**Supplementary materials for:**

**Pharmacokinetics and safety of candidate tocilizumab biosimilar CT-P47 versus reference tocilizumab: a randomized, double-blind, single-dose phase I study**

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# Supplementary methods

## Supplementary Table 1. Study centers and Institutional Review Boards (Part 2).

|  |  |
| --- | --- |
| Study center | Institutional Review Board |
| Anonymized, Seoul, Republic of Korea | Anonymized Hospital Institutional Review Board  |
| Anonymized Bundang Hospital, Seongnam, Republic of Korea | **Anonymized** Hospital Institutional Review Board |
| Anonymized, Seoul, Republic of Korea | **Anonymized** Institutional Review Board |
| Anonymized, Incheon, Republic of Korea | **Anonymized** Institutional Review Board |
| Anonymized, Cheongju, Republic of Korea | **Anonymized** Institutional Review Board  |
| Anonymized, Jeonju, Republic of Korea | **Anonymized** Institutional Review Board |
| Anonymized Hospital, Busan, Republic of Korea | **Anonymized** Hospital Institutional Review Board |

### Full inclusion and exclusion criteria

#### Inclusion criteria

1. Healthy males or females aged 19–55 years (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and heart rate measurement, 12-lead electrocardiogram, and clinical laboratory tests).
2. Body weight ≥60–≤100 kg (males) or ≥50–≤100 kg (females), with body mass index 18.5–28.0 kg/m2 (inclusive).
3. Participant is able to understand and comply with protocol requirements, instructions, and any restrictions.
4. Participant voluntarily agrees to participate and provides a signed and dated informed consent form prior to screening.
5. Individuals of childbearing potential (i.e., biologically capable of having children and sexually active) must use a highly effective method of contraception throughout the study and for 3 months after study drug administration. If an individual or their partner has been surgically sterilized for less than 24 weeks prior to informed consent, they must agree to use a medically acceptable method of contraception. Postmenopausal females must have experienced their last period more than 1 year prior to the date of informed consent without an alternative medical cause to be classified as not of childbearing potential.

#### Exclusion criteria

1. A medical history and/or current presence of disease, including ≥1 of the following:
* Atopy (e.g., allergic asthma, eczematous, and dermatitis), judged by the investigator to be clinically significant.
* Known or suspected clinically relevant hypersensitivity or allergic reaction to any of the excipients of the study drug, or other human, humanized, and murine monoclonal antibodies.
* Medical condition classed as significant by the investigator, including cardiac, gastrointestinal (including diverticulitis), renal, endocrine, neurologic, immune, hepatic, hematologic (including pancytopenia, aplastic anemia or blood dyscrasia), metabolic (including diabetes mellitus), or pulmonary disease.
* Any malignancy except adequately treated squamous or basal cell carcinoma of the skin.
* Bacterial infections, viral infections, and/or invasive fungal infections (including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis), and/or other opportunistic infections that are clinically significant by the investigator’s judgement, including local fungal infections or a history of herpes zoster.
* Known infection with hepatitis B or hepatitis C (active or carrier state) or human immunodeficiency virus, or syphilis.
* Systemic or local infection; a known risk for developing sepsis; and/or known active inflammatory process or evidence of infection, requiring inpatient hospitalization or intravenous antibiotics within 24 weeks prior to study drug administration.
1. Any of the following laboratory abnormalities at screening or on Day −1:
* Alanine aminotransferase >1.5 × the upper limit of normal (ULN)
* Aspartate aminotransferase >1.5 × ULN
* Total bilirubin >1.5 × ULN
* Absolute neutrophil count <2,000/mm3 (2.0×103/µL)
* Platelet count <100,000/mm3 (100.0×103/µL)
1. History of surgical intervention or an operation within 4 weeks prior to study drug administration, or planned surgical procedure during the study.
2. Active tuberculosis, latent tuberculosis (defined as a positive result for interferon-gamma release assay [IGRA] with no active lesion on examination of chest X‑ray, and without any sign or symptom of tuberculosis), a history of tuberculosis, or close contact with a person with active tuberculosis or travel to areas within a high incidence of tuberculosis within 8 weeks prior to study drug administration, or planned travel to an area with a high incidence of tuberculosis during the study period. In the case of an indeterminate IGRA result at screening, one retest will be allowed during the screening period. If the repeated IGRA result is again indeterminate or positive, the participant will be excluded from the study. If the repeated IGRA result is negative, the participant can be included in the study.
3. Previous exposure to tocilizumab, any biosimilar of tocilizumab, or any drug that directly targets interleukin-6.
4. Previous exposure to an investigational drug, any monoclonal antibody, or fusion protein; current use of a biologic agent (except for coronavirus disease 2019 [COVID-19] vaccines); or participation in another clinical trial within 6 months prior to study drug administration.
5. Treatment with prescription medications (excluding hormonal birth control), over-the-counter drugs, dietary supplements, or herbal remedies that could affect the outcome of the study, within 2 weeks prior to study drug administration.
6. Administration of a live or attenuated vaccine within 4 weeks prior to study drug administration, during the study, or planned until the 3 months after study drug administration. Use of an authorized, non-live-attenuated COVID-19 vaccine was permitted, if the vaccination was completed 2 weeks prior to study drug administration and no clinically significant adverse reaction occurred after vaccination.
7. A history and/or current presence of medical problems or findings from physical examination or laboratory testing identified as clinically significant by the investigator (other than those listed above) within 4 weeks prior to first study drug administration.
8. Whole blood donation within 8 weeks or donation of blood components within 4 weeks prior to study drug administration, or planned donation of whole blood or blood components during the study.
9. Males planning to have children or donate sperm within 3 months after study drug administration. Females currently pregnant or lactating, or planning to be pregnant or breastfeed within 3 months after study drug administration.
10. Participants with reasonable evidence or history of drug abuse, alcohol use, or smoking prior to study drug administration, as judged by the investigator or on the basis of any of the following:
* A positive urine drug test result during screening or prior to study drug administration.
* A history or presence of regular alcohol consumption exceeding an average weekly intake of 21 units in the 4 weeks prior to first administration of the study drug and/or participant unwilling to avoid taking alcohol or alcohol-containing foods, medications, or beverages during clinic attendance as well as within 24 hours prior to screening and each study visit.
* Consumption of >10 cigarettes (or equivalent) per day within 4 weeks prior to study drug administration and/or participant is unable to refrain from smoking during clinic attendance.
1. Presence of tattoos, sunburn, or other skin disturbances (i.e., cuts, bruises, redness, hardness, tenderness) on the outer upper arm, which may interfere with a medical assessment of the injection site both prior to and following study drug administration.
2. Evidence of a psychological or emotional condition or any resultant therapy that is likely to invalidate informed consent, or limit the ability of the individual to comply with the protocol requirements, in the opinion of the investigator. Individuals who are unable to understand the protocol requirements, instructions, study related restrictions, and/or the nature, scope, and possible consequences of the clinical study, or are unable to give written informed consent or to comply fully with the protocol, will be excluded.
3. Vulnerable individuals (e.g., any individuals [or their immediate family members] involved in the conduct of the study; incarcerated or institutionalized individuals).

### Capture logic for treatment-emergent adverse events of special interest (TEAESIs)

TEAESIs were recorded as follows:

* *Infection*: treatment-emergent adverse events (TEAEs) coded with a system organ class of 'infections and infestations'.
* *Hypersensitivity, including anaphylaxis:* TEAEs recorded as ‘hypersensitivity’ in the electronic case report form (eCRF). Anaphylaxis was medically reviewed according to Sampson criteria [[14](#_ENREF_14)].
* *Injection-site reaction:* TEAEs recorded as ‘injection site reaction’ in the eCRF.
* *Hepatic event*: standardized Medical Dictionary for Regulatory Activities queries (SMQ) of ‘hepatic disorder’ (narrow).
* *Hemorrhage (medically significant bleeding events):* SMQ of ‘hemorrhage’ (narrow), excluding laboratory terms.
* *Gastrointestinal perforation:* SMQ of ‘GI [gastrointestinal] perforation’ (narrow), followed by medical review.
* *Malignancy:* SMQ of ‘malignant or unspecified tumors’ (narrow).
* *Demyelinating disorder:* SMQ of ‘demyelination’ (narrow).

### Analysis sets

Analyses were conducted in the intent-to-treat (ITT), safety, and pharmacokinetic (PK) sets, as defined below:

* *ITT set:* all randomly assigned participants. Participants were analyzed according to the study drug to which they had been randomized.
* *Safety set:* all randomly assigned participants who received a complete or partial dose of study drug. Participants were analyzed according to the study drug received.
* *PK set:* all randomly assigned participants who received a complete dose of study drug and had ≥1 post-treatment PK concentration measurement above the lower limit of quantification. Participants were analyzed according to the study drug received.

# Supplementary results

## Supplementary Table 2. Baseline demographics and characteristics (intent-to-treat set; Part 1).

|  |  |  |
| --- | --- | --- |
|  | **CT-P47(N=14)** | **EU-tocilizumab (N=15)** |
| Age (years), median (range) | 28.0 (22–41) | 30.0 (25–42) |
| Sex, n (%)a |  |  |
| Male | 13 (92.9) | 13 (86.7) |
| Female | 1 (7.1) | 2 (13.3) |
| Body weight at Day −1, n (%)a,b |  |  |
| <70 kg | 7 (50.0) | 7 (46.7) |
| 70 to <90 kg | 6 (42.9) | 6 (40.0) |
| ≥90 kg | 1 (7.1) | 2 (13.3) |
| Weight at screening (kg), median (range) | 71.2 (55.0–99.1) | 71.9 (50.2–91.9) |
| Height at screening (cm), median (range) | 172.95 (165.7–190.0) | 174.20 (159.3–192.9) |
| BMI at screening (kg/m2), median (range) | 23.4 (18.8–27.5) | 22.7 (19.8–27.8) |
| Asian race, n (%) | 14 (100.0) | 15 (100.0) |
| Non-Hispanic or Non-Latino ethnicity, n (%) | 14 (100.0) | 15 (100.0) |
| Smoking history, n (%) |  |  |
| Yes | 4 (28.6) | 2 (13.3) |
| No | 10 (71.4) | 13 (86.7) |
| Average cigarette consumption for smokers (cigarettes/day), median (range) | 6 (5–8) | 9 (8–10) |

aStratification factor for randomization.
bFor participants whose Day −1 assessments were omitted, screening body weight was used.
BMI = body mass index. EU-tocilizumab = European Union-approved reference tocilizumab.

## Supplementary Table 3. Summary of TEAEs (safety set; Part 1).

|  |  |  |
| --- | --- | --- |
|  | **CT-P47****(N=14)** | **EU-tocilizumab****(N=15)** |
| Total number of TEAEs | 6 | 11 |
| Participants with ≥1 TEAE, n (%) | 5 (35.7) | 7 (46.7) |
| ≥1 study drug-related TEAE | 5 (35.7) | 6 (40.0) |
| ≥1 grade 3 TEAE | 1 (7.1)a | 0 |
| ≥1 grade 4 TEAE | 0 | 2 (13.3)b |
| Participants with ≥1 TESAE, n (%) | 0 | 0 |
| Participants with ≥1 TEAE leading to study drug discontinuation, n (%) | 0 | 0 |
| Participants with ≥1 TEAE leading to death, n (%) | 0 | 0 |
| Participants with ≥1 TEAESI, n (%) |  |  |
| Infectionc | 0 | 3 (20.0) |
| Study drug-related | 0 | 2 (13.3) |
| Injection-site reactionc | 1 (7.1) | 0 |
| Study drug-related | 1 (7.1) | 0 |
| Hypersensitivity (including anaphylaxis) | 0 | 1 (6.7) |
| Study drug-related | 0 | 1 (6.7) |
| Demyelinating disorder | 0 | 0 |
| Gastrointestinal perforation | 0 | 0 |
| Hemorrhage | 0 | 0 |
| Hepatic event | 0 | 0 |
| Malignancy  | 0 | 0 |

aTEAE of blood creatine phosphokinase increased, reported based on local laboratory assessments. The parameter recovered to normal range without any treatment.

bOne TEAE each of neutropenia and hypertriglyceridemia, reported based on local laboratory assessments. The parameters recovered to normal range without any treatment.

cAll grade 1 in intensity.

EU-tocilizumab = European Union-approved reference tocilizumab. TEAE = treatment-emergent adverse event. TEAESI = treatment-emergent adverse event of special interest. TESAE = treatment-emergent serious adverse event.

## Supplementary Table 4. Summary of immunogenicity results (safety set; Part 2).

|  |  |  |
| --- | --- | --- |
|  | **CT-P47(N=144)** | **EU-tocilizumab(N=140)** |
| Participants with ≥1 positive post-baseline ADA result, n (%) | 20 (13.9) | 29 (20.7) |
| Participants with ≥1 positive post-baseline NAb result, n (%) | 17 (11.8) | 20 (14.3) |
| Participants with a positive ADA result, n (%) |  |  |
| Baseline | 1 (0.7) | 1 (0.7) |
| Day 13 | 0 | 4 (2.9) |
| Day 43 | 20 (13.9) | 28 (20.0) |
| Participants with a positive NAb result, n (%) |  |  |
| Baseline | 0 | 0 |
| Day 13 | 0 | 1 (0.7) |
| Day 43 | 17 (11.8) | 19 (13.6) |

ADA = anti-drug antibody. EU-tocilizumab = European Union-approved reference tocilizumab. NAb = neutralizing antibody.

## Supplementary Figure 1. Mean (SD) serum concentrations by ADA status (PK set; Part 2).

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ADA = anti-drug antibody. EU-tocilizumab = European Union-approved reference tocilizumab. PK = pharmacokinetic. SD = standard deviation.

## Supplementary Table 5. Summary of PK variables by ADA status (PK set; Part 2).

|  |  |  |
| --- | --- | --- |
|  | **ADA positive** | **ADA negative** |
| **CT-P47 (N=20)** | **EU-tocilizumab (N=29)** | **CT-P47 (N=124)** | **EU-tocilizumab (N=111)** |
| AUC0–inf (day\*μg/mL) |   |   |   |   |
| n | 19a | 29 | 119a | 107a,b |
| Mean (SD) | 85.85 (50.36) | 82.19 (28.80) | 95.70 (39.32) | 87.01 (38.05) |
| AUC0–last (day\*μg/mL) |   |   |   |   |
| n | 20 | 29 | 124 | 110b |
| Mean (SD) | 83.24 (46.54) | 81.12 (28.67) | 94.07 (39.18) | 85.09 (37.07) |
| Cmax (μg/mL) |  |  |  |  |
| n | 20 | 29 | 124 | 111 |
| Mean (SD) | 9.54 (4.44) | 9.35 (3.34) | 10.46 (3.94) | 9.95 (3.64) |
| Tmax (day) |   |   |   |   |
| n | 20 | 29 | 124 | 111 |
| Median (range) | 4.00 (2.02–6.00) | 3.98 (1.97–6.99) | 3.99 (1.00–8.98) | 3.99 (1.00–6.99) |
| t1/2 (day) |   |   |   |   |
| n | 19a | 29 | 119a | 107a,b |
| Mean (SD) | 1.83 (0.94) | 1.62 (0.41) | 1.62 (0.63) | 1.68 (0.76) |
| %AUCext (%) |  |  |  |  |
| n | 19a | 29 | 119a | 107a,b |
| Mean (SD) | 1.37 (2.45) | 1.30 (3.50) | 1.24 (4.45) | 1.29 (3.30) |
| λz (1/day) |   |   |   |   |
| n | 19a | 29 | 119a | 107a,b |
| Mean (SD) | 0.4340 (0.1191) | 0.4499 (0.09157) | 0.4589 (0.09196) | 0.4550 (0.1064) |
| CL/F (L/h) |   |   |   |   |
| n | 19a | 29 | 119a | 107a,b |
| Mean (SD) | 0.1240 (0.09936) | 0.09833 (0.05630) | 0.09851 (0.1371) | 0.09884 (0.07690) |
| Vz/F (L) |  |  |  |  |
| n | 19a | 29 | 119a | 107a,b |
| Mean (SD) | 7.29 (6.22) | 5.69 (3.97) | 5.91 (12.04) | 5.70 (5.16) |

aλz and its associated variables (i.e., t1/2, AUC0–inf,%AUCext,CL/F and Vz/F) were not evaluable for nine participants: eight participants (CT-P47, n=5; EU-tocilizumab, n=3) were excluded from the AUC0–inf analysis owing to adjusted coefficients of determination (adjustedR2) <0.85; one participant in the CT-P47 group did not have ≥3 PK evaluations after Cmax, thus AUC0–inf was not evaluable.

bOne participant in the EU-tocilizumab group was excluded from all PK analyses other than Cmax and Tmax due to increased serum tocilizumab concentrations observed after 360 hours post-dose. These results were not considered physiologically plausible; no reasons for the impact on these PK parameters could be identified.

%AUCext = percentage of area under the concentration–time curve from time zero to infinity obtained by extrapolation. λz = terminal elimination rate constant. ADA = anti-drug antibody. AUC0–inf = area under the concentration–time curve from time zero to infinity. AUC0–last = area under the concentration–time curve from time zero to the last quantifiable concentration. CL/F = apparent total body clearance. Cmax = maximum serum concentration. EU-tocilizumab = European Union-approved reference tocilizumab. PK = pharmacokinetic. SD = standard deviation. t1/2 = terminal half-life. Tmax = time to maximum serum concentration. Vz/F = apparent volume of distribution during the terminal phase.

## Supplementary Table 6. TEAEs by system organ class (safety set; Part 2).

|  |  |  |
| --- | --- | --- |
| **Participants, n (%)** | **CT-P47** **(N=144)** | **EU-tocilizumab (N=140)** |
| Investigations | 17 (11.8) | 23 (16.4) |
| Infections and infestations | 10 (6.9) | 25 (17.9) |
| General disorders and administration site conditions | 16 (11.1) | 10 (7.1) |
| Nervous system disorders | 9 (6.3) | 13 (9.3) |
| Gastrointestinal disorders | 5 (3.5) | 14 (10.0) |
| Musculoskeletal and connective tissue disorders | 3 (2.1) | 10 (7.1) |
| Respiratory, thoracic, and mediastinal disorders | 7 (4.9) | 4 (2.9) |
| Injury, poisoning, and procedural complications | 4 (2.8) | 6 (4.3) |
| Immune system disorders | 4 (2.8) | 2 (1.4) |
| Skin and subcutaneous tissue disorders | 4 (2.8) | 2 (1.4) |
| Blood and lymphatic system disorders | 1 (0.7) | 1 (0.7) |
| Renal and urinary disorders | 1 (0.7) | 1 (0.7) |
| Ear and labyrinth disorders | 0 | 1 (0.7) |
| Reproductive system and breast disorders | 0 | 1 (0.7) |

EU-tocilizumab = European Union-approved reference tocilizumab. TEAE = treatment-emergent adverse event.

## Supplementary Table 7. TEAEs reported by ≥2% participants in either treatment group (safety set; Part 2).

|  |  |  |
| --- | --- | --- |
| **Participants, n (%)** | **CT-P47** **(N=144)** | **EU-tocilizumab (N=140)** |
| Neutrophil count decreased | 14 (9.7) | 15 (10.7) |
| COVID-19 | 8 (5.6) | 19 (13.6) |
| Headache | 7 (4.9) | 11 (7.9) |
| White blood cell count decreased | 8 (5.6) | 6 (4.3) |
| Injection-site reaction | 4 (2.8) | 5 (3.6) |
| Hypersensitivity | 4 (2.8) | 2 (1.4) |
| Alanine aminotransferase increased | 2 (1.4) | 3 (2.1) |
| Aspartate aminotransferase increased | 2 (1.4) | 3 (2.1) |
| Cough | 4 (2.8) | 1 (0.7) |
| Ligament sprain | 1 (0.7) | 4 (2.9) |
| Oropharyngeal pain | 4 (2.8) | 1 (0.7) |
| Nausea | 3 (2.1) | 2 (1.4) |
| Diarrhea | 1 (0.7) | 3 (2.1) |
| Arthralgia | 0 | 3 (2.1) |

COVID-19 = coronavirus disease 2019. EU-tocilizumab = European Union-approved reference tocilizumab. TEAE = treatment-emergent adverse event.

## Supplementary Table 8. TEAEs of grade ≥3 in intensity, by relationship to study drug (safety set; Part 2).

|  |  |  |
| --- | --- | --- |
| **Participants, n (%)** | **CT-P47** **(N=144)** | **EU-tocilizumab (N=140)** |
| Neutrophil count decreased |  4 (2.8) | 7 (5.0) |
| Study drug-related | 4 (2.8) | 7 (5.0) |
| Blood creatine phosphokinase increased | 2 (1.4)a | 2 (1.4)a |
| Study drug-related | 0 | 1 (0.7)a |
| Aspartate aminotransferase increased | 0 | 2 (1.4)b |
| Study drug-related | 0 | 1 (0.7) |
| Neutropenia | 1 (0.7)a | 1 (0.7)a |
| Study drug-related | 1 (0.7)a | 1 (0.7)a |
| White blood cell count decreased | 0 | 1 (0.7) |
| Study drug-related | 0 | 1 (0.7) |
| Blood pressure increased | 0 | 1 (0.7) |
| Study drug-related | 0 | 1 (0.7) |
| Alanine aminotransferase increased | 0 | 1 (0.7)a |
| Study drug-related | 0 | 0 |
| Headache | 0 | 1 (0.7) |
| Study drug-related | 0 | 1 (0.7) |

aGrade 4 in intensity.

bGrade 4 in intensity for 1 (0.7%) participant; the event was not considered related to study drug.

EU-tocilizumab = European Union-approved reference tocilizumab. TEAE = treatment-emergent adverse event.

## Supplementary Table 9. Hematology and clinical chemistry variables of CTCAE grade ≥3 in intensity (safety set; Part 2).

|  |  |  |
| --- | --- | --- |
| **Participants, n (%)** | **CT-P47 (N=144)** | **EU-tocilizumab** **(N=140)** |
| White blood cell decreased | 2 (1.4) | 2 (1.4) |
| Neutrophil count decreased | 14 (9.7) | 23 (16.4) |
| Lymphocyte count decreased | 1 (0.7) | 0 |
| Hypermagnesemia | 2 (1.4) | 0 |
| Alanine aminotransferase increased | 0 | 1 (0.7) |
| Aspartate aminotransferase increased | 1 (0.7) | 2 (1.4) |
| Creatine phosphokinase increased | 7 (4.9) | 2 (1.4) |
| Hypertriglyceridemia | 7 (4.9) | 4 (2.9) |

CTCAE = Common Terminology Criteria for Adverse Events. EU-tocilizumab = European Union-approved reference tocilizumab.