Clinical trial results:
A Phase I Pharmacokinetic and Safety Study of Tocilizumab (TCZ) in Patients Less Than 2 Years Old with Active Systemic Juvenile Idiopathic Arthritis (sJIA)

Summary

EudraCT number	2015-000435-33
Trial protocol	DE HU BE ES PL GB FR
Global end of trial date	13 July 2017

Results information

Result version number	v2
This version publication date	10 August 2017
First version publication date	12 February 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	NP25737

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01455701
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)	No
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	Interim
Date of interim/final analysis	28 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2016
Global end of trial reached?	Yes
Global end of trial date	13 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics of tocilizumab over 12 weeks in participants less than 2 years of age with sJIA.

Protection of trial subjects:

The investigator ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in current "Guideline for Good Clinical Practice" International Conference on Harmonization (ICH) Tripartite Guideline or with local law if it afforded greater protection to the participant.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2012
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: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	11
EEA total number of subjects	5

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)	11

Children (2-11 years)	0
Adolescents (12-17 years)	0
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:

Total 11 participants were enrolled, all of which were treated by tocilizumab.

Period 1

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

Arms

Arm title	Tocilizumab

Arm description:

Participants received tocilizumab intravenous (IV) infusion at a dose of 12 milligrams per kilogram (mg/kg) every two weeks (Q2W) during main evaluation period of 12 weeks (a total of 6 infusions including one at baseline visit). Participants had the option to be treated in an optional extension period after completion of main evaluation period. In optional extension period, participants received tocilizumab 12 mg/kg IV infusion Q2W from Week 12 until the participant reached 2 years of age or had been treated for one year from baseline, whichever was longer.

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

Dosage and administration details:

Tocilizumab was administered as indicated in the arm description.

Number of subjects in period 1	Tocilizumab
Started	11
Completed	7
Not completed	4
Adverse event	4

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab

Reporting group description:

Participants received tocilizumab intravenous (IV) infusion at a dose of 12 milligrams per kilogram (mg/kg) every two weeks (Q2W) during main evaluation period of 12 weeks (a total of 6 infusions including one at baseline visit). Participants had the option to be treated in an optional extension period after completion of main evaluation period. In optional extension period, participants received tocilizumab 12 mg/kg IV infusion Q2W from Week 12 until the participant reached 2 years of age or had been treated for one year from baseline, whichever was longer.

Reporting group values	Tocilizumab	Total	
Number of subjects	11	11	
Age Categorical Units: Subjects			
Infants and toddlers (28 days - 23 months)	11	11	
Age Continuous Units: months			
arithmetic mean	15.9		
standard deviation	± 4	-	
Gender Categorical Units: Subjects			
Female	7	7	
Male	4	4	

End points

End points reporting groups

Reporting group title	Tocilizumab

Reporting group description:

Participants received tocilizumab intravenous (IV) infusion at a dose of 12 milligrams per kilogram (mg/kg) every two weeks (Q2W) during main evaluation period of 12 weeks (a total of 6 infusions including one at baseline visit). Participants had the option to be treated in an optional extension period after completion of main evaluation period. In optional extension period, participants received tocilizumab 12 mg/kg IV infusion Q2W from Week 12 until the participant reached 2 years of age or had been treated for one year from baseline, whichever was longer.

Primary: Maximum Serum Concentration (Cmax) of Tocilizumab

End point title	Maximum Serum Concentration (Cmax) of Tocilizumab[1]

End point description:

Pharmacokinetic profile of tocilizumab was evaluated in terms of model predicted Cmax at steady state. Pharmacokinetic-evaluable population included all participants who provided at least one serum pharmacokinetic sample with valid concentration data.

End point type	Primary

End point timeframe:

Pre-infusion (Hour 0) on Days 1, 15, 29, 43, 57, 71, and 85; at the end of infusion on Days 1, 29 and 71; and anytime on Days 8, 36, and 78 (infusion length = 1 hour)

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: No statistical analysis was planned for this study.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)	288 (± 40.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Minimum Serum Concentration (Cmin) of Tocilizumab

End point title	Minimum Serum Concentration (Cmin) of Tocilizumab[2]

End point description:

Pharmacokinetic profile of tocilizumab was evaluated in terms of observed Cmin at day 85. Pharmacokinetic-evaluable population.

End point type	Primary

End point timeframe:

Pre-infusion (Hour 0) on day 85; (infusion length = 1 hour)

Notes:

[2] - 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: No statistical analysis was planned for this study.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mcg/mL				
arithmetic mean (standard deviation)	69.21 (± 42.02)			

Statistical analyses

No statistical analyses for this end point

Primary: Model predicted Area Under the Serum Concentration-Time Curve from Time Zero to End of Dosing (AUCtau) of Tocilizumab

End point title	Model predicted Area Under the Serum Concentration-Time Curve from Time Zero to End of Dosing (AUCtau) of Tocilizumab[3]

End point description:

AUCtau is the model-predicted area under the tocilizumab serum concentration versus time curve from time zero to the end of dosing interval (2 weeks). Pharmacokinetic-evaluable population.

End point type	Primary

End point timeframe:

Pre-infusion (Hour 0) on Days 1, 15, 29, 43, 57, 71, and 85; at the end of infusion on Days 1, 29 and 71; and anytime on Days 8, 36, and 78 (infusion length = 1 hour)

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: No statistical analysis was planned for this study.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: micrograms*day per milliliter				
arithmetic mean (standard deviation)	947.4 (± 231.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs) and Serious AEs

End point title	Number of Participants With Adverse Events (AEs) and Serious AEs

End point description:

Number of participants with categorized AEs and serious AEs is reported. Detailed information of AEs is

provided in the AEs section.

End point type	Secondary

End point timeframe:

Baseline up to end of the study (up to approximately 60 weeks)

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants				
AE with fatal outcome	0			
Serious AE	3			
Serious AE leading to withdrawal	3			
Serious AE leading to dose modification	0			
Related Serious AE	3			
AE leading to withdrawal	4			
AE leading to dose modification	1			
Related AE	6			
Related AE leading to withdrawal	4			
Related AE leading to dose modification	1			
Total number of patients with at least one AE	10			
Total number of deaths	0			
Total number of patients withdrawn due an AE	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of the study (up to approximately 60 weeks)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Tocilizumab

Reporting group description:

Participants received tocilizumab intravenous (IV) infusion at a dose of 12 milligrams per kilogram (mg/kg) every two weeks (Q2W) for up to 10 weeks (a total of 6 infusions including one at baseline visit) in main evaluation period (12-week period) and 12 mg/kg every Q2W from week 12 until participant reached 2 years of age or had been treated for one year from baseline in optional extension period.

Serious adverse events	Tocilizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 11 (27.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Juvenile idiopathic arthritis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tocilizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)		
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastrointestinal disorders			
Chapped lips			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vomiting			

subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Allergic respiratory symptom			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Endocrine disorders			
Cushingoid			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Infections and infestations			
Ear infection			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Respiratory tract infection viral			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypercalcaemia			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 October 2011	Protocol was amended for removal of sampling for anti-tocilizumab antibody, tocilizumab pharmacokinetics, and soluble interleukin-6 receptor (sIL-6R) at Week 18.
30 January 2012	Protocol was amended for making steroid tapering non-mandatory to remain stable for 6 weeks.
29 October 2014	Protocol was amended to change the time between diagnosis of sJIA and treatment with biologics from a 3-month delay to a 1-month delay.
01 June 2015	Protocol was amended to address concerns raised in the protocol review during the voluntary harmonization procedure in Europe. An exclusion criterion was amended to clarify that previous history of significant allergic or infusion reactions to any of the excipients listed in tocilizumab product labeling documents was part of this exclusion criterion.
10 February 2016	Protocol was amended mainly to clarify an inclusion criterion that it was intended to refer to the 1 month period of symptoms subsequent to the diagnosis of sJIA, before being considered for treatment with a biologic therapy, consistent with the updated American College of Rheumatology (ACR) recommendations for the treatment of sJIA that outlined the use of biologic therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported