group description:

Participants with body weight <30 kg received 162 milligrams (mg) of tocilizumab either Q10D or Q2W for 52 weeks.

Reporting group title	Tocilizumab 162 mg - QW
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Reporting group description:

Participants with body weight =>30 kg received 162 mg of tocilizumab QW, for 52 weeks.

Serious adverse events	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 25 (20.00%)	2 / 26 (7.69%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PULMONARY HAEMORRHAGE			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			

JUVENILE IDIOPATHIC ARTHRITIS			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABSCCESS SOFT TISSUE			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORAL CANDIDIASIS			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

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

Non-serious adverse events	Tocilizumab 162 mg - Q10D or Q2W	Tocilizumab 162 mg - QW	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 25 (92.00%)	24 / 26 (92.31%)	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 25 (8.00%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	3	0	

Injury, poisoning and procedural complications			
ARTHROPOD BITE			
subjects affected / exposed	3 / 25 (12.00%)	2 / 26 (7.69%)	
occurrences (all)	3	3	
CONTUSION			
subjects affected / exposed	3 / 25 (12.00%)	2 / 26 (7.69%)	
occurrences (all)	3	2	
FALL			
subjects affected / exposed	2 / 25 (8.00%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 25 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	0 / 25 (0.00%)	6 / 26 (23.08%)	
occurrences (all)	0	15	
Blood and lymphatic system disorders			
LEUKOPENIA			
subjects affected / exposed	1 / 25 (4.00%)	5 / 26 (19.23%)	
occurrences (all)	1	8	
NEUTROPENIA			
subjects affected / exposed	5 / 25 (20.00%)	8 / 26 (30.77%)	
occurrences (all)	21	11	
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	2 / 25 (8.00%)	3 / 26 (11.54%)	
occurrences (all)	2	4	
INJECTION SITE SWELLING			
subjects affected / exposed	0 / 25 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	9	
INJECTION SITE REACTION			
subjects affected / exposed	0 / 25 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	10	
INJECTION SITE PRURITUS			

subjects affected / exposed	0 / 25 (0.00%)	6 / 26 (23.08%)	
occurrences (all)	0	12	
INJECTION SITE PAPULE			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	41	
INJECTION SITE PAIN			
subjects affected / exposed	1 / 25 (4.00%)	5 / 26 (19.23%)	
occurrences (all)	1	11	
INJECTION SITE INDURATION			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
INJECTION SITE OEDEMA			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	3	
INJECTION SITE ERYTHEMA			
subjects affected / exposed	1 / 25 (4.00%)	9 / 26 (34.62%)	
occurrences (all)	6	18	
Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	2 / 25 (8.00%)	4 / 26 (15.38%)	
occurrences (all)	2	6	
CONSTIPATION			
subjects affected / exposed	2 / 25 (8.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
DIARRHOEA			
subjects affected / exposed	4 / 25 (16.00%)	3 / 26 (11.54%)	
occurrences (all)	5	5	
NAUSEA			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
ODYNOPHAGIA			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>VOMITING</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 25 (0.00%)</p> <p>0</p> <p>3 / 25 (12.00%)</p> <p>4</p>	<p>2 / 26 (7.69%)</p> <p>5</p> <p>6 / 26 (23.08%)</p> <p>6</p>	
<p>Hepatobiliary disorders</p> <p>HYPERTRANSAMINASAEMIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 25 (8.00%)</p> <p>3</p>	<p>1 / 26 (3.85%)</p> <p>1</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>COUGH</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>OROPHARYNGEAL PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>RHINORRHOEA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>BRONCHOSPASM</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 25 (24.00%)</p> <p>13</p> <p>2 / 25 (8.00%)</p> <p>2</p> <p>2 / 25 (8.00%)</p> <p>4</p> <p>2 / 25 (8.00%)</p> <p>4</p>	<p>6 / 26 (23.08%)</p> <p>9</p> <p>4 / 26 (15.38%)</p> <p>5</p> <p>1 / 26 (3.85%)</p> <p>2</p> <p>0 / 26 (0.00%)</p> <p>0</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>PRURITUS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>RASH</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 25 (8.00%)</p> <p>2</p> <p>4 / 25 (16.00%)</p> <p>4</p>	<p>2 / 26 (7.69%)</p> <p>2</p> <p>4 / 26 (15.38%)</p> <p>5</p>	
<p>Musculoskeletal and connective tissue disorders</p> <p>ARTHRALGIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ARTHRITIS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 25 (0.00%)</p> <p>0</p> <p>2 / 25 (8.00%)</p> <p>3</p>	<p>2 / 26 (7.69%)</p> <p>3</p> <p>0 / 26 (0.00%)</p> <p>0</p>	

BACK PAIN			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
JUVENILE IDIOPATHIC ARTHRITIS			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
NECK PAIN			
subjects affected / exposed	1 / 25 (4.00%)	2 / 26 (7.69%)	
occurrences (all)	2	3	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
EAR INFECTION			
subjects affected / exposed	0 / 25 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	5	
GASTROENTERITIS			
subjects affected / exposed	3 / 25 (12.00%)	2 / 26 (7.69%)	
occurrences (all)	3	2	
GASTROENTERITIS VIRAL			
subjects affected / exposed	3 / 25 (12.00%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
HAND-FOOT-AND-MOUTH DISEASE			
subjects affected / exposed	4 / 25 (16.00%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
PARONYCHIA			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
PHARYNGITIS			
subjects affected / exposed	0 / 25 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
RHINITIS			
subjects affected / exposed	2 / 25 (8.00%)	4 / 26 (15.38%)	
occurrences (all)	2	4	
SINUSITIS			

subjects affected / exposed	0 / 25 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	6 / 25 (24.00%)	5 / 26 (19.23%)	
occurrences (all)	16	7	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	8 / 25 (32.00%)	5 / 26 (19.23%)	
occurrences (all)	16	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2013	Protocol Version 2 removed the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) as a PRO tool for legal reasons, and replaced it with the CHAQ functional ability instrument. As the CHAQ uses 100 mm VAS scales as opposed to the 21-circle scale used in JAMAR, all other assessments using the 21-circle scale were switched to the 100 mm VAS scale for the purposes of consistency. Additionally, the immunogenicity testing requirements were updated for patients who withdrew due to hypersensitivity or anaphylaxis, and the dose interval changes for patients whose BW increased or decreased above or below the 30 kg threshold were clarified.
08 May 2013	Protocol Version 3 was a country specific amendment for Russia, which revised the inclusion criteria for the age range of patients to 12–17 years of age.
05 August 2013	The key changes in Protocol Version 4 were to limit the number of patients switching from TCZ IV to TCZ SC to no more than 50% of the total number of subjects and to include the request to collect information on the prior four IV infusions for patients switching from TCZ IV to TCZ SC.
02 March 2015	Protocol Version 5 changed the dosing regimen for patients weighing < 30 kg from Q10D to Q2W following the review of the planned interim analysis. This change was applicable to all newly enrolled patients weighing < 30 kg as well as to patients weighing ≥ 30 kg already enrolled in the study and receiving Q10D as per the initial dosing regimen. It should be noted that this Protocol Amendment was finalized but not submitted to the Health Authorities or study sites as further updates were identified prior to submission.
23 June 2015	Protocol Version 6 included the change in dosing regimen for patients weighing < 30 kg (i.e., Q10D to Q2W) as described in Version 5 and was submitted to the Health Authorities and study sites. It was planned that patients weighing < 30 kg enrolled prior to the interim analysis would switch from a Q10D to a Q2W dosing regimen; however, these patients had completed the study by the time this protocol amendment was approved and implemented. Additional minor changes were included in this Protocol Amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported