Clinical trial results:
A Double-Blind, Randomized, Parallel-Group, Active Control Study to Compare the Efficacy and Safety of CHS-0214 Versus Enbrel® in Subjects With Chronic Plaque Psoriasis (CHS-0214-04) (RaPsOdy)

Summary

EudraCT number	2014-000444-14
Trial protocol	DE GB PL
Global end of trial date	27 April 2016

Results information

Result version number	v1 (current)
This version publication date	13 May 2017
First version publication date	13 May 2017

Trial information

Trial identification

Sponsor protocol code	CHS-0214-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02134210
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Coherus BioSciences, Inc.
Sponsor organisation address	333 Twin Dolphin Drive, Suite 600, Redwood City, United States, CA 94065
Public contact	Barbara K. Finck, Coherus BioSciences, Inc., +1 650 649 3530,
Scientific contact	Barbara K. Finck, Coherus BioSciences, Inc., +1 650 649 3530,

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	31 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 July 2015
Global end of trial reached?	Yes
Global end of trial date	27 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Part 1 of this study was to compare the efficacy and safety of CHS-0214 and Enbrel (EU) 50 mg given twice a week (BIW) for 12 weeks.

The primary objective of Part 2 of this study was to compare the safety and durability of response of CHS-0214 and Enbrel (EU) 50 mg given once a week (QW) from 13 weeks up to 47 weeks of treatment.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with the International Conference on Harmonisation E6 Good Clinical Practice Guidelines.
The rationale of the study, procedural details, and investigational goals were explained to each subject, along with potential risks and benefits. Each subject was assured of his/her right to withdraw from the study at any time. Prior to the initiation of any study procedures, each subject signed and dated an approved informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 201
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Canada: 74
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	South Africa: 48
Country: Number of subjects enrolled	United States: 142
Worldwide total number of subjects	521
EEA total number of subjects	225

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	486
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

4-week screening period (Weeks -4 to 0)

Period 1

Period 1 title	Part 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CHS-0214

Arm description:

Subjects were assigned the treatment as randomized.

Arm type	Experimental
Investigational medicinal product name	CHS-0214
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A 50 mg dose of CHS-0214 was administered twice a week (BIW) by subcutaneous (SC) injection, from Week 0 Day 0 through Week 12.

Arm title	Enbrel (EU)

Arm description:

Subjects were assigned the treatment as randomized.

Arm type	Active comparator
Investigational medicinal product name	Enbrel (EU)
Investigational medicinal product code	
Other name	etanercept
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A 50 mg dose of Enbrel (EU) was administered twice a week (BIW) by subcutaneous (SC) injection, from Week 0 Day 0 through Week 12.

Number of subjects in period 1	CHS-0214	Enbrel (EU)
Started	261	260
Completed	255	241
Not completed	6	19
Consent withdrawn by subject	4	8
TB test positive	-	1
Physician decision	-	1
Disease progression	-	1
Adverse event, non-fatal	-	5
other	-	2
Lost to follow-up	2	-
Protocol deviation	-	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CHS-0214

Arm description: -

Arm type	Experimental
Investigational medicinal product name	CHS-0214
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects continued in the blinded groups to which they were originally randomized.
A 50 mg dose of CHS-0214 was administered once a week (QW) by subcutaneous (SC) injection, for maintenance, from Week 13 through Week 47.

Arm title	Enbrel (EU)

Arm description: -

Arm type	Safety
Investigational medicinal product name	Enbrel (EU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects continued in the blinded groups to which they were originally randomized.

A 50 mg dose of Enbrel (EU) was administered once a week (QW) by subcutaneous (SC) injection, for maintenance, from Week 13 through Week 47.

Number of subjects in period 2	CHS-0214	Enbrel (EU)
Started	255	241
Completed	227	211
Not completed	28	30
TB test positive	1	3
Consent withdrawn by subject	14	8
Disease progression	2	5
Adverse event, non-fatal	5	4
Development of malignancy	-	1
Pregnancy	1	-
Did not return for follow up visit	1	1
Lost to follow-up	4	7
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	CHS-0214
Reporting group description:	
Subjects were assigned the treatment as randomized.	
Reporting group title	Enbrel (EU)
Reporting group description:	
Subjects were assigned the treatment as randomized.	

Reporting group values	CHS-0214	Enbrel (EU)	Total
Number of subjects	261	260	521
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	246	240	486
From 65-84 years	15	20	35
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	76	80	156
Male	185	180	365

Subject analysis sets	
Subject analysis set title	CHS-0214 - FAP Part 1
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Population (FAP) included all subjects randomized prior to the dosing suspension who had completed 12 weeks of study drug at the time of the suspension, and subjects randomized after dosing was resumed and received 1 or more doses of study drug. This was the primary efficacy analysis population.	
Subject analysis set title	Enbrel (EU) - FAP Part 1
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Population (FAP) included all subjects randomized prior to the dosing suspension who had completed 12 weeks of study drug at the time of the suspension, and subjects randomized after dosing was resumed and received 1 or more doses of study drug. This was the primary efficacy analysis population.	

Reporting group values	CHS-0214 - FAP Part 1	Enbrel (EU) - FAP Part 1	
Number of subjects	228	228	

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)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	217	213	
From 65-84 years	11	15	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	66	71	
Male	162	157	

End points

End points reporting groups

Reporting group title	CHS-0214
Reporting group description:	
Subjects were assigned the treatment as randomized.	
Reporting group title	Enbrel (EU)
Reporting group description:	
Subjects were assigned the treatment as randomized.	
Reporting group title	CHS-0214
Reporting group description: -	
Reporting group title	Enbrel (EU)
Reporting group description: -	
Subject analysis set title	CHS-0214 - FAP Part 1
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Population (FAP) included all subjects randomized prior to the dosing suspension who had completed 12 weeks of study drug at the time of the suspension, and subjects randomized after dosing was resumed and received 1 or more doses of study drug. This was the primary efficacy analysis population.	
Subject analysis set title	Enbrel (EU) - FAP Part 1
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Population (FAP) included all subjects randomized prior to the dosing suspension who had completed 12 weeks of study drug at the time of the suspension, and subjects randomized after dosing was resumed and received 1 or more doses of study drug. This was the primary efficacy analysis population.	

Primary: Mean percent change in PASI from baseline (last non-missing value prior to first dose) at Week 12.

End point title	Mean percent change in PASI from baseline (last non-missing value prior to first dose) at Week 12.
End point description:	
This was the primary endpoint intended to support the Marketing Authorization Application in the European Union.	
End point type	Primary
End point timeframe:	
Baseline (last non-missing value prior to first dose) to Week 12.	

End point values	CHS-0214 - FAP Part 1	Enbrel (EU) - FAP Part 1		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	228	228		
Units: Mean percent change				
arithmetic mean (standard deviation)	-76.7 (± 21.1)	-73.4 (± 25)		

Statistical analyses

Statistical analysis title	Analysis of Mean Percent Change in PASI at Week 12
Comparison groups	CHS-0214 - FAP Part 1 v Enbrel (EU) - FAP Part 1
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Estimated treatment difference, weighted
Point estimate	-3.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.67
upper limit	0.84
Variability estimate	Standard error of the mean
Dispersion value	2.171

Notes:

[1] - Cochran-Mantel-Haenszel (CMH) procedure stratified by the randomization strata. Equivalence was established if the limits of the 2-sided 95% CI were completely within the pre-specified equivalence range.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline to Week 48	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	CHS-0214
Reporting group description: -	
Reporting group title	Enbrel (EU)
Reporting group description: -	

Serious adverse events	CHS-0214	Enbrel (EU)	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 261 (2.68%)	10 / 260 (3.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 261 (0.77%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 261 (0.38%)	0 / 260 (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			
Chest pain			
subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	1 / 261 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 261 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pickwickian syndrome			
subjects affected / exposed	1 / 261 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 261 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 260 (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			
Bartholin's abscess			

subjects affected / exposed	1 / 261 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	CHS-0214	Enbrel (EU)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	191 / 261 (73.18%)	198 / 260 (76.15%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 261 (2.30%)	4 / 260 (1.54%)	
occurrences (all)	7	5	
Blood creatine phosphokinase increased			
subjects affected / exposed	11 / 261 (4.21%)	11 / 260 (4.23%)	
occurrences (all)	12	11	
Hepatic enzyme increased			
subjects affected / exposed	5 / 261 (1.92%)	7 / 260 (2.69%)	
occurrences (all)	5	9	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 261 (4.98%)	14 / 260 (5.38%)	
occurrences (all)	13	14	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 261 (3.07%)	10 / 260 (3.85%)	
occurrences (all)	8	16	
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	7 / 261 (2.68%)	8 / 260 (3.08%)	
occurrences (all)	13	8	

Injection site reaction			
subjects affected / exposed	11 / 261 (4.21%)	46 / 260 (17.69%)	
occurrences (all)	18	80	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 261 (2.30%)	3 / 260 (1.15%)	
occurrences (all)	6	3	
Toothache			
subjects affected / exposed	2 / 261 (0.77%)	6 / 260 (2.31%)	
occurrences (all)	2	7	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 261 (3.07%)	9 / 260 (3.46%)	
occurrences (all)	9	9	
Psoriasis			
subjects affected / exposed	10 / 261 (3.83%)	13 / 260 (5.00%)	
occurrences (all)	10	13	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 261 (2.68%)	4 / 260 (1.54%)	
occurrences (all)	7	5	
Back pain			
subjects affected / exposed	6 / 261 (2.30%)	4 / 260 (1.54%)	
occurrences (all)	6	4	
Infections and infestations			
Influenza			
subjects affected / exposed	11 / 261 (4.21%)	11 / 260 (4.23%)	
occurrences (all)	12	12	
Nasopharyngitis			
subjects affected / exposed	40 / 261 (15.33%)	42 / 260 (16.15%)	
occurrences (all)	54	56	
Pharyngitis			
subjects affected / exposed	5 / 261 (1.92%)	7 / 260 (2.69%)	
occurrences (all)	5	7	
Sinusitis			

subjects affected / exposed	4 / 261 (1.53%)	10 / 260 (3.85%)	
occurrences (all)	4	12	
Upper respiratory tract infection			
subjects affected / exposed	24 / 261 (9.20%)	27 / 260 (10.38%)	
occurrences (all)	25	29	
Urinary tract infection			
subjects affected / exposed	8 / 261 (3.07%)	13 / 260 (5.00%)	
occurrences (all)	11	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2014	- Study name RaPsOdy was added at the end of the study title - All secondary endpoints were added - Inclusion and exclusion criteria were edited to better define the selection of the study population - Added development of malignancy while on study as a reason for subject withdrawal - Added instruction that subjects who discontinued early would return for all Part 1 study visits - Clarified that "dropouts" referred to subjects who discontinued early and who were randomized but not treated - Revised instructions for used syringes - Edited language around prior and concomitant medications - Clarified that the same Investigator/clinician should have conducted the PASI for each subject at each visit - Added clarification that injection site reactions should have only been reported as adverse events if they were observed by study personnel - Changed Grade 4 adverse event definition from "severe" to "life-threatening" - Clarified that subjects with an indeterminate QuantiFERON-TB Gold test result could have had the test repeated once, and if negative, could have participated in the study
06 November 2014	- Prohibited administration of a live vaccine within 4 weeks prior to screening - Added language to clarify text around study drug accountability and retention as a safety measure, and to maintain consistency with the product insert of etanercept - Updated testing methods for positive HIV results
11 March 2015	- Revised enrollment numbers - Clarified that a subject's last dose is at Week 47 - Added text to clarify requirements for the use of abstinence as a means of birth control - Added requirement that study personnel should visually inspect syringes for particulate matter and/or discoloration prior to dispensing study drug - Clarified TB testing entry criteria and what results permitted a repeat test - Clarified when subjects should have returned for follow-up after last dose of study drug - Added an explanation on how to manage subjects who were enrolled prior to study drug suspension - Prohibited systemic steroids within 4 weeks of randomization - Clarified that subjects who were off study drug during the study drug suspension period could have resumed study drug regardless of how many doses were missed - Expanded the 2 primary endpoints of the study - Added a description of adverse event outcomes - Added language to allow continuation into an open-label extension study in select countries - Redefined the Full Analysis Population and Safety Population
21 September 2015	- Added durability of response as an efficacy variable for Part 2 - Added detailed information to the interpretation of QuantiFERON-TB Gold testing and how subjects who had an intermediate or low positive result should be managed - Added language stating that the Sponsor may review A/B unblinded Part 1 analyses to assess if the results can support the project regulatory strategy and may release the assessment publically

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 October 2014	During the conduct of the study, enrollment and dosing of subjects was voluntarily suspended by the Sponsor. During routine visual inspection of study drug in storage, 4 syringes containing CHS-0214 from a lot in use in Study CHS-0214-04 were observed to contain small dark particles. In the interest of patient safety, dosing of the ongoing Phase 3 clinical trials was immediately stopped, and an investigation was initiated to determine the cause and incidence of the observed particulate. A chemical analysis by an independent laboratory determined that the particles were not the result of drug product instability or formulation. Upon conclusion of the investigation, the lot was replaced in clinical inventory, and enrollment and dosing were resumed.	05 November 2014

Notes:

Limitations and caveats

None reported