# 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) |
|---|---|

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

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 9 | 130 | 139 |
| Male | 3 | 37 | 37 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 391 | | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 337 | | |
| Elderly (≥65 years) | 54 | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>full range (min-max) | - | | |
| Gender categorical<br>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<br>Units: Subjects | | | |
| Adults (18-64 years) | 296 | 292 | 293 |
| Elderly (≥65 years) | 47 | 47 | 47 |
| Age continuous<br>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<br>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<br>Units: Subjects | | | |
| Adults (18-64 years) | 296 | 296 | |
| Elderly (≥65 years) | 47 | 47 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 51.4 | 51.4 | |
| full range (min-max) | 18 to 74 | 18 to 74 | |
| Gender categorical<br>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) | | |

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<br>occurrences (all) | 7 / 168 (4.17%)<br>7 | 4 / 175 (2.29%)<br>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:<br>• Deleted primary PK objective for Part 2, therefore DAS28 (CRP) would only be considered as primary endpoint for Part 2.<br>• Added biomarker as one of the secondary objective assessment item for Part 2.<br>• Updated the study design for Part 2 with double-blind and double-dummy design.<br>• Revised the cut-off point of body weight at Week 6 for Part 2.<br>• Specified the unbinding process.<br>• Allowed one more rescreening.<br>• Added the joint count assessments by an independent joint count assessor to minimize bias.<br>• Revised the PK sampling time point table for Part 2 to reflect the design change (double-blind).<br>• Specified the assessment time points of hypersensitivity monitoring for Part 2 to reflect the design change (double-blind).<br>• Specified the assessment time points of patient's assessments of local site pain to reflect the design change (double-blind).<br>• Updated the method of assigning patients to treatment arms and treatments administered for Part 2 as per the updated design.<br>• Added the identity of CT-P13 placebo product as per the updated design (double-blind, double-dummy).<br>• Other administrative changes. |
| 13 January 2017 | Summary of significant changes included the following:<br>• Revised biomarker to the tertiary objective assessment item for Part 2, and not limited to FcgRIIIa.<br>• Specified the sampling time point in case of the patient who could not be possible to be dispensed on the dosing day.<br>• Revised the exclusion condition for diabetes mellitus to match with the updated condition in the exclusion criteria.<br>• Added the exclusion condition for hepatitis C, HIV-1 and HIV-2 to provide more specific information.<br>• Added the storage condition for keeping CT-P13 SC PFS.<br>• Updated the New York Heart Association Functional Classification followed by the latest version<br>• Other administrative changes |
| 21 July 2017 | Summary of significant changes included the following:<br>• Revised the posology for part 2 from 'every 4 weeks' to 'every 2 weeks' as per the result of interim PK-PD modelling analysis.<br>• Other administrative changes. |

| | |
|---|---|
| 02 February 2018 | Summary of significant changes included the following:<br>• Updated the ICH guideline E6.<br>• 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.<br>• Specified the description about study drug randomisation for Part 2 and added the table.<br>• Clarified the premedication for Part 1 and Part 2.<br>• Added the word 'PFS' to clarify the study product regimen for Part 2.<br>• Revised visit window for Part 2.<br>• 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.<br>• Added PK endpoints for Part 1 to sufficiently investigate PK of CT-P13 SC.<br>• Revised PK endpoints for Part 2 to clarify.<br>• Revised to collect detailed 12-lead ECG results for safety investigation.<br>• 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.<br>• Added case of not to take IGRA test if it was not needed.<br>• 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.<br>• Other administrative changes. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported