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 Rheumatoid Arthritis and Inadequate Response to Treatment With Methotrexate (CHS-0214-02) (RApsody)

Summary

EudraCT number	2014-000443-33
Trial protocol	HU IT GB ES DE 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-0214-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02115750
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	21 October 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 to Enbrel (EU) at 24 weeks in subjects with rheumatoid arthritis (RA) who had an inadequate response to methotrexate and no more than 3 other non-biologic disease-modifying anti-rheumatic drugs and who were naïve to biologic therapies.

The objectives of Part 2 of the study were to evaluate the longer-term safety and the durability of response to open-label CHS-0214.

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	13 May 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: 83
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Belarus: 75
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Japan: 193
Country: Number of subjects enrolled	Russian Federation: 80
Country: Number of subjects enrolled	South Africa: 56

Country: Number of subjects enrolled	United States: 125
Worldwide total number of subjects	647
EEA total number of subjects	112

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)	568
From 65 to 84 years	79
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 group 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 once a week (QW) by subcutaneous (SC) injection, from Week 0 Day 0 through Week 24.

Arm title	Enbrel (EU)

Arm description:

Subjects were assigned the treatment group 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 once a week (QW) by subcutaneous (SC) injection, from Week 0 Day 0 through Week 24.

Number of subjects in period 1	CHS-0214	Enbrel (EU)
Started	324	323
Completed	312	301
Not completed	12	22
Consent withdrawn by subject	7	7
Disease progression	-	1
Adverse event, non-fatal	2	10
Other	1	4
Lost to follow-up	1	-
Protocol deviation	1	-

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CHS-0214/CHS-0214

Arm description:

Part 2 was an open-label period.

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:

Following Part 1 (during which a 50 mg dose of CHS-0214 was administered QW by SC injection, from Week 0 Day 0 through Week 24), subjects continued on CHS-0214 in Part 2.
A 50 mg dose of CHS-0214 was administered QW by SC injection, starting at Week 25, through Week 47.

Arm title	Enbrel (EU)/CHS-0214

Arm description:

Part 2 was an open-label period.

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:

Following Part 1 (during which a 50 mg dose of Enbrel (EU) was administered QW by SC injection, from Week 0 Day 0 through Week 24), subjects switched to CHS-0214 in Part 2.

A 50 mg dose of CHS-0214 was administered QW by SC injection, starting at Week 25, through Week 47.

Number of subjects in period 2[1]	CHS-0214/CHS-0214	Enbrel (EU)/CHS-0214
Started	284	280
Completed	272	269
Not completed	12	11
Consent withdrawn by subject	3	2
Physician decision	1	1
Adverse event, non-fatal	5	5
ACR20 not met at Week 24	-	1
Other	1	-
Conversion of TB test to positive	1	1
Lost to follow-up	-	1
Protocol deviation	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects qualified for Part 2. Only subjects who completed the 24-week, double-blind portion of the study (Part 1), attained at least a 20% improvement according to American College of Rheumatology (ACR) criteria (ie, ACR20) response at Week 24, and tolerated study drug in Part 1 with no serious adverse events or unresolved Grade 3 or higher adverse events related to study drug (per Investigator) were eligible for Part 2 and received open-label CHS-0214 50 mg QW SC beginning at Week 25.

Baseline characteristics

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

Reporting group values	CHS-0214	Enbrel (EU)	Total
Number of subjects	324	323	647
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)	285	283	568
From 65-84 years	39	40	79
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	260	257	517
Male	64	66	130

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 who received 1 or more doses of the study drug after the study was restarted, and 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 who received 1 or more doses of the study drug after the study was restarted and was the primary efficacy analysis population.	

Reporting group values	CHS-0214 - FAP Part 1	Enbrel (EU) - FAP Part 1	
Number of subjects	256	256	
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)	231	226	
From 65-84 years	25	30	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	208	206	
Male	48	50	

End points

End points reporting groups

Reporting group title	CHS-0214
Reporting group description:	
Subjects were assigned the treatment group as randomized.	
Reporting group title	Enbrel (EU)
Reporting group description:	
Subjects were assigned the treatment group as randomized.	
Reporting group title	CHS-0214/CHS-0214
Reporting group description:	
Part 2 was an open-label period.	
Reporting group title	Enbrel (EU)/CHS-0214
Reporting group description:	
Part 2 was an open-label period.	
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 who received 1 or more doses of the study drug after the study was restarted, and 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 who received 1 or more doses of the study drug after the study was restarted and was the primary efficacy analysis population.	

Primary: ACR20 at Week 24

End point title	ACR20 at Week 24
End point description:	
The primary efficacy endpoint in Part 1 was the percentage of subjects who achieved ACR20 at Week 24 compared to baseline (last non-missing value prior to first dose). Subjects were considered an ACR20 responder if, when compared to baseline (last non-missing value prior to first dose), they achieved a 20% decrease in SJC, 20% decrease in TJC, and 20% improvement in 3 of the following 5 measures: • High sensitivity C-reactive protein (hs-CRP); • Health Assessment Questionnaire-Disability Index (HAQ-DI); • Subject's global assessment of pain (ie, subject's pain assessment [SPA]-visual analog scale [VAS]); • Subject's global assessment of disease activity (SGA-VAS); and • Physician's global assessment of disease activity (PGA-VAS).	
End point type	Primary
End point timeframe:	
From Baseline to Week 24	

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	256	256		
Units: percent				
number (not applicable)	91	90.6		

Statistical analyses

Statistical analysis title	Percentage of subjects achieving ACR20
Comparison groups	CHS-0214 - FAP Part 1 v Enbrel (EU) - FAP Part 1
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Estimated treatment difference, weighted
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.55
upper limit	5.37
Variability estimate	Standard error of the mean
Dispersion value	2.531

Notes:

[1] - Cochran-Mantel-Haenszel (CMH) test for bioequivalence, weight adjusted. Equivalence was based upon the 95% (2-sided) confidence interval (CI) for the difference in ACR20 rates at Week 24 compared to baseline (last non-missing value prior to first dose). If the 95% CI was contained within the pre-specified equivalence range, equivalence was established.

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/CHS-0214, Parts 1 and 2
Reporting group description: -	
Reporting group title	Enbrel (EU)/CHS-0214, Parts 1 and 2
Reporting group description: -	

Serious adverse events	CHS-0214/CHS-0214, Parts 1 and 2	Enbrel (EU)/CHS-0214, Parts 1 and 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 324 (4.63%)	24 / 320 (7.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign ovarian tumour			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 324 (0.00%)	2 / 320 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			

subjects affected / exposed	1 / 324 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 324 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Alveolitis allergic			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			

subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral nerve injury			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	2 / 324 (0.62%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Age-related macular degeneration			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (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			
Skin ulcer			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
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			
Osteoarthritis			
subjects affected / exposed	1 / 324 (0.31%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			

subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 324 (0.31%)	0 / 320 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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/CHS-0214, Parts 1 and 2	Enbrel (EU)/CHS-0214, Parts 1 and 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	240 / 324 (74.07%)	243 / 320 (75.94%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 324 (4.01%)	15 / 320 (4.69%)	
occurrences (all)	14	16	
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 324 (2.16%)	13 / 320 (4.06%)	
occurrences (all)	7	14	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 324 (3.40%)	12 / 320 (3.75%)	
occurrences (all)	12	12	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 324 (6.17%)	8 / 320 (2.50%)	
occurrences (all)	30	10	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	9 / 324 (2.78%)	44 / 320 (13.75%)	
occurrences (all)	11	78	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	7 / 324 (2.16%)	8 / 320 (2.50%)	
occurrences (all)	8	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 324 (1.85%)	7 / 320 (2.19%)	
occurrences (all)	6	7	
Nausea			
subjects affected / exposed	9 / 324 (2.78%)	5 / 320 (1.56%)	
occurrences (all)	9	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 324 (3.70%)	11 / 320 (3.44%)	
occurrences (all)	12	11	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 324 (2.16%)	4 / 320 (1.25%)	
occurrences (all)	8	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 324 (1.54%)	7 / 320 (2.19%)	
occurrences (all)	6	11	
Back pain			
subjects affected / exposed	8 / 324 (2.47%)	10 / 320 (3.13%)	
occurrences (all)	8	10	
Rheumatoid arthritis			
subjects affected / exposed	10 / 324 (3.09%)	11 / 320 (3.44%)	
occurrences (all)	11	13	
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 324 (3.09%)	13 / 320 (4.06%)	
occurrences (all)	10	14	
Cystitis			
subjects affected / exposed	8 / 324 (2.47%)	7 / 320 (2.19%)	
occurrences (all)	8	7	
Herpes zoster			

subjects affected / exposed	7 / 324 (2.16%)	5 / 320 (1.56%)	
occurrences (all)	7	5	
Nasopharyngitis			
subjects affected / exposed	46 / 324 (14.20%)	39 / 320 (12.19%)	
occurrences (all)	58	49	
Oral herpes			
subjects affected / exposed	7 / 324 (2.16%)	10 / 320 (3.13%)	
occurrences (all)	7	12	
Respiratory tract infection viral			
subjects affected / exposed	8 / 324 (2.47%)	3 / 320 (0.94%)	
occurrences (all)	10	4	
Sinusitis			
subjects affected / exposed	9 / 324 (2.78%)	10 / 320 (3.13%)	
occurrences (all)	11	11	
Upper respiratory tract infection			
subjects affected / exposed	16 / 324 (4.94%)	32 / 320 (10.00%)	
occurrences (all)	19	39	
Urinary tract infection			
subjects affected / exposed	22 / 324 (6.79%)	17 / 320 (5.31%)	
occurrences (all)	31	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2014	- Revised study objectives to specify subjects should be naïve to biologic therapies and clarified how study drug was to be referenced - Specified how study drug dosing was transitioned from Part 1 to Part 2 and from Part 2 to OLSES - Inclusion and exclusion criteria were edited to better define the selection of the study population - Clarified removal of subjects from therapy or assessment - Clarified treatments administered, selection, and timing of doses in study - Specified blind was to be maintained until last subject completed Part 2 - Added details regarding study drug dispensing - Clarified prior and concomitant medications - Explained serum samples regarding treatment compliance - Added instructions for dosing subjects in Part 2 - Specified requirement to assess all previous injection sites at all visits after Day 0 - Added further specification and explanation regarding primary efficacy variables (ACR20, 66/68 SJC/TJC, CRP, HAQ-DI, subject's pain assessment, SGA, and PGA) - Added instructions for calculating DAS28-CRP(4) and explained scores - Defined response duration variables for Part 2 - Added respiratory rate to vital sign measurements and clarified methods and timing of vital signs and electrocardiogram assessments - Clarified use for and retention of serum samples - Specified analyses to be performed by local and central laboratories - Defined the PK Concentration Population and described use of serum samples for PK analysis - Added details regarding Data Safety Monitoring Board evaluation at end of Part 1
22 May 2014	- Added instruction that subjects who discontinue study drug for any reason during Part 1 should return for all Part 1 study visits per protocol - Inclusion and exclusion criteria were edited to better define the selection of the study population: added approved kinase inhibitors as DMARDs; added that subjects with recent known exposure to a patient with TB should be excluded; added that patients with an indeterminate QuantiFERON-TB Gold test could be rescreened 1 time and if a negative result, the subject could participate in the study; and added that male subjects whose partners may become pregnant or who may breastfeed during the study are not eligible to participate - Clarified removal of subjects from therapy or assessment - Revised handling of used syringes and specified subjects were not required to bring unused syringes to each visit - Clarified that oral corticosteroids and methotrexate doses could be reduced during the study for safety considerations only - Clarified ISRs regarding first dose of study drug and reporting as an "ISR" adverse event - Specified that if the subject's normal dosing schedule coincides with a study visit the subject should be reminded to hold their dose until after the study visit - Added that the online DAS28-CRP(4) calculator was provided to sites by Medpace - Clarified QuantiFERON-TB Gold test screening and chest x-ray

26 August 2014	- Clarified that joints injected at screening will not be calculated in the screening joint count assessment but will be included in the baseline joint count assessment - Clarified that joints injected during Part 2 will not be eliminated in subsequent joint counts but should be noted as swollen and tender - Inclusion and exclusion criteria were edited to better define the selection of the study population: removed CRP criteria from the definition of active disease and added DAS28-CRP(4) as an inclusion criterion; added abstinence as an allowable form of birth control for women of childbearing potential; clarified that other disease processes, not only evidence of TB, demonstrated on abnormal chest x-ray would exclude subjects; also clarified that a chest x-ray should be obtained during screening if one is not available with in the previous 6 months; and clarified possible regional infections that may be covered by regional guidelines - Added that a positive QuantiFERON-TB Gold test at any time during the study is cause for termination of the subject from the study - Added that females using abstinence as birth control will have a urine pregnancy test at each study visit; also added for Argentina only that females of childbearing potential and not surgically sterile will have a monthly urine pregnancy test - Clarified instructions for subject disposal of used syringes - Clarified that baseline labs did not need to be repeated if screening labs were drawn within 2 weeks prior to baseline visit - Added clarification for recording ISRs as adverse events
06 November 2014	Excluded Japan. - Removed language that 200 subjects had to complete Part 2 for the Part 1 database to be cleaned and locked and that the Data Safety Monitoring Board had to meet after the last subject completes the 24-week evaluations during Part 1 - Prohibited administration of a live vaccine within 4 weeks prior to screening - Specified that study drug syringes were to be inspected by study personnel prior to dispensation - Revised for consistency that a steroid injection for a single joint at or after Week 24 should be noted as swollen and tender going forward - Updated testing methods for positive HIV results
26 February 2015	- Added information defining when subjects should have returned for their Follow-up Visit in relation to when they discontinued study drug - Revised text throughout to reflect the decision to offer OLSES in selected countries - Specified that for subjects who were taking leflunomide, cholestyramine should have been administered to facilitate excretion of leflunomide 2 weeks prior to screening - Clarified the requirements for the use of abstinence as a means of birth control - Clarified the TB testing entry criteria and what results permitted a repeat test - Increased sample size to account for the number of subjects who were randomized prior to study drug suspension - Clarified use of a topical NSAID as an allowed NSAID - Added verbiage to comply with Japanese Society of Hematology guidelines for management of hepatitis B - Specified that subjects were to bring back all unused study drug at their Week 24 Visit - Added definition for unexpected adverse events - Added that adverse event outcomes were to be recorded by the Investigator - Clarified Sponsor reporting requirements of serious adverse events and/or suspected unexpected serious adverse events - Updated analysis plan based on study drug dosing suspension - Specified that Population 1 and Population 2 were to be analyzed separately - Revised definitions of Full Analysis and Safety Populations and Japanese Population based on study drug dosing suspension - Clarified restrictions for administration of live vaccines to be within 4 week prior to screening or at any time during the course of the study

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