Clinical trial results:
A Randomized, Parallel-Group, Phase I/III Study to Evaluate Efficacy, Pharmacokinetics and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Rheumatoid Arthritis

Summary

EudraCT number	2016-002125-11
Trial protocol	LV EE HU CZ BG ES
Global end of trial date	15 April 2019

Results information

Result version number	v1 (current)
This version publication date	23 February 2020
First version publication date	23 February 2020

Trial information

Trial identification

Sponsor protocol code	CT-P13 3.5

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03147248
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CELLTRION Inc.
Sponsor organisation address	23, Academy-ro, Yeonsu-gu, Incheon, Korea, Republic of, 22014
Public contact	Su Eun Song, Clinical Operation Department, CELLTRION Inc., +82 32 850 5776, SuEun.Song@celltrion.com
Scientific contact	Sung Hyun Kim, Clinical Planning Department, CELLTRION Inc., +82 32 850 5778, SungHyun.Kim@celltrion.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	15 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2018
Global end of trial reached?	Yes
Global end of trial date	15 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1
•To find the optimal dose of CT-P13 subcutaneous (SC) over the first 30 weeks as determined by the area under the concentration-time curve (AUC_T) at steady state between Week 22 and Week 30
Part 2
•To demonstrate that CT-P13 SC is noninferior to CT-P13 intravenous (IV) at Week 22, in terms of efficacy, as determined by clinical response according to change from baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (C-reactive protein [CRP])

Protection of trial subjects:

The CT-P13 SC via prefilled syringe (PFS) was injected by the investigator or his/her designee at each study center visit at the time points specified in the schedule of events. CT-P13 SC via PFS was injected at a slow, steady rate. For each new injection, a different injection site was used. The same injection sites could be used only if the other sites were unavailable due to safety reasons and in that case, it was recommended that the new injection was given at least 3 cm away from the most recent area injected. After proper training in injection technique, patients could self-inject with CT-P13 SC via PFS if their investigator determined that it was appropriate. For patients in specific countries in Part 2, CT-P13 SC via auto-injector (AI) was self-injected by the patients after proper training in AI injection technique. If healthcare professional determined or the patient requested it, additional training was given prior to the self-injection of CT-P13 SC via PFS or AI. Hypersensitivity was assessed by vital sign monitoring on each visit day at the time points: Prior to the beginning of the study drug administration and 1h after the end of the study drug administration. Hypersensitivity was assessed at the time points from Week 0 to Week 30 in Part 2: Prior to the beginning of the SC formulation injection and 1h after the end of the IV formulation infusion. Hypersensitivity was monitored by routine continuous clinical monitoring, incl. patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment (adrenaline, antihistamines, corticosteroids, and respiratory support incl. inhalational therapy, oxygen, and artificial ventilation) was available and any types of ECG could have been performed. For patients who experienced or developed life-threatening treatment-related anaphylactic reactions, infliximab treatment was stopped immediately and the patient withdrawn from the study.

Background therapy:

Throughout the study, methotrexate (MTX) were coadministered at a dosage of between 12.5 to 25 mg/week (between 10 to 25 mg/week in Korea), oral or parenteral dose. Folic acid were co-administered at a dosage of at least 5 mg/week for as long as MTX treatment was continued.

Evidence for comparator:

CT-P13 IV is an approved biosimilar to EU-approved Remicade and US-licensed Remicade. A new formulation of CT-P13 SC is developed as liquid type filled aseptically into 1 mL PFS and is an alternative to the IV regimen where SC infliximab injection typically takes less than 2 minutes. Therefore, this study was designed to evaluate efficacy, pharmacokinetic (PK), pharmacodynamic (PD) and safety between CT-P13 SC and CT-P13 IV in patients with active Rheumatoid Arthritis (RA).

Actual start date of recruitment	12 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bosnia and Herzegovina: 21
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Peru: 44
Country: Number of subjects enrolled	Russian Federation: 78
Country: Number of subjects enrolled	Ukraine: 62
Country: Number of subjects enrolled	Poland: 114
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Bulgaria: 29
Country: Number of subjects enrolled	Estonia: 9
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Latvia: 4
Worldwide total number of subjects	391
EEA total number of subjects	173

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)	337
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study consisted of 2 parts. 48 patients from 15 study centers were randomly assigned in 1 of 4 cohorts in Part 1 and 343 patients from 68 study centers were randomly assigned to 1 of 2 treatment arms in Part 2.

Pre-assignment

Screening details:

Key Inclusion Criteria:
- Patient is male or female between 18 and 75 years old, incl., with a diagnosis of RA according to the 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR).
- Patient has active disease as defined by the presence of ≥6 swollen joints (of 28 assessed), ≥6 tender joints (of 28 assessed).

Period 1

Period 1 title	Part 1 + Part 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Subject

Blinding implementation details:

Blinding was not included in Part 1 of the study because it was an open-label study. Part 2 was blinded during the study. All the patient and physician and predefined blinded team remained blinded until all patients had completed the study and the database had been finalized for study termination. The blindness has been maintained throughout the study period except the appointed unblinded teams. The blind should not be broken under normal circumstances.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: CT-P13 IV 3 mg/kg (Part 1)

Arm description:

CT-P13 (3 mg/kg) by IV infusion administered as a 2 hour IV infusion per dose.

Arm type	Active comparator
Investigational medicinal product name	CT-P13 (infliximab)
Investigational medicinal product code	
Other name	Infliximab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CT-P13 IV (3 mg/kg) administered as a 2 hour IV infusion at Weeks 0 and 2, then administered with further 7 doses of CT-P13 IV at Week 6 and every 8 weeks thereafter. MTX between 12.5 to 25 mg/week (10 to 25 mg/week in Korea), oral or parenteral dose and folic acid (≥ 5 mg/week) were coadministered.

Arm title	Cohort 2: CT-P13 SC 90 mg (Part 1)

Arm description:

CT-P13 (90 mg) by single SC injection via PFS.

Arm type	Experimental
Investigational medicinal product name	CT-P13 (infliximab)
Investigational medicinal product code	
Other name	Infliximab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

CT-P13 IV (3 mg/kg) administered as a 2 hour IV infusion at Weeks 0 and 2, then CT-P13 SC (90 mg) by SC injection via PFS with a 2-week interval from Week 6. The dose of SC 90 mg was adjusted to SC 120 mg every 2 weeks after Week 30 in applicable patients in Cohort 2: CT-P13 SC 90 mg. MTX between 12.5 to 25 mg/week (10 to 25 mg/week in Korea), oral or parenteral dose and folic acid (≥ 5 mg/week) were coadministered.

Arm title	Cohort 3: CT-P13 SC 120 mg (Part 1)

Arm description:

CT-P13 (120 mg) by single SC injection via PFS.

Arm type	Experimental
Investigational medicinal product name	CT-P13 (infliximab)
Investigational medicinal product code	
Other name	Infliximab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

CT-P13 IV (3 mg/kg) administered as a 2 hour IV infusion at Weeks 0 and 2, then CT-P13 SC (120 mg) by SC injection via PFS with a 2-week interval from Week 6. MTX between 12.5 to 25 mg/week (10 to 25 mg/week in Korea), oral or parenteral dose and folic acid (≥ 5 mg/week) were coadministered.

Arm title	Cohort 4: CT-P13 SC 180 mg (Part 1)

Arm description:

CT-P13 (180 mg) by double SC injections via PFS.

Arm type	Experimental
Investigational medicinal product name	CT-P13 (infliximab)
Investigational medicinal product code	
Other name	Infliximab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

CT-P13 IV (3 mg/kg) administered as a 2 hour IV infusion at Weeks 0 and 2, then CT-P13 SC (180 mg) by SC injection via PFS with a 2-week interval from Week 6. The dose of SC 180 mg was adjusted to SC 120 mg every 2 weeks after Week 30 in applicable patients in Cohort 4: CT-P13 SC 180 mg. MTX between 12.5 to 25 mg/week (10 to 25 mg/week in Korea), oral or parenteral dose and folic acid (≥ 5 mg/week) were coadministered.

Arm title	Arm 1: CT-P13 SC 120 mg (Part 2)

Arm description:

CT-P13 (120 mg) by single SC injection every other week with placebo IV at Weeks 6, 14 and 22.

Arm type	Experimental
Investigational medicinal product name	CT-P13 (infliximab)
Investigational medicinal product code	
Other name	Infliximab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

CT-P13 IV (3 mg/kg) administered as a 2 hour IV infusion at Weeks 0 and 2, then CT-P13 SC (120 mg) by SC injection via PFS with a 2-week interval from Week 6 up to Week 54 with placebo IV at Weeks 6, 14 and 22. Patients in specific countries were administered CT-P13 SC via AI at Week 46 and every 2 weeks up to Week 54, and were switched back to CT-P13 SC via PFS at Week 56 and every 2 weeks up to Week 64. MTX between 12.5 to 25 mg/week (10 to 25 mg/week in Korea), oral or parenteral dose and folic acid (≥ 5 mg/week) were coadministered.

Arm title	Arm 2: CT-P13 IV 3 mg/kg (Part 2)

Arm description:

CT-P13 (3 mg/kg) by IV infusion administered as a 2 hour IV infusion per dose every 8 weeks with placebo SC at Week 6 and every other week up to Week 28. CT-P13 (120 mg) by single SC injection was administered every other week from Week 30.

Arm type	Active comparator
Investigational medicinal product name	CT-P13 (infliximab)
Investigational medicinal product code	
Other name	Infliximab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CT-P13 IV (3 mg/kg) administered as a 2 hour IV infusion at Weeks 0 and 2, then administered with further 3 doses of CT-P13 IV at Week 6 and every 8 weeks thereafter (Weeks 6, 14 and 22) with placebo SC at Week 6 and every 2 weeks up to Week 28. CT-P13 IV was switched to CT-P13 SC via PFS at Week 30, and further doses with CT-P13 SC every other week were given up to Week 54 (up to Week 44 for specific countries). Patients in specific countries were administered CT-P13 SC via AI at Week 46 and every 2 weeks up to Week 54, and were switched back to CT-P13 SC via PFS at Week 56 and every 2 weeks up to Week 64. MTX between 12.5 to 25 mg/week (10 to 25 mg/week in Korea), oral or parenteral dose and folic acid (≥ 5 mg/week) were coadministered.

Number of subjects in period 1	Cohort 1: CT-P13 IV 3 mg/kg (Part 1)	Cohort 2: CT-P13 SC 90 mg (Part 1)	Cohort 3: CT-P13 SC 120 mg (Part 1)
Started	13	11	12
Completed	12	9	10
Not completed	1	2	2
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	2	2
Other	-	-	-
Death	-	-	-
Pregnancy	-	-	-
Lost to follow-up	-	-	-
Patient develops signs of disease progression	1	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Cohort 4: CT-P13 SC 180 mg (Part 1)	Arm 1: CT-P13 SC 120 mg (Part 2)	Arm 2: CT-P13 IV 3 mg/kg (Part 2)
Started	12	167	176
Completed	10	141	145
Not completed	2	26	31
Consent withdrawn by subject	-	12	9
Adverse event, non-fatal	2	6	11
Other	-	3	5
Death	-	-	4
Pregnancy	-	1	-
Lost to follow-up	-	2	-

Patient develops signs of disease progression	-	-	2
Protocol deviation	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: CT-P13 IV 3 mg/kg (Part 1)
Reporting group description:	
CT-P13 (3 mg/kg) by IV infusion administered as a 2 hour IV infusion per dose.	
Reporting group title	Cohort 2: CT-P13 SC 90 mg (Part 1)
Reporting group description:	
CT-P13 (90 mg) by single SC injection via PFS.	
Reporting group title	Cohort 3: CT-P13 SC 120 mg (Part 1)
Reporting group description:	
CT-P13 (120 mg) by single SC injection via PFS.	
Reporting group title	Cohort 4: CT-P13 SC 180 mg (Part 1)
Reporting group description:	
CT-P13 (180 mg) by double SC injections via PFS.	

Reporting group title	Arm 1: CT-P13 SC 120 mg (Part 2)
Reporting group description:	
CT-P13 (120 mg) by single SC injection every other week with placebo IV at Weeks 6, 14 and 22.	
Reporting group title	Arm 2: CT-P13 IV 3 mg/kg (Part 2)
Reporting group description:	
CT-P13 (3 mg/kg) by IV infusion administered as a 2 hour IV infusion per dose every 8 weeks with placebo SC at Week 6 and every other week up to Week 28. CT-P13 (120 mg) by single SC injection was administered every other week from Week 30.	

Reporting group values	Cohort 1: CT-P13 IV 3 mg/kg (Part 1)	Cohort 2: CT-P13 SC 90 mg (Part 1)	Cohort 3: CT-P13 SC 120 mg (Part 1)
Number of subjects	13	11	12
Age categorical			
Units: Subjects			
Adults (18-64 years)	12	9	10
Elderly (≥65 years)	1	2	2
Age continuous			
Units: years			
arithmetic mean	43.6	53.5	49.7
full range (min-max)	24 to 69	39 to 68	30 to 65
Gender categorical			
Units: Subjects			
Female	11	9	9
Male	2	2	3

Reporting group values	Cohort 4: CT-P13 SC 180 mg (Part 1)	Arm 1: CT-P13 SC 120 mg (Part 2)	Arm 2: CT-P13 IV 3 mg/kg (Part 2)
Number of subjects	12	167	176
Age categorical			
Units: Subjects			
Adults (18-64 years)	10	148	148
Elderly (≥65 years)	2	19	28
Age continuous			
Units: years			
arithmetic mean	50.7	50.9	51.9

full range (min-max)	32 to 68	19 to 74	18 to 74

Gender categorical Units: Subjects			
Female	9	130	139
Male	3	37	37

Reporting group values	Total		
Number of subjects	391		
Age categorical Units: Subjects			
Adults (18-64 years)	337		
Elderly (≥65 years)	54		
Age continuous Units: years arithmetic mean full range (min-max)	--		
Gender categorical Units: Subjects			
Female	307		
Male	84		

Subject analysis sets

Subject analysis set title	All-randomised population (Part 2)
Subject analysis set type	Full analysis

Subject analysis set description:

The all-randomised population consisted of all randomly assigned patients at Week 6, regardless of whether or not any study drug dosing was completed. It was also applied for Part 1.

Subject analysis set title	Efficacy population (Part 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The efficacy population consisted of the all-randomised population who received at least one full dose of study drug (CT-P13 SC or CT-P13 IV) at Week 6 or thereafter and who had at least one efficacy evaluation result after Week 6 or thereafter treatment. It was also applied for Part 1. Additionally, for the primary endpoint of Part 2, the efficacy analysis set consisted of the patients who were included in efficacy population and had DAS28 (CRP) result at Week 22.

Subject analysis set title	Pharmacokinetics population (Part 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population consisted of the all-randomised population who received at least one full dose of study drug (CT-P13 SC or CT-P13 IV) at Week 6 or thereafter and who had at least one PK concentration result after Week 6 or thereafter treatment. It was also applied for Part 1. Additionally, for the primary endpoint of Part 1, the PK analysis set consisted of the patients who received all doses (full) of study drug up to Week 30 (prior to Week 30) in the PK population.

Subject analysis set title	Pharmacodynamics population (Part 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PD population consisted of the all-randomised population who received at least one full dose of study drug (CT-P13 SC or CT-P13 IV) at Week 6 or thereafter and who had at least one PD result (rheumatoid factor, anti-cyclic citrullinated peptide [anti-CCP], CRP, or erythrocyte sedimentation rate) after Week 6 or thereafter treatment. It was also applied for Part 1.

Subject analysis set title	Safety population (Part 2)

Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of all patients who received at least one dose (partial or full) of study drug (CT-P13 SC or CT-P13 IV) at Week 6 or thereafter. It was also applied for Part 1.

Reporting group values	All-randomised population (Part 2)	Efficacy population (Part 2)	Pharmacokinetics population (Part 2)
Number of subjects	343	339	340
Age categorical			
Units: Subjects			
Adults (18-64 years)	296	292	293
Elderly (≥65 years)	47	47	47
Age continuous			
Units: years			
arithmetic mean	51.4	51.4	51.4
full range (min-max)	18 to 74	18 to 74	18 to 74
Gender categorical			
Units: Subjects			
Female	269	265	267
Male	74	74	73

Reporting group values	Pharmacodynamics population (Part 2)	Safety population (Part 2)	
Number of subjects	343	343	
Age categorical			
Units: Subjects			
Adults (18-64 years)	296	296	
Elderly (≥65 years)	47	47	
Age continuous			
Units: years			
arithmetic mean	51.4	51.4	
full range (min-max)	18 to 74	18 to 74	
Gender categorical			
Units: Subjects			
Female	269	269	
Male	74	74	

End points

End points reporting groups

Reporting group title	Cohort 1: CT-P13 IV 3 mg/kg (Part 1)
Reporting group description: CT-P13 (3 mg/kg) by IV infusion administered as a 2 hour IV infusion per dose.	
Reporting group title	Cohort 2: CT-P13 SC 90 mg (Part 1)
Reporting group description: CT-P13 (90 mg) by single SC injection via PFS.	
Reporting group title	Cohort 3: CT-P13 SC 120 mg (Part 1)
Reporting group description: CT-P13 (120 mg) by single SC injection via PFS.	
Reporting group title	Cohort 4: CT-P13 SC 180 mg (Part 1)
Reporting group description: CT-P13 (180 mg) by double SC injections via PFS.	

Reporting group title	Arm 1: CT-P13 SC 120 mg (Part 2)
Reporting group description: CT-P13 (120 mg) by single SC injection every other week with placebo IV at Weeks 6, 14 and 22.	
Reporting group title	Arm 2: CT-P13 IV 3 mg/kg (Part 2)
Reporting group description: CT-P13 (3 mg/kg) by IV infusion administered as a 2 hour IV infusion per dose every 8 weeks with placebo SC at Week 6 and every other week up to Week 28. CT-P13 (120 mg) by single SC injection was administered every other week from Week 30.	
Subject analysis set title	All-randomised population (Part 2)
Subject analysis set type	Full analysis
Subject analysis set description: The all-randomised population consisted of all randomly assigned patients at Week 6, regardless of whether or not any study drug dosing was completed. It was also applied for Part 1.	
Subject analysis set title	Efficacy population (Part 2)
Subject analysis set type	Sub-group analysis
Subject analysis set description: The efficacy population consisted of the all-randomised population who received at least one full dose of study drug (CT-P13 SC or CT-P13 IV) at Week 6 or thereafter and who had at least one efficacy evaluation result after Week 6 or thereafter treatment. It was also applied for Part 1. Additionally, for the primary endpoint of Part 2, the efficacy analysis set consisted of the patients who were included in efficacy population and had DAS28 (CRP) result at Week 22.	
Subject analysis set title	Pharmacokinetics population (Part 2)
Subject analysis set type	Sub-group analysis
Subject analysis set description: The PK population consisted of the all-randomised population who received at least one full dose of study drug (CT-P13 SC or CT-P13 IV) at Week 6 or thereafter and who had at least one PK concentration result after Week 6 or thereafter treatment. It was also applied for Part 1. Additionally, for the primary endpoint of Part 1, the PK analysis set consisted of the patients who received all doses (full) of study drug up to Week 30 (prior to Week 30) in the PK population.	
Subject analysis set title	Pharmacodynamics population (Part 2)
Subject analysis set type	Sub-group analysis
Subject analysis set description: The PD population consisted of the all-randomised population who received at least one full dose of study drug (CT-P13 SC or CT-P13 IV) at Week 6 or thereafter and who had at least one PD result (rheumatoid factor, anti-cyclic citrullinated peptide [anti-CCP], CRP, or erythrocyte sedimentation rate) after Week 6 or thereafter treatment. It was also applied for Part 1.	
Subject analysis set title	Safety population (Part 2)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of all patients who received at least one dose (partial or full) of study drug (CT-P13 SC or CT-P13 IV) at Week 6 or thereafter. It was also applied for Part 1.

Primary: Analysis of Change (Decrease) From Baseline of Disease Activity Score Using 28 Joint Counts (DAS28) (CRP) at Week 22 (ANCOVA) (Part 2)

End point title	Analysis of Change (Decrease) From Baseline of Disease Activity Score Using 28 Joint Counts (DAS28) (CRP) at Week 22 (ANCOVA) (Part 2)[1]

End point description:

The primary efficacy endpoint was the mean change (decrease) from baseline of DAS28 (CRP) at Week 22 (ANCOVA) for the efficacy population. All patients included in the efficacy population were analyzed according to the treatment they received. The least squares means and standard errors, estimate of treatment difference (CT-P13 SC 120 mg - CT-P13 IV 3 mg/kg), and 2-sided 95% CI obtained from the ANCOVA model.

End point type	Primary

End point timeframe:

At Week 22

Notes:

[1] - 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: ANCOVA Statistical analysis was presented for this endpoint of Part 2.

End point values	Arm 1: CT-P13 SC 120 mg (Part 2)	Arm 2: CT-P13 IV 3 mg/kg (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	168		
Units: Score				
least squares mean (standard error)	2.21 (± 0.221)	1.94 (± 0.209)		

Statistical analyses

Statistical analysis title	ANCOVA Statistical analysis

Statistical analysis description:

Primary efficacy analysis were analyzed using an ANCOVA considering the treatment as fixed effect and country, serum CRP concentration at Week 2 (≤0.6 mg/dL vs. >0.6 mg/dL), and body weight at Week 6 (≤100 kg vs. >100 kg) as covariates. The non-inferiority was to be concluded if the lower limit of the two-sided 95% CI for the difference in the mean change (decrease) from baseline of DAS28 (CRP) at Week 22 was greater than the pre-specified non-inferiority margin of -0.6.

Comparison groups	Arm 2: CT-P13 IV 3 mg/kg (Part 2) v Arm 1: CT-P13 SC 120 mg (Part 2)
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	Difference of Least square means
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.52

Primary: Descriptive Statistics of AUCτ of Infliximab at Steady State (Part 1)

End point title	Descriptive Statistics of AUCτ of Infliximab at Steady State (Part 1)[2][3]

End point description:

For Part 1, the primary PK endpoint of the AUCτ at steady state between Week 22 and Week 30 was analyzed in patients who received all doses (full) of study drug up to Week 30 (prior to Week 30) in the PK population. AUCτ is calculated at Week 22 for the IV cohort, Week 22 and 26 for Group A of SC cohorts, and Week 24 and 28 for Group B of SC cohorts.

End point type	Primary

End point timeframe:

From Week 22 to Week 30. Week 24, 26 and 28 are not applicable for cohort 1.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive Statistics was presented for this endpoint of Part 1.

[3] - 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: Descriptive Statistics was presented for this endpoint of Part 1.

End point values	Cohort 1: CT-P13 IV 3 mg/kg (Part 1)	Cohort 2: CT-P13 SC 90 mg (Part 1)	Cohort 3: CT-P13 SC 120 mg (Part 1)	Cohort 4: CT-P13 SC 180 mg (Part 1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	10	11	12
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Week 22	12032957.514 (± 5345598.5883)	5047724.204 (± 2449771.8620)	7333766.999 (± 2765064.1854)	9930696.560 (± 3208367.3670)
Week 24	0 (± 0)	3272936.820 (± 2847811.5999)	4835631.915 (± 2156587.2518)	9322764.345 (± 2704651.4449)
Week 26	0 (± 0)	4722645.212 (± 2434832.1852)	7295570.506 (± 2261574.6345)	10402980.887 (± 3316415.1055)
Week 28	0 (± 0)	3231316.559 (± 2582286.8805)	5076458.747 (± 2733359.4502)	10578411.810 (± 3443240.8206)

Statistical analyses

No statistical analyses for this end point

Secondary: Descriptive Statistics for Actual Value in Serum CRP Concentration (Pharmacodynamic Parameter) (Part 2)

End point title	Descriptive Statistics for Actual Value in Serum CRP Concentration (Pharmacodynamic Parameter) (Part 2)[4]

End point description:

For evaluation of pharmacodynamic (PD), the secondary endpoint was defined as concentration of CRP between 2 treatment groups up to Week 54. The blood samples for CRP were collected at Weeks 0, 2 and 6, and every 8 weeks up to Week 54. All enrolled patients received CT-P13 IV infusions at Weeks 0 and 2. Then, patients in CT-P13 SC group were administered with CT-P13 SC at Week 6 and every 2

weeks thereafter up to Week 54. Patients in the CT-P13 IV group were administered with CT-P13 IV at Week 6 and every 8 weeks thereafter up to Week 22 (Weeks 14 and 22). And then, CT-P13 IV was switched to CT-P13 SC at Week 30, and further doses with CT-P13 SC were given up to Week 54. All patients in the PD population were analyzed according to the treatment they received. The actual PD population was 168 for CT-P13 SC arm and 175 for CT-P13 IV arm. One patient in the CT-P13 IV arm who was mis-randomized was analyzed as CT-P13 SC arm.

End point type	Secondary

End point timeframe:

Up to Week 54

Notes:

[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: Descriptive Statistics was presented for this endpoint of Part 2.

End point values	Arm 1: CT-P13 SC 120 mg (Part 2)	Arm 2: CT-P13 IV 3 mg/kg (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	176		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline	1.822 (± 2.3669)	2.230 (± 3.5181)		
Week 2	0.474 (± 0.7761)	0.619 (± 1.4288)		
Week 6	0.740 (± 1.3774)	0.977 (± 1.8369)		
Week 14	0.811 (± 1.9631)	1.144 (± 2.5256)		
Week 22	0.723 (± 1.3343)	1.161 (± 2.1265)		
Week 30	0.666 (± 1.2609)	1.168 (± 2.1426)		
Week 38	0.714 (± 1.2759)	1.078 (± 2.9450)		
Week 46	0.600 (± 1.0143)	0.786 (± 1.4681)		
Week 54	0.601 (± 1.0051)	0.779 (± 1.4846)		

Statistical analyses

No statistical analyses for this end point

Secondary: Descriptive Statistics of Observed Ctrough (Trough Concentration [Before the Next Study Drug Administration] of Infliximab (Part 2)

End point title	Descriptive Statistics of Observed Ctrough (Trough Concentration [Before the Next Study Drug Administration] of Infliximab (Part 2)[5]

End point description:

For evaluation of pharmacokinetics (PK), the secondary endpoint was defined as the analysis of trough concentration of Infliximab up to Week 54. The samples were collected at Weeks 0, 2 and 6, and every 8 weeks up to Week 54. During PK monitoring visit (Weeks 22-30), samples were collected every 2 weeks according steady state PK sampling time point. All enrolled patients received CT-P13 IV infusions at Weeks 0 and 2. Patients in SC group were administered with CT-P13 SC at Week 6 and every 2 weeks thereafter up to Week 54. Patients in IV group were administered with CT-P13 IV at Week 6 and every 8 weeks thereafter up to Week 22. Then, CT-P13 IV was switched to CT-P13 SC at Week 30, and further

doses with CT-P13 SC were given up to Week 54. No PK results were obtained at Weeks 6 and 14 for SC group and Weeks 12, 20, 24, 26 and 28 for IV group due to 2 weeks and 8 weeks dosing interval, respectively. All patients in PK population were analyzed according to the treatment they received.

End point type	Secondary

End point timeframe:

Up to Week 54. Not applicable visits are as follows: Arm 1 - Week 6 and 14; Arm 2 - Week 12, 20, 24, 26 and 28.

Notes:

[5] - 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: Descriptive Statistics was presented for this endpoint of Part 2.

End point values	Arm 1: CT-P13 SC 120 mg (Part 2)	Arm 2: CT-P13 IV 3 mg/kg (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	174		
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 0	15.7346 (± 5.83064)	16.0028 (± 5.98981)		
Week 2	8.6402 (± 5.96562)	8.8058 (± 7.13489)		
Week 6	0 (± 0)	1.8922 (± 2.61129)		
Week 12	12.3338 (± 8.20393)	0 (± 0)		
Week 14	0 (± 0)	3.2044 (± 11.13945)		
Week 20	12.7203 (± 9.13334)	0 (± 0)		
Week 22	13.1921 (± 10.56596)	1.0302 (± 1.85362)		
Week 24	12.3212 (± 8.54834)	0 (± 0)		
Week 26	10.7290 (± 7.07566)	0 (± 0)		
Week 28	12.2747 (± 9.75026)	0 (± 0)		
Week 36	12.2038 (± 9.43936)	8.7911 (± 8.62922)		
Week 44	11.2449 (± 8.50602)	9.9692 (± 9.65035)		
Week 52	10.9761 (± 8.81064)	10.2342 (± 10.08052)		

Statistical analyses

No statistical analyses for this end point

Secondary: Descriptive Statistics for Actual Value of DAS28 (CRP) (Part 2)

End point title	Descriptive Statistics for Actual Value of DAS28 (CRP) (Part

End point description:

For evaluation of efficacy, the secondary endpoint was defined as descriptive statistics of actual value in disease activity measured by DAS28 (CRP) up to Week 54 (efficacy population) between 2 treatment

groups. The results up to Week 6 represented the efficacy of CT-P13 IV loading dose (3 mg/kg) regardless of randomized treatment group (CT-P13 SC or CT-P13 IV) in both treatment groups. Patients in the CT-P13 IV group were administered with CT-P13 IV at Week 6 and every 8 weeks thereafter up to Week 22. And then, CT-P13 IV was switched to CT-P13 SC at Week 30. All patients in the efficacy population were analyzed according to the treatment they received.

End point type	Secondary

End point timeframe:

Up to Week 54

Notes:

[6] - 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: Descriptive Statistics was presented for this endpoint of Part 2.

End point values	Arm 1: CT-P13 SC 120 mg (Part 2)	Arm 2: CT-P13 IV 3 mg/kg (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	174		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	6.008 (± 0.7541)	5.863 (± 0.8090)		
Week 2	4.702 (± 0.9361)	4.643 (± 1.0460)		
Week 6	3.983 (± 1.2021)	4.112 (± 1.2105)		
Week 14	3.483 (± 1.1996)	3.677 (± 1.2510)		
Week 22	3.338 (± 1.0958)	3.482 (± 1.2329)		
Week 30	3.047 (± 1.1272)	3.521 (± 1.2339)		
Week 54	2.796 (± 1.1414)	2.913 (± 1.1648)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patients achieving Response according to ACR20 Criteria (Part 2)

End point title	Patients achieving Response according to ACR20 Criteria (Part 2)[7]

End point description:

For evaluation of efficacy, the secondary endpoint was defined as proportions of patients achieving clinical response according to ACR20 (20% response, as defined by the ACR) between CT-P13 SC and CT-P13 IV groups. The results up to Week 6 represented the efficacy of CT-P13 IV loading dose (3 mg/kg) regardless of randomized treatment group (CT-P13 SC or CT-P13 IV) in both treatment groups. Patients in the CT-P13 IV group were administered with CT-P13 IV at Week 6 and every 8 weeks thereafter up to Week 22. And then, CT-P13 IV was switched to CT-P13 SC at Week 30. All patients in the efficacy population were analyzed according to the treatment they received.

End point type	Secondary

End point timeframe:

Up to Week 54

Notes:

[7] - 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: No statistical analysis was presented for this endpoint of Part 2.

End point values	Arm 1: CT-P13 SC 120 mg (Part 2)	Arm 2: CT-P13 IV 3 mg/kg (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	174		
Units: Patients				
Week 2	63	57		
Week 6	107	103		
Week 14	124	130		
Week 22	139	137		
Week 30	142	133		
Week 54	132	125		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed from the date the informed consent form was signed until the last assessment date or End-of-Study visit (Treatment period).

Adverse event reporting additional description:

The investigator was responsible for reporting all AEs that were observed or reported during the study, regardless of their relationship to the study drug or clinical significance. A participant is counted once if they reported 1 or more events. Only the most severe events is counted. TEAEs collected from Part 2 are shown in this table.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Arm 1: CT-P13 SC 120 mg (Part 2)
Reporting group description: -	
Reporting group title	Arm 2: CT-P13 IV 3 mg/kg (Part 2)

Reporting group description: -

Serious adverse events	Arm 1: CT-P13 SC 120 mg (Part 2)	Arm 2: CT-P13 IV 3 mg/kg (Part 2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 168 (3.57%)	14 / 175 (8.00%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hereditary haemochromatosis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 168 (0.00%)	2 / 175 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
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			
Neutropenia			

subjects affected / exposed	1 / 168 (0.60%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 168 (0.00%)	2 / 175 (1.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			

subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pertussis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 168 (1.19%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device loosening			
subjects affected / exposed	1 / 168 (0.60%)	0 / 175 (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: 3 %

Non-serious adverse events	Arm 1: CT-P13 SC 120 mg (Part 2)	Arm 2: CT-P13 IV 3 mg/kg (Part 2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 168 (45.24%)	73 / 175 (41.71%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 168 (4.76%)	11 / 175 (6.29%)	
occurrences (all)	8	11	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 168 (1.79%)	7 / 175 (4.00%)	
occurrences (all)	3	8	
Injury, poisoning and procedural complications			

Infusion related reaction			
subjects affected / exposed	2 / 168 (1.19%)	9 / 175 (5.14%)	
occurrences (all)	3	9	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 168 (4.17%)	11 / 175 (6.29%)	
occurrences (all)	9	13	
General disorders and administration site conditions			
Localised injection site reaction			
subjects affected / exposed	30 / 168 (17.86%)	22 / 175 (12.57%)	
occurrences (all)	119	61	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	6 / 168 (3.57%)	4 / 175 (2.29%)	
occurrences (all)	6	5	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	8 / 168 (4.76%)	8 / 175 (4.57%)	
occurrences (all)	9	8	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	13 / 168 (7.74%)	16 / 175 (9.14%)	
occurrences (all)	16	17	
Upper respiratory tract infection			
subjects affected / exposed	9 / 168 (5.36%)	13 / 175 (7.43%)	
occurrences (all)	12	16	
Latent tuberculosis			
subjects affected / exposed	8 / 168 (4.76%)	10 / 175 (5.71%)	
occurrences (all)	8	10	
Urinary tract infection			
subjects affected / exposed	9 / 168 (5.36%)	9 / 175 (5.14%)	
occurrences (all)	14	11	
Bronchitis			
subjects affected / exposed	7 / 168 (4.17%)	4 / 175 (2.29%)	
occurrences (all)	8	5	
Oral herpes			

subjects affected / exposed occurrences (all)	7 / 168 (4.17%) 7	4 / 175 (2.29%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2016	Summary of significant changes included the following: • Deleted primary PK objective for Part 2, therefore DAS28 (CRP) would only be considered as primary endpoint for Part 2. • Added biomarker as one of the secondary objective assessment item for Part 2. • Updated the study design for Part 2 with double-blind and double-dummy design. • Revised the cut-off point of body weight at Week 6 for Part 2. • Specified the unbinding process. • Allowed one more rescreening. • Added the joint count assessments by an independent joint count assessor to minimize bias. • Revised the PK sampling time point table for Part 2 to reflect the design change (double-blind). • Specified the assessment time points of hypersensitivity monitoring for Part 2 to reflect the design change (double-blind). • Specified the assessment time points of patient's assessments of local site pain to reflect the design change (double-blind). • Updated the method of assigning patients to treatment arms and treatments administered for Part 2 as per the updated design. • Added the identity of CT-P13 placebo product as per the updated design (double-blind, double-dummy). • Other administrative changes.
13 January 2017	Summary of significant changes included the following: • Revised biomarker to the tertiary objective assessment item for Part 2, and not limited to FcgRIIIa. • Specified the sampling time point in case of the patient who could not be possible to be dispensed on the dosing day. • Revised the exclusion condition for diabetes mellitus to match with the updated condition in the exclusion criteria. • Added the exclusion condition for hepatitis C, HIV-1 and HIV-2 to provide more specific information. • Added the storage condition for keeping CT-P13 SC PFS. • Updated the New York Heart Association Functional Classification followed by the latest version • Other administrative changes
21 July 2017	Summary of significant changes included the following: • Revised the posology for part 2 from 'every 4 weeks' to 'every 2 weeks' as per the result of interim PK-PD modelling analysis. • Other administrative changes.

02 February 2018	Summary of significant changes included the following: • Updated the ICH guideline E6. • Modified the time point of EOS visit from '8 weeks from the last dose was received' to '2 weeks from the last dose was received' considering administration of CT-P13 SC. • Specified the description about study drug randomisation for Part 2 and added the table. • Clarified the premedication for Part 1 and Part 2. • Added the word 'PFS' to clarify the study product regimen for Part 2. • Revised visit window for Part 2. • Added the description that joint taken any surgical procedure would be excluded from the joint count assessment, and to reflect this change, the description also added that patient history would be informed to independent joint assessor. • Added PK endpoints for Part 1 to sufficiently investigate PK of CT-P13 SC. • Revised PK endpoints for Part 2 to clarify. • Revised to collect detailed 12-lead ECG results for safety investigation. • Revised to inhibit IGRA retest during the study. Guide added for resume of study drug and in case of exposure to person with active TB. • Added case of not to take IGRA test if it was not needed. • Added the reporting and follow-up of serious adverse drug reactions for part 2 since the EOS visit was done only after 2 weeks from last dose of study drug. • Other administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported