Clinical trial results:
An Open-Label Safety Extension Study (OLSES) Evaluating the Long term Safety and Durability of Response of CHS 0214 (CHS 0214-05)

Summary

EudraCT number	2015-000665-30
Trial protocol	GB ES DE IT
Global end of trial date	18 October 2017

Results information

Result version number	v1 (current)
This version publication date	26 October 2018
First version publication date	26 October 2018

Trial information

Trial identification

Sponsor protocol code	CHS-0214-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, MD Chief Medical Officer, Coherus BioSciences, Inc., 001 650-649-3530, bfinck@coherus.com
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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	03 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2017
Global end of trial reached?	Yes
Global end of trial date	18 October 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this open-label safety extension study (OLSES) was to evaluate the longer-term safety and durability of response of subjects who completed 48 weeks of evaluations in the confirmatory safety and efficacy studies, CHS 0214-02 or CHS 0214-04, evaluating CHS 0214 in rheumatoid arthritis (RA) and plaque psoriasis (PsO), respectively.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and with all applicable local and country laws and regulations where the study was conducted, and in compliance with the International Council for 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 (ICF). Informed consent was obtained from subjects again if the ICF was revised during their study participation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 July 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: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Canada: 50
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Japan: 164
Country: Number of subjects enrolled	South Africa: 86
Worldwide total number of subjects	359
EEA total number of subjects	28

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)	319
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Within 1 month of their Week 48 Visit of the parent study (either CHS-0214-02 or CHS-0214-04).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	RA Population

Arm description:

The RA Population included all subjects with RA who completed Study CHS-0214-02, met the entry criteria for enrollment into Study CHS-0214-05, received at least 1 dose of CHS-0214, and had any efficacy measurements.

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 received open-label study drug (CHS-0214) 50 mg every week in prefilled syringes with passive needle guard by self-injection or by a caregiver at home as a subcutaneous injection. Subjects received study drug for 48 weeks except in Japan, where subjects were allowed to receive study drug until marketing approval. Subsequently, the study was terminated prior to any application for marketing approval.

Arm title	PsO Population

Arm description:

The PsO Population included all subjects with PsO who completed Study CHS-0214-04, met the entry criteria for enrollment into Study CHS-0214 05, received at least 1 dose of CHS-0214, and had any efficacy measurements.

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 received open-label study drug (CHS-0214) 50 mg every week in prefilled syringes with passive needle guard by self-injection or by a caregiver at home as a subcutaneous injection. Subjects received study drug for 48 weeks.

Number of subjects in period 1[1]	RA Population	PsO Population
Started	224	132
Completed	205	112
Not completed	19	20
Consent withdrawn by subject	9	10
Requires medical treatment excluded by protocol	-	2
Adverse event, non-fatal	3	1
Other	3	1
Conversion of TB test to positive	3	-
Disease progression requiring additional therapy	1	3
Lost to follow-up	-	1
Protocol deviation	-	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 359 subjects were enrolled in the trial, but only 356 subjects were included in the Full Analysis Population (FAP), this included all subjects who received 1 or more doses of study drug and had any efficacy measurements. From Parent Study CHS-0214-04 (PsO), 2 subjects did not receive at least 1 dose of study drug and 1 subject from Parent Study CHS-0214-02 (RA) did not have any efficacy measurements. As these 3 subjects did not meet the FAP criteria they were not reported in the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	356	356	
Age categorical Units: Subjects			
Adults (18-64 years)	316	316	
From 65-84 years	40	40	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	201	201	
Male	155	155	

Subject analysis sets

Subject analysis set title	Japanese RA Population
Subject analysis set type	Full analysis

Subject analysis set description:

The Japanese RA Population included all subjects with RA who completed Study CHS-0214-02 at Japanese sites, met the entry criteria for enrollment into Study CHS-0214-05, received at least 1 dose of CHS-0214, and had any efficacy measurements.

Reporting group values	Japanese RA Population		
Number of subjects	163		
Age categorical Units: Subjects			
Adults (18-64 years)	143		
From 65-84 years	20		
85 years and over	0		
Gender categorical Units: Subjects			
Female	119		
Male	44		

End points

End points reporting groups

Reporting group title	RA Population

Reporting group description:

The RA Population included all subjects with RA who completed Study CHS-0214-02, met the entry criteria for enrollment into Study CHS-0214-05, received at least 1 dose of CHS-0214, and had any efficacy measurements.

Reporting group title	PsO Population

Reporting group description:

The PsO Population included all subjects with PsO who completed Study CHS-0214-04, met the entry criteria for enrollment into Study CHS-0214 05, received at least 1 dose of CHS-0214, and had any efficacy measurements.

Subject analysis set title	Japanese RA Population
Subject analysis set type	Full analysis

Subject analysis set description:

The Japanese RA Population included all subjects with RA who completed Study CHS-0214-02 at Japanese sites, met the entry criteria for enrollment into Study CHS-0214-05, received at least 1 dose of CHS-0214, and had any efficacy measurements.

Primary: Durability of response (maintenance of an ACR20 response or greater)

End point title	Durability of response (maintenance of an ACR20 response or greater)[1][2]

End point description:

In subjects with RA, the primary efficacy endpoint was the durability of response (maintenance of an ACR20 response or greater), which was measured at each visit. The ACR20 is a composite endpoint based on the following assessments:
· 66/68 swollen joint count (SJC) or tender joint count (TJC),
· Subject's pain assessment (SPA)-visual analog scale (VAS),
· Subject's global assessment of disease activity (SGA)-VAS,
· Physician's global assessment of disease activity (PGA)-VAS,
· Health Assessment Questionnaire-Disability Index (HAQ-DI), and
· High sensitivity C-reactive protein (hs-CRP).

The baseline value to assess the ACR20 during this study was the same baseline value used to assess the ACR20 during the parent study (ie, the Week 0 assessment in the parent study).

ACR20 = 20% improvement according to American College of Rheumatology criteria.

End point type	Primary

End point timeframe:

For 48 weeks from the start of treatment. In the Japanese population, subjects were allowed to receive study drug until marketing approval. Subsequently, the study was terminated prior to any application for marketing approval.

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: In this study, the changes in ACR score over time were compared to the baseline values measured at Week 0 of the parent study (CHS-0214-02) in order to measure the maintenance over time of a response already obtained in the parent study. Hence, the baseline values used to calculate the maintenance of this response were the same between Studies CHS0214-02 and CHS-0214-05 (OLSES) for subjects with RA.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary efficacy endpoint of durability of response is defined differently for subjects with RA and subjects with PsO, which explains why not all the baseline period arms are reported on.

End point values	RA Population	Japanese RA Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	224	163		
Units: percent				
number (not applicable)	76.3	82.2		

Statistical analyses

No statistical analyses for this end point

Primary: Durability of response (maintenance of PASI-50 response or greater)

End point title	Durability of response (maintenance of PASI-50 response or greater)[3][4]

End point description:

For subjects with PsO, the primary efficacy endpoint was the durability of response (maintenance of PASI-50 response or greater), which was measured at each visit.

End point type	Primary

End point timeframe:

For 48 weeks from the start of treatment.

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: In this study, the changes in PASI scores over time were compared to the baseline values measured at Week 0 of the parent study (CHS-0214-04) in order to measure the maintenance over time of a response already obtained in the parent study. Hence, the baseline values used to calculate the maintenance of this response were the same between Studies CHS021404 and CHS0214-05 (OLSES) for subjects with PsO.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary efficacy endpoint of durability of response is defined differently for subjects with RA and subjects with PsO, which explains why not all the baseline period arms are reported on.

End point values	PsO Population			
Subject group type	Reporting group			
Number of subjects analysed	131			
Units: percent				
number (not applicable)	71.8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Week 0 Day 0 Visit through the Follow-up Visit 28 days after last dose of study drug. Ongoing adverse event from the subject's involvement in Studies CHS-0214-02 or CHS-0214-04 was continued as TEAEs in OLSES.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	RA & PsO Population

Reporting group description: -

Serious adverse events	RA & PsO Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 357 (7.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle strain			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pain			

subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper Limb fracture				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic aneurysm				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina unstable				
subjects affected / exposed	2 / 357 (0.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	1 / 357 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				

subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Temporal lobe epilepsy			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cystocele			

subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spondylolisthesis			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 357 (0.56%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary tuberculosis			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Appendicitis			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 357 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	RA & PsO Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	291 / 357 (81.51%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	15 / 357 (4.20%)		
occurrences (all)	20		
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 357 (3.64%)		
occurrences (all)	14		
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	14 / 357 (3.92%)		
occurrences (all)	16		
Nausea			
subjects affected / exposed	10 / 357 (2.80%)		
occurrences (all)	10		
Dental caries			
subjects affected / exposed	9 / 357 (2.52%)		
occurrences (all)	9		
Gastritis			
subjects affected / exposed	9 / 357 (2.52%)		
occurrences (all)	9		
Hepatobiliary disorders			

Hepatic function abnormal			
subjects affected / exposed	11 / 357 (3.08%)		
occurrences (all)	13		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	17 / 357 (4.76%)		
occurrences (all)	18		
Arthralgia			
subjects affected / exposed	11 / 357 (3.08%)		
occurrences (all)	14		
Rheumatoid arthritis			
subjects affected / exposed	8 / 357 (2.24%)		
occurrences (all)	11		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	37 / 357 (10.36%)		
occurrences (all)	40		
Nasopharyngitis			
subjects affected / exposed	86 / 357 (24.09%)		
occurrences (all)	120		
Influenza			
subjects affected / exposed	24 / 357 (6.72%)		
occurrences (all)	26		
Bronchitis			
subjects affected / exposed	16 / 357 (4.48%)		
occurrences (all)	20		
Pharyngitis			
subjects affected / exposed	15 / 357 (4.20%)		
occurrences (all)	17		
Urinary tract infection			
subjects affected / exposed	15 / 357 (4.20%)		
occurrences (all)	16		
Sinusitis			
subjects affected / exposed	8 / 357 (2.24%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2015	-Revised Early Termination Visit to Follow-up Visit 28 days after the last dose of study drug -Diaries to be electronic -For eligible subjects to the OLSES: .Data collected Week 48 Visit of parent study will consider Week 0 Day 0 data in the OLSES .If eligibility isn't determined and consent isn't obtained Week 48 Visit of parent study, subjects will come back within 1 month of Week 48 Visit to complete procedures/testing required for OLSES Subject to be given study drug supply -Subjects removed from therapy or assessment if positive viral screen results (Week 48 laboratory results referred to CHS-0214-02 or CHS-0214-04) -Removed not meeting enrollment goals as reason Sponsor's temporary suspension or premature termination of the study -Added text recommended Enbrel dose subjects with RA and PsO -If injection is planned on the day of a study visit, should be performed after the completion all visit procedures, blood sample collected represents trough serum sample -Concomitant medications changes NSAID, prednisone, and MTX doses -Glucocorticoids prohibited concomitant medications subject could be on a stable dose of drugs that may cause new onset or exacerbation of psoriasis -Check dosing per protocol and provision of retraining -Added guidelines for the management hepatitis B infection -SGA-VAS performed after PGA-VAS for RA and after PSGA for PsO at Weeks 4, 24, 48, and 52 -Medical and surgical history will not be collected but referenced from the parent study -PASI score assessors demonstrate proficiency performing PASI attempts to use same assessor -Added secondary efficacy endpoints for the RA Population -Ongoing AEs from CHS-0214-02 or CHS 0214-04 should continue -RA durability of response definition and correct baseline values -PsO durability of response definition and correct baseline values -Sponsor written permission for publication and study-related info -Removed pregnancy test language for subjects in Argentina

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported