# Electronic Supplementary Material

## Supplementary Methods

**Original Research Article for *Drug Safety***

**Title**

Real-world safety and efficacy of biosimilar CT-P13 in patients with immune-mediated inflammatory diseases: Integrated analysis of three Japanese prospective observational studies

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**Outlines of the Protocol and Statistical Analysis Plan of the Post-Marketing Surveillance Studies**

**(A) PMS on patients with rheumatoid arthritis (Code: IFX 11)**

**1. Objectives**

The objectives of this study are to collect safety, efficacy, and other relevant data on the use of CT-P13 in daily medical practice and confirm its safety profile and efficacy.

**2. Patients (*approved indication*)**

*Indication: Rheumatoid arthritis in patients who had shown an inadequate response to conventional non-biologic treatments (including for prevention of structural damage to joints).*

The prescribers of CT-P13 should adhere to the warnings, contraindications, and various precautions stated in the package insert. Additionally, CT-P13 should be used in accordance with the latest "Guidelines for the Use of TNF Inhibitors in the Treatment of Rheumatoid Arthritis" established by the Japan College of Rheumatology.

Contraindications: 1) Severe infections, including active tuberculosis

2) NYHA class III or higher congestive heart failure; patients with NYHA class II or below congestive heart failure require careful observation

3) Malignancies or demyelinating disorders.

Projected number of patients: 1000

**3. Dosage and administration**

The drug should be used at the approved dosage and regimen of administration.

*Dosage and Administration: The usual dosage is 3 mg/kg administered as an intravenous infusion. After the initial dose, administer doses at weeks 2 and 6, and then every 8 weeks. If the effect is insufficient or decreases after 6 weeks of treatment, the dose can be increased, or the dosing interval can be shortened. These increases in doses and/or reductions in dosing intervals will be made in a stepwise manner. The maximum dose is 10 mg/kg if the dosing interval is 8 weeks or 6 mg/kg if the dosing interval is shortened. The minimum dosing interval is 4 weeks.*

*This drug should be used in combination with methotrexate.*

4. **Requirements for medical institutions and physicians**

The medical institutions must:

1) Be capable of providing adequate emergency care (medical institutions can collaborate with other hospitals)
2) Have specialists in rheumatoid arthritis
3) Be able to participate in this survey.

Physicians must:

1) Be qualified as specialists in the Japanese Society of Rheumatology or certificated as rheumatologists by the Japanese Orthopedic Society

2) Have extensive experience in treatment with biologics
3) Have extensive experience in treatment with methotrexate
4) Be able to cooperate with this survey and meet with the sponsor representative.

**5. Observation period**

1) One year from the initial administration of CT-P13. To ensure the safety and efficacy during a one-year observation period, information will be collected until the initial administration date beyond the first year of treatment.
2) Up to 2 months after the last administration for patients who discontinue CT-P13 therapy within 1 year (for any reason excluding "patient death," "no visit," or "hospital transfer").

**6. Outcome**

Based on the reported/collected patient information, the following analyses will be conducted according to the statistical analysis plan:

1) Patient disposition
2) Patient background
3) Drug administration (number of doses, dosage, infusion time, dose enhancement) and weekly dosage of methotrexate
4) Safety evaluation

   The following data will be processed, and the output data will be stratified by patient background factors, patient groups, pregnancy and lactation status, and presence of comorbidities:

   1 Incidence of adverse events/adverse drug reactions
   2 Incidence of serious adverse events/serious adverse drug reactions
   3 Incidence of adverse events/adverse drug reactions leading to discontinuation
   4 Incidence of adverse drug reactions of special interest (severe infections, infusion reactions, interstitial lung disease, tuberculosis, severe hematologic disorders, malignant tumors)
5) Efficacy evaluation

   The following data will be output for each patient group at the specified time points during the observation period:

   1 Change in the following disease activity parameters:

   DAS28-CRP, DAS28-ESR, tender joint count, swollen joint count, physician global assessment of disease activity (VAS), patient global assessment of disease activity (VAS), CRP, ESR, rheumatoid factor, MMP-3, SDAI, CDAI

   2 Change in proportion of patients categorized by level of the following disease activity parameters:

   CDAI, SDAI, DAS28-CRP, DAS28- ESR, EULAR (CRP) response, EULAR (ESR) response
6) Drug persistence and reasons for discontinuation

   The cumulative rates of drug persistence using the Kaplan-Meier method, considering treatment discontinuation as an event, will be assessed according to patient groups.

**(B) PMS on patients with inflammatory bowel disease (Code: IFX 21)**

**1. Objectives**

The objectives of this study are to collect safety, efficacy, and other relevant data on the use of CT-P13 in daily medical practice and confirm its safety profile and efficacy.

**2. Patients (*approved indication*)**

Crohn's disease (CD):

*Indication: CD indicating one of the following conditions (limited to patients with inadequate response to conventional non-biologic treatments):*

- *Moderate to severe active phase CD*
- *Fistulas*

Ulcerative colitis (UC):

*Indication: Moderate to severe UC (limited to patients with inadequate response to conventional non-biologic treatments).*

Prescribers of CT-P13 should adhere to the warnings, contraindications, and various precautions stated in the package insert.

Projected number of patients: 300 patients who received CT-P13 therapy for 120 days or more (over 100 patients with CD and over 100 patients with UC).

**3. Dosage and administration**

The drug should be used at the approved dosage and regimen of administration.

CD:

*Dosage and Administration: The usual dosage is 5 mg/kg administered as an intravenous infusion. After the initial dose, administer doses at weeks 2 and 6, and then every 8 weeks. If the effect is insufficient or decreases after 6 weeks of treatment, the dose can be increased to 10 mg/kg. If the dosing interval is shortened, 5 mg/kg can be administered at intervals of at least 4 weeks.*

UC:

*Dosage and Administration: The usual dosage is 5 mg/kg administered as an intravenous infusion. After the initial dose, administer at weeks 2 and 6, and then every 8 weeks.*

4. **Requirements for medical institutions and physicians**

The medical institutions must:

1) Be capable of providing adequate emergency care (medical institutions can collaborate with other hospitals)
2) Have specialists in CD and UC
3) Be able to participate in this survey.

Physicians must:

1) Qualify as specialists in the Japanese Society of Gastroenterology, certified specialists in the Japan Gastroenterological Endoscopy Society, or specialists in the Japanese Society of Coloproctology

2) Have extensive experience in treatment with biologics
3) Be able to participate in this survey and meet with the sponsor representative.

**5. Observation period**

1) Two years from administration of the initial dose of CT-P13. To ensure the safety and efficacy during a two-year observation period, information will be collected until the initial administration date beyond the first two years of treatment.
2) Up to 2 months after the last administration for patients who discontinue CT-P13 therapy within 2 years (for any reason excluding "patient death," "no visit," or "hospital transfer").

**6. Outcome**

Based on the reported/collected patient information, the following analyses will be conducted according to the statistical analysis plan:

1) Patient disposition
2) Patient background
3) Drug administration (number of doses, dosage, infusion time, dose enhancement)
4) Safety evaluation

   The following data will be processed, and the output data will be stratified by patient background factors, patient groups, pregnancy and lactation status, and presence of comorbidities:

   1 Incidence of adverse events/adverse drug reactions
   2 Incidence of serious adverse events/serious adverse drug reactions
   3 Incidence of adverse events/adverse drug reactions leading to discontinuation
   4 Incidence of adverse drug reactions of special interest (severe infections, infusion reactions, interstitial lung disease, tuberculosis, severe hematologic disorders, malignant tumors)
5) Efficacy evaluation

   The following data will be output for each patient group at the specified time points during the observation period:

   1 Changes in the following disease activity parameters:
   Body weight, CRP, hematocrit, CDAI for CD, partial Mayo score for UC
   2 Change in proportion of patients categorized by level of the following disease activity parameters:
   Physician Global Assessment of Improvement, endoscopic evaluation, and CDAI for CD
6) Drug persistence and reasons for discontinuation

   The cumulative rates of drug persistence using the Kaplan-Meier method, considering treatment discontinuation as an event, will be assessed according to patient groups.

**(C) PMS on patients with psoriasis (Code: IFX 22)**

**1. Objectives**

The objectives of this study are to collect safety, efficacy, and other relevant data on the use of CT-P13 in daily medical practice and confirm its safety profile and efficacy.

**2. Patients (*approved indication*)**

*Indication: Plaque psoriasis, psoriatic arthritis, pustular psoriasis, and psoriatic erythroderma in patients who had shown an inadequate response to conventional non-biologic treatments.*

Prescribers of CT-P13 should adhere to the warnings, contraindications, and various precautions stated in the package insert.

Projected number of patients: 100 patients who received CT-P13 therapy for 180 days or more.

**3. Dosage and administration**

The drug should be used at the approved dosage and regimen of administration.

*Dosage and Administration: The usual dosage is 5 mg/kg administered as an intravenous infusion. After the initial dose, administer doses at weeks 2 and 6, and then every 8 weeks. If the effect is insufficient or decreases after 6 weeks of treatment, the dose can be increased, or the dosing interval can be shortened. These increases in dose and/or reductions in dosing intervals will be made in a stepwise manner. The maximum dose per kg body weight is 10 mg/kg if the dosing interval is 8 weeks or 6 mg/kg if the dosing interval is shortened. The minimum dosing interval is 4 weeks.*

4. **Requirements for medical institutions and physicians**

The medical institutions must:

1) Be either primary training facilities or training facilities certified by the Japanese Dermatological Association, or facilities (primarily core hospitals) approved by the Japanese Dermatological Association Biologics Evaluation Committee to meet similar facility conditions. Additionally, facilities previously approved as TNFα inhibitor-eligible facilities will be acceptable.
2) Participate in this survey and have specialists who can participate in this survey.

**5. Observation period**

1) One year from administration of the initial dose of CT-P13. To ensure the safety and efficacy during a one-year observation period, information will be collected until the initial administration date beyond the first year of treatment.
2) Up to 2 months after the last administration for patients who discontinue CT-P13 therapy within 1 year (for any reason excluding "patient death," "no visit," or "hospital transfer").

**6. Outcome**

Based on the reported/collected patient information, the following analyses will be conducted according to the statistical analysis plan:

1) Patient disposition
2) Patient background
3) Drug administration (number of doses, dosage, infusion time, dosing enhancement)
4) Safety evaluation

   The following data will be processed, and the output data will be stratified by patient background factors, patient groups, pregnancy and lactation status, and presence of comorbidities:

   1 Incidence of adverse events/adverse drug reactions
   2 Incidence of serious adverse events/serious adverse drug reactions
   3 Incidence of adverse events/adverse drug reactions leading to discontinuation
   4 Incidence of adverse drug reactions of special interest (severe infections, infusion reactions, interstitial lung disease, tuberculosis, severe hematologic disorders, malignant tumors)

5) Efficacy evaluation

   The following data will be output for each patient group at the specified time points during the observation period:

   1 Changes in the following disease activity parameters:
   PASI, PASI response, BSA, PGA, DLQI, ΔDLQI, NAPI
   Additionally, for patients with psoriatic arthritis:
   DAS28-CRP, DAS28-ESR, tender joint count, swollen joint count, physician global assessment of disease activity (VAS), patient global assessment of disease activity (VAS), CRP, ESR
   2 Change in proportion of patients categorized by level of the following disease activity parameters:
   PASI, PASI response, BSA, PGA, DLQI, ΔDLQI, NAPSI
   Additionally, for patients with psoriatic arthritis:
   DAS28-CRP, DAS28- ESR, EULAR (CRP) response, EULAR (ESR) response

6) Drug persistence and reasons for discontinuation

   The cumulative rates of drug persistence using the Kaplan-Meier method, considering treatment discontinuation as an event, will be assessed according to patient groups.