CLINICAL AT

Randomized Controlled Trial: Subcutaneous vs Intravenous Infliximab CT-P13 Maintenance in Inflammatory Bowel Disease

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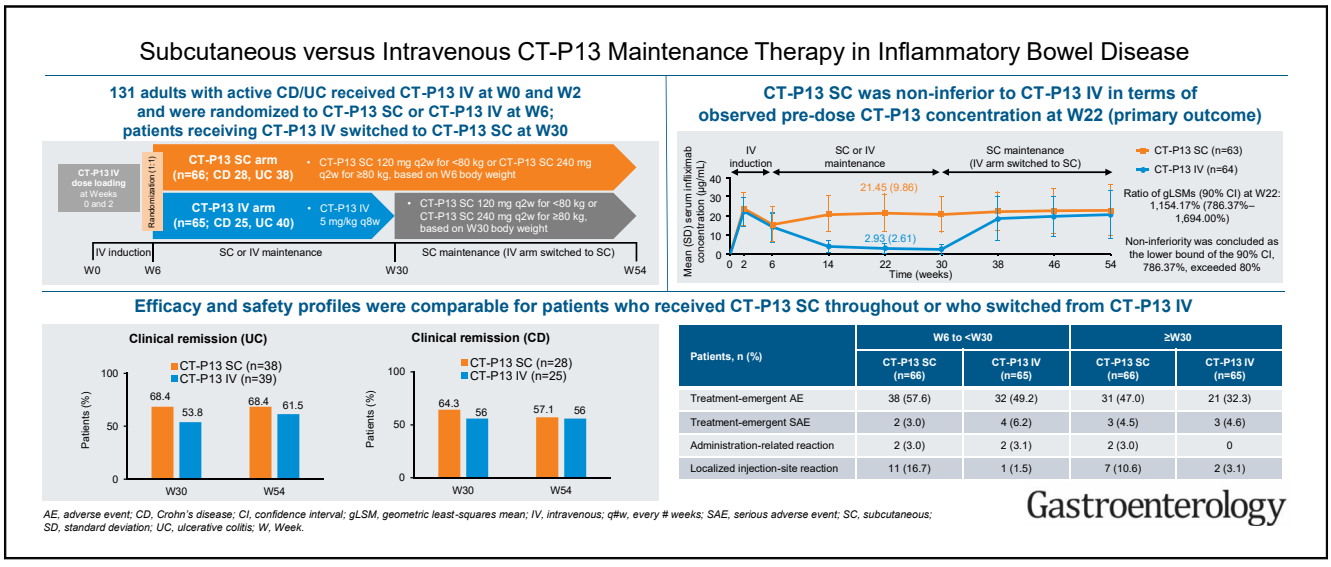

Patients, n (%)	W6 to <W30		≥W30	
	CT-P13 SC (n=66)	CT-P13 IV (n=65)	CT-P13 SC (n=66)	CT-P13 IV (n=65)
Treatment-emergent AE	38 (57.6)	32 (49.2)	31 (47.0)	21 (32.3)
Treatment-emergent SAE	2 (3.0)	4 (6.2)	3 (4.5)	3 (4.6)
Administration-related reaction	2 (3.0)	2 (3.1)	2 (3.0)	0
Localized injection-site reaction	11 (16.7)	1 (1.5)	7 (10.6)	2 (3.1)

AE, adverse event; CD, Crohn's disease; CI, confidence interval; gLSM, geometric least-squares mean; IV, intravenous; q#w, every # weeks; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation; UC, ulcerative colitis; W, Week.

See editorial on page 2244.

BACKGROUND & AIMS: This study compared pharmacokinetics, symptomatic and endoscopic efficacy, safety, and immunogenicity of a subcutaneous formulation of the infliximab biosimilar CT-P13 (CT-P13 SC) vs intravenous CT-P13 (CT-P13 IV) in patients with inflammatory bowel disease (IBD). **METHODS:** This randomized, multicenter, open-label, parallel-group, phase 1 study enrolled tumor necrosis factor inhibitor–naïve patients with active ulcerative colitis (total Mayo score 6–12 points with endoscopic subscore ≥2) or Crohn's disease (Crohn's Disease Activity Index 220–450 points) at 50 centers. After CT-P13 IV induction at Week (W) 0/W2, patients were randomized (1:1) to receive CT-P13 SC every 2 weeks (q2w) from W6 to W54 or CT-P13 IV every 8 weeks from W6 to W22. At W30, all patients receiving CT-P13 IV switched to CT-P13 SC q2w until W54. The primary endpoint was noninferiority of CT-P13 SC to CT-P13 IV for observed predose CT-P13 concentration at W22 ($C_{trough,W22}$), concluded if the lower bound of the 2-sided 90% confidence interval (CI) for the ratio of geometric least-squares means exceeded 80%. **RESULTS:** Overall, 66 and 65 patients were randomized to CT-P13 SC and CT-P13 IV, respectively. The primary endpoint of noninferiority was met with a geometric least-squares means ratio for $C_{trough,W22}$ of 1154.17% (90% CI 786.37–1694.00; n = 59 [CT-P13 SC]; n = 57 [CT-P13 IV]). W30/W54 clinical remission rates were comparable between arms. Other efficacy,

safety, and immunogenicity assessments were also broadly comparable between arms, including after switching. **CONCLUSIONS:** The pharmacokinetic noninferiority of CT-P13 SC to CT-P13 IV, and the comparable efficacy, safety, and immunogenicity profiles, support the potential suitability of CT-P13 SC treatment in IBD. ClinicalTrials.gov ID: NCT02883452.

Keywords: Crohn's disease; CT-P13; Infliximab; Subcutaneous; Ulcerative Colitis.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Subcutaneous infliximab (CT-P13 SC) could enable patients to self-administer infliximab therapy. This open-label, randomized, controlled trial evaluated CT-P13 SC maintenance in patients with active Crohn's disease and ulcerative colitis.

NEW FINDINGS

CT-P13 SC was noninferior to intravenous infliximab (CT-P13 IV) in terms of mean observed predose serum concentration at Week 22 ($C_{trough,W22}$). Efficacy and safety profiles were comparable between arms.

LIMITATIONS

Although the primary endpoint was objective, the open-label design limits interpretation of some findings. The study was powered for primary endpoint assessment: sample size was insufficient for secondary endpoint analyses.

IMPACT

CT-P13 SC could provide efficacious maintenance therapy for patients with active Crohn's disease or ulcerative colitis who are in need of infliximab treatment, with a tolerable safety profile.

Inflammatory bowel disease (IBD) is a heterogeneous group of chronic inflammatory disorders: the main phenotypes comprise ulcerative colitis (UC) and Crohn's disease (CD).[1,2] Biologic therapies, including tumor necrosis factor (TNF) inhibitors, have markedly affected IBD treatment.[3] Key treatment guidelines recommend TNF inhibitors, including infliximab, for the treatment of moderately to severely active UC and CD that have not responded to conventional therapy.[4–8] As reference product patents have expired, infliximab biosimilars have been developed and had increasing uptake for the treatment of IBD.[3] The infliximab biosimilar CT-P13, administered as an intravenous (IV) formulation (CT-P13 IV), has an established safety and efficacy profile in the treatment of IBD.[9–11]

A subcutaneous (SC) CT-P13 formulation has been developed,[10] containing 120 mg/mL infliximab, providing opportunities for CT-P13 self-administration and examination of the clinical impact of SC vs IV dosing schemes.[12] In terms of pharmacokinetics, IV-administered biologics lead to immediate drug exposure in the systemic circulation and high initial peak concentrations, compared with the slow absorption, incomplete bioavailability, and lower peak concentrations with SC-administered biologics.[13,14] However, SC biologics may benefit patients with IBD, including through improved ease of use increasing convenience, and reduced requirement for medical visits and associated travel.[15–18] SC biologics also offer potential benefits for health care systems, by optimizing medical resources and reducing associated costs.[19–21] Societal costs of IV biologic treatment, related to travel and loss of productivity, must also be considered.[21]

CT-P13 SC has received regulatory approval from the European Medicines Agency for all indications previously approved for CT-P13 IV, including IBD.[22] Given the differences in pharmacokinetic profile between IV and SC biologic administration, the CT-P13 SC clinical development program to date combines IV dose loading, to achieve high drug concentrations, with SC maintenance therapy, to create a constant exposure and minimize variation in serum concentration levels. During CT-P13 SC clinical development in IBD, Part 1 of the CT-P13 SC 1.6 study compared 54 weeks of treatment with CT-P13 IV (5 mg/kg every 8 weeks [q8w]) with either of 3 doses of CT-P13 SC (120, 180, or 240 mg every 2 weeks [q2w]) in 44 patients with active CD.[23,24] After 1 year of treatment, overall efficacy and safety profiles were comparable between CT-P13 SC and CT-P13 IV, although clinical remission rates were numerically higher in CT-P13 SC cohorts at week (W) 54.[23,24] Mean predose serum concentrations (C_{trough}) were higher for CT-P13 SC vs CT-P13 IV, and exceeded the 5 μg/mL target therapeutic concentration throughout the study.[23,24] Based on the proof-of-principle and dose-selection findings in Part 1, Part 2 was initiated: results are presented here. The primary objective of Part 2 was to demonstrate noninferiority of CT-P13 SC to CT-P13 IV, in terms of pharmacokinetics, in patients with active UC or CD. In addition, efficacy, pharmacodynamics, safety, and immunogenicity were evaluated up to W54. These parameters were evaluated for patients who received CT-P13 SC treatment up to W30 (after CT-P13 IV dose loading), compared with patients who received continued CT-P13 IV treatment. Comparisons also were made between patients who switched from CT-P13 IV to CT-

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Abbreviations used in this paper: **ADA, antidrug antibody; AE, adverse event; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDAI-70, decrease of ≥70 points from baseline in Crohn's Disease Activity Index score; CDAI-100, decrease of ≥100 points from baseline in Crohn's Disease Activity Index score; CI, confidence interval; CRP, C-reactive protein; C_{trough}, trough serum concentrations; $C_{trough,W22}$, predose serum concentration at Week 22; FC, fecal calprotectin; IBD, inflammatory bowel disease; IRR, infusion-related reaction; ISR, injection-site reaction; IV, intravenous; LSM, least-squares mean; NAb, neutralizing antibody; q#w, every # weeks; RA, rheumatoid arthritis; SC, subcutaneous; SIBDQ, Simplified Inflammatory Bowel Disease Questionnaire; SIR, systemic injection reaction; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TNF, tumor necrosis factor; UC, ulcerative colitis; W, week.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2021.02.068

P13 SC treatment at W30 and those who received CT-P13 SC up to W54.

Materials and Methods

Study Design

Part 2 of this open-label, randomized, multicenter, parallel-group phase 1 study (NCT02883452) was initiated following the independent Data Safety Monitoring Board review of data up to W30 from Part 1 of the study. Patients were screened at 62 hospitals and clinical study centers in 16 countries (Supplementary Table 1) and enrolled at 50 sites in 15 countries. During the induction/dose-loading phase (W0–W6), all patients received CT-P13 5 mg/kg IV at W0 and W2. At W6, patients who had received 2 full doses of CT-P13 IV without safety concerns (per investigator's judgment) were randomized (1:1) to CT-P13 SC or CT-P13 IV (see Supplementary Materials for details including stratification). During the maintenance phase (W6–W54), patients in the CT-P13 SC arm received CT-P13 120 mg (patients <80 kg) or 240 mg (patients ≥80 kg) SC q2w. Patients in the CT-P13 IV arm received CT-P13 5 mg/kg IV q8w from W6 until W22, when the primary endpoint was evaluated. Clinical observation following the randomized treatment period continued until W30 (ie, 8 weeks after the last CT-P13 IV dose). From W30, patients in the CT-P13 IV arm switched to receive CT-P13 SC q2w up to W54 (dose 120 mg or 240 mg for patients <80 kg or ≥80 kg, respectively). The end-of-study visit was 2 weeks after the last dose of CT-P13 SC, or 8 weeks after the last dose of CT-P13 IV (for patients who discontinued early and last received CT-P13 IV). The study protocol and ethics approval information are included in the Supplementary Materials. All authors had access to the study data and reviewed and approved the final manuscript.

Patients

Full inclusion and exclusion criteria are provided in the Supplementary Materials. Briefly, patients were aged 18 to 75 years with active UC or CD (defined in Supplementary Materials), had disease duration ≥3 months before first administration of study drug, were TNF inhibitor naïve, and had received no prior biologics for UC or CD. Patients with tuberculosis exposure or diagnosis were excluded. Patients had received conventional therapy for active UC (corticosteroids alone or in combination with thiopurines and 5-aminosalicylates) or CD (corticosteroids and/or immunomodulators) but had not responded despite an adequate course of therapy. Immunomodulators were allowed if stable doses were received for ≥8 weeks (thiopurines) or ≥6 weeks (methotrexate) before first administration of study drug (Day 0) and were maintained throughout the study.

Study Treatment

CT-P13 IV (5 mg/kg) was administered as a 2-hour (+15 minutes) IV infusion. CT-P13 SC was administered via prefilled syringe containing 120 mg CT-P13 SC. Patients <80 kg (at W6 [CT-P13 SC arm] or W30 [CT-P13 IV arm]) received 120 mg CT-P13 SC q2w via a single SC injection; patients ≥80 kg received 240 mg CT-P13 SC q2w via 2 SC injections. For patients receiving CT-P13 SC 120 mg q2w, dose escalation to CT-P13 SC 240 mg q2w was permitted from W30 if an initial response was lost (defined in the Supplementary Materials). CT-P13 SC injections were administered by a health care professional at each study center visit, or could be self-administered from W8, after adequate training. Patients could receive pre-medications 30 to 60 minutes before CT-P13 IV or CT-P13 SC treatment, including antihistamine, hydrocortisone, and/or paracetamol, at the discretion of the investigator.

Study Endpoints

The primary endpoint was a pharmacokinetic endpoint. Specifically, it was defined as noninferiority of observed predose concentration of CT-P13 at W22 ($C_{trough,W22}$) for CT-P13 SC vs CT-P13 IV. An additional exploratory endpoint was comparison of target therapeutic concentration of 5 μg/mL for mean predicted C_{trough}, which was defined as a conservative threshold to evaluate CT-P13 SC based on previous publications.[25,26] Secondary endpoints were to evaluate efficacy, pharmacokinetics, biomarker responses, and safety (including immunogenicity) of CT-P13 SC and CT-P13 IV over the first 30 weeks, and of CT-P13 SC (including switching results from the CT-P13 IV arm) up to W54.

Pharmacokinetic and Efficacy Assessments

Predose blood samples for pharmacokinetic assessment were obtained at all study visits from W0 to W54, including a pharmacokinetic monitoring visit occurring between W22 and W30 (Supplementary Table 2). Biomarker responses (C-reactive protein [CRP] and fecal calprotectin [FC]) were evaluated at all study visits (except pharmacokinetic monitoring visit). Serum infliximab levels were quantitatively measured using Meso Scale Discovery electrochemiluminescence (Meso Scale Diagnostics, LLC, Rockville, MD). Efficacy assessments (defined in the Supplementary Materials and conducted predose, where relevant) included Simplified Inflammatory Bowel Disease Questionnaire (SIBDQ), Mayo score (patients with UC only), or Simplified Endoscopic Activity Score for CD and Crohn's Disease Activity Index (CDAI) scores (patients with CD only). All endoscopy data included in the manuscript were by central review, conducted by independent reviewers blinded to treatment allocations using a paired read with adjudication algorithm.

Safety and Immunogenicity Assessments

Safety assessments (detailed in Supplementary Materials) included monitoring adverse events (AEs) and prior/concomitant medications throughout the study. AEs of special interest included administration-related reactions (classified as infusion-related reactions [IRRs; following CT-P13 IV administration], systemic injection reactions [SIRs; following CT-P13 SC administration], or delayed hypersensitivity reactions), localized injection-site reactions (ISRs), infection, and malignancy. Immunogenicity (antidrug antibody [ADA] and neutralizing antibody [NAb]) assays were also conducted (see Supplementary Materials).

Statistical Analyses

For the primary endpoint, a sample size of 104 patients (52 per arm) was determined to provide 90% power to demonstrate noninferiority of CT-P13 SC to CT-P13 IV based on the

95% 1-sided confidence interval (CI) for the geometric least-squares mean (LSM) ratio of $C_{trough,W22}$ for CT-P13 SC to CT-P13 IV. This assumed an 80% noninferiority margin, 5% 1-sided alpha level, expected ratio of 1.3, and percentage coefficient of variation of 100%. Considering a 20% dropout rate, a total of 130 patients would have been required. This target sample size was maintained per Data Safety Monitoring Board recommendation, based on data up to W30 in Part 1 of the study.

Analysis populations are described in the Supplementary Materials. The primary endpoint was assessed by analysis of covariance in patients who received all doses (full) of study drug before W22 in the pharmacokinetic population; noninferiority of CT-P13 SC to CT-P13 IV was concluded if the lower bound of the 2-sided 90% CI for the ratio of geometric LSMs was higher than 80%. A population pharmacokinetic model was used to estimate pharmacokinetic parameters for individual patients (except $C_{trough,W22}$) using a nonlinear mixed-effect pharmacokinetic model (see Supplementary Figures 1–5 and Supplementary Tables 3 and 4 in the Supplementary Materials). The pharmacokinetic parameters were obtained using both NONMEM, version 7.3.0 (ICON Development Solutions, Hanover, MD) and R software package, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). Post hoc exploratory statistical analyses were conducted to compare pharmacokinetics, efficacy, and safety between treatment arms, using the Student *t* test, Welch's *t* test, and Fisher's exact test. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

Results

Patient Disposition

Patients were screened between March 27, 2018, and August 8, 2018. Study visits took place between May 7, 2018, and October 2, 2019, and follow-up for all patients concluded on January 17, 2020, when the database was locked. Overall, 136 patients were enrolled and initiated the dose-loading phase (Figure 1). Five patients withdrew during the dose-loading phase. Thus, 131 patients (78 UC; 53 CD) entered the maintenance phase at W6, when 66 and 65 patients were randomized to CT-P13 SC and CT-P13 IV, respectively. Correspondingly, 11 (16.7%) and 15 (23.1%) patients discontinued the study between randomization and W54, most frequently due to disease progression (9 [34.6%] of 26 patients), defined as disease exacerbation lasting >8 weeks. The proportion of patients discontinuing study treatment between randomization and assessment of the primary endpoint at W22 was comparable between arms (CT-P13 SC: 7 [10.6%] patients; CT-P13 IV: 8 [12.3%] patients).

Baseline demographics, disease characteristics, and stratification factors were generally balanced between arms (Table 1); demographic characteristics were also well balanced by indication (Supplementary Table 5).

The proportion of patients discontinuing study treatment in the maintenance phase was relatively similar between arms for each indication, and between indications overall (Supplementary Figure 6).

Results up to W30

This section includes pharmacokinetics, efficacy, biomarker responses, and immunogenicity and safety data assessed up to W30 for the CT-P13 SC and CT-P13 IV arms.

Pharmacokinetics. For the primary outcome, mean (percentage coefficient of variation) observed $C_{trough,W22}$ was higher in the CT-P13 SC arm than in the CT-P13 IV arm (21.45 [45.98] μg/mL vs 2.93 [88.98] μg/mL) (Table 2). By analysis of covariance, the ratio of geometric LSMs (90% CI) was 1154.17% (786.37–1694.00), resulting in the lower bound of the 90% CI exceeding 80%, thereby meeting the primary outcome of noninferiority of CT-P13 SC compared with CT-P13 IV in terms of $C_{trough,W22}$. Mean observed $C_{trough,W22}$ exceeded the 5 μg/mL therapeutic target for patients receiving CT-P13 SC 120 or 240 mg, but this was below the threshold for patients receiving CT-P13 IV (Supplementary Table 6).

Mean predose serum infliximab concentrations were similar between arms during the dose-loading phase until W6, when patients in both arms received CT-P13 IV (Figure 2). From W6 onward, patients in the CT-P13 SC arm received CT-P13 SC treatment q2w. For the CT-P13 IV arm, mean predose serum infliximab concentrations gradually decreased up to W30 as the dosing interval increased (Figure 2). During the pharmacokinetic intense-monitoring period (W22–W30), at steady state, mean serum concentrations were relatively stable and minimally undulating in the CT-P13 SC arm (Figure S7). In contrast, during this 8-week intense-monitoring interval, mean serum concentrations in the CT-P13 IV arm reflected the q8w dosing (Supplementary Figure 7). As expected, highest values were observed immediately after the W22 infusion; thereafter, steeply decreasing until W30. In terms of secondary pharmacokinetic endpoints, after the dose-loading phase, mean predicted and observed C_{trough} were higher for CT-P13 SC vs CT-P13 IV up to W30 (Supplementary Table 7). Mean predicted C_{trough} in the CT-P13 SC arm consistently exceeded the target therapeutic concentration (5 μg/mL) during the steady-state period (W22–W30). Mean predicted maximum serum concentration after dose administration ($C_{max,ss}$) was lower for CT-P13 SC than CT-P13 IV at W22. Mean predicted area under the concentration–time curve exposure normalized to the 8-week interval from W22 to W30 (AUC_{ss8w}) was slightly higher for CT-P13 SC vs CT-P13 IV.

Clinical efficacy and biomarker response. For patients with UC, clinical response by partial Mayo score was similar between arms up to W30, with response rates not statistically significantly different at W30 in the CT-P13 SC vs CT-P13 IV arm (33 [86.8%] vs 29 [74.4%] patients, respectively; $P = .2501$) (Figure 3*A*). Clinical remission rates were also not statistically significantly different between arms up to W30, with remission rates at W22 of 23 (60.5%) and 15 (38.5%) patients in the CT-P13 SC and CT-P13 IV arms, respectively ($P = .0694$) (Figure 3*B*). The proportions of patients achieving clinical response (CT-P13 SC: 24 [63.2%] patients; CT-P13 IV: 17 [43.6%] patients; $P = .1113$) and clinical remission (CT-P13 SC: 17 [44.7%] patients; CT-P13 IV: 10 [25.6%] patients; $P = .0977$) according to total Mayo score were not statistically significantly

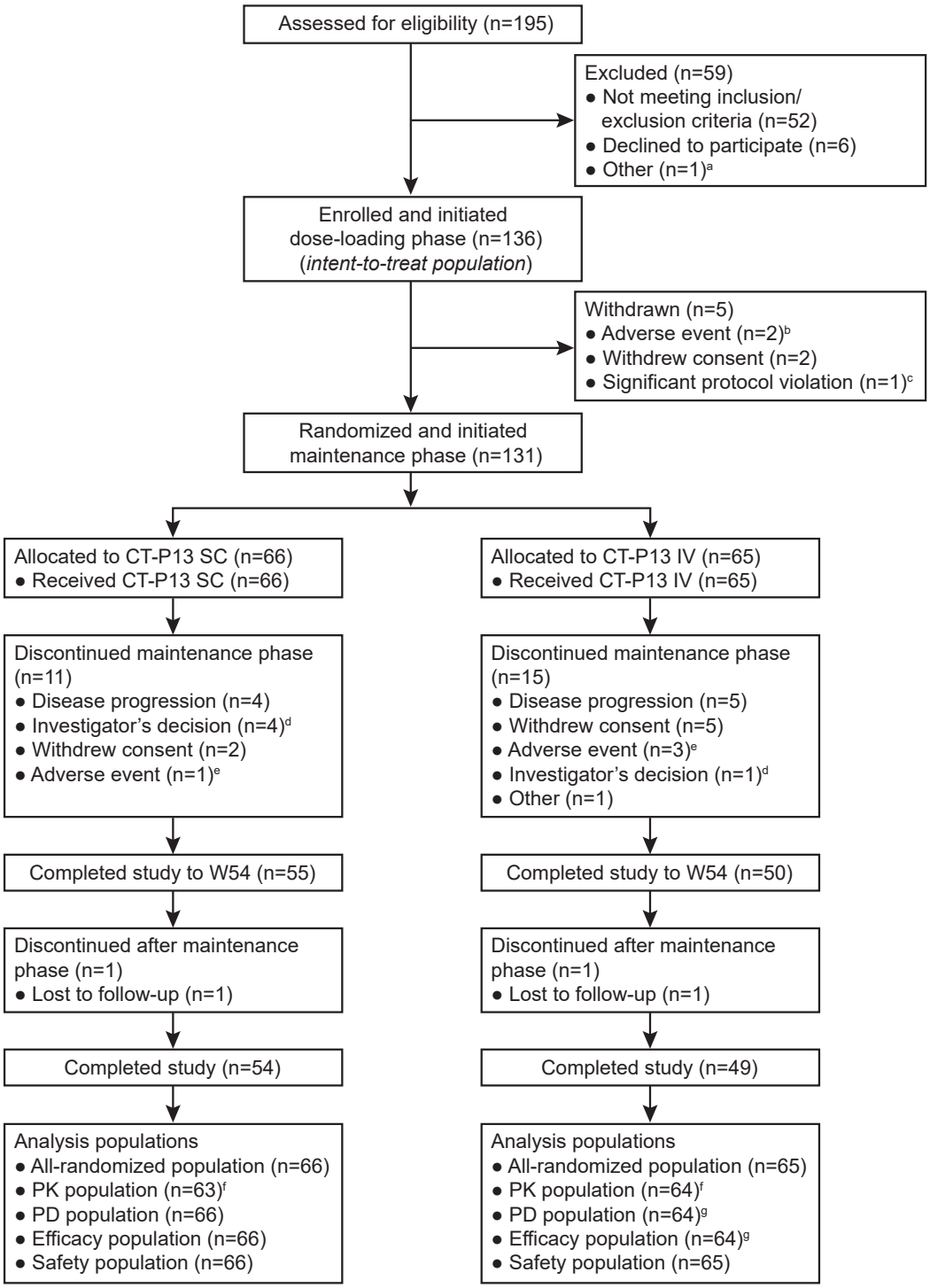

Figure 1. Patient disposition. PD, pharmacodynamic; PK, pharmacokinetic. [a]Patient failed to provide test results required for screening. [b]During the dose-loading phase, 2 patients discontinued due to AEs (CD aggravation and administration-related reaction). [c]Patient had previously received infliximab treatment; this information was received on the day of first study treatment administration. [d]Discontinuations were due to lack of efficacy or insufficient benefit from the treatment per investigator's decision. [e]During the maintenance phase, 1 patient in the CT-P13 SC arm discontinued after W50 study drug administration due to grade 3 non–small-cell lung cancer; 3 patients in the CT-P13 IV arm discontinued after W14 study drug administration due to grade 2 infusion-related reaction, grade 3 psoriasis, and grade 3 disseminated tuberculosis. [f]Four patients (3 CT-P13 SC arm; 1 CT-P13 IV arm) were excluded from the PK population due to absence of PK concentration results after W6 study drug administration due to early discontinuation. [g]One patient (CT-P13 IV arm) was excluded from the PD and efficacy populations due to absence of PD and efficacy evaluation results after W6 study drug administration due to early discontinuation.

Table 1. Baseline Patient Demographics and Disease Characteristics and Stratification Details (All-Randomized Population)

	CT-P13 SC (n = 66)	CT-P13 IV (n = 65)
Baseline patient demographics and disease characteristics		
Age (*y*), median (range)	33.0 (18–69)	36.0 (18–70)
Sex, n (%)		
Male	36 (54.5)	35 (53.8)
Female	30 (45.5)	30 (46.2)
Race, n (%)[a]		
Asian	3 (4.5)	4 (6.2)
White	62 (93.9)	60 (92.3)
Other	1 (1.5)	1 (1.5)
Ethnicity, n (%)		
Hispanic/Latino	3 (4.5)	0
Non-Hispanic/Non-Latino	62 (93.9)	65 (100.0)
Unknown	1 (1.5)	0
Screening height (*cm*), median (range)	170.00 (144.0–187.0)	171.00 (157.0–198.0)
Screening weight (*kg*), median (range)	66.10 (45.2–117.0)	69.00 (43.2–116.2)
Screening BMI (kg/m^2), median (range)	23.57 (16.40–34.94)	23.63 (15.31–38.28)
Time since IBD diagnosis (*y*), mean (SD)	5.70 (6.01)	5.85 (6.29)
CRP (*mg/dL*), mean (SD)[b]	0.81 (1.44)	0.98 (1.67)
FC (*μg/g*), mean (SD)[b]	2094.2 (4114.17)	2605.2 (8757.77)
Total Mayo score (patients with UC), mean (SD)[c]	7.9 (1.60)	8.2 (1.66)
Partial Mayo score (patients with UC), mean (SD)[c]	5.4 (1.31)	5.9 (1.21)
CDAI score (patients with CD), mean (SD)[d]	296.38 (59.21)	294.75 (59.90)
SES-CD score (patients with CD), mean (SD)[d]	10.86 (8.28)	8.06 (5.82)
SIBDQ score, mean (SD)		
UC[c]	38.1 (9.91)	34.8 (10.89)
CD[d]	37.1 (12.73)	37.8 (11.37)
Patients receiving concomitant corticosteroids indicated for UC/CD treatment, n (%)[e]	22 (33.3)	25 (38.5)
Stratification factors		
Current treatment with 6-MP, AZA, or MTX, n (%)		
Used	29 (43.9)	29 (44.6)
Not used	37 (56.1)	36 (55.4)
Disease, n (%)		
UC	38 (57.6)	40 (61.5)
CD	28 (42.4)	25 (38.5)
Clinical response at W6, n (%)[f]		
Responder	49 (74.2)	52 (80.0)
Nonresponder	17 (25.8)	13 (20.0)
Body weight at W6, n (%)		
<80 kg	48 (72.7)	45 (69.2)
≥80 kg	18 (27.3)	20 (30.8)

6-MP, 6-mercaptopurine; AZA, azathioprine; BMI, body mass index; MTX, methotrexate; PD, pharmacodynamic; SD, standard deviation; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease.
[a]No patients were Black.
[b]Evaluated in the PD population.
[c]Evaluated in the efficacy population—UC.
[d]Evaluated in the efficacy population—CD.
[e]Evaluated in the safety population.
[f]Assessed using partial Mayo score (≥2-point decrease in partial Mayo score with accompanying ≥1-point decrease in rectal bleeding subscore or an absolute rectal bleeding subscore of 0 or 1) for patients with UC and CDAI-70 (≥70-point decrease in CDAI score) for patients with CD.

Table 2. Observed $C_{trough,W22}$ of Infliximab as Assessed by ANCOVA (PK Population)

	CT-P13 SC (n = 63)	CT-P13 IV (n = 64)
n	59[a,b]	57[a,c]
Median (range)	21.80 (0.10–54.40)	2.45 (0.10–9.17)
Mean (SD)	21.45 (9.86)	2.93 (2.61)
%CV	45.98	88.98
Geometric mean	16.98	1.49
Geometric LSM	20.98	1.82
Ratio of geometric LSMs (90% CI)[d]	1154.17% (786.37%–1694.00%)	

NOTE. Concentrations below the lower limit of quantification were set equal to the lower limit of quantification.
%CV, percent coefficient of variation; 6-MP, 6-mercaptopurine; ANCOVA, analysis of covariance; AZA, azathioprine; $C_{trough,W22}$, pre-dose serum concentration at W22; MTX, methotrexate; PK, pharmacokinetic; SD, standard deviation.
[a]One patient was excluded from the analysis due to not receiving all full doses of study drug before W22.
[b]Three patients were excluded from the analysis due to study discontinuation before W22.
[c]Six patients were excluded from the analysis due to study discontinuation before W22.
[d]Analyzed by ANCOVA with treatment as a fixed effect. Covariates were current use of treatment with 6-MP, AZA, or MTX (used vs not used), indication (CD vs UC), clinical response at W6 (responder vs nonresponder), and body weight at W6 (<80 vs ≥80 kg).

different in the CT-P13 SC vs CT-P13 IV arm at W22 (Supplementary Table 8). The proportion of patients achieving mucosal healing (endoscopic improvement) was not significantly different between the CT-P13 SC and CT-P13 IV arms at W22 (18 [47.4%] vs 12 [30.8%] patients; $P = .1646$) (Supplementary Table 8). Similar levels of improvement in mean scores on the SIBDQ were observed in both arms up to W30 (Supplementary Table 9).

For patients with CD, mean CDAI scores and the proportions of patients achieving clinical response (by CDAI-100, a decrease of ≥100 points from baseline in CDAI score) and clinical remission were all similar between arms up to W30 (Figure 3*C* and *D*; Supplementary Table 10). Simplified Endoscopic Activity Score for Crohn's Disease scores decreased to similar values in each arm at W22 (Supplementary Table 11). The proportions of patients achieving endoscopic response or endoscopic remission were not statistically significantly different in the CT-P13 SC vs CT-P13 IV arm at W22 (endoscopic response: 78.6% [n = 11/14] vs 42.9% [n = 3/7]; $P = .1564$; endoscopic remission: 35.7% [n = 5/14] vs 14.3% [n = 1/7]; $P = .6126$) (Supplementary Table 8). Similar levels of improvement in mean SIBDQ scores were observed in both arms up to W30 (Supplementary Table 9).

During the dose-loading phase, mean CRP concentration decreased from baseline to W2 in both arms (Supplementary Figure 8*A*). In general, the low CRP concentration was maintained until W30. CRP concentrations were not statistically significantly different in the CT-P13 IV vs CT-P13 SC arm during the maintenance phase up to W30, except for a higher CRP level in the CT-P13 IV vs CT-P13 SC arm at W14 ($P = .0279$). Mean FC concentration decreased from baseline to W2; low levels were maintained up to W30

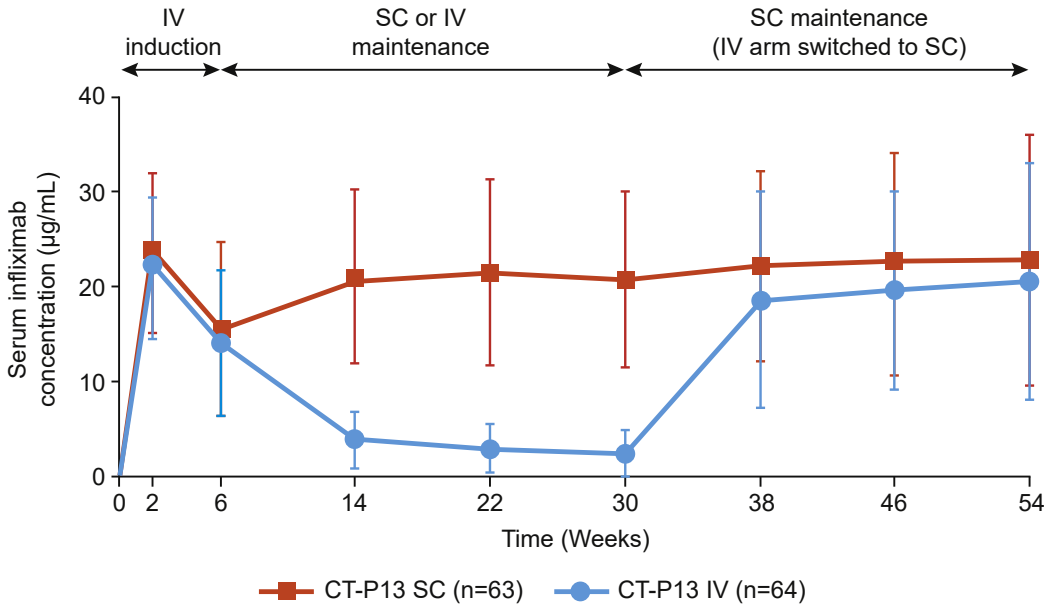

Figure 2. Mean (±SD) predose serum infliximab concentration[a] for CT-P13 SC and CT-P13 IV arms (PK population). PK, pharmacokinetic; SD, standard deviation. [a]Concentrations below the lower limit of quantification (BLQ) before W0 were set to zero; other concentrations BLQ were set to the lower limit of quantification.

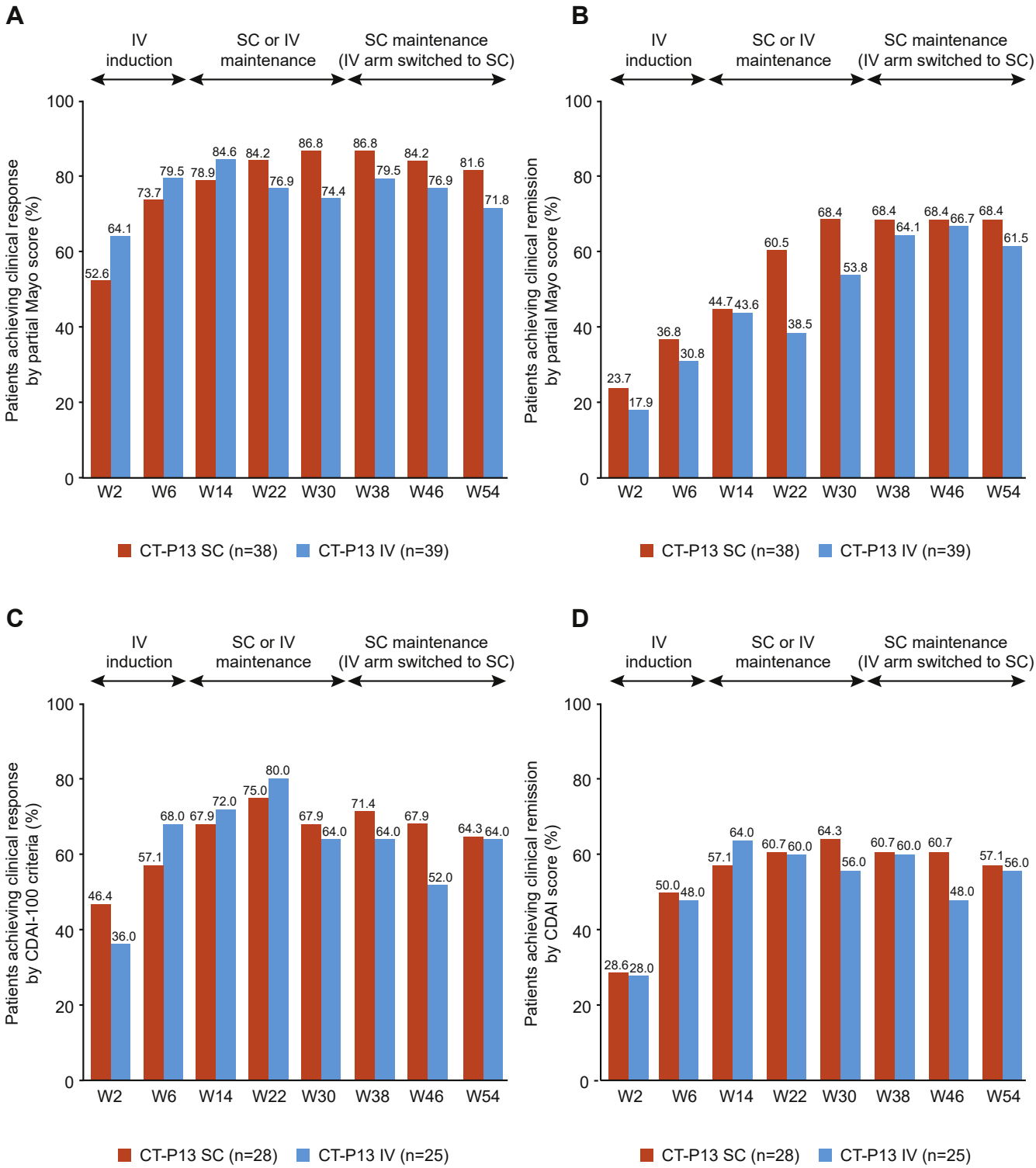

Figure 3. Clinical response and remission rates in patients with CD and UC. (*A*) Proportion of patients achieving clinical response by partial Mayo score (efficacy population—UC). (*B*) Proportion of patients achieving clinical remission by partial Mayo score (efficacy population—UC). (*C*) Proportion of patients achieving clinical response by CDAI-100 criteria (efficacy population—CD). (*D*) Proportion of patients achieving clinical remission by CDAI score (efficacy population—CD).

to a comparable degree in both arms (Supplementary Figure 8*B*).

Immunogenicity. In both arms, the proportion of ADA-positive patients increased after the dose-loading phase. The proportion of ADA-positive patients was not statistically significantly different in the CT-P13 SC arm compared with the CT-P13 IV arm up to W30 (W14: $P = .3197$; W22: $P = .0510$; W30: $P = .0805$; Supplementary Table 12). At W22,

Table 3. Summary of TEAEs During the Maintenance Phase (Safety Population)

	W6 to <W30		≥W30	
	CT-P13 SC (n = 66)	CT-P13 IV (n = 65)	CT-P13 SC (n = 66)	CT-P13 IV (n = 65)
Total number of TEAEs	111	80	121	58
Patients with ≥1 TEAE, n (%)	38 (57.6)	32 (49.2)	31 (47.0)	21 (32.3)
Study drug-related	22 (33.3)	15 (23.1)	13 (19.7)	12 (18.5)
Study drug-unrelated	26 (39.4)	27 (41.5)	27 (40.9)	13 (20.0)
Total number of TESAEs	2	4	3	5
Patients with ≥1 TESAE, n (%)	2 (3.0)	4 (6.2)	3 (4.5)	3 (4.6)
Study drug-related	0	1 (1.5)[a]	1 (1.5)[b]	2 (3.1)[c]
Study drug-unrelated	2 (3.0)	3 (4.6)	2 (3.0)	2 (3.1)
Total number of TEAEs leading to study drug discontinuation	0	3	1	0
Patients with ≥1 TEAE leading to study drug discontinuation, n (%)	0	3 (4.6)	1 (1.5)	0
Study drug-related	0	3 (4.6)	1 (1.5)	0
Total number of TEAEs classified as IRR	N/A	2	N/A	N/A
Patients with ≥1 TEAE classified as IRR, n (%)	N/A	2 (3.1)	N/A	N/A
Total number of TEAEs classified as SIR	1	N/A	1	0
Patients with ≥1 TEAE classified as SIR, n (%)	1 (1.5)	N/A	1 (1.5)	0
Total number of TEAEs classified as delayed hypersensitivity	1	0	1	0
Patients with ≥1 TEAE classified as delayed hypersensitivity, n (%)	1 (1.5)	0	1 (1.5)	0
Total number of TEAEs classified as localized ISR	25	1	25	13
Patients with ≥1 TEAE classified as localized ISR, n (%)	11 (16.7)	1 (1.5)	7 (10.6)	2 (3.1)
Total number of TEAEs classified as infection	15	12	19	12
Patients with ≥1 TEAE classified as infection, n (%)	11 (16.7)	11 (16.9)	12 (18.2)	9 (13.8)
Total number of TEAEs classified as malignancy	0	0	1	0
Patients with ≥1 TEAE classified as malignancy, n (%)	0	0	1 (1.5)	0

N/A, not applicable.
[a]One patient with UC experienced a grade 3 TESAE of disseminated tuberculosis after W14; the event recovered after treatment, but the patient was withdrawn from the study.
[b]One patient with CD experienced a grade 3 TESAE of non–small-cell lung cancer after W50; the event led to study treatment discontinuation.
[c]One patient with UC experienced both a grade 3 TESAE of pneumonia after W32 and a grade 3 TESAE of bronchitis after W52, and another patient experienced a grade 3 TESAE of spontaneous abortion after W54.

the time point for the primary endpoint evaluation, a greater proportion of patients in the CT-P13 IV vs CT-P13 SC arm were NAb positive.

Safety. Table 3 shows safety findings for the maintenance phase. During the first part of the maintenance phase (W6 to <W30), treatment-emergent adverse events (TEAEs) were reported by 38 (57.6%) and 32 (49.2%) patients in the CT-P13 SC and CT-P13 IV arms, respectively ($P = .3833$), with study drug–related TEAEs reported by 22 (33.3%) and 15 (23.1%) patients, respectively ($P = .2448$; Table 3). Treatment-emergent serious adverse events (TESAEs) were reported by 2 (3.0%) and 4 (6.2%) patients in the CT-P13 SC and CT-P13 IV arms, respectively ($P = .4403$). TEAEs leading to study drug discontinuation were reported by 3 (4.6%) patients in the CT-P13 IV arm only. No deaths were reported during the study.

Considering AEs of special interest, IRRs were reported for 2 (3.1%) patients in the CT-P13 IV arm during the maintenance phase before W30 (Table 3). Patients were ADA and NAb positive at IRR occurrence in both cases. Both events were grade 2 in intensity; 1 IRR, occurring during W14 of study drug infusion, led to the patient being withdrawn from the study. One (1.5%) patient in the CT-P13 SC arm reported an SIR (grade 1 in intensity) during the maintenance phase before W30 (Table 3). This patient reported the SIR following the W20 injection; the ADA and

NAb results measured at W22 were positive and negative, respectively. One (1.5%) patient in the CT-P13 SC arm reported delayed hypersensitivity during this period (Table 3). The event was grade 1 in intensity and occurred 2 days after W6 study drug injection; the patient was ADA negative at occurrence. Localized ISRs, all grade 1–2 in intensity, were reported by a greater proportion of patients in the CT-P13 SC vs CT-P13 IV arm (11 [16.7%] vs 1 [1.5%] patients) (Table 3).

Similar proportions of patients in the CT-P13 SC and CT-P13 IV arms experienced TEAEs of infection during the maintenance phase before W30: 11 (16.7%) and 11 (16.9%), respectively. Most infections were grade 1 to 2 in intensity.

Local site pain was higher in the CT-P13 SC vs CT-P13 IV arm at W6, when these patients received the first SC injection (Supplementary Table 13). Local site pain generally decreased with repeated CT-P13 SC administration and remained fairly consistent in the CT-P13 IV arm up to W22.

Results After W30

This section includes pharmacokinetics, efficacy, biomarker responses, and immunogenicity and safety data assessed after W30 for patients in the CT-P13 SC arm, who continued CT-P13 SC treatment, and for patients in the CT-P13 IV arm, who switched to CT-P13 SC treatment from W30.

Pharmacokinetics. After switching to CT-P13 SC at W30, mean predose serum CT-P13 concentrations in the CT-P13 IV arm increased and, from W38 onward, became similar to those in the CT-P13 SC arm (Figure 2). In addition, observed C_{trough} was similar between arms after patients in the CT-P13 IV arm switched to CT-P13 SC; the difference in concentrations between arms continued to decrease during the subsequent treatment period (Supplementary Table 7).

Clinical efficacy and biomarker response. For patients with UC, the proportions of patients achieving clinical response (CT-P13 SC: 31 [81.6%] patients; CT-P13 IV: 28 [71.8%] patients; W54) and clinical remission (CT-P13 SC: 26 [68.4%] patients; CT-P13 IV: 24 [61.5%] patients; W54) by partial Mayo score were similar between arms up to W54 (Figure 3*A* and *B*). The proportions of patients achieving clinical response and remission according to total Mayo score were similar between arms at W54 (Supplementary Table 8). A similar proportion of patients in each arm achieved mucosal healing (endoscopic improvement) at W54 (CT-P13 SC: 21 [55.3%] patients; CT-P13 IV: 22 [56.4%] patients) (Supplementary Table 8). Improvements in mean SIBDQ scores were similar between arms throughout (Supplementary Table 9).

For patients with CD, mean CDAI scores were generally comparable between arms up to W54 (Supplementary Table 10). The proportions of patients achieving clinical response (by CDAI-100) and clinical remission were also similar between arms after patients in the CT-P13 IV arm switched to CT-P13 SC at W30 (Figure 3*C* and *D*). The proportions of patients achieving endoscopic response and remission were similar between arms at W54 (Supplementary Table 8). The improvement in mean scores on the SIBDQ was similar between arms up to W54 (Supplementary Table 9).

Mean CRP concentrations were similar between arms after patients in the CT-P13 IV arm switched to CT-P13 SC treatment at W30, and were maintained at a consistent level in both arms until W54 (Supplementary Figure 8*A*). Mean FC concentrations remained similar between arms between W30 and W54 (Supplementary Figure 8*B*).

Immunogenicity. The proportion of ADA-positive patients gradually increased in the CT-P13 SC arm throughout the study and did not increase in the CT-P13 IV arm after switching to CT-P13 SC. From W38 to W54, the proportions of ADA-positive patients were not statistically significantly different for the CT-P13 IV vs CT-P13 SC arm (W38: $P = .8603$; W46: $P = .1576$; W54: $P = .3787$) (Supplementary Table 12). During the entire study from W0 to W54, similar proportions of patients in each arm converted to ADA-positive status (CT-P13 SC: 69.7% [n = 46/66]; CT-P13 IV: 63.5% [n = 40/63]). A smaller proportion of patients in the CT-P13 SC arm converted to NAb-positive status compared with the CT-P13 IV arm: 18.2% (n = 12/66) vs 36.9% (n = 24/65), respectively ($P = .0194$).

Safety. After the switch from CT-P13 IV to CT-P13 SC at W30, treatment was well maintained in the CT-P13 IV arm, as it was with patients receiving CT-P13 SC throughout. On and after W30, TEAEs were reported by 31 (47.0%) and 21 (32.3%) patients in the CT-P13 SC and CT-P13 IV arms, respectively ($P = .1085$), whereas 13 (19.7%) and 12 (18.5%) patients, correspondingly, reported study drug–related TEAEs (Table 3). Similar proportions of patients reported TESAEs in each arm (CT-P13 SC: 3 [4.5%] patients; CT-P13 IV: 3 [4.6%] patients). One (1.5%) patient in the CT-P13 SC arm experienced a TEAE leading to study drug discontinuation.

No patients in the CT-P13 IV arm experienced SIRs or delayed hypersensitivity after switching to CT-P13 SC. One (1.5%) patient in the CT-P13 SC arm experienced a grade 1 SIR at W52; the patient was ADA negative throughout the study. In addition, 1 (1.5%) patient in the CT-P13 SC arm reported delayed hypersensitivity 1 day after W52 study drug administration. The event was grade 1 in intensity; W46 and W54 ADA results were positive, whereas NAb results were negative. The proportion of patients in the CT-P13 SC arm reporting localized ISRs on and after W30 (7 [10.6%] patients) was not statistically significantly different from the CT-P13 IV arm (2 [3.1%] patients; $P = .1645$). Infections were reported at a comparable frequency between arms (CT-P13 SC: 12 [18.2%] patients; CT-P13 IV: 9 [13.8%] patients).

As anticipated, local site pain increased in the CT-P13 IV arm at W30, when patients switched to CT-P13 SC treatment (Supplementary Table 13). In general, local site pain decreased with repeated CT-P13 SC administration up to W54.

Safety findings for the overall treatment period are shown in Supplementary Table 14. During the maintenance phase as a whole, the most frequent TEAEs were localized ISRs, UC (ie, disease aggravation), neutropenia, and rash

(Supplementary Table 15). As anticipated, localized ISRs were reported by a greater proportion of patients in the CT-P13 SC vs CT-P13 IV arm (15 [22.7%] vs 3 [4.6%] patients). Most TEAEs were grade 1 to 2 in intensity; study drug–related grade 3 TEAEs were reported by 2 (3.0%) and 7 (10.8%) patients in the CT-P13 SC and CT-P13 IV arms, respectively. Grade 4 TEAEs were reported by 2 (3.0%) and 1 (1.5%) patients in the CT-P13 SC and CT-P13 IV arms, respectively, comprising neutropenia (1 patient per arm) and appendicitis (CT-P13 SC); all were considered unrelated to study drug.

There were no notable differences between arms or any new safety findings in clinical laboratory results, vital sign measurements, or electrocardiogram results.

Discussion

In this study, the pharmacokinetic noninferiority of CT-P13 SC to CT-P13 IV was demonstrated because the lower bound of the 90% CI for the geometric LSM observed $C_{trough,W22}$ exceeded the lower bound of the predefined noninferiority margin. As such, the primary endpoint was met. In addition, clinical efficacy, biomarker responses, and safety and immunogenicity profiles were broadly comparable between the CT-P13 SC and CT-P13 IV arms, including following a switch at W30 to CT-P13 SC treatment for patients in the CT-P13 IV arm.

Our findings build on those previously reported from Part 1 of the study, which was designed to find the optimal dose of CT-P13 SC in patients with active CD with comparison to CT-P13 IV treatment.[23,24] In line with findings from Part 1 of the study,[23,24] mean predicted C_{trough} consistently exceeded the target therapeutic concentration (5 μg/mL) in the CT-P13 SC arm in Part 2. In terms of mean observed $C_{trough,W22}$, the higher value in the CT-P13 SC arm vs the CT-P13 IV arm was not only due to the inclusion of patients receiving the 240 mg dose, as mean $C_{trough,W22}$ for patients receiving 120 mg (19.83 μg/mL) still exceeded the concentration in the CT-P13 IV arm (2.93 μg/mL) (Supplementary Table 6). The relatively stable mean serum concentrations observed at steady state with CT-P13 SC treatment were as anticipated based on the pharmacokinetic properties of the SC formulation.[27] Mean observed C_{trough} consistently exceeded the target after patients in the CT-P13 IV arm switched to CT-P13 SC at W30. The increased C_{trough} for CT-P13 SC vs CT-P13 IV may be postulated to translate into higher efficacy. However, given higher peak serum concentrations with CT-P13 IV vs CT-P13 SC, the overall drug exposure was ultimately comparable between arms. In addition, it is currently unknown which pharmacokinetic parameter is most critical for conferring the biological and immunological effect of the drug. In our study, the differences in secondary pharmacokinetic parameters (C_{trough} and $C_{max,ss}$) between arms were as expected given the different administration routes and dosing schedules.[13] Alongside dose and schedule, bioavailability also affects C_{trough}; reported bioavailability for CT-P13 SC is approximately 60%.[12,27] Our findings illustrate the potential benefits of CT-P13 SC in terms of providing remarkably stable systemic exposure, with C_{trough} maintained above the target therapeutic concentration, when administered more frequently and at a lower dosage than CT-P13 IV. For comparison, CT-P13 IV maintenance dosing generated a larger difference between C_{max} and C_{trough}; however, the proposed dosing scheme for CT-P13 SC led to efficacy findings similar to those with CT-P13 IV. The potential pharmacokinetic benefits of CT-P13 SC are also supported by the higher mean C_{trough} and consistent exceeding of the target therapeutic concentration (1 μg/mL) for patients with rheumatoid arthritis (RA) receiving CT-P13 SC compared with CT-P13 IV.[28,29]

Clinical response and remission rates and SIBDQ scores for both indications were generally comparable between arms throughout, and our efficacy findings were similar to historical data for reference infliximab.[30] Our clinical and endoscopic response and remission findings are limited by the relatively higher rate of missing endoscopy data for patients with UC in the CT-P13 IV vs CT-P13 SC arm and the small number of evaluable patients. Following the switch from CT-P13 IV to CT-P13 SC treatment at W30, findings for these efficacy parameters remained similar between arms. The similarity at W54 suggests comparable efficacy between sustained treatment with CT-P13 SC and CT-P13 IV treatment followed by a switch to CT-P13 SC, in patients with either UC or CD. This conclusion is also supported by the similarity in biomarker responses between arms throughout.

In this study, overall safety was comparable between arms, as previously demonstrated in patients with RA who received CT-P13 SC or CT-P13 IV treatment.[28,29] The proportions of patients reporting TEAEs overall (75.8% and 64.6% in the CT-P13 SC and CT-P13 IV arms, respectively) were comparable to those previously reported for patients with CD treated with CT-P13 IV or reference infliximab (including switching between these treatments) in the PLANETCD study, in which 67% of patients reported TEAEs overall.[9] With reference to the known safety profile of infliximab,[30,31] there were no new safety findings in this study.

Treatment was well maintained both for patients in the CT-P13 SC arm who continued CT-P13 SC treatment up to W54, and for patients in the CT-P13 IV arm whose treatment was switched from CT-P13 IV to CT-P13 SC at W30. Following the switch in the CT-P13 IV arm, similar proportions of patients in each arm reported study drug–related TEAEs and TESAEs. In addition, despite the prevailing view that SC formulations pose an increased risk of ADA formation,[32] the overall immunogenicity results demonstrated that CT-P13 SC was not more immunogenic than CT-P13 IV. Similar immunogenicity between CT-P13 SC and CT-P13 IV has been demonstrated in a larger study in patients with RA.[29] Similar immunogenicity was also observed with SC- and IV-administered vedolizumab in the VISIBLE 1 study.[33] Various explanations are possible, including high zone tolerance, designating immune tolerance induced by high concentrations of the antigen (here the monoclonal antibody) and/or favorable drug–TNF ratios leading to reduced immune complex formation and

diminished ADA generation.[34–36] Nevertheless, our findings suggest that switching from CT-P13 IV to CT-P13 SC during maintenance therapy does not result in increased immunogenicity relative to continuing maintenance therapy with CT-P13 SC.

The incidence of study drug administration-related reactions (IRRs, SIRs, and delayed hypersensitivity) during the whole study treatment period was low (5 [7.6%] and 3 [4.6%] patients in CT-P13 SC and CT-P13 IV arms, respectively, in total). These incidences are comparable with or lower than the ≥10% reported for IRRs in the Summary of Product Characteristics for reference infliximab[30] and the pooled estimates of 5% (95% CI 3%–9%) and 11% (95% CI 5%–23%) for the incidence of infusion reactions in a meta-analysis of studies evaluating CT-P13 treatment in biologic-naïve patients with UC and CD, respectively.[11] Localized ISRs were the most frequent TEAE reported during the full maintenance phase and, as expected, were more common in the CT-P13 SC arm. The higher incidence of localized ISRs in the CT-P13 SC vs CT-P13 IV arm is in keeping with an SC mode of biologic administration, and echoed by the higher frequency of ISRs reported with SC vedolizumab compared with IV vedolizumab in the VISIBLE 1 study.[33]

The interpretation of our findings is limited by the open-label study design; however, the primary endpoint was objective, and endoscopic assessments, performed by independent central review, were comparable between arms, albeit with small numbers of patients. Due to the size of the study population, the study was also underpowered to sufficiently evaluate the secondary clinical and immunogenicity outcomes, meaning that differences between arms may not have been detected due to type 2 error. The ongoing CT-P13 SC 3.7 and CT-P13 SC 3.8 studies, which are evaluating CT-P13 SC maintenance therapy (vs placebo SC) in patients with active UC and CD, respectively, will provide further data regarding CT-P13 SC treatment in patients with IBD.[37,38] In the present study, the efficacy and safety of a single switch of maintenance treatment from CT-P13 IV to CT-P13 SC has been demonstrated in TNF inhibitor–naïve patients with IBD. These findings are in line with the comparable efficacy and safety demonstrated for patients with RA after 1 year of therapy in a phase 1/3 randomized controlled trial, for patients who switched maintenance therapy from CT-P13 IV to CT-P13 SC at W30, compared with those who received CT-P13 IV throughout.[29] However, further studies evaluating treatment in TNF inhibitor–experienced patients and multiple- or cross-switching between CT-P13 IV and CT-P13 SC might be valuable.

In conclusion, this study demonstrated the non-inferiority of CT-P13 SC to CT-P13 IV in terms of pharmacokinetics (assessed by $C_{trough,W22}$) in patients with active IBD. Infliximab trough levels achieved with CT-P13 SC treatment were consistently maintained above the target therapeutic concentration throughout the study, independently of whether patients had received CT-P13 SC directly after dose loading or had switched to CT-P13 SC at W30 to continue maintenance therapy. Efficacy, safety, and immunogenicity outcomes did not differ between patients receiving CT-P13 SC or the licensed infliximab biosimilar CT-P13 IV. Furthermore, efficacy and safety profiles were comparable between patients who had received CT-P13 SC throughout (after CT-P13 IV dose loading) and those who had switched from CT-P13 IV to CT-P13 SC treatment at W30. These findings support the novel CT-P13 SC formulation as a suitable therapeutic agent to expand and improve treatment options for patients with IBD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online, version of *Gastroenterology* at www.gastrojournal.org, and at, https://doi.org/10.1053/j.gastro.2021.02.068.

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Received September 23, 2020. Accepted February 28, 2021.

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Acknowledgments
The authors thank all study investigators, staff, and patients who contributed to this study. Supplementary Table 1 presents all principal investigators who participated in the study. Selected data up to Week 30 of the study were presented as a late-breaking abstract at United European Gastroenterology (UEG) Week 2019 (October 19–23, 2019, Barcelona, Spain). Selected data up to Week 54 were presented in an oral presentation at the European Crohn's and Colitis Organisation (ECCO) Congress 2020 (February 12–15, 2020, Vienna, Austria) and were presented in an oral presentation at Digestive Disease Week (DDW) 2020 (May 5, 2020, online).

Medical writing support, including support in the development of a draft outline and subsequent drafts in consultation with the authors, collating author comments, copyediting, fact checking, and referencing, was provided by Beatrice Tyrrell, DPhil at Aspire Scientific Limited (Bollington, UK). Funding for medical writing support for this article was directly provided by Celltrion, Inc. (Incheon, Republic of Korea).

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Conflict of interest
These authors disclose the following: Stefan Schreiber has received personal fees from AbbVie, Arena, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Inc., Falk, Fresenius, Gilead, IMAB, Janssen, MSD, Mylan, Pfizer, Protagonist, Provention Bio, Takeda, and Theravance outside the submitted work. Shomron Ben-Horin has received consultancy/advisory board fees from AbbVie, Celltrion, Falk, Ferring, GSK, Janssen, Pfizer, and Takeda, and research support from AbbVie, Celltrion, Janssen, Pfizer, and Takeda. Jaroslaw Leszczyszyn has received speaker's fees from Astra Zeneca, MSD, and Janssen. Robert Dudkowiak has received investigator fees from AbbVie, Ferring, GSK, Janssen, and Pfizer. Adi Lahat has received consultancy or advisory board fees from AbbVie, Celltrion, and Takeda. Beata Gawdis-Wojnarska has received fees from Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Inc., Gilead, Harbor, Janssen, Pfizer, Shire, Takeda, and Theravance. Aldis Pukitis has served as a consultant for AbbVie, Johnson & Johnson, and Takeda. Katalin Farkas has received advisory board fees from Bayer. Jaroslaw Kierkus has received consultation fees, research grants, or honoraria from AbbVie, Egis, Janssen, Nestlé, Nutricia, and Takeda. Sang Joon Lee, Sung Hyun Kim, Jee Hye Suh, Mi Rim Kim, and Seul Gi Lee are employees of Celltrion, Inc. Byong Duk Ye has received a research grant from Celltrion and Pfizer Korea; consulting fees from AbbVie Korea, Celltrion, Chong Kun Dang Pharm., Daewoong Pharma., Ferring Korea, IQVIA, Janssen Korea, Kangstem Biotech, LG Chem, Medtronic Korea, Shire Korea, Takeda, and Takeda Korea; speaking fees from AbbVie Korea, Celltrion, Ferring Korea, IQVIA, Janssen Korea, Pfizer Korea, Shire Korea, and Takeda Korea. Walter Reinisch has served as a speaker for Abbott Laboratories, AbbVie, AESCA, Aptalis, Astellas, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, PLS Education, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult; as a consultant for 4SC, Abbott Laboratories, AbbVie, AESCA, Algernon, Amgen, AM Pharma, AMT, AOP Orphan, Arena Pharmaceuticals, Astellas, AstraZeneca, Avaxia, Roland Berger, Bioclinica, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Cellerix, ChemoCentryx, Celgene, Centocor, Celltrion, Covance, Danone Austria, DSM, Elan, Eli Lilly, Ernst & Young, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Intrinsic Imaging, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt, MEDahead, MedImmune, Millennium, Mitsubishi Tanabe Pharma, MSD, Nash Pharmaceuticals, Nestlé, Nippon Kayaku, Novartis, Ocera, OMass, Otsuka, PAREXEL, PDL, PERI Consulting, Pharmacosmos, Philip Morris Institute, Pfizer, Procter & Gamble, Prometheus, Protagonist, Provention, Robarts Clinical Trial, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics, SetPoint Medical, Sigmoid, Sublimity, Takeda, Therakos, Theravance, TiGenix, UCB, Vifor, Zealand, and Zyngenia; as an advisory board member for 4SC, Abbott Laboratories, AbbVie, AESCA, Amgen, AM Pharma, Astellas, AstraZeneca, Avaxia, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Cellerix, ChemoCentryx, Celgene, Centocor, Celltrion, Danone Austria, DSM, Elan, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millennium, Mitsubishi Tanabe Pharma, MSD, Nestlé, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Sandoz, Schering-Plough, Second Genome, SetPoint Medical, Takeda, Therakos, TiGenix, UCB, Zealand, and Zyngenia; and has received research funding from Abbott Laboratories, AbbVie, AESCA, Centocor, Falk Pharma, Immundiagnostik, and MSD. The remaining authors disclose no conflicts.

Funding
The study was funded by Celltrion, Inc. (Incheon, Republic of Korea).

The sponsor contributed to the design and conduct of the study; collection, management, analysis, and interpretation of the data; and the preparation, review, and approval/decision to submit the manuscript. All authors, including employees of the sponsor, provided intellectual contribution to the manuscript development.