Switching From Reference Infliximab to Biosimilar CT-P13 Did Not Change Quality of Life in Stable Inflammatory Bowel Disease Patients

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Background: Quality of life (QoL) data for patients with inflammatory bowel disease switched from the reference infliximab to biosimilar CT-P13 is lacking. This study aims to demonstrate noninferiority for QoL and efficacy after switching.

Methods: OoL and clinical efficacy were measured prior to and after 2, 4, and 6 CT-P13 infusions.

Results: One hundred seventy-eight patients were included. Noninferiority was established for QoL [ratio 97.95% (95% confidence interval 95.93 to 100.01)] and efficacy [difference −0.02 (95% confidence interval −0.68 to 0.64)]. Five patients reported 6 nonrelated, serious adverse events.

Conclusions: Switching from reference infliximab to CT-P13 did not affect the QoL or disease activity and was well tolerated.

Lay Summary

Patients with inflammatory bowel disease were switched from the originator infliximab to the biosimilar CT-P13. Before and after switching they filled in questionnaires. The study showed that switching did not reduce the quality of life and efficacy of the treatment.

Key Words: quality of life, infliximab, biosimilar, inflammatory bowel disease

INTRODUCTION

The inflammatory bowel diseases (IBDs), ulcerative colitis (UC), and Crohn disease (CD) are chronic and life-long and their impact on patients' quality of life (QoL) but also on healthcare budgets is considerable.[1,2] The introduction of biologicals for treatment of IBD greatly improved patient outcomes and QoL.[3,4] However, TNF-α inhibitors and other biologicals are costly compared with conventional treatments and have resulted in increased healthcare costs.[5] For this reason, less expensive biosimilar products have been developed. A biotherapeutic product that is similar in quality, safety, and efficacy to an already licensed reference biotherapeutic product is called a biosimilar.[6,7] The use of less expensive biosimilars will therefore substantially reduce healthcare costs.[8]

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CT-P13 (Remsima, Celltrion, Incheon, South Korea) is one of the world's first biosimilars to infliximab approved by the European Medicines Agency (EMA) in 2013 for similar indications as the reference infliximab (Remicade; Johnson & Johnson, New Brunswick, NJ, USA).[9] After approval by EMA, several studies were performed that assessed the effect of switching from reference infliximab to biosimilar CT-P13.[8] The NOR-SWITCH study was a randomized, noninferiority, double-blind, phase 4 study with 52 weeks of follow-up in which 482 patients treated with reference infliximab either continued treatment with reference infliximab or were switched to biosimilar CT-P13.[10] The NOR-SWITCH study included 93 UC and 155 CD patients and showed that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to a prespecified noninferiority margin of 15%. The study was not powered to show noninferiority in individual diseases.[10] Several case series of IBD patients also showed that switching from the reference to the biosimilar CT-P13 is safe and does not affect the efficacy or the immunogenicity.[11–14] Patient reported outcome data like QoL are seen as important parameters for patients since this has an immediate impact on their daily activities whereas efficacy is often less meaningful to patients.[15] So QoL data can assure the patients that the biosimilar treatment is similar to the reference product. Most switch studies lack QoL and no study reported QoL as primary endpoint. Furthermore, the follow-up of the patients in this study was 1 year, where most switch studies are short-term reports.

In this prospective, observational study executed in daily clinical practice in The Netherlands, QoL as primary objective and efficacy and safety of CT-P13 as secondary objectives were investigated following a switch from reference infliximab in patients with IBD (either CD or UC) in stable remission.

MATERIALS AND METHODS

Study Population

Adult patients (≥18 years) with a confirmed diagnosis of IBD (CD or UC), who started treatment with CT-P13 were eligible for the study. Furthermore, patients had to be in stable remission, defined as stable and continuous treatment with reference infliximab during the last 3 infusions and no foreseen changes in treatment schedule or dose adjustment for the coming 2 months for infliximab. Concomitant medications, except for another biological drug or a nonregistered new chemical entity, were permitted provided that doses were stable for 2 months and no foreseen changes in medications. *Exclusion criteria included* pregnant patients as well as nursing patients, patients with severe cardiovascular disease (New York Heart Association class 3 or 4), with mental or psychiatric disorders, with substance abuse (and/or history of opioid abuse), with language barriers or patients who were not able to adhere to the study procedures for other reasons.

The reason to switch from the reference infliximab to the biosimilar CT-P13 was savings of the healthcare budget and not medical. The hospital decided to switch the patients because the significantly lower cost of the biosimilar without expected change in efficacy and safety. The patients were informed by the treating physician about the reason for the switch and were allowed to continue treatment with the reference infliximab.

Study Design

This was an open-label observational, prospective, multicenter study at 12 sites in The Netherlands. For each patient, the data for the reference infliximab treatment served as baseline. Patients were followed for 6 intravenous infusions with CT-P13 (approximately 1 year) after switching from reference infliximab. The dose and dosing frequency of CT-P13 were identical to those of the previous reference infliximab treatment (~5 mg/kg, every 6–8 weeks). The duration of the first CT-P13 infusion was the same as for the reference infliximab according to the standard hospital protocol for infliximab. Changes in duration of subsequent infusions were allowed.

The primary objective of the first phase of the study was to evaluate QoL in patients with IBD after 2 infusions of CT-P13 compared with the previous reference infliximab treatment. The objective of the second phase of the study was to evaluate efficacy and safety after 6 infusions of CT-P13.

Demographics, prior medications, QoL, and disease activity were documented at the baseline visit before the first CT-P13 infusion (visit 1). QoL and disease activity were further assessed at follow-up visits after the second, fourth, and sixth CT-P13 infusion (visits 2, 3, and 4, respectively). These visits occurred 14–0 days prior to the third, fifth, and seventh CT-P13 infusion.

QoL was evaluated with the inflammatory bowel disease questionnaire (IBDQ) either using a telemedicine system "mijnIBDcoach"[16] or a paper version of the questionnaire, as preferred by the investigator.[17,18] Disease activity was rated with the Harvey–Bradshaw index (HBI) for CD patients[19,20] and with the simple clinical colitis activity index (SCCAI) for UC patients.[21–23] In all patients, the measurement of serum C-reactive protein[24] and fecal calprotectin[25] was optional.

Throughout the study, concomitant medications and adverse events were collected and adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 21.1).

Endpoints

The primary endpoint of the first study phase was change in QoL measured by IBDQ after 2 infusions of CT-P13 compared with baseline (the reference infliximab treatment). The primary endpoint of the second study phase was change in

clinical efficacy measured with HBI or SCCAI after 6 CT-P13 infusions compared with baseline.

Secondary endpoints were changes in QoL and disease activity; serum C-reactive protein and calprotectin after 2, 4, and 6 infusions with CT-P13. Safety endpoints comprised type, incidence, relation, and severity of adverse events, evaluated up to 30 days after discontinuation.

Statistical Analyses

Noninferiority for both primary endpoints was tested at a 2.5% significance level with a 1-sided paired *t* test. Noninferiority of the primary phase 1 endpoint was established, if the lower limit of the 2-sided 95% confidence interval (CI) for the geometric mean of the IBDQ ratio (last visit vs baseline) was above 85%, which is in line with the registration studies of CT-P13.[17] Noninferiority of the primary phase 2 endpoint was established, if the upper limit of the 2-sided 95% CI of the mean difference was <2 for HBI or <2.5 for SCCAI.[26]

For the secondary endpoints, least squares mean estimates of the within group effect (with 95% CI) and the corresponding *P*-values using an approximate *t* test were calculated by a repeated measures ANOVA. All primary and secondary efficacy analyses were performed on the per protocol population (PPP) and repeated for full analysis population (FAP). The FAP population was defined in the study protocol as all patients who received at least 1 dose of CT-P13 treatment during the study and who had at least 1 postdose efficacy evaluation.

The primary efficacy endpoints were tested for the total IBD group as well as the CD and UC groups separately provided that the number of evaluable patients per group was sufficient. The sample size required to achieve 90% power of the primary outcome in the PPP analysis was calculated to be 91 patients per disease group (CD or UC) for phase 1—and 47 patients per disease group for phase 2. Assuming exclusion of 10% of patients from the enrolled population, a minimum of 102 enrolled patients per indication was required.

Because the actual number of recruited UC patients was lower than required, the primary endpoint of phase 1 was tested for the total (CD and UC) population and for the CD population only. For the primary endpoint of phase 2, the 2 subgroups could not be combined as different disease activity scores were used. Exploratory analyses were performed in the UC group for primary outcomes in both phases.

The safety population defined as all patients who received at least 1 dose of CT-P13 treatment and had at least 1 safety assessment after that dose was used for the safety endpoints.

Ethical Consideration

Written, informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The study was approved by the ethical review board "adviescommissie nWMO Brabant" on February 23, 2016 (approval number A15.111).

RESULTS

Between June 24, 2016 and October 24, 2017, a total of 180 IBD patients (122 CD and 58 UC) were enrolled in the study. Two CD patients did not receive CT-P13 treatment. The safety population included 120 CD and 58 UC patients and the FAP population 114 CD and 55 UC patients. In the first phase of the study the PPP included 100 CD and 52 UC patients and in the second phase of the study the PPP included 84 CD and 38 UC patients. Detailed patient disposition is provided in Figure 1. The main reason for exclusion in phase 1 was lack of data, because the patients did not to fill in the QoL questionnaire. The main reasons for discontinuation in phase 2 were treatment with another biological and/or adverse events. The adverse events leading to discontinuation are discussed in the safety section.

Overall 49.7% male and 50.3% female patients participated with mean age of 43.2 years and mean duration of disease 12.4 years. More demographic details and baseline characteristics are provided in Table 1. The median duration of infliximab treatment before inclusion in this study was 57.2 months for the IBD group. Changes in duration of subsequent infusions were allowed and occurred in 1%–4% of the patients. Comedication was used by 71% of the patients and included azathioprine (27.2%).

Primary Efficacy Endpoints

Phase 1: QoL—IBDQ

The geometric mean ratio of the total IBDQ score after 2 CT-P13 infusions compared with baseline in the PP population was 97.95% (95% CI 95.93, 100.01) for the IBD group, 99.04% (95% CI 96.24, 101.93) for the CD group, and 95.94% (95% CI 93.40, 98.55) for the UC group in the exploratory analysis (Table 2). Because the lower limit of the 95% CI was >85, noninferiority of CT-P13 compared to reference infliximab was established in the CD and IBD groups.

Phase 2: disease activity—HBI and SCCAI

The mean difference of the disease activity as measured by HBI after 6 CT-P13 infusions compared with baseline in the PP population was −0.02 (95% CI −0.68, 0.64) in the CD group (Table 2). Because the upper limit of the 95% CI was below 2, noninferiority of CT-P13 compared with reference infliximab was established in the CD group. The mean difference of the disease activity as measured by SCCAI result for the UC group was 0.50 (95% CI −0.27, 1.27) in the exploratory analysis.

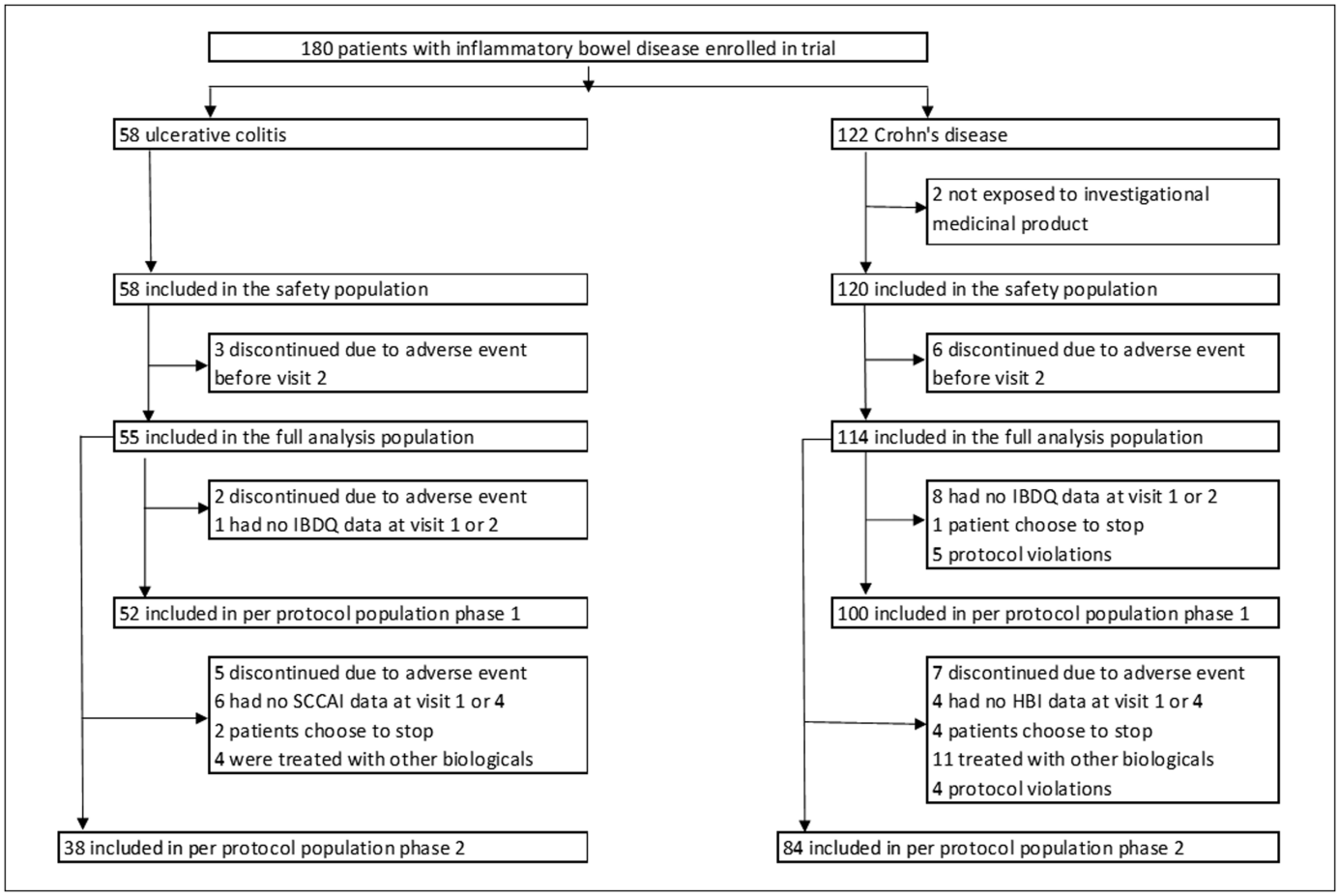

FIGURE 1. Trial flow diagram.

Secondary Efficacy Endpoints

There were no significant overall changes over time in the IBDQ score for the IBD population ($P = 0.339$; Fig. 2). Also, no significant overall changes were observed for the disease activity for the CD and UC populations ($P = 0.443$ and $P = 0.308$ respectively; Table 3).

With respect to disease activity, remission of CD is defined as a HBI score below 5 and remission of UC is defined as a SCCAI score below 2.5.[26] The number of patients in remission was stable during the study period in both populations (Table3).

The range of fecal calprotectin levels varied during the study while C-reactive protein levels were more consistent and no statistically significant changes from baseline were observed in the disease groups (Table 3).

Safety

A total of 216 adverse events (Table 4) were reported, the majority [60 (28%)] were of gastrointestinal nature. Fatigue was the most frequently reported adverse event, reported by 18 (10%) patients, followed by upper abdominal pain and musculoskeletal discomfort [10 (6%) patients each] and nausea [6 (3%) patients]. Most adverse events were mild to moderate in severity.

Five patients reported 6 serious adverse events: 1 UC patient with melanoma, 3 CD patients with, respectively, abdominal hernia repair, urinary calculus, and subarachnoid hemorrhage and 1 CD patient with both fever and perirectal abscesses. All patients recovered from their serious events except the patient with subarachnoid hemorrhage who died. None of these serious adverse events were considered related to CT-P13 treatment according to the treating physician.

A total of 16 (9%) patients [10 (8%) in the CD group and 6 (10%) in the UC group] discontinued from the study due to adverse events such as abdominal pain, nausea, fatigue, and musculoskeletal discomfort; most of these events were considered related to CT-P13 treatment.

DISCUSSION

This study confirmed the noninferiority of the biosimilar CT-P13 compared with reference infliximab with regard to QoL and disease activity in stable IBD patients.

TABLE 1. Demographics and Baseline Characteristics of Intention to Treat (ITT) Population

	IBD (n = 169)	CD (n = 114)	UC (n = 55)
Gender			
Male, n (%)	84 (49.7)	50 (43.9)	34 (61.8)
Female, n (%)	85 (50.3)	64 (56.1)	21 (38.2)
Age, y			
Mean (SD)	43.2 (14.54)	41.5 (13.92)	46.7 (15.30)
Median (IQR)	44.0 (30.0, 53.0)	41.5 (29.0, 50.0)	49.0 (34.0, 58.0)
Range	18–79	18–79	18–79
Duration disease, y	162	109	53
Mean (SD)	12.4 (8.48)	12.4 (8.45)	12.5 (8.62)
Median (IQR)	10.2 (5.8, 16.7)	10.5 (6.0, 16.4)	9.9 (5.7, 17.6)
Range	0.9–47.9	1.6–47.9	0.9–41.5
Reference infliximab treatment duration, months			
Mean (SD)	61.3 (34.3)	64.9 (36.7)	53.9 (27.7)
Median (IQR)	57.2 (35.4, 80.8)	58.8 (37.7, 82.0)	47.9 (27.4, 78.9)
Range	9–202	9–202	10–118
Reference infliximab dose, mg/kg			
Mean (SD)	5.2 (1.5)	5.3 (1.6)	5.1 (1.2)
Median (IQR)	5.0 (5.0, 5.0)	5.0 (5.0, 5.0)	5.0 (5.0, 5.0)
Range	3–10	3–10	3–10

IQR, interquartile range; SD, standard deviation.

TABLE 2. Primary Efficacy Endpoints for Phase 1 and Phase 2 PPPs

Disease	Parameter	n			Assessment
Primary Endpoint Phase 1			Ratio (%)		
QoL			(Test/Reference)*	95% CI of Ratio	
IBD	IBDQ	149	97.95	(95.93, 100.01)	Noninferior
CD	IBDQ	97	99.04	(96.24, 101.93)	Noninferior
UC	IBDQ	52	95.94	(93.40, 98.55)	Noninferior‡
Primary Endpoint Phase 2			Difference	95% CI of Difference	
Disease Activity			(Test/Reference)†		
CD	HBI	84	−0.02	(−0.68, 0.64)	Noninferior
UC	SCCAI	38	0.50	(−0.27, 1.27)	Noninferior‡

*Visit 2 vs baseline.
†Visit 4 vs baseline.
‡Exploratory analysis.
Parameters were analyzed on a log scale using ANOVA. The ratio was calculated by transforming the difference between the natural log LS means back to the original scale and multiplying by 100.
n, number of subjects with data available for both visits; SD, standard deviation.

CT-P13 treatment was well tolerated. Noninferiority was also established in the subgroup of CD patients. However, due to the limited number of UC patients included in this study, subanalysis for this group was only exploratory. All primary and secondary efficacy analyses were performed on the PPP and repeated on the FAP population and showed similar results for the both populations, demonstrating robustness of the data.

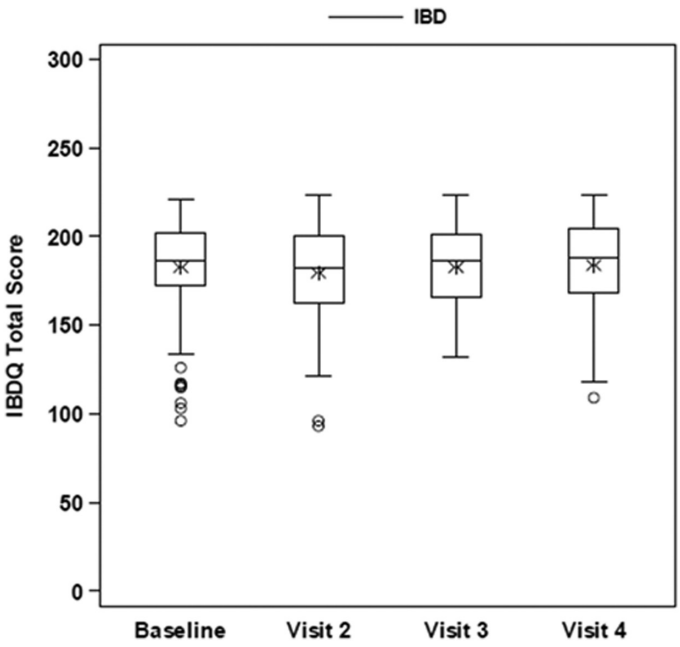

FIGURE 2. QoL measured with the IBDQ score during the study period for the intention to treat (ITT) population. The box represents the interquartile range. The line in the middle of the box represents the median. The asterisk represents the mean. The whiskers represent the maximum value (1.5 times higher than the 75th percentile) and minimum (1.5 times lower than the 25th percentile) values. The circles outside the whiskers represent outliers.

The patient's perspective on switching from medication can be different as the physician perspective, therefore patient reported outcome measurements are very important.[15] In this study, QoL was the primary endpoint in contrast to other switch studies were the efficacy data were the primary endpoint. We showed that switching from reference infliximab to CT-P13 did not affect the QoL of the IBD patients, these data are in line with 3 other studies.[14,27,28] Only Strik et al and Bergqvist et al collected QoL data as secondary endpoint.[14,27] In a large observational study in 313 IBD patients, QoL was measured by the Short Health Scale and no significant differences in QoL were reported 1 year after switching to CT-P13.[27] In an open-label, prospective, interventional, noninferiority study QoL was assessed by EQ-5D and no significant differences in QoL were demonstrated 16 weeks after switching to CT-P13.[14] The third study showed no difference in patients' perspectives after switching from infliximab to CT-P13 in a 12-month prospective cohort study including 113 IBD patients. In this study, only patient reported outcomes were used, 2 general questionnaires and 1 IBD questionnaire, however no efficacy endpoints were included.[28] Other clinical studies in which patients switched from reference infliximab to CT-P13 focused on efficacy and safety and did not include a patient reported outcome.

No change in clinically important efficacy or safety was observed in previous real-world and randomized, controlled studies 1 year after switching from the reference infliximab to

TABLE 3. Disease Activity at Baseline, After 2, 4, and 6 Infusions With CT-P13 Intention to Treat (ITT) Population

Parameter	Statistic	Baseline	Visit 2	Visit 3	Visit 4
HBI score					
CD	n	114	113	105	92
	Mean (SD)	3.47 (3.51)	3.42 (3.73)	3.11 (3.53)	3.12 (3.39)
	Median (IQR)	3.0 (1.0, 5.0)	3.0 (1.0, 5.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)
	Range	0–23	0–25	0–25	0–24
SCCAI score					
UC	n	55	50	43	38
	Mean (SD)	1.93 (2.01)	1.96 (2.38)	2.28 (2.12)	2.42 (2.98)
	Median (IQR)	2.0 (0.0, 3.0)	1.0 (0.0, 3.0)	2.0 (1.0, 4.0)	1.5 (0.0, 3.0)
	Range	0–9	0–11	0–8	0–13
Fecal calprotectin					
IBD	n	60	40	35	36
	Mean (SD)	178 (384)	165 (330)	189 (507)	104 (232)
	Median (IQR)	31 (15, 121)	42 (21, 107)	49 (15, 175)	32 (15, 87)
	Range	0–1865	9–1714	0–3000	0–1266
CRP					
IBD	n	87	75	83	73
	Mean (SD)	4.5 (5.0)	3.9 (4.8)	4.1 (7.7)	4.2 (6.4)
	Median (IQR)	3.0 (1.0,8.0)	2.0 (1.0,5.0)	1.0 (1.0,4.0)	1.0 (1.0,6.0)
	Range	0–28	0–24	0–48	0–36

CRP, C-reactive protein; IQR, interquartile range; n, number of subjects; SD, standard deviation.

TABLE 4. Overall Summary of Adverse Events During CT-P13 Treatment Safety Population

	IBD (n =178)	CD (n = 120)	UC (n = 58)
Patients with at least 1 adverse event	80 (45%)	60 (50%)	20 (35%)
Adverse events	216	167	49
Patients with at least 1 treatment-related adverse event	37 (21%)	26 (22%)	11 (19%)
Treatment-related adverse events	90	70	20
Patients with at least 1 severe adverse event	13 (7%)	10 (8%)	3 (5%)
Severe adverse events	16	12	4
Patients with at least 1 treatment-related severe adverse event	8 (5%)	7 (6%)	1 (2%)
Treatment-related severe adverse events	10	9	1
Patients with at least 1 serious adverse event	5 (3%)	4 (3%)	1 (2%)
Serious adverse events	6	5	1
Related serious adverse event	—	—	—
Patients who died to a nonrelated event	1 (1%)	1 (1%)	—
Patients with at least 1 adverse event leading to discontinuation from study	16 (9%)	10 (8%)	6 (10%)

CT-P13.[8,10,11,27] The NOR-SWITCH study, the only randomized study so far, with 482 patients suffering from different autoimmune diseases including IBD, showed noninferiority of efficacy of CT-P13 compared with patients remaining on the reference infliximab. However, the NOR-SWITCH study was underpowered to show noninferiority in individual diseases.[10]

A limitation of the present study is its prospective, observational, open-label design instead of a randomized controlled design with control groups. However, since strict in- and exclusion criteria are not used in this noninterventional study, the findings are applicable to real-life patient populations. Moreover, patients served as their own control, reflecting daily clinical practice for patients switching from the reference infliximab to CT-P13. However, because patients served as their own control it is difficult to compare discontinuation rates with other studies since they might have continued CT-P13. The discontinuation rate in an open-label study is expected to be higher compared to double-blind studies because patients are aware of the switch (nocebo effect).[29]

Most events in this study were of gastrointestinal nature, whereas in the NOR-SWITCH study most adverse events were infection related (nasopharyngitis and urinary tract infection). A possible explanation is that the NOR-SWITCH study did not only include patients with IBD, but also patients with rheumatic arthritis and psoriasis.

In conclusion, QoL was not impacted in patients with stable IBD who started using biosimilar CT-P13 instead of reference infliximab in daily clinical practice and CT-P13 was shown to be clinically effective and well tolerated in these patients.

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DATA AVAILABILITY

Data not publicly available.

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