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ORIGINAL RESEARCH ARTICLE

Post-Marketing Pooled Safety Analysis for CT-P13 Treatment of Patients with Immune-Mediated Inflammatory Diseases in Observational Cohort Studies

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Abstract

Background At EU marketing authorisation, safety data for CT-P13 (biosimilar infliximab) were limited, particularly in some indications, and uncommon adverse events (AEs) could not be evaluated among relatively small analysis populations.

Objectives Our objective was to investigate the overall safety profile and incidence rate of AEs of special interest (AESIs), including serious infections and tuberculosis, in CT-P13-treated patients.

Methods Data were pooled from six observational studies representing authorised indications of CT-P13 (ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, adult and paediatric Crohn's disease and ulcerative colitis). Patients were analysed by indication and treatment (patients who received CT-P13 or those who switched from reference infliximab to CT-P13 ≤ 6 months prior to enrolment or during the study).

Results Overall, 4393 patients were included ($n = 3677$ CT-P13 group; $n = 716$ switched group); 64.03% of patients had inflammatory bowel disease and 6.31% of patients were antidrug antibody positive. Overall, 32.94% and 9.58% of patients experienced treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs, respectively. Across indications, TEAEs were more frequent with CT-P13 than with the switched group. Infections including tuberculosis were the most frequent serious AESI overall (2.48%) and by treatment group or indication. In total, 14 patients (0.32%) reported active tuberculosis. Overall incidence rates per 100 patient-years (95% confidence interval) were 3.40 (2.788–4.096) for serious infections including tuberculosis and 0.44 (0.238–0.732) for active tuberculosis. Infusion-related reactions were the second most frequent AESI following infection including tuberculosis.

Conclusion The CT-P13 safety profile appears consistent with previous studies for CT-P13 and reference infliximab, supporting the favourable risk/benefit balance for CT-P13 treatment.

1 Introduction

CT-P13 is a biosimilar of infliximab that had received regulatory approval in 86 countries as of September 2019. Authorisation was received from the Ministry of Food and Drug Safety in Korea (2012), the European Medicines Agency (2013) and the US FDA (2016) [1–4]. CT-P13 is licensed for use in all indications approved for reference infliximab: ankylosing spondylitis (AS), rheumatoid arthritis (RA; in combination with methotrexate), psoriatic arthritis (PsA), plaque psoriasis (Ps), adult and paediatric Crohn's disease (CD) and ulcerative colitis (UC) [5–9].

Regulatory approval of CT-P13 was supported by two randomised, double-blind studies that compared CT-P13 with reference infliximab in patients with RA (PLANETRA) and those with AS (PLANETAS) [10, 11]. In the phase III PLANETRA study, CT-P13 had equivalent efficacy

Previous Presentation Selected data from four of the contributing studies were reported in a poster (FRI0104) at the European League Against Rheumatism (EULAR) Annual Congress 2019 (12–15 June; Madrid, Spain). Selected data for patients with inflammatory bowel disease were reported in a poster (P0422) at United European Gastroenterology (UEG) Week 2019 (19–23 October; Barcelona, Spain).

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Key Points

Safety data for 4393 patients were pooled from six post-marketing, open-label, observational cohort studies including patients treated with CT-P13 (biosimilar infliximab) for all authorised indications.

Incidence rates of serious infections including tuberculosis and infusion-related reactions were lower for patients who switched from reference infliximab to CT-P13 than for other CT-P13-treated patients; these adverse events were most frequent in patients with rheumatoid arthritis.

The overall safety profile and the incidence of serious infections, tuberculosis and infusion-related reactions were comparable to those in previous observational studies for CT-P13 and reference infliximab and should be representative of the safety profile for adult patients treated with CT-P13 in clinical practice.

to reference infliximab in patients with RA (treated with concomitant methotrexate and folic acid), with comparable pharmacokinetic and safety profiles [10]. The phase I PLANETAS study demonstrated the equivalence of the pharmacokinetic profiles for CT-P13 and reference infliximab; efficacy and safety profiles were also comparable [11].

Following regulatory approval, several observational and real-world studies investigated the safety profile of CT-P13. However, many studies published to date included an insufficient number of patients to assess the absolute risk of uncommon adverse events (AEs), anticipated to occur in 1/100 to 1/1000 patients. For CT-P13, uncommon AEs include infections, such as tuberculosis, and immune system disorders, such as serum sickness and anaphylactic reactions [5, 7]. For inflammatory bowel disease (IBD), multiple studies enrolling over 100 patients investigated the safety of CT-P13 [12–24], likely reflecting the need for safety data in these indications, for which regulatory approval was based on extrapolation [25]. In contrast, few such studies have evaluated the safety profile of CT-P13 in patients with AS or RA [26–29], and data for PsA and Ps are lacking. To evaluate the safety profile of CT-P13 in the post-marketing setting, we present data pooled from six observational studies representing all authorised indications of CT-P13.

2 Methods

2.1 Analysis Population

This manuscript reports an analysis of safety data from six post-marketing, non-interventional, open-label, observational cohort studies in which patients with RA, AS, PsA, Ps, UC or CD were administered CT-P13 according to prescribing recommendations in the authorised product information. CT-P13 infusions were performed as outpatient procedures in a clinic setting. Included studies were the CT-P13 4.2 Korea/EU registry for patients with RA (ClinicalTrials.gov: NCT02557295 [30]), the CT-P13 4.3 Korea/EU registry for patients with CD or UC (NCT02326155 [31]), the CT-P13 4.4 Korea/EU registry for patients with AS (NCT02557308 [32]), the KOREA-PMS study for all indications (not registered with ClinicalTrials.gov), the CONNECT-IBD study for patients with CD or UC (NCT02539368 [33]) and the PERSIST study for patients with RA, AS or PsA (NCT02605642 [34]). Full study details are provided in Table S1 in the electronic supplementary material (ESM). Briefly, the CT-P13 4.3 Korea/EU registry and KOREA-PMS study enrolled patients treated with CT-P13, regardless of prior biologic therapies. PERSIST enrolled patients treated with CT-P13, some of whom were switched from stable reference infliximab treatment at enrolment. CONNECT-IBD enrolled patients treated with CT-P13 or reference infliximab but permitted switching between CT-P13 and other anti-tumour necrosis factor (TNF) agents during the study. The CT-P13 4.4 Korea/EU registry and the CT-P13 4.2 Korea/EU registry enrolled patients receiving CT-P13 or anti-TNF agents. In Korea only, the CT-P13 4.2 study also enrolled a biologic-naïve patient population. All patients included in this analysis received one or more CT-P13 dose prior to data cut-off (27 December 2017).

2.2 Objectives

The primary objective was to investigate the incidence rate (IR) of tuberculosis and serious infections in patients treated with CT-P13. The secondary objective was to investigate the IR of AEs of special interest (AESIs) in patients treated with CT-P13.

2.3 Assessments

The duration of exposure to CT-P13 was determined for all patients (whether they had discontinued treatment, completed treatment or were continuing treatment). Duration of CT-P13 exposure (in days) was calculated as the date of the last CT-P13 dose minus the date of the first CT-P13 dose plus 1, regardless of dose interruptions or changes. For participants in ongoing studies, the first dose after study initiation and the last dose prior to data cut-off were used. For patients switched from CT-P13 to other therapies, the date of administration of the first dose of the other therapeutic was taken as the date of last CT-P13 exposure. For patients switched to CT-P13 from other anti-TNF agents, the date of the first CT-P13 dose was taken as the first dosing date.

AEs were classified as pre-treatment AEs or treatment-emergent AEs (TEAEs). TEAEs were AEs that either

occurred after the first dose of study treatment or that presented before but worsened in severity after the first dose of study treatment. Only TEAEs associated with CT-P13 (AEs that occurred after the first dose of CT-P13 or presented before but worsened in severity after the first dose of CT-P13) were included in the analysis, regardless of prior reference infliximab or other anti-TNF treatment. In patients who switched between anti-TNF agents, only AEs that occurred during the CT-P13 treatment period (between the first CT-P13 dose and the day before the first dose of the switched medication) were included. Serious AEs (SAEs) were defined as death, life-threatening event (including events that put patients at risk of death at the time of the event but not events that may have caused patient death if more severe), inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, and important medical events based on appropriate medical judgement. Only treatment-emergent SAEs (TESAEs) associated with CT-P13 were included in the analysis, regardless of prior reference infliximab or other anti-TNF treatment. All AEs and medical/surgical history were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) version 20.1.

AESIs were based on safety concerns identified in the CT-P13 risk-management plan [35, 36]. Infusion-related reactions (IRRs) were analysed as an independent AESI. Algorithms were developed to identify AESI cases (Table S2, ESM) based primarily on reported AE terms from MedDRA. Some algorithms incorporated additional variables, such as time to event onset, to enable identification of relevant case reports. Algorithms could not be developed for some safety concerns because information was unavailable (e.g. infusion reaction associated with shortened infusion, serious infusion reactions during a re-induction regimen following disease flare, Bacillus Calmette–Guérin breakthrough infection and agranulocytosis in infants with *in utero* exposure to CT-P13).

In the CT-P13 4.2, CT-P13 4.3 and CT-P13 4.4 Korea/EU registries, blood samples were collected prior to drug administration (for patients receiving CT-P13 or reference infliximab) for optional immunogenicity testing at day 0, 6 months (week 30; CT-P13 4.2 registries only), once a year during treatment and at the end-of-study (EOS) visit. An enzyme-linked immunosorbent assay method was used to detect anti-infliximab antibodies in human serum. Results were considered positive if they were positive on both screening and confirmatory assays. Some CONNECT-IBD study sites conducted voluntary immunogenicity analysis as part of routine clinical care. Thus, patients who received CT-P13 could opt to provide immunogenicity data obtained from the most recent test before study enrolment and at any time during the study. Immunogenicity testing was not conducted for patients with PsA/Ps. Patients were included in the antidrug antibody (ADA)-positive subgroup if they had one or more positive ADA result during the study; ADA-negative patients had only negative ADA results.

For this pooled analysis, reasons for study discontinuation were organised into common terms between studies (Table S3, ESM). Study duration to discontinuation (in days) was calculated as the date of permanent discontinuation of study treatment minus the date of informed consent (or the first visit date for KOREA-PMS) plus 1. Study duration to discontinuation was calculated only for patients who had discontinued prior to data cut-off (completed or continuing patients were not included).

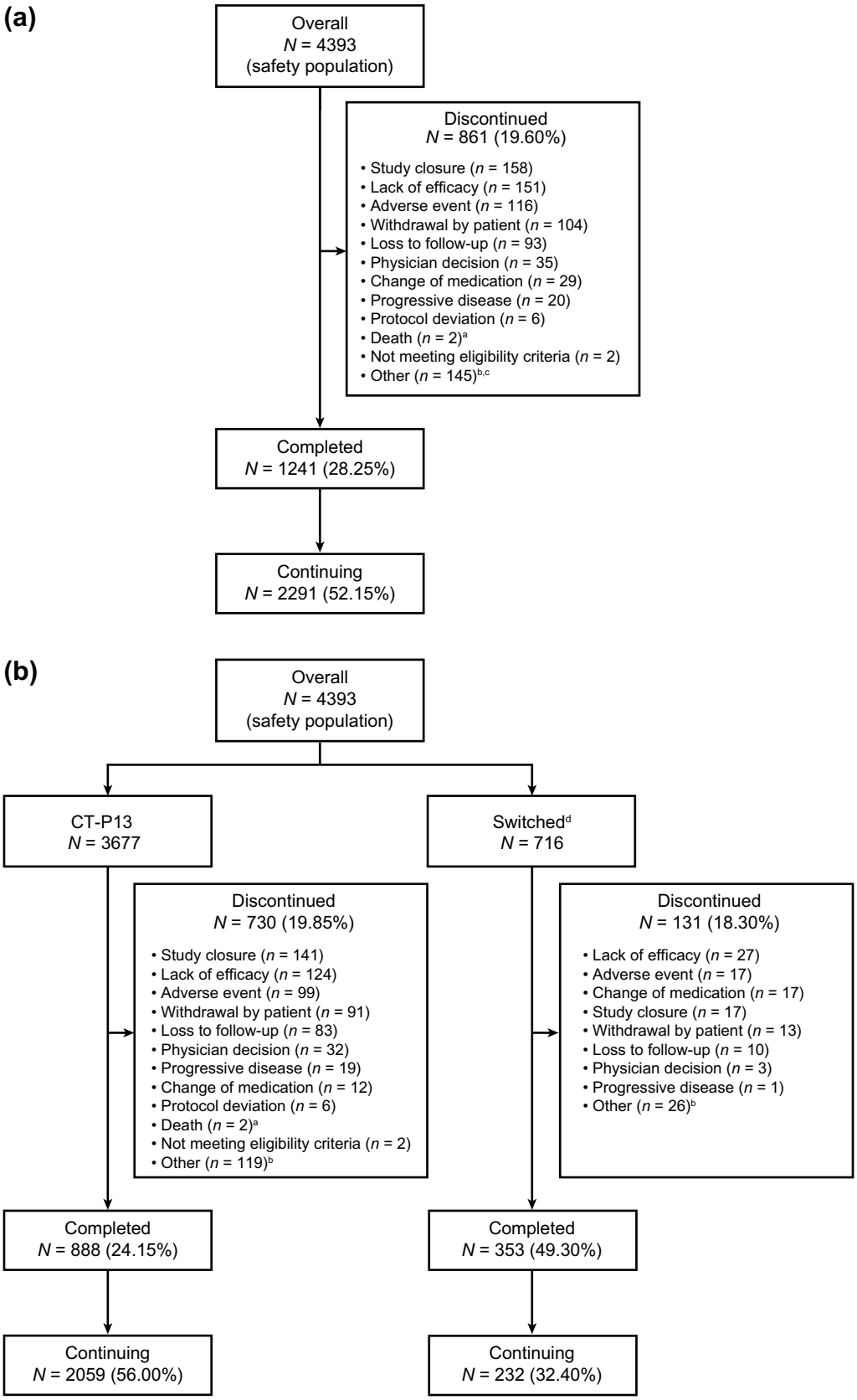
2.4 Data Collection

For the CT-P13 4.2 and CT-P13 4.4 Korea/EU registries, data were collected until the EOS for patients who switched to CT-P13 or until 1 year from the date of switch (or EOS, whichever was earlier) for patients who switched to other anti-TNF agents. For patients in the CT-P13 4.2 Korea/EU registry who switched to disease-modifying antirheumatic drugs, no further assessment was required after the switch. Patients enrolled in the CT-P13 4.3 Korea/EU registry were not permitted to switch. For the CT-P13 4.2, CT-P13 4.3 and CT-P13 4.4 Korea/EU registries, safety data were collected for 6 months from the date of withdrawal for patients who discontinued CT-P13. In KOREA-PMS, data were collected for the 4-year post-marketing surveillance period according to Korean regulations. In CONNECT-IBD and PERSIST, the maximum follow-up duration was 2 years. All studies, apart from KOREA-PMS and data collection at Korean sites for the CT-P13 4.2 and CT-P13 4.4 registries, were ongoing at data cut-off. Data cut-off was defined based on achievement of the target sample size in order to meet the objectives of the analysis for the purpose of regulatory submission.

2.5 Statistical Methods

We aimed to use a sufficiently large dataset to be able to assess the absolute risk of tuberculosis and serious infections, and the risk relative to appropriate controls, in patients receiving CT-P13. A target sample size of 3100 patients was calculated to achieve 80% power at the 5% one-sided significance level to detect an additional 0.247% incidence of tuberculosis based on the post-marketing surveillance sample size calculation procedure of PASS 12 (NCSS, LLC., Kaysville, UT, USA). The relative risk ratio was 2.108 based on a tuberculosis incidence of 0.223% derived from published registry data [37, 38].

Continuous variables were summarised using descriptive statistics; categorical variables were summarised using frequencies and percentages. Data were analysed descriptively. No hypothesis testing was performed.


(a)
Overall
N = 4393
(safety population)
Discontinued
N = 861 (19.60%)
• Study closure (n = 158)
• Lack of efficacy (n = 151)
• Adverse event (n = 116)
• Withdrawal by patient (n = 104)
• Loss to follow-up (n = 93)
• Physician decision (n = 35)
• Change of medication (n = 29)
• Progressive disease (n = 20)
• Protocol deviation (n = 6)
• Death (n = 2)a
• Not meeting eligibility criteria (n = 2)
• Other (n = 145)b,c
Completed
N = 1241 (28.25%)
Continuing
N = 2291 (52.15%)
(b)
Overall
N = 4393
(safety population)
CT-P13
N = 3677
Switchedd
N = 716
Discontinued
N = 730 (19.85%)
• Study closure (n = 141)
• Lack of efficacy (n = 124)
• Adverse event (n = 99)
• Withdrawal by patient (n = 91)
• Loss to follow-up (n = 83)
• Physician decision (n = 32)
• Progressive disease (n = 19)
• Change of medication (n = 12)
• Protocol deviation (n = 6)
• Death (n = 2)a
• Not meeting eligibility criteria (n = 2)
• Other (n = 119)b
Discontinued
N = 131 (18.30%)
• Lack of efficacy (n = 27)
• Adverse event (n = 17)
• Change of medication (n = 17)
• Study closure (n = 17)
• Withdrawal by patient (n = 13)
• Loss to follow-up (n = 10)
• Physician decision (n = 3)
• Progressive disease (n = 1)
• Other (n = 26)b
Completed
N = 888 (24.15%)
Completed
N = 353 (49.30%)
Continuing
N = 2059 (56.00%)
Continuing
N = 232 (32.40%)

◂**Fig. 1** Patient disposition (**a**) overall and (**b**) by treatment group (safety population). [a]Seven deaths were reported in total, with death recorded as the reason for discontinuation for two patients. The remaining five patients reported adverse events as the reason for discontinuation. [b]Recovery was not the primary reason for discontinuation for any patient. [c]For CONNECT-IBD, 'other' reasons for discontinuation with an incidence ≥ 5 were move to another city or country ($n = 18$); switching to biologic or unknown treatment ($n = 16$); patient decision ($n = 16$); change hospital ($n = 13$); change to infliximab biosimilar SB2 (Samsung Bioepis, Incheon, Korea; $n = 12$); insufficient money ($n = 10$); investigator decision ($n = 5$); and screen failure ($n = 5$). [d]Patients switched from reference infliximab to CT-P13 ≤ 6 months prior to enrolment or during the study, regardless of the reference infliximab treatment period

Datasets from contributing studies (Table S1, ESM) were combined for analysis. Because of the small sample size of paediatric patients with CD or UC enrolled in the CT-P13 4.3 EU registry and the KOREA-PMS study, their data were analysed in combination with data for adult patients.

AESIs were summarised by the IR per 100 patient-years (calculated as the total number of patients who reported the AESI divided by the total exposure duration of all patients multiplied by 100) and the 95% confidence interval (CI) based on the Poisson distribution. IR per 100 patient-years was not calculated for IRRs and acute hypersensitivity. IRs were calculated overall, by treatment group and by indication. IRs for TEAEs were also calculated. If a patient experienced the same AE more than once, the AE was included only once in the most severe category for calculating incidence. A subgroup analysis was conducted to determine the incidence and maximum severity of tuberculosis for all combined indications for data from countries with a high or low incidence of tuberculosis according to World Health Organization 2016 estimates [39]. Statistical analyses were conducted using SAS Software version 9.4 (SAS Institute, Inc., Cary, NC, USA). No special method for handling missing data was employed in the analysis other than those for missing dates (described in Sect. 1.1 of the ESM).

The safety population ('overall') comprised all patients who received one or more CT-P13 dose during the study, analysed by treatment actually received. If there was any doubt about whether a patient was treated or not, they were assumed to have been treated for the purpose of this analysis. The ADA-positive population comprised all patients in the safety population who had one or more ADA-positive result during the study.

Patients were also analysed by indication and by treatment group. The 'CT-P13' group included patients naïve to CT-P13, patients treated continuously with CT-P13, patients treated with anti-TNF agents other than reference infliximab or CT-P13 who switched to CT-P13, patients treated with CT-P13 who switched to other anti-TNF agents or non-biologic treatment or patients previously treated with reference infliximab (> 6 months prior to enrolment) who switched to CT-P13. The 'switched' group included patients who switched from reference infliximab to CT-P13 ≤ 6 months prior to enrolment or during the study, regardless of the reference infliximab treatment period.

3 Results

3.1 Patients

The overall safety population included 4393 patients with RA, AS, PsA, Ps, UC or CD who were treated with one or more dose of CT-P13 across the six post-marketing observational studies (Fig. 1a). At data cut-off (27 December 2017), approximately half ($n = 2291$; 52.15%) of patients in the overall safety population were continuing in their respective study; 28.25% ($n = 1241$) had completed their respective studies and 19.60% ($n = 861$) had discontinued. The median (range) study duration to discontinuation, calculated only for patients who discontinued treatment prior to data cut-off, was 214 (1–1233) days in the overall safety population and 217 (1–1233) and 177 (1–707) days in the CT-P13 and switched groups, respectively (Table S4, ESM). Study closure (3.60%; $n = 158/4393$) and lack of efficacy (3.44%; $n = 151/4393$) were the most common primary reasons for discontinuation in the overall safety population; AEs only led to discontinuation in 2.64% of patients ($n = 116/4393$). AEs accounted for discontinuation of 2.69% ($n = 99/3677$) and 2.37% of patients ($n = 17/716$) in the CT-P13 and switched groups, respectively (Fig. 1b). Overall, death was reported as the primary reason for discontinuation for only two patients, whereas AEs were reported as the primary reason for discontinuation for the five additional patients who died.

Altogether, 64.03% of patients had IBD (CD, $n = 1814$; UC, $n = 999$), whereas 18.64% ($n = 819$) of patients had AS, 15.25% ($n = 670$) of patients had RA and 2.05% ($n = 90$) of patients had PsA/Ps (Fig. S1, ESM). Median (range) study duration to discontinuation ranged from 172 days (3–712) for patients with PsA/Ps to 262 days (1–728) for patients with AS; however, the number of evaluable patients varied substantially between indications (Table S4, ESM). Study discontinuation was most common in patients with RA (38.51% of patients discontinued; Fig. S1, ESM). Across indications, the most common reasons for discontinuation included study closure, lack of efficacy, AEs and withdrawal by the patient.

Of the 918 patients with immunogenicity results available, 277 (30.17%) were ADA positive (Fig. S2 and Table S7, ESM). In the ADA-positive population, the median study duration to discontinuation (480 days [range 31–913]) was approximately double that of the overall safety population. More ADA-positive patients discontinued their study than

patients in the overall safety population (54.09% [Fig. S2b, ESM] vs. 19.85% (Fig. 1b) for the CT-P13 group; 90.00% [Fig. S2b, ESM] vs. 18.30% (Fig. 1b) for the switched group). Study closure was the main reason for the difference in discontinuation rate between ADA-positive and overall populations (29.24% [Fig. S2a, ESM] vs. 3.60% [Fig. 1a]). This was anticipated since study closure did not apply to PERSIST and KOREA-PMS, in which immunogenicity testing was not conducted. Among non-operational reasons, the largest differences in primary discontinuation reason between the ADA-positive and overall populations were lack of efficacy (7.94 vs. 3.44%) and AEs (5.42 vs. 2.64%).

Overall, baseline characteristics were broadly similar between treatment groups (Table 1). Adult patients (≥ 18 years) accounted for 96.79% of the safety population, and the median age was 40.0 years. Overall, most patients were White or Asian (46.78 and 41.27%, respectively), reflecting the regional split in study participation. Reflecting the treatment switch, time since first diagnosis was longer in patients who switched from reference infliximab than in those initiating treatment with CT-P13 (median 7.10 vs. 4.20 years). Overall, 62.28% of patients had received prior biologic therapy, accounting for 54.94 and 100.00% of patients in the CT-P13 and switched groups, respectively. Prior biologic immunosuppressant therapy had been received by 62.21% of patients overall (Table S5, ESM). Table S6 (ESM) shows baseline characteristics by indication.

Overall, the mean ± standard deviation duration of CT-P13 exposure was 266.9 ± 194.25 days, and the maximum duration of exposure was 1296 days (Table S4, ESM). Most (80.38%) patients were exposed to CT-P13 for between 3 months and 2 years, whereas 1025 (23.33%) of patients were exposed for > 1 year. Overall, 380 (8.65%) patients had received only one dose of CT-P13. Mean duration of exposure was broadly comparable across treatment groups and across indications except for PsA/Ps, where it was longer (322.1 vs. 254.0–280.3 days). Overall, the median (range) maximum CT-P13 dose was 5.00 (1.5–12.9) mg/kg, and this varied between indications. Median CT-P13 dose was highest in patients with CD (5.50 mg/kg) and lowest in patients with RA (3.50 mg/kg), in line with the lower dose specified for RA treatment in the product information.

3.2 Immunogenicity

Overall, immunogenicity results were available for 20.90% ($n = 918$) of patients. Of these patients, 30.17% ($n = 277$) were ADA positive and 69.83% ($n = 641$) were ADA negative (Table S7, ESM). The proportion of patients with immunogenicity results was similar between indications other than for PsA/Ps, for which no immunogenicity testing was performed. Among indications, the proportion of ADA-positive patients was highest for RA (50.40% of evaluable patients).

3.3 Treatment-Emergent Adverse Events (AEs) and Treatment-Emergent Serious AEs

Overall, 32.94% of patients experienced one or more TEAE (AEs that occurred or worsened after the first dose of CT-P13), and 9.58% of patients experienced one or more TESAE (Table 2). Overall, 13.09 and 2.73% of patients experienced one or more TEAE and TESAE that were considered by the investigator to be related to CT-P13. Across indications, the proportion of patients experiencing one or more TEAEs was greatest for patients with RA (50.15%) and lowest for patients with PsA/Ps (26.67%; Table S8, ESM). Proportions of patients who experienced one or more TEAEs were slightly higher in the CT-P13 group than in the switched group (34.08 vs. 27.09% for all indications combined). This was also the case for TESAEs for indications other than PsA/Ps, for which only three patients experienced one or more TESAE. Overall, the maximum severity of TEAEs was mild for 47.96% of patients, with 12.58% of patients experiencing one or more severe TEAE (Table S9, ESM). TEAEs and TESAEs were distributed across a number of system organ classes (SOCs), with infections and infestations and gastrointestinal disorders the most frequent SOCs for both TEAEs and TESAEs (Table S9, ESM).

Overall, 6.49% of patients experienced one or more TEAE leading to permanent discontinuation, whereas the proportions differed between treatment groups (6.99% CT-P13; 3.91% switched; Table 2). By indication, the proportion of patients who experienced one or more TEAE leading to discontinuation was lowest for AS (3.42%) and highest for RA and UC (8.81%; Table S8, ESM).

Overall, seven (0.16%) of the 4393 patients died during study participation, all of whom were in the CT-P13 group (Table S8, ESM). By indication, three patients (0.30%) with UC, two (0.30%) with RA, one (0.12%) with AS and one (0.06%) with CD died. Five deaths were considered unrelated to study treatment: one due to acute respiratory distress syndrome (considered unlikely to be related to CT-P13 treatment; patient with RA), one laceration of abdominal aortic aneurysm (patient with CD), one sudden death with unknown cause (patient with AS), one sudden heart death (patient with UC) and one unknown cause (patient with UC). Two deaths were considered possibly related to CT-P13: one from pneumonia (patient with RA) and one from sepsis due to pneumonia (patient with UC).

Among ADA-positive patients, 54.87% of patients experienced TEAEs overall, with the incidence similar between CT-P13 and switched groups (Table S10, ESM). The incidence of TEAEs was highest for patients with RA (85.71%). TESAEs occurred in 12.27% of patients, with a higher incidence in the switched versus CT-P13 group (20.00 vs. 11.67%). Overall, 9.39% (8.17% CT-P13 group; 25.00% switched group) of patients experienced one or more

Table 1 Baseline patient demographics and disease characteristics by treatment group (safety population)

Demographics and characteristics	Overall ($N=4393$)		CT-P13 ($n=3677$)		Switched[a] ($n=716$)	
	n	Result	*n*	Result	*n*	Result
Age (years)	4393	40.0 (7–87)	3677	40.0 (7–87)	716	40.0 (8–82)
Age group (years)						
< 18	4393	141 (3.21)	3677	112 (3.05)	716	29 (4.05)
≥ 18		4252 (96.79)		3565 (96.95)		687 (95.95)
Sex						
Male	4393	2356 (53.63)	3677	1949 (53.01)	716	407 (56.84)
Female		2036 (46.35)		1727 (46.97)		309 (43.16)
Missing		1 (0.02)		1 (0.03)		0
Race[b]						
White	4393	2055 (46.78)	3677	1796 (48.84)	716	259 (36.17)
Asian[c]		1813 (41.27)		1405 (38.21)		408 (56.98)
Black or African American		10 (0.23)		9 (0.24)		1 (0.14)
Other		329 (7.49)		303 (8.24)		26 (3.63)
Missing		186 (4.23)		164 (4.46)		22 (3.07)
Region						
EU	4393	2520 (57.36)	3677	2220 (60.38)	716	300 (41.90)
Non-EU		1873 (42.64)		1457 (39.62)		416 (58.10)
Height (cm)[d]	946	168.00 (116.5–195.0)	811	168.00 (116.5–195.0)	135	170.20 (145.1–193.0)
Weight (kg)[e]	2405	63.00 (19.8–146.0)	1906	62.80 (20.3–139.0)	499	65.00 (19.8–146.0)
BMI (kg/m^2)	946	24.00 (12.9–52.5)	811	23.80 (12.9–48.7)	135	25.00 (14.1–52.5)
Years since first diagnosis	4350	4.80 (0.0–55.0)	3641	4.20 (0.0–55.0)	709	7.10 (0.0–42.8)
Prior medical or surgical history[f]	4393	1865 (42.45)	3677	1538 (41.83)	716	327 (45.67)
Surgical and medical procedures		706 (16.07)		601 (16.34)		105 (14.66)
Musculoskeletal and connective tissue disorders		399 (9.08)		324 (8.81)		75 (10.47)
Infections and infestations		375 (8.54)		337 (9.17)		38 (5.31)
Gastrointestinal disorders		363 (8.26)		290 (7.89)		73 (10.20)
Metabolism and nutrition disorders		297 (6.76)		236 (6.42)		61 (8.52)
Vascular disorders		292 (6.65)		234 (6.36)		58 (8.10)
Prior biologic therapy[g,h]	4393	2736 (62.28)	3677	2020 (54.94)	716	716 (100.00)
Immunosuppressants		2733 (62.21)		2017 (54.85)		716 (100.00)
Antineoplastic agents[i]		3 (0.07)		3 (0.08)		0
Antidiarrheals, intestinal anti-inflammatory or anti-infective agents[j]		3 (0.07)		3 (0.08)		0

Data are presented as median (range) or *n* (%) unless otherwise indicated

Baseline was defined as the last non-missing result on or prior to the first administration of study treatment

BMI body mass index, *eCRF* electronic case report form, *EU* European Union, *PMS* post-marketing surveillance, *SOC* system organ class

[a]Patients switched from reference infliximab to CT-P13 ≤ 6 months prior to enrolment or during the study, regardless of the reference infliximab treatment period

[b]Reported as 'ethnicity' in the PERSIST study

[c]Includes all patients in the KOREA-PMS study

[d]Not recorded in the KOREA-PMS or CONNECT-IBD studies

[e]Not recorded in the CONNECT-IBD study

[f]Prior medical or surgical history is shown for SOCs where the incidence is ≥ 5% in any group

[g]In the switched group, patients who were treated with reference infliximab prior to CT-P13 before enrolment were not analysed as patients with prior biologics

[h]In the CT-P13 4.2, CT-P13 4.3 and CT-P13 4.4 studies conducted in the EU, prior biologics were recorded separately from prior/concomitant medications on the eCRF and only these prior biologics were included in the analysis. For other studies, prior biologics were defined as medications discontinued prior to the first dose of study treatment, which were coded to the World Health Organization Drug Dictionary preferred terms infliximab, adalimumab, etanercept, certolizumab, vedolizumab, ustekinumab, tocilizumab, sarilumab, etrolizumab, abatacept, secukinumab, natalizumab, golimumab, anakinra or rituximab

[i]Patients received rituximab

[j]Patients received etrolizumab

Table 2 Summary of treatment-emergent adverse events and treatment-emergent serious adverse events overall, by treatment group and by indication (safety population)

N (%)	Overall (*N* = 4393)	By treatment group		By indication[a]				
		CT-P13 (*n* = 3677)	Switched[b] (*n* = 716)	RA (*n* = 670)	AS (*n* = 819)	PsA/Ps (*n* = 90)	UC (*n* = 999)	CD (*n* = 1814)
Patients experiencing one or more TEAE[c]	1447 (32.94)	1253 (34.08)	194 (27.09)	336 (50.15)	309 (37.73)	24 (26.67)	274 (27.43)	504 (27.78)
Related	575 (13.09)	509 (13.84)	66 (9.22)	134 (20.00)	117 (14.29)	14 (15.56)	133 (13.31)	177 (9.76)
Unrelated	1057 (24.06)	910 (24.75)	147 (20.53)	267 (39.85)	232 (28.33)	13 (14.44)	170 (17.02)	375 (20.67)
Patients experiencing one or more TESAE[c]	421 (9.58)	373 (10.14)	48 (6.70)	83 (12.39)	37 (4.52)	3 (3.33)	100 (10.01)	198 (10.92)
Related	120 (2.73)	104 (2.83)	16 (2.23)	28 (4.18)	17 (2.08)	1 (1.11)	36 (3.60)	38 (2.09)
Unrelated	322 (7.33)	287 (7.81)	35 (4.89)	59 (8.81)	22 (2.69)	2 (2.22)	72 (7.21)	167 (9.21)
Patients with one or more TEAE[c] leading to discontinuation	285 (6.49)	257 (6.99)	28 (3.91)	59 (8.81)	28 (3.42)	7 (7.78)	88 (8.81)	103 (5.68)
Patients with one or more TEAE[c] leading to death	7 (0.16)	7 (0.19)	0	2 (0.30)	1 (0.12)	0	3 (0.30)	1 (0.06)

AE adverse event, *AS* ankylosing spondylitis, *CD* Crohn's disease, *Ps* psoriasis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *TEAE* treatment-emergent adverse event, *TESAE* treatment-emergent serious adverse event, *UC* ulcerative colitis

[a]Indication was missing for one patient in CONNECT-IBD, thus 'by indication' information is presented for 4392 patients in total

[b]Patients switched from reference infliximab to CT-P13 ≤ 6 months prior to enrolment or during the study, regardless of the reference infliximab treatment period

[c]TEAEs and TESAEs included only AEs that occurred after the first dose of CT-P13 or worsened in severity after the date of the first dose of CT-P13

TEAE that led to discontinuation. As for all TEAEs, the proportion of patients who experienced one or more TEAE leading to discontinuation was higher in those with RA (15.87%) than in those with other indications.

3.4 AEs of Special Interest

The most frequently reported AESI was infections including tuberculosis, with an incidence of 9.74% in the overall population (10.14% CT-P13 group; 7.68% switched group; Table 3). This was the case across indications, although the incidence of infections ranged from 6.01 to 19.10% of patients with UC and RA, respectively (Table S8, ESM). Infections including tuberculosis were reported more frequently in the CT-P13 group than in the switched group for all indications, apart from RA. IRRs were the second most frequent AESI overall, experienced by 4.17% of the overall population (Table 3).

In terms of serious AESIs, infections including tuberculosis were reported most frequently, with an incidence of 2.48% in the overall population, whereas seven (0.16%) patients experienced serious acute hypersensitivity reactions (after manual review of cases; Table 3). The IRs per 100 patient-years for AESIs and serious AESIs are also shown in Table 3.

In common with the safety population, the most frequent AESIs in the ADA-positive population were infections including tuberculosis (67 patients; 24.19%) and IRRs (32 patients; 11.55%). Across indications, the AESI with the highest incidence was infections including tuberculosis, followed by IRRs, in line with the safety population. The incidence of these AESIs was highest for patients with RA, with 29 (46.03%) patients experiencing infections including tuberculosis and 19 (30.16%) patients experiencing IRRs.

Table 3 Summary of the incidence and incidence rate for adverse events of special interest and serious adverse events of special interest overall, by treatment group and by indication (safety population)

Incidence and incidence rate	Overall ($N=4393$)	By treatment group		By indication[a]				
		CT-P13 ($n=3677$)	Switched[b] ($n=716$)	RA ($n=670$)	AS ($n=819$)	PsA/Ps ($n=90$)	UC ($n=999$)	CD ($n=1814$)
AESIs[c]								
Infection including TB	428 (9.74)	373 (10.14)	55 (7.68)	128 (19.10)	88 (10.74)	12 (13.33)	60 (6.01)	140 (7.72)
	13.33 (12.101–14.659)	13.74 (12.377–15.203)	11.13 (8.382–14.483)	24.90 (20.772–29.604)	15.45 (12.392–19.036)	15.12 (7.812–26.409)	8.29 (6.326–10.671)	10.58 (8.902–12.487)
IRR[d] [*n* (%)]	183 (4.17)	164 (4.46)	19 (2.65)	65 (9.70)	29 (3.54)	5 (5.56)	37 (3.70)	47 (2.59)
Hepatobiliary event	67 (1.53)	58 (1.58)	9 (1.26)	22 (3.28)	34 (4.15)	0	4 (0.40)	7 (0.39)
	2.087 (1.601–2.623)	2.136 (1.622–2.762)	1.821 (0.833–3.457)	3.695 (2.225–5.771)	5.970 (4.134–8.342)	0 (0–4.648)	0.553 (0.151–1.415)	0.529 (0.213–1.09)
Haematologic reactions	42 (0.96)	36 (0.98)	6 (0.84)	8 (1.19)	5 (0.61)	2 (2.22)	4 (0.40)	23 (1.27)
	1.31 (0.943–1.769)	1.33 (0.929–1.835)	1.21 (0.445–2.642)	1.56 (0.672–3.066)	0.88 (0.285–2.049)	2.52 (0.305–9.102)	0.55 (0.151–1.415)	1.74 (1.102–2.608)
Exposure during pregnancy	25 (0.57)	22 (0.60)	3 (0.42)	0	0	0	8 (0.80)	17 (0.94)
	0.779 (0.504–1.15)	0.810 (0.508–1.227)	0.607 (0.125–1.774)	0 (0–0.717)	0 (0–0.648)	0 (0–4.648)	1.105 (0.477–2.178)	1.285 (0.748–2.057)
Acute hypersensitivity reaction[d,e]	21 (0.48)	18 (0.49)	3 (0.42)	3 (0.45)	1 (0.12)	0	7 (0.70)	10 (0.55)
Manual review[f]	7 (0.16)	6 (0.16)	1 (0.14)	1 (0.15)	1 (0.12)	0	3 (0.30)	2 (0.11)
Non-haematologic malignancy[g]	18 (0.41)	17 (0.46)	1 (0.14)	6 (0.90)	0	0	5 (0.50)	7 (0.39)
	0.56 (0.332–0.886)	0.63 (0.365–1.002)	0.20 (0.005–1.127)	1.17 (0.428–2.540)	0 (0–0.648)	0 (0–4.648)	0.69 (0.224–1.612)	0.53 (0.213–1.09)
Active TB	14 (0.32)	13 (0.35)	1 (0.14)	3 (0.45)	5 (0.61)	0	2 (0.20)	4 (0.22)
	0.44 (0.238–0.732)	0.48 (0.255–0.819)	0.20 (0.005–1.127)	0.58 (0.12–1.705)	0.88 (0.285–2.049)	0 (0–4.648)	0.28 (0.033–0.998)	0.30 (0.082–0.774)
SLE lupus-like syndrome	5 (0.11)	5 (0.14)	0	0	0	1 (1.11)	1 (0.10)	3 (0.17)
	0.156 (0.051–0.363)	0.184 (0.06–0.43)	0 (0–0.746)	0 (0–0.717)	0 (0–0.648)	1.260 (0.032–7.02)	0.138 (0.003–0.77)	0.227 (0.047–0.663)
Demyelinating disorder	2 (0.05)	1 (0.03)	1 (0.14)	0	0	0	0	2 (0.11)
	0.06 (0.008–0.225)	0.04 (0.001–0.205)	0.20 (0.005–1.127)	0 (0–0.717)	0 (0–0.648)	0 (0–4.648)	0 (0–0.51)	0.15 (0.018–0.546)
Congestive heart failure	1 (0.02)	1 (0.03)	0	0	1 (0.12)	0	0	0
	0.031 (0.001–0.174)	0.037 (0.001–0.205)	0 (0–0.746)	0 (0–0.717)	0.176 (0.004–0.978)	0 (0–4.648)	0 (0–0.51)	0 (0–0.279)
HBV reactivation	1 (0.02)	1 (0.03)	0	0	1 (0.12)	0	0	0
	0.031 (0.001–0.174)	0.037 (0.001–0.205)	0 (0–0.746)	0 (0–0.717)	0.176 (0.004–0.978)	0 (0–4.648)	0 (0–0.51)	0 (0–0.279)

Table 3 (continued)

Incidence and incidence rate	Overall ($N=4393$)	By treatment group		By indication[a]				
		CT-P13 ($n=3677$)	Switched[b] ($n=716$)	RA ($n=670$)	AS ($n=819$)	PsA/Ps ($n=90$)	UC ($n=999$)	CD ($n=1814$)
Serum sickness (delayed hypersensitivity reactions)	1 (0.02)	1 (0.03)	0	0	0	0	1 (0.10)	0
	0.03 (0.001–0.174)	0.04 (0.001–0.205)	0 (0–0.746)	0 (0–0.717)	0 (0–0.648)	0 (0–4.648)	0.14 (0.003–0.77)	0 (0–0.279)
Intestinal or perianal abscess in patients with CD								
	31 (1.71)	30 (1.91)	1 (0.40)	–	–	–	–	31 (1.71)
	2.34 (1.592–3.326)	2.56 (1.724–3.648)	0.67 (0.017–3.737)	–	–	–	–	–
Serious AESIs								
Infection including TB	109 (2.48)	94 (2.56)	15 (2.09)	27 (4.03)	17 (2.08)	1 (1.11)	24 (2.40)	40 (2.21)
	3.40 (2.788–4.096)	3.46 (2.797–4.236)	3.03 (1.698–5.005)	5.25 (3.461–7.641)	2.98 (1.739–4.779)	1.26 (0.032–7.020)	3.32 (2.125–4.934)	3.02 (2.160–4.117)
Acute hypersensitivity reaction[d,e]	15 (0.34)	12 (0.33)	3 (0.42)	3 (0.45)	1 (0.12)	0	5 (0.50)	6 (0.33)
Manual review[f]	7 (0.16)	6 (0.16)	1 (0.14)	1 (0.15)	1 (0.12)	0	3 (0.30)	2 (0.11)
Haematologic reactions	8 (0.18)	7 (0.19)	1 (0.14)	2 (0.30)	0	0	1 (0.10)	5 (0.28)
	0.25 (0.108–0.491)	0.26 (0.104–0.531)	0.20 (0.005–1.127)	0.39 (0.047–1.405)	0 (0–0.648)	0 (0–4.648)	0.14 (0.003–0.770)	0.38 (0.123–0.882)
Hepatobiliary events	5 (0.11)	5 (0.14)	5 (0.14)	2 (0.30)	2 (0.24)	0	1 (0.10)	0
	0.156 (0.051–0.363)	0	0 (0–0.746)	0.389 (0.047–1.405)	0.351 (0.043–1.269)	0 (0–4.648)	0.138 (0.003–0.77)	0 (0–0.279)

Data are presented as *n* (%); IR per 100 py (95% exact CI) unless otherwise indicated

AESI adverse event of special interest, *AS* ankylosing spondylitis, *CD* Crohn's disease, *CI* confidence interval, *HBV* hepatitis B virus, *IR* incidence rate, *IRR* infusion-related reaction, *Ps* psoriasis, *PsA* psoriatic arthritis, *PT* preferred term, *py* patient-years, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *TB* tuberculosis, *UC* ulcerative colitis

[a]Indication was missing for one patient in CONNECT-IBD, so 'by indication' information is presented for 4392 patients in total

[b]Patients switched from reference infliximab to CT-P13 ≤ 6 months prior to enrolment or during the study, regardless of the reference infliximab treatment period

[c]There were no cases of haematologic malignancy or sarcoidosis/sarcoid-like reaction

[d]IR per 100 py was not calculated

[e]Includes anaphylactic shock

[f]Manual review for anaphylactic shock comprised confirming that the event fulfilled Sampson criteria [59] and that the patient was treated with adrenaline or other rescue medications because of the event

[g]The most commonly reported non-haematological malignancies were coded to the PTs neoplasm malignant ($n=6$) and gastric cancer ($n=5$). All other non-haematological malignancies were reported in one patient each (<0.02% incidence)

3.5 Serious Infections

Infection including tuberculosis was the most frequent serious AESI overall and in both treatment groups (2.56% CT-P13 group; 2.09% switched group; Table 3). This was also the most frequent serious AESI across indications, with incidence ranging from 1.11% for patients with PsA/Ps to 4.03% for patients with RA. The IR per 100 patient-years (95% CI) for serious infections including tuberculosis was 3.40 (2.788–4.096) in the safety population (Table 3). Overall, the most frequent severe infections were opportunistic infection, anal abscess ($n=4$ each; 0.09%) and pneumonia ($n=3$; 0.07%; Table S11, ESM). The opportunistic infections were herpes zoster, oral fungal infection, pneumonia legionella and vulvovaginal mycotic infection ($n=1$ each).

3.6 Active Tuberculosis

Overall, active tuberculosis was reported in 14 (0.32%) patients (0.35% CT-P13 group; 0.14% switched group; Table 3). Most active tuberculosis cases were reported in patients with AS ($n=5$; 0.61%), whereas three patients (0.45%) with RA, two (0.20%) with UC and four (0.22%) with CD also reported this infection (Table S8, ESM). No patients with PsA/Ps reported active tuberculosis. Overall, the IR per 100 patient-years (95% CI) for active tuberculosis was 0.44 (0.238–0.732). Corresponding IRs by indication were 0.58 (0.12–1.705) in RA, 0.88 (0.285–2.049) in AS, 0.28 (0.033–0.998) in UC, 0.30 (0.082–0.774) in CD and 0 (0–4.648) in PsA/Ps. Active tuberculosis was reported by 13 (0.71%) patients from a high-incidence country (all in Korea) and by one (0.04%) patient from a low-incidence country (Portugal) (Table S12, ESM). The incidences of active tuberculosis by country were 0.72% ($n=13/1797$) and 0.71% ($n=1/140$) in Korea and Portugal, respectively.

3.7 Infusion-Related Reactions

In the safety population, 183 (4.17%) patients experienced one or more TEAE of IRRs overall, whereas, in the ADA-positive population, 32 (11.55%) patients experienced IRRs (Table 4). In both analysis populations, the proportion of patients experiencing IRRs was higher in the CT-P13 group than in the switched group. Most IRRs were non-severe. However, 13 (0.30%) patients experienced severe IRRs overall, most of which were classified in the immune system disorders SOC ($n=8$; 0.18%). In the ADA-positive population, all severe IRRs were immune system disorders ($n=2$; 0.72%). Of all IRRs, the most frequently reported preferred term was hypersensitivity in both the safety and the ADA-positive population, reported by 1.53 and 7.22% of patients, respectively. Analysing the safety population by indication, IRRs were reported most frequently in patients with RA (9.70%) and least frequently in patients with CD (2.59%; Table S8, ESM). Across indications, IRRs were reported more frequently in the CT-P13 group than in the switched group.

In the safety population, ten (0.23%) patients reported one or more TESAE of IRRs overall, including two (0.72%) patients in the ADA-positive population (Table 4). The preferred terms for the ten reported IRRs in the safety population were hypersensitivity ($n=4$), anaphylactic shock ($n=2$), anaphylactic reaction ($n=1$), IRR ($n=1$) and rash generalised ($n=1$) in the CT-P13 group and anaphylactic reaction ($n=1$) in the switched group.

4 Discussion

This post-marketing pooled analysis combined data from six observational studies of patients treated with CT-P13. Data were analysed for 4393 patients, representing all authorised indications for CT-P13, including 1025 patients who were treated for over 1 year. The objectives of this analysis were to investigate the IRs of serious infections, tuberculosis and other AESIs in patients treated with CT-P13.

In this analysis, 32.94% of patients treated with one or more dose of CT-P13 experienced one or more TEAE, whereas 9.58% of patients experienced one or more TESAE. Acknowledging the limitations of cross-trial comparisons, these incidences appear in line with published large observational studies of CT-P13 treatment (that enrolled more than 100 patients), which reported incidences of AEs ranging from 7.19 to 48.36% [15–17, 19, 23, 26] and incidences of SAEs ranging from 1.80 to 12.07% [13, 16, 17, 19, 20, 23]. The overall safety profile for CT-P13 identified in our analysis is also similar to registry data for reference infliximab treatment, for example, 43.32 and 10.02% of 838 patients with RA included in a Canadian registry experienced one or more AE and SAE, respectively [40]. In contrast, the incidence of TEAEs in our analysis was lower than the 84.36% of patients with CD who reported any AE [41] and the 77.53% of patients with UC who reported one or more pre-specified AE [42] in other registries, which may be due to their longer median follow-up times and longer durations of exposure to reference infliximab. Overall, the incidence of AESIs was consistent with the reference infliximab prescribing information [8]. In the case of intestinal or perianal abscess, for which incidence is not specified in the prescribing information, the incidence in our analysis (1.71% of patients with CD) was lower than that reported in a retrospective analysis of reference infliximab-treated patients with CD ($n=15/258$; 5.81%) [43].

In our analysis, serious infections including tuberculosis were experienced by 2.48% of patients ($n=109$) in the safety population. This is comparable to the incidence reported in

Table 4 Infusion-related reactions by maximum severity, system organ class and preferred term with a frequency of ≥0.25% (safety and antidrug antibody-positive populations)

SOC PT, *n* (%)	Safety population						ADA-positive population					
	Overall (*N* = 4393)		CT-P13 (*n* = 3677)		Switched[a] (*n* = 716)		Overall (*n* = 277)		CT-P13 (*n* = 257)		Switched[a] (*n* = 20)	
Patients with one or more TEAE[b] of IRR	183 (4.17)		164 (4.46)		19 (2.65)		32 (11.55)		31 (12.06)		1 (5.00)	
Maximum severity	Severe	Total	Severe	Total	Severe	Total	Severe	Total	Severe	Total	Severe	Total
Immune system disorders	8 (0.18)	74 (1.68)	7 (0.19)	66 (1.79)	1 (0.14)	8 (1.12)	2 (0.72)	21 (7.58)	1 (0.39)	20 (7.78)	1 (5.00)	1 (5.00)
Hypersensitivity	6 (0.14)	67 (1.53)	6 (0.16)	60 (1.63)	0	7 (0.980)	1 (0.36)	20 (7.22)	1 (0.39)	20 (7.78)	0	0
Anaphylactic reaction	1 (0.02)	5 (0.11)	0	4 (0.11)	1 (0.14)	1 (0.14)	1 (0.36)	1 (0.36)	0	0	1 (5.00)	1 (5.00)
Skin and subcutaneous tissue disorders	1 (0.02)	49 (1.12)	1 (0.03)	44 (1.20)	0	5 (0.70)	0	5 (1.81)	0	5 (1.95)	0	0
Pruritus	0	18 (0.41)	0	15 (0.41)	0	3 (0.42)	0	1 (0.36)	0	1 (0.39)	0	0
Urticaria	0	15 (0.34)	0	13 (0.35)	0	2 (0.28)	0	3 (1.08)	0	3 (1.17)	0	0
Rash	0	12 (0.27)	0	12 (0.33)	0	0	0	2 (0.72)	0	2 (0.78)	0	0
Injury, poisoning and procedural complications	3 (0.07)	35 (0.80)	3 (0.08)	33 (0.90)	0	2 (0.28)	0	5 (1.81)	0	5 (1.95)	0	0
IRR	2 (0.05)	34 (0.77)	2 (0.05)	32 (0.87)	0	2 (0.28)	0	5 (1.81)	0	5 (1.95)	0	0
Gastrointestinal disorders	1 (0.02)	6 (0.14)	0	3 (0.08)	1 (0.14)	3 (0.42)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	0	4 (0.09)	0	4 (0.11)	0	0	0	1 (0.36)	0	1 (0.39)	0	0
Arthralgia	0	2 (0.05)	0	2 (0.05)	0	0	0	1 (0.36)	0	1 (0.39)	0	0
Patients with one or more TESAE[b] of IRR	10 (0.23)		9 (0.24)		1 (0.14)		2 (0.72)		1 (0.39)		1 (5.00)	

Data are presented as *n* (%) unless otherwise indicated

ADA antidrug antibody, *AE* adverse event, *IRR* infusion-related reaction, *PT* preferred term, *SOC* system organ class, *TEAE* treatment-emergent adverse event, *TESAE* treatment-emergent serious adverse event

[a]Patients switched from reference infliximab to CT-P13 ≤6 months prior to enrolment or during the study, regardless of the reference infliximab treatment period

[b]TEAEs and TESAEs included only AEs that occurred after the first dose of CT-P13 or worsened in severity after the date of the first dose of CT-P13

previous large observational studies of CT-P13 treatment. Of 2499 patients with CD who were treated with CT-P13 in a nationwide French study, 83 (3.32%) experienced serious infections [18]. Of 547 patients with IBD enrolled in the PROSIT-BIO cohort, five (0.73%) experienced SAEs of infection [13], whereas 1.16% of patients ($n = 2/173$) with IBD experienced serious TEAEs of infection in a Korean post-marketing study [17]. The incidence of serious infections in our analysis was within the range previously reported for reference infliximab (0.91–8.48%) [41, 44–52], including 7.30% ($n = 42/575$) for patients with RA in the REMITRACT study [45] and 8.16% ($n = 150/1839$) for patients with CD in the ENCORE registry [41].

Among infections, tuberculosis is a particular safety concern related to anti-TNF treatment [53]. In our analysis, 428 (9.74%) patients in the safety population reported infections including tuberculosis and 14 (0.32%) patients reported active tuberculosis (comprising 13 patients from Korea and one from Portugal). As expected, our subgroup analysis showed that the frequency of active tuberculosis was higher in countries that, per World Health Organization 2016 estimates, have a high incidence of tuberculosis than in countries with a low incidence (0.71 vs. 0.04%) [39]. The incidence of active tuberculosis in our analysis was consistent with data from observational studies. A large observational study of CT-P13 treatment in patients with IBD identified no cases of active tuberculosis among 353 patients after 54 weeks of follow-up [15], whereas tuberculosis was reported in 0.24% of patients ($n = 6/2499$) with CD who were treated with CT-P13 in a nationwide French study [18]. A post-marketing study of CT-P13 in the Republic of Korea reported one patient with active tuberculosis (of 113 [0.88%]) after 30 weeks of follow-up [17], whereas a Japanese post-marketing surveillance study with a 2-year follow-up period reported two patients (of 523; 0.38%) with tuberculosis [19]. In a Korean registry study of 244 CT-P13-treated patients with AS, two (0.82%) patients reported tuberculosis infection after 4 years of follow-up [26]. The incidence of active tuberculosis in our analysis was within the range previously reported (0–5.00%) for patients with AS, PsA and RA treated with reference infliximab [45, 49–52, 54–58].

IRRs are another important safety concern related to CT-P13 treatment. In our analysis, 4.17% of patients reported IRRs. This is consistent with the incidence of IRRs reported in large observational studies of CT-P13 treatment in patients with IBD (2.56–9.37%) [12, 13, 15–17, 19, 23, 24], although definitions for IRRs are likely to vary between studies. The incidence of IRRs in our analysis was also similar to that of infusion or injection-site reactions in the Korean registry of patients with AS ($n = 10/244$; 4.10%) after up to 4 years of follow-up [26]. In addition, the incidence of IRRs in this analysis was lower than that described in the summary of product characteristics (SmPC) for reference infliximab of $\geq 1/10$ (very common) [8] when administered with concomitant immunosuppressant therapy as recommended. However, the case definition for IRR in this analysis differed from that used for reference infliximab in the SmPC: the observation interval post-administration was 1 day for CT-P13 versus 1 h in clinical studies for reference infliximab [8]. In the ADA-positive population in our analysis, 11.55% of patients experienced IRRs, suggesting a higher frequency of IRRs in ADA-positive patients. This would be consistent with findings for reference infliximab, as a two- to threefold increase in the frequency of IRRs is listed in the product information for ADA-positive patients [8]. However, the results of our analyses in the ADA-positive population should be interpreted with caution. The values may not be representative of the general population, as ADAs were not measured in all patients and were derived from studies where immunogenicity testing was optional, although the proportion of ADA-positive patients (30.17% of those with immunogenicity results) identified in our study was within the range reported in previous large observational studies of CT-P13 treatment [12, 15, 22, 24]. In addition, results of our analyses in the ADA-positive population are limited by the fact that patients in the ADA-positive population were also included in the safety population.

In this analysis, data cut-off was defined based on achievement of the target sample size in order to meet the objectives of the analysis rather than being aligned with the duration of treatment in the contributing observational studies. As such, data were obtained from annual or interim reports for ongoing studies. It is important to note that CT-P13 exposure duration was independent of study duration to discontinuation in this analysis. CT-P13 exposure duration was determined for all patients, including those who had discontinued treatment, completed treatment or were continuing treatment. Study duration to discontinuation was calculated only for patients who had discontinued prior to data cut-off; patients who were continuing or had completed therapy were not included. As such, study duration to discontinuation and CT-P13 exposure duration could differ for a given indication or analysis population.

This analysis included a large safety dataset collected systematically for 4393 patients who were administered CT-P13 under the conditions recommended in the authorised product information in observational studies. This sample size is sufficient to enable quantification of AEs occurring with a true frequency of approximately 1/1500 or greater. Thus, the frequency of uncommon AEs and a proportion of rare AEs can be estimated confidently using this dataset. However, any comparisons with published data for CT-P13 and reference infliximab should be made with caution because case definitions for AEs are likely to differ between studies, and other differences between study designs could

also influence the comparability of the data. Patients with CD, UC, AS and RA were well represented in the safety population, although there were relatively few patients with PsA/Ps, meaning that further safety analyses might be warranted in this indication. Adult patients comprised most of the safety population (96.79%), so the incidences and IRs of AEs following CT-P13 treatment identified in our analysis should be representative of those expected in adult patients treated in the long term in clinical practice. As only 141 paediatric patients (3.21%) were included in the overall safety population, a separate analysis of paediatric data could not be conducted and should be a focus of future research. In addition, the findings of our analysis are limited by the open-label, observational design of the six contributing studies, as there were no concurrent controls. However, the inclusion of 716 patients who switched treatment from reference infliximab to CT-P13 provides valuable information on the safety profile for patients making this switch in treatments, although none of the contributing studies were designed to assess the interchangeability of CT-P13 and reference infliximab. As such, no conclusions can be drawn from the current analysis regarding the safety of unrestricted switching between reference infliximab and CT-P13, or switching involving any other infliximab biosimilars or TNF inhibitors, or regarding the interchangeability of reference infliximab and CT-P13.

5 Conclusion

The IRs identified in this analysis for important safety concerns associated with CT-P13 administration, including serious infections, tuberculosis and other AESIs, should be representative of those observed in adult patients who are treated in clinical practice for the authorised indications of CT-P13 (RA, AS, PsA, Ps, UC or CD). Comparisons must be made cautiously, but the safety profile of CT-P13 appears consistent with that of reference infliximab. Overall, these results support the favourable risk/benefit balance for CT-P13 when administered under the conditions of use recommended in the authorised product information.

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Author Contributions SJL and KMB: made substantial contributions to the conception or design of study. All authors made a substantial contribution to the acquisition, analysis, and interpretation of the data and manuscript development and gave final approval of the manuscript for submission.

Data Availability Most of the data generated or analysed during this study are included in this published article (and its supplementary information files). Other datasets associated with the current study are not publicly available due to confidentiality but are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

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Conflict of interest SJL, KMB, SL, YJL, JEP, and SGL are employees of CELLTRION, Inc. (Incheon, Republic of Korea). SJL and KMB are shareholders in CELLTRION, Inc.

Ethical Approval This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and with all International Council for Harmonisation good clinical practice guidelines. In addition, all local regulatory requirements were followed. The final protocol, any amendments and informed consent documentation were reviewed and approved by the institutional review boards and/or independent ethics committees at each of the investigational centres participating in the study.

Informed Consent Informed consent was obtained from all individual participants included in the studies.

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