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	

Results information

Result version number	v1
This version publication date	12 February 2017
First version publication date	12 February 2017

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	Trial Information Support Line-TISL, F.Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	Trial Information Support Line-TISL, F.Hoffmann-La Roche AG, 41 616878333, 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?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics of Tocilizumab (TCZ) over 12 weeks in patients less than 2 years of age with sJIA.

Protection of trial subjects:

The investigator will ensure that this study is 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 is conducted, whichever affords the greater protection to the individual.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
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	Spain: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Argentina: 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:

Patients whose guardian has given written informed consent underwent a thorough screening examination between -21 and -1 days before the start of the study. During the screening visit(s), inclusion/exclusion criteria were checked, a medical examination was performed.

Period 1

Period 1 title	12 weeks treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	12 mg/kg TCZ infusions

Arm description:

Patients received tocilizumab 12 mg/kg by intravenous infusion every 2 weeks for a total of 6 infusions.

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

Dosage and administration details:

Tocilizumab (200 mg/10 mL) was administered by intravenous infusion every two weeks.

Number of subjects in period 1	12 mg/kg TCZ infusions
Started	11
Completed	7
Not completed	4
Adverse event, non-fatal	4

Baseline characteristics

Reporting groups	
Reporting group title	12 weeks treatment period
Reporting group description:	
Patients received 12 mg/kg TCZ infusions every two weeks for 12 weeks	

Reporting group values	12 weeks treatment period	Total	
Number of subjects	11	11	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	11	11	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
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	12 mg/kg TCZ infusions

Reporting group description:

Patients received tocilizumab 12 mg/kg by intravenous infusion every 2 weeks for a total of 6 infusions.

Primary: Systemic exposure (AUC 2 weeks)

End point title	Systemic exposure (AUC 2 weeks)[1]

End point description:

Computed steady-state systemic exposure (AUC 2 weeks) defined as the area under the serum concentration-time profile during a dosing interval

End point type	Primary

End point timeframe:

Data used for analysis were collected during visits at week 0, 2, 4, 6, 8, 10.

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.

End point values	12 mg/kg TCZ infusions			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: µg/mL×day				
arithmetic mean (standard deviation)	919.2 (± 214.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Systemic exposure (Cmin)

End point title	Systemic exposure (Cmin)[2]

End point description:

Systemic exposure to TCZ is evaluated in terms of computed steady-state concentration at the end of a dosing interval (Cmin)

End point type	Primary

End point timeframe:

Blood samples used for analysis were collected before infusion during visits at week 0, 2, 4, 6, 8, 10.

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: Descriptive statistics only were planned for this endpoint.

End point values	12 mg/kg TCZ infusions			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: µg/mL				
arithmetic mean (standard deviation)	38.2 (± 12.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Systemic exposure (Cmax)

End point title	Systemic exposure (Cmax)[3]

End point description:

Systemic exposure to TCZ is evaluated in terms of computed steady-state maximum observed serum concentration post infusion (Cmax)

End point type	Primary

End point timeframe:

Blood samples used for analysis were collected after infusion during visits at week 0, 4, 10.

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.

End point values	12 mg/kg TCZ infusions			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: µg/mL				
arithmetic mean (standard deviation)	276.1 (± 45.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Adverse Events

End point title	Incidence of Adverse Events

End point description:

Categorized serious and non serious adverse events (AEs) are reported. Detailed listing of AEs is provided in the AEs section.

End point type	Secondary

End point timeframe:

Adverse Events were reported throughout the entire study period.

End point values	12 mg/kg TCZ infusions			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Number of patients				
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 events	32			
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:

All serious and non-serious Adverse Events are reported throughout the entire study period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	12 mg/kg TCZ infusions

Reporting group description:

Patients received tocilizumab 12 mg/kg by intravenous infusion every 2 weeks for a total of 6 infusions.

Serious adverse events	12 mg/kg TCZ infusions		
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	0		
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	12 mg/kg TCZ infusions		
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			
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Chapped lips			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dental caries			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Allergic respiratory symptom			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Dermatitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Endocrine disorders			
Cushingoid			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	4		
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		
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	Removal of sampling for anti-TCZ antibody, TCZ PK and sIL-6R at Week 18
30 January 2012	Steroid tapering not longer mandated to remain stable for 6 weeks
29 October 2014	Change of the time between diagnosis of sJIA and treatment with biologics from a 3-month delay to a 1-month delay
01 June 2015	Clarification that previous history of significant allergic or infusion reactions to any of the excipients listed in TCZ product labeling documents is part of this exclusion criterion No4.
10 February 2016	Clarification that inclusion criterion 3 was intended to refer to the 1 month period of symptoms subsequent to the diagnosis of sJIA

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported