Clinical trial results:
A Multicenter Postmarketing Study to Evaluate the Placental Transfer of Certolizumab Pegol in Pregnant Women Receiving Treatment with Cimzia® (Certolizumab Pegol)

Summary

EudraCT number	2013-003812-30
Trial protocol	NL
Global end of trial date	21 November 2016

Results information

Result version number	v1 (current)
This version publication date	07 December 2017
First version publication date	07 December 2017

Trial information

Trial identification

Sponsor protocol code	UP0017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02019602
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES Inc.
Sponsor organisation address	8010 Arco Corporate Drive, Raleigh, United States, 27617
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether there was transfer of Certolizumab Pegol (CZP) across the placenta to infants from mothers by evaluating the concentration of CZP in the plasma of infants at birth.

Protection of trial subjects:

During the conduct of the study all mothers and infants were closely monitored. Additionally, for the comfort and convenience of the mother and her baby, the study allowed home healthcare nurses to perform study procedures in the mothers' homes.

Background therapy:

Background therapy was permitted as defined in the study protocol.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	09 January 2014
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	France: 7
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Switzerland: 12
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	37
EEA total number of subjects	9

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	16
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in January 2014 and concluded in November 2016.

Pre-assignment

Screening details:

The Participant Flow refers to the Safety Set for Mothers [SS-M] and the Safety Set for Infants [SS-I]. For mothers, Baseline is defined as their screening visit. Since babies are regarded as study participants once they are born, baseline for the infants is considered to be the day of their birth.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SS-M

Arm description:

This arm consisted of all participating mothers who entered the screening period and received at least 1 dose of Certolizumab Pegol (CZP) less than or equal to 35 days prior to delivery.

Arm type	Experimental
Investigational medicinal product name	Cimzia
Investigational medicinal product code	CZP
Other name	Certolizumab pegol
Pharmaceutical forms	Lyophilisate for solution for injection, Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

This study only included pregnant women who started or decided to continue treatment with CZP for an approved indication in accordance with their treating physician prior to participating in the study. The CZP was not provided by the Sponsor. The CZP dose and administration schedule were per the physician's instructions.

Arm title	SS-I

Arm description:

This arm consisted of all infants born to mothers in the SS-M group.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	SS-M	SS-I
Started	21	16
Completed	16	16
Not completed	5	0
Adverse event, non-fatal	1	-
Ineligibility	4	-

Period 2

Period 2 title	Sampling Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	SS-M

Arm description:

This arm consisted of all participating mothers who entered the screening period and received at least 1 dose of Certolizumab Pegol (CZP) less than or equal to 35 days prior to delivery.

Arm type	Experimental
Investigational medicinal product name	Cimzia
Investigational medicinal product code	CZP
Other name	Certolizumab pegol
Pharmaceutical forms	Solution for injection in pre-filled syringe, Lyophilisate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

This study only included pregnant women who started or decided to continue treatment with CZP for an approved indication in accordance with their treating physician prior to participating in the study. The CZP was not provided by the Sponsor. The CZP dose and administration schedule were per the physician's instructions.

Arm title	SS-I

Arm description:

This arm consisted of all infants born to mothers in the SS-M group.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	SS-M	SS-I
Started	16	16
Completed	16	16

Baseline characteristics

Reporting groups	
Reporting group title	SS-M
Reporting group description:	
This arm consisted of all participating mothers who entered the screening period and received at least 1 dose of Certolizumab Pegol (CZP) less than or equal to 35 days prior to delivery.	
Reporting group title	SS-I
Reporting group description:	
This arm consisted of all infants born to mothers in the SS-M group.	

Reporting group values	SS-M	SS-I	Total
Number of subjects	21	16	37
Age Categorical			
Units: Subjects			
<=18 years	0	16	16
Between 18 and 65 years	21	0	21
>=65 years	0	0	0
Age Continuous			
Units: years			
arithmetic mean	31.4	0	
standard deviation	± 5.0	± 0	-
Gender Categorical			
Units: Subjects			
Male	0	6	6
Female	21	10	31

End points

End points reporting groups

Reporting group title	SS-M
Reporting group description:	
This arm consisted of all participating mothers who entered the screening period and received at least 1 dose of Certolizumab Pegol (CZP) less than or equal to 35 days prior to delivery.	
Reporting group title	SS-I
Reporting group description:	
This arm consisted of all infants born to mothers in the SS-M group.	
Reporting group title	SS-M
Reporting group description:	
This arm consisted of all participating mothers who entered the screening period and received at least 1 dose of Certolizumab Pegol (CZP) less than or equal to 35 days prior to delivery.	
Reporting group title	SS-I
Reporting group description:	
This arm consisted of all infants born to mothers in the SS-M group.	
Subject analysis set title	PKS-M
Subject analysis set type	Full analysis
Subject analysis set description:	
This arm consisted of all mothers from the SS-M analysis set who provided the CZP concentration sample at delivery.	
Subject analysis set title	PKS-U
Subject analysis set type	Full analysis
Subject analysis set description:	
This arm consisted of all umbilical cords of infants from the SS-I analysis set from which a CZP concentration sample was obtained at birth.	
Subject analysis set title	PK-PPS-I
Subject analysis set type	Per protocol
Subject analysis set description:	
This arm consisted of all infants from the SS-I analysis set who provided a CZP concentration sample at birth and had no important protocol deviations that would have impacted the primary PK analysis.	

Primary: The plasma concentration of Certolizumab Pegol (CZP) in the Infant(s) at birth

End point title	The plasma concentration of Certolizumab Pegol (CZP) in the Infant(s) at birth[1]
End point description:	
Blood samples will be taken within 24 hours after birth from the infant(s). -999 = below limit of quantification.	
End point type	Primary
End point timeframe:	
Day 0	

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 formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	PK-PPS-I			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: µg/mL				
median (full range (min-max))				
median (full range)	-999 (-999 to 0.0422)			

Statistical analyses

No statistical analyses for this end point

Secondary: The plasma concentration of Certolizumab Pegol (CZP) in the mother at delivery

End point title	The plasma concentration of Certolizumab Pegol (CZP) in the mother at delivery

End point description:

Blood samples will be taken within 24 hours before/after delivery from the mothers.

End point type	Secondary

End point timeframe:

Day 0

End point values	PKS-M			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: µg/mL				
median (full range (min-max))				
median (full range)	24.40 (4.96 to 49.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: The ratio of plasma concentration of Certolizumab Pegol (CZP) between the infant(s) and mother at delivery/birth

End point title	The ratio of plasma concentration of Certolizumab Pegol (CZP) between the infant(s) and mother at delivery/birth

End point description:

Blood samples will be taken within 24 hours before/after delivery from the mothers and within 24 hours after birth from the infant(s). Values below limit of quantification (BLQ) are replaced by values of lower limit of quantification/2=0.016 in calculations of ratios, however if both concentrations for a subject are BLQ then the ratio for that subject will not be calculated.

End point type	Secondary

End point timeframe:

Day 0

End point values	PK-PPS-I			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: ratio				
median (full range (min-max))				
median (full range)	0.0007634 (0.000403 to 0.00323)			

Statistical analyses

No statistical analyses for this end point

Secondary: The plasma concentration of Certolizumab Pegol (CZP) in the umbilical cord at birth

End point title	The plasma concentration of Certolizumab Pegol (CZP) in the umbilical cord at birth

End point description:

Blood samples will be taken directly after delivery (within <= 1 hour) from the umbilical cord.
-999 = below limit of quantification.

End point type	Secondary

End point timeframe:

Day 0

End point values	PKS-U			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: µg/mL				
median (full range (min-max))				
median (full range)	-999 (-999 to 0.0477)			

Statistical analyses

No statistical analyses for this end point

Secondary: The plasma concentration level of anti-CZP antibodies in the mother at delivery

End point title	The plasma concentration level of anti-CZP antibodies in the mother at delivery

End point description:

Blood samples will be taken within 24 hours before/after delivery from the mothers.

-999 = below limit of quantification.

End point type	Secondary

End point timeframe:

Day 0

End point values	PKS-M			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: units/mL				
median (full range (min-max))				
median (full range)	-999 (-999 to -999)			

Statistical analyses

No statistical analyses for this end point

Secondary: The plasma concentration level of anti-CZP antibodies in the umbilical cord(s) at birth

End point title	The plasma concentration level of anti-CZP antibodies in the umbilical cord(s) at birth

End point description:

Blood samples will be taken directly after delivery (within <= 1 hour) from the umbilical cord.
-999 = below limit of quantification.

End point type	Secondary

End point timeframe:

Day 0

End point values	PKS-U			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: units/mL				
median (full range (min-max))				
median (full range)	-999 (-999 to -999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected during the whole study period (from Week 0 up to Week 25)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	SS-I

Reporting group description:

This arm consisted of all infants born to mothers in the SS-M group.

Reporting group title	SS-M

Reporting group description:

This arm consisted of all participating mothers who entered the screening period and received at least 1 dose of Certolizumab Pegol (CZP) less than or equal to 35 days prior to delivery.

Serious adverse events	SS-I	SS-M	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	7 / 21 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Vaginal laceration			
subjects affected / exposed	0 / 16 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Arrested labour			
subjects affected / exposed	0 / 16 (0.00%)	2 / 21 (9.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational diabetes			
subjects affected / exposed	0 / 16 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placental insufficiency			

subjects affected / exposed	0 / 16 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyhydramnios			
subjects affected / exposed	0 / 16 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature baby			
subjects affected / exposed	0 / 16 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolonged labour			
subjects affected / exposed	0 / 16 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meconium in amniotic fluid			
subjects affected / exposed	1 / 16 (6.25%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Macrosomia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Perineal abscess			
subjects affected / exposed	0 / 16 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SS-I	SS-M	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 16 (25.00%)	3 / 21 (14.29%)	
Pregnancy, puerperium and perinatal conditions			
Foetal hypokinesia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Umbilical cord around neck			
subjects affected / exposed	2 / 16 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 16 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 16 (6.25%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 16 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	3	
Infections and infestations			
Candida infection			

subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	0 / 21 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2014	Protocol Amendment 1, approved on 04 Nov 2014, was a substantial amendment implemented to provide clarification to aid smooth running of the study, to address inconsistencies between this study and the closely related breast milk study, UP0016, and to address some operational challenges observed or presented to UCB as feedback from Independent Ethics Committees/Institutional Review Boards and partner operations personnel, as well as Investigators and study site personnel. The main changes included: •Update of the text regarding the approval status for CZP, per the latest Investigator's brochure, to include additional indications for CZP treatment – psoriatic arthritis, ankylosing spondylitis, and axial spondyloarthritis. •Clarification of infant consent/assent. •Clarification of the requirements for blood sampling for the infant. •Clarification of the procedures for analysis of blood samples. •Clarification of the noninterventional design of the study as it related to CZP therapy. •Clarifications of tuberculosis (TB) testing requirements and procedures for subjects who developed latent TB or active TB. •Clarification of the definitions of the analysis sets. •Analysis of the ratios of CZP and polyethylene glycol concentrations in maternal and umbilical cord were added as exploratory pharmacokinetic variables. •Minor changes were made for consistency with updated Sponsor document templates. •Some changes were made based on feedback from the Swiss Ethics Committee on Protocol UP0016: addition of names and addresses of central and local laboratories, and clarification of data confidentiality regarding data anonymization and retraction of consent. •Some changes were made in the statistical analysis sections (safety analyses and handling of protocol deviations) based on discussions during preparation of the Statistical Analysis Plan for UP0016. •Correction of typographical errors, minor inconsistencies, and editorial updates to aid clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29030361