# Electronic Supplementary Material

## Supplementary Results

**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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**Table S1** Comparison of patient characteristics between all patients and those included in the primary efficacy analysis

| | All patients (Safety set) | Primary efficacy analysis set |
|---|---|---|
| | *n*=1816 | *n*=1150 |
| **Patient characteristics** | | |
| Sex (Male rate) | 44% | 45% |
| Age (years) | 51.9 ± 16.6 | 52.3 ± 16.5 |
| Disease duration (years) | 10.2 ± 9.5 | 10.6 ± 9.5 |
| BMI (kg/m$^2$) | 22.5 ± 4.0 | 22.5 ± 3.9 |
| Current smoker | 13% | 13% |
| Past smoker | 13% | 13% |
| History of allergy | 16% | 16% |
| Comorbidities | 45% | 46% |
| History of interstitial lung disease | 2% | 1% |
| Other respiratory comorbidities | 4% | 5% |
| **Disease activity** | | |
| Moderate-to-high disease activity [a)] | 38% | 35% |
| CRP (mg/dL) | 1.2 ± 2.3 | 1.0 ± 2.12 |
| **Prior biologics** | | |
| None (Naïve to biologics) | 40% | 37% |
| Switched from IFX | 49% | 54% |
| Switched from other biologics | 11% | 9% |
| **Concomitant medication** | | |
| Steroid [b)] | 31% | 31% |
| Methotrexate | 57% | 57% |
| Immunomodulator [c)] | 9% | 8% |
| Immunosuppressant [d)] | 16% | 17% |
| 5-aminosalicylic acid | 31% | 34% |

Values are expressed as % or mean ± standard deviation.
[a)] Patients with DAS28-CRP >3.2 for RA, CDAI >220 for CD, partial Mayo score ≥5 for UC, and PASI >5 for PS.
[b)] Steroid used for the target disease, excluding prophylaxis and treatment for comorbidities or adverse events.
[c)] Immunomodulator includes csDMARDs, but not methotrexate.
[d)] Immunosuppressant includes azathioprine, mercaptopurine, and mycophenolic acid.

**Table S2** Incidence of ADRs and serious ADRs to CT-P13 in 1,816 patients in the safety analysis set during the observation period of 1,854 patient-years

| System Organ Class | All ADRs | | | Serious ADRs | | |
|---|---|---|---|---|---|---|
| | No. of ADRs | Incidence % | Incidence rate /100PY (95%CI) | No. of SADRs | Incidence % | Incidence rate /100PY (95%CI) |
| Total | 439 | 24.2% | 23.7 (21.5 - 25.9) | 84 | 4.6% | 4.5 (3.6 - 5.5) |
| Blood and lymphatic system disorders | 9 | 0.5% | 0.5 (0.2 - 0.8) | 2 | 0.1% | 0.1 (0.0 - 0.3) |
| Cardiac disorders | 4 | 0.2% | 0.2 (0.0 - 0.4) | 3 | 0.2% | 0.2 (0.0 - 0.3) |
| Ear and labyrinth disorders | 1 | 0.1% | 0.1 (0.0 - 0.2) | 1 | 0.1% | 0.1 (0.0 - 0.2) |
| Endocrine disorders | 1 | 0.1% | 0.1 (0.0 - 0.2) | 1 | 0.1% | 0.1 (0.0 - 0.2) |
| Eye disorders | 2 | 0.1% | 0.1 (0.0 - 0.3) | 1 | 0.1% | 0.1 (0.0 - 0.2) |
| Gastrointestinal disorders | 34 | 1.9% | 1.8 (1.2 - 2.5) | 11 | 0.6% | 0.6 (0.2 - 0.9) |
| General disorders & administration site conditions | 23 | 1.3% | 1.2 (0.7 - 1.7) | 3 | 0.2% | 0.2 (0.0 - 0.3) |
| Hepatobiliary disorders | 32 | 1.8% | 1.7 (1.1 - 2.3) | 4 | 0.2% | 0.2 (0.0 - 0.4) |
| Infections and infestations | 110 | 6.1% | 5.9 (4.8 - 7.0) | 33 | 1.8% | 1.8 (1.2 - 2.4) |
| Injury, poisoning and procedural complications | 150 | 8.3% | 8.1 (6.8 - 9.4) | 13 | 0.7% | 0.7 (0.3 - 1.1) |
| Investigations | 40 | 2.2% | 2.2 (1.5 - 2.8) | 1 | 0.1% | 0.1 (0.0 - 0.2) |
| Metabolism and nutrition disorders | 7 | 0.4% | 0.4 (0.1 - 0.7) | 0 | 0.0% | 0.0 |
| Musculoskeletal and connective tissue disorders | 12 | 0.7% | 0.7 (0.3 - 1.0) | 1 | 0.1% | 0.1 (0.0 - 0.2) |
| Neoplasms benign, malignant and unspecified | 6 | 0.3% | 0.3 (0.1 - 0.6) | 5 | 0.3% | 0.3 (0.0 - 0.5) |
| Nervous system disorders | 19 | 1.0% | 1.0 (0.6 - 1.5) | 4 | 0.2% | 0.2 (0.0 - 0.4) |
| Psychiatric disorders | 1 | 0.1% | 0.1 (0.0 - 0.2) | 0 | 0.0% | 0.0 - |
| Renal and urinary disorders | 7 | 0.4% | 0.4 (0.1 - 0.7) | 0 | 0.0% | 0.0 - |
| Reproductive system and breast disorders | 1 | 0.1% | 0.1 (0.0 - 0.2) | 1 | 0.1% | 0.1 (0.0 - 0.2) |
| Respiratory, thoracic and mediastinal disorders | 48 | 2.6% | 2.6 (1.9 - 3.3) | 14 | 0.8% | 0.8 (0.4 - 1.2) |
| Skin and subcutaneous tissue disorders | 48 | 2.6% | 2.6 (1.9 - 3.3) | 2 | 0.1% | 0.1 (0.0 - 0.3) |
| Vascular disorders | 5 | 0.3% | 0.3 (0.0 - 0.5) | 0 | 0.0% | 0.0 - |

*ADR* adverse drug reaction, *CI* confidence interval, *SADR*. serious adverse drug reaction, *PY* patient-years

**Table S3** Effect of steroid use on occurrence of infusion reactions

| | Number of | | | Incidence of IRs/infusions | | | |
|---|---|---|---|---|---|---|---|
| | Patients | Infusions | IRs | % | OR | 95%CI | *p* value |
| **First IRs from start of CT-P13 therapy** | | | | | | | |
| No steroid | 1207 | 10780 | 103 | 1.0% | 1.00 | | |
| Steroid for target disease [a)] | 548 | 3361 | 33 | 1.0% | 1.03 | 0.69-1.52 | 0.890 |
| Steroid for prophylaxis [b)] | 46 | 336 | 11 | 3.3% | 3.51 | 1.87-6.60 | <0.001*** |
| Total | 1816 | 14661 | 149 | 1.0% | | | |
| **Second IRs after recovery from first IRs** | | | | | | | |
| No steroid | 42 | 134 | 26 | 19.4% | 1.00 | | |
| Steroid for target disease | 14 | 32 | 9 | 28.1% | 1.63 | 0.67-3.93 | 0.280 |
| Steroid for prophylaxis | 25 | 99 | 8 | 8.1% | 0.37 | 0.16-0.85 | 0.019* |
| Total | 81 | 265 | 43 | 16.2% | | | |

*p<0.05, ***p<0.001 by the Wald test
[a)] Steroid use for treatment of target disease, excluding use for prophylaxis, comorbidities, or adverse drug reactions
[b)] Steroid use for prophylaxis of infusion reactions, irrespective of other purposes
*IRs* infusion reactions, *OR* odds ratio, *CI* confidence interval

**Table S4** Incidence of common infections and serious infections in 1,816 patients in the safety analysis set during the observation period of 1,854 patient-years

| Infection [a] | Infection | | | Serious infection | | |
|---|---|---|---|---|---|---|
| | No. of infetion | Incidence % | Incidence rate /100PY (95%CI) | No. of infetion | Incidence % | Incidence rate /100PY (95%CI) |
| Bacterial pneumonia [b] | 22 | 1.2% | 1.2 (0.7 - 1.7) | 15 | 0.8% | 0.8 (0.4 - 1.2) |
| Nasopharyngitis | 21 | 1.2% | 1.1 (0.7 - 1.6) | 0 | 0.0% | 0.0 - |
| Herpes zoster | 15 | 0.8% | 0.8 (0.4 - 1.2) | 4 | 0.2% | 0.2 (0.0 - 0.4) |
| Bronchitis | 7 | 0.4% | 0.4 (0.1 - 0.7) | 0 | 0.0% | 0.0 - |
| Cellulitis | 5 | 0.3% | 0.3 (0.0 - 0.5) | 3 | 0.2% | 0.2 (0.0 - 0.4) |
| Influenza | 5 | 0.3% | 0.3 (0.0 - 0.5) | 0 | 0.0% | 0.0 - |
| Cystitis | 5 | 0.3% | 0.3 (0.0 - 0.5) | 0 | 0.0% | 0.0 - |
| Tuberculosis | 4 | 0.2% | 0.2 (0.0 - 0.4) | 4 | 0.2% | 0.2 (0.0 - 0.4) |
| Sepsis | 3 | 0.2% | 0.2 (0.0 - 0.4) | 3 | 0.2% | 0.2 (0.0 - 0.4) |
| Cytomegalovirus infection | 3 | 0.2% | 0.2 (0.0 - 0.4) | 2 | 0.1% | 0.1 (0.0 - 0.3) |
| Total | 110 | 6.1% | 5.9 (4.8 - 7.0) | 33 | 1.8% | 1.8 (1.2 - 2.4) |

[a] Infection occurred in ≥5 patients or caused ≥2 serious reactions
[b] Bacterial pneumonia includes pneumonia, pneumonia bacterial, and pneumonia pneumococcal
*CI* confidence interval, *PY* patient-years

**Table S5** Univariate Cox regression analysis of number and type of comorbidities associated with infections

| Comorbidities | Category | Incidence of infections (%) | | Cox analysis | | |
|---|---|---|---|---|---|---|
| | | | | HR | (95% CI) | *p* value |
| Total | | 110/1816 | (6.1%) | | | |
| Comorbidities | No | 38/995 | (3.8%) | 1.00 | (reference) | |
| | Yes | 72/821 | (8.8%) | 2.48 | (1.67-3.67) | <0.001 *** |
| Number of comorbidities | 0 | 38/995 | (3.8%) | 1.00 | (reference) | |
| | 1 | 27/369 | (7.3%) | 2.05 | (1.25-3.35) | 0.004 ** |
| | 2 | 19/184 | (10.3%) | 3.23 | (1.86-5.61) | <0.001 *** |
| | 3+ | 26/268 | (9.7%) | 2.60 | (1.58-4.29) | <0.001 *** |
| Pre-existing Infections | No | 98/1744 | (5.6%) | 1.00 | (reference) | |
| | Yes | 12/72 | (16.7%) | 3.35 | (1.84-6.10) | <0.001 *** |
| Immune system disorders | No | 106/1797 | (5.9%) | 1.00 | (reference) | |
| | Yes | 4/19 | (21.1%) | 3.25 | (1.20-8.81) | 0.021 * |
| Anemia | No | 99/1738 | (5.7%) | 1.00 | (reference) | |
| | Yes | 11/78 | (14.1%) | 2.42 | (1.30-4.51) | 0.006 ** |
| Cardiac disorders | No | 105/1783 | (5.9%) | 1.00 | (reference) | |
| | Yes | 5/33 | (15.2%) | 2.70 | (1.10-6.63) | 0.030 * |
| Respiratory disorders | No | 102/1709 | (6.0%) | 1.00 | (reference) | |
| | Yes | 8/107 | (7.5%) | 1.49 | (0.73-3.07) | 0.276 |
| Renal disorders | No | 106/1777 | (6.0%) | 1.00 | (reference) | |
| | Yes | 4/39 | (10.3%) | 1.77 | (0.65-4.80) | 0.263 |
| Hepatobiliary disorder | No | 102/1720 | (5.9%) | 1.00 | (reference) | |
| | Yes | 8/96 | (8.3%) | 1.41 | (0.69-2.90) | 0.346 |
| Diabetes mellitus | No | 103/1721 | (6.0%) | 1.00 | (reference) | |
| | Yes | 7/95 | (7.4%) | 1.40 | (0.65-3.02) | 0.389 |
| Hypertension | No | 98/1639 | (6.0%) | 1.00 | (reference) | |
| | Yes | 12/177 | (6.8%) | 1.26 | (0.69-2.29) | 0.459 |
| Hyperlipidemia | No | 98/1685 | (5.8%) | 1.00 | (reference) | |
| | Yes | 12/131 | (9.2%) | 1.52 | (0.83-2.77) | 0.171 |

*CI* confidence interval, *HR* hazard ratio,

**Table S6** Detailed information on 4 patients who developed tuberculosis on CT-P13 therapy

| Patient | #1 | #2 | #3 | #4 |
|---|---|---|---|---|
| Sex | Male | Male | Male | Male |
| Age | 65 years | 61 years | 61 years | 60 years |
| Disease | RA | CD | UC | RA |
| Prior biologics | Naïve to biologics | Naïve to biologics | Naïve to biologics | Switched from golimumab |
| Tuberculosis examination before CT-P13 therapy | | | | |
| Tuberculin skin test | not tested | not tested | 1+ | not tested |
| Interferon-gamma releasing assay | not tested | - | - | + [b] |
| Chest radiograph or CT | NAD | NAD | NAD | NAD |
| History of tuberculosis | - | - | + [a] | + |
| Prophylactic use of anti-tuberculosis drug | - | - | - | - [c] |
| Occurrence of tuberculosis | Tuberculous peritonitis | Tuberculous meningitis | Tuberculous | Pulmonary tuberculosis |
| Days to occurrence of tuberculosis | 178 | 303 | 43 | 224 |
| Number of administrations of CT-P13 | 5 | 7 | 2 | 5 |
| Outcome (Confirmed day after occurrence) | Improvement (day 12) | Sequelae (day 107) | Recovery (day 203) | Unclear (day 38) |

[a] Tuberculosis at age 24
[b] Positive on prior examination to golimumab treatment
[c] Completed 6 months of prophylaxis with isoniazid along with golimumab therapy
*CD* Crohn's disease, *CT* computed tomography, *NAD* no abnormality detected, *PS* psoriasis, *RA* rheumatoid arthritis, *UC* ulcerative colitis

**Table S7** Prior examination for tuberculosis, prophylactic drug use for tuberculosis, and incidence of tuberculosis

| | Total | RA | CD | UC | PS | Naïve to biologics | Switched from IFX | Switched from other biologics |
|---|---|---|---|---|---|---|---|---|
| | *n* =1816 | *n* =987 | *n* =342 | *n* =322 | *n* =165 | *n* =725 | *n* =894 | *n* =197 |
| Implementation rate of prior examination | 92.4% | 93.1% | 87.4% | 91.9% | 99.4% | 98.1% | 86.7% | 97.4% |
| Tuberculin skin test | 27.4% | 20.7% | 31.6% | 35.1% | 43.0% | 20.6% | 35.1% | 17.3% |
| Interferon-gamma releasing assay | 73.1% | 73.9% | 67.3% | 67.7% | 90.3% | 88.1% | 57.7% | 87.8% |
| Chest radiograph or CT | 89.2% | 90.5% | 83.0% | 86.6% | 98.2% | 95.6% | 83.2% | 93.4% |
| Positive rate in the prior examination | 9.3% | 7.9% | 10.4% | 8.1% | 17.1% | 6.6% | 12.5% | 6.3% |
| Tuberculin skin test | 22.6% | 21.6% | 23.1% | 18.6% | 31.0% | 19.5% | 24.9% | 14.7% |
| Interferon-gamma releasing assay | 3.0% | 3.1% | 2.6% | 1.4% | 5.4% | 2.2% | 3.9% | 3.0% |
| Chest radiograph or CT | 1.2% | 1.2% | 1.8% | 0.0% | 2.5% | 1.0% | 1.3% | 1.6% |
| History of tuberculosis | 1.5% | 1.7% | 1.5% | 0.9% | 1.8% | 1.1% | 1.5% | 3.6% |
| Prophylactic use of anti-tuberculosis drug | 2.9% | 4.1% | 0.9% | 0.9% | 4.2% | 3.6% | 1.9% | 5.1% |
| (for high-risk patients) [a)] | 14.0% | 17.1% | 6.3% | 11.5% | 16.1% | 24.0% | 6.7% | 31.3% |
| Occurrence of tuberculosis | 4 (0.2%) | 2 (0.2%) | 1 (0.3%) | 1 (0.3%) | 0 (0%) | 3 (0.4%) | 0 (0%) | 1 (0.5%) |

[a)] Prophylactic drug use for patients who had positive results in the prior examination or history of tuberculosis

*CD* Crohn's disease, *CT* computed tomography, *IFX* infliximab, *PS* psoriasis, *RA* rheumatoid arthritis, *UC* ulcerative colitis

**Table S8** Univariate Cox regression analysis of baseline factors associated with interstitial lung disease

| Baseline factor | Category | Incidence (%) | | Cox analysis | | |
|---|---|---|---|---|---|---|
| | | | | HR | (95% CI) | *p* value |
| Total | | 16/1816 | (0.9%) | | | |
| Disease | RA | 11/987 | (1.1%) | 1.00 | (reference) | |
| | CD | 1/342 | (0.3%) | 0.24 | (0.03-1.88) | 0.175 |
| | UC | 1/322 | (0.3%) | 0.30 | (0.04-2.34) | 0.252 |
| | PS | 3/165 | (1.8%) | 1.67 | (0.47-6.00) | 0.430 |
| Prior biologics | Naïve | 7/725 | (1.0%) | 1.00 | (reference) | |
| | Switched from IFX | 6/894 | (0.7%) | 0.60 | (0.20-1.79) | 0.361 |
| | Switched from other biologics | 3/197 | (1.5%) | 1.86 | (0.48-7.19) | 0.370 |
| Sex | Female | 8/1015 | (0.8%) | 1.00 | (reference) | |
| | Male | 8/801 | (1.0%) | 1.27 | (0.48-3.39) | 0.629 |
| Age (years) | ＜45 | 0/602 | (0.0%) | | | |
| | 45≦ ＜65 | 9/728 | (1.2%) | 1.00 | (in 1-year increments) | |
| | 65≦ | 7/486 | (1.4%) | 1.05 | (1.02-1.10) | 0.006 ** |
| Disease duration (years) | ＜5 | 4/626 | (0.6%) | 1.00 | (in 1-year increments) | |
| | 5≦ | 12/1052 | (1.1%) | 0.99 | (0.94-1.04) | 0.683 |
| BMI (kg/m2) | Normal (18.5-25) | 11/1093 | (1.0%) | | | |
| | Underweight (<18.5) | 2/228 | (0.9%) | 1.00 | (in 1 kg/$m^2$ increments) | |
| | Overweight (25≦) | 1/364 | (0.3%) | 0.95 | (0.82-1.10) | 0.465 |
| CRP （mg/dL） | < 0.5 | 4/971 | (0.4%) | 1.00 | (reference) | |
| | ≧ 0.5 | 9/601 | (1.5%) | 4.28 | (1.32-13.9) | 0.016 * |
| Smoking history | No | 5/1023 | (0.5%) | 1.00 | (reference) | |
| | Yes | 5/369 | (1.4%) | 2.79 | (0.81-9.62) | 0.105 |
| History of allergy | No | 13/1522 | (0.9%) | 1.00 | (reference) | |
| | Yes | 3/294 | (1.0%) | 1.23 | (0.35-4.32) | 0.745 |
| Comorbidities | No | 3/995 | (0.3%) | 1.00 | (reference) | |
| | Yes | 13/821 | (1.6%) | 5.33 | (1.52-18.7) | 0.009 ** |
| History of interstitial lung disease | No | 12/1779 | (0.7%) | 1.00 | (reference) | |
| | Yes | 4/37 | (10.8%) | 18.59 | (5.99-57.7) | <0.001 *** |
| Comorbidities of other respiratory comorbidities | No | 14/1742 | (0.8%) | 1.00 | (reference) | |
| | Yes | 2/74 | (2.7%) | 3.87 | (0.88-17.0) | 0.073 |
| Concomitant methotrexate use | No | 4/774 | (0.5%) | 1.00 | (reference) | |
| | Yes | 12/1042 | (1.2%) | 2.21 | (0.71-6.85) | 0.170 |
| Concomitant steroid use [a)] | No | 11/1245 | (0.9%) | 1.00 | (reference) | |
| | Yes | 5/571 | (0.9%) | 1.08 | (0.37-3.10) | 0.892 |

* $p$ <0.05, ** $p$ <0.01, *** $p$ <0.001

[a)] Steroid use for the treatment of target disease, excluding use for prophylaxis, comorbidities, or adverse drug reactions

*BMI* body mass index, *CD* Crohn's disease, *CI* confidence interval, *CRP* C-reactive protein, *HR* hazard ratio, *IFX* infliximab, *PS* psoriasis, *RA* rheumatoid arthritis, *UC* ulcerative colitis

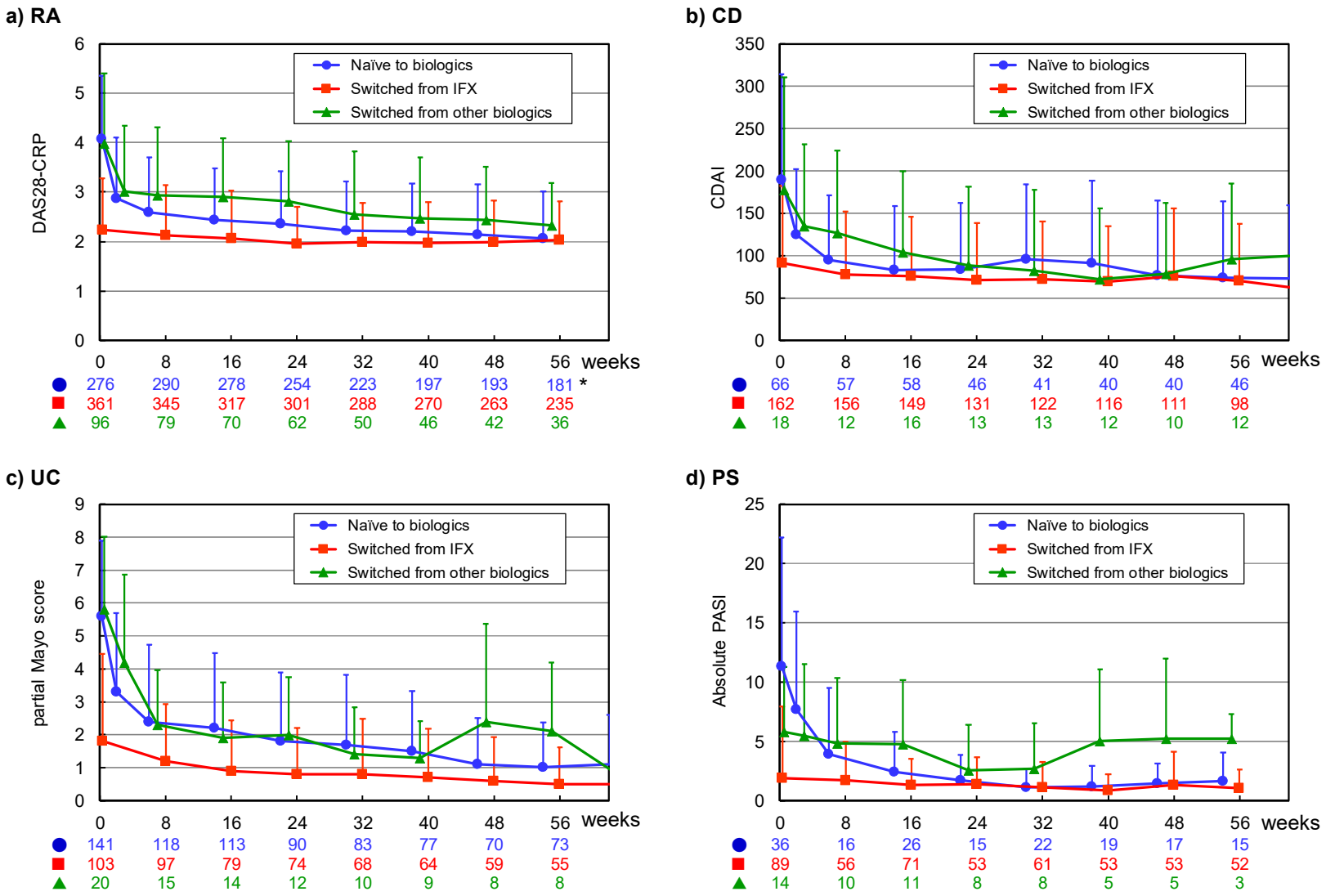


**Fig. S1** Effect of CT-P13 on disease activity parameters (mean ± SD) in patients with (a) RA, (b) CD, (c) UC, and (d) PS
* Number of analyzed patients at each time point
*CD* Crohn's disease, *CDAI* Crohn's Disease Activity Index, *DAS28-CRP* Disease Activity Score in 28 joints with C-reactive protein, *IFX* infliximab, *PASI* Psoriasis Area and Severity Index, *PS* psoriasis, *RA* rheumatoid arthritis, *UC* ulcerative colitis

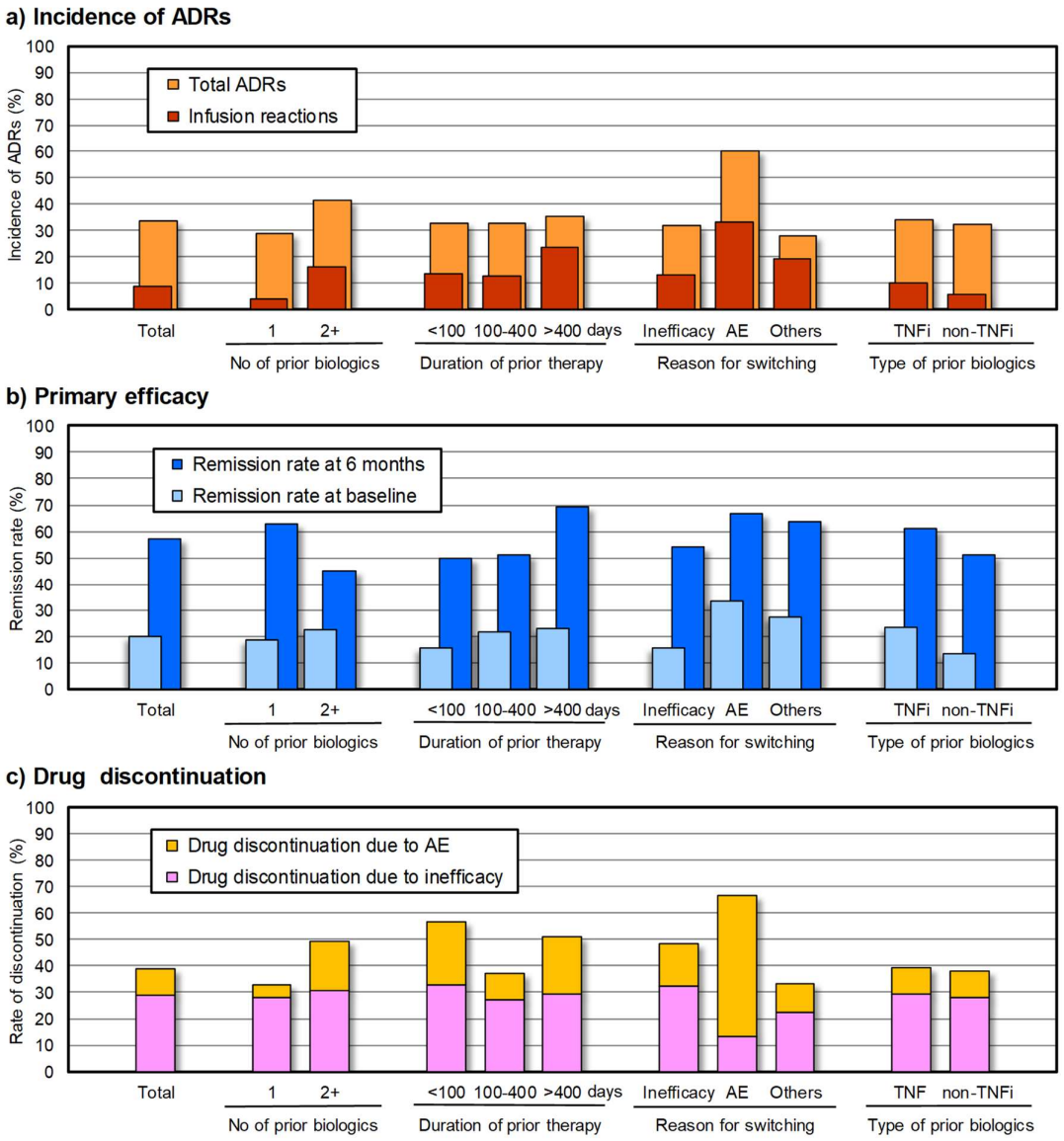


**Fig. S2** Impact of differences in prior biologic therapy on (a) incidence of ADRs, (b) primary efficacy, and (c) drug discontinuation in patients who switched from other biologics to CT-P13
*ADR* adverse drug reaction, *AE* adverse event, *TNFi* inhibitor of tumor necrosis factor