Original Article

Efficacy and Safety of the Biosimilar Infliximab CT-P13 Treatment in Inflammatory Bowel Diseases: A Prospective, Multicentre, Nationwide Cohort


Abstract

Background and Aims: Biosimilar infliximab CT-P13 is approved for all indications of the originator product in Europe. Prospective data on its efficacy, safety, and immunogenicity in inflammatory bowel diseases are lacking.

Methods: A prospective, nationwide, multicentre, observational cohort was designed to examine the efficacy, safety, and immunogenicity of CT-P13 infliximab biosimilar in the induction treatment of Crohn’s disease [CD] and ulcerative colitis [UC]. Demographic data were collected and a harmonised monitoring strategy was applied. Early clinical remission, response, and early biochemical response were evaluated at Week 14, steroid-free clinical remission was evaluated at Week 30. Therapeutic drug level was monitored using a conventional enzyme-linked immunosorbent assay.

Results: In all, 210 consecutive inflammatory bowel disease [126 CD and 84 UC] patients were included in the present cohort. At Week 14, 81.4% of CD and 77.6% of UC patients showed clinical response and 53.6% of CD and 58.6% of UC patients were in clinical remission. Clinical remission rates at Week 14 were significantly higher in CD and UC patients who were infliximab naïve, compared with those with previous exposure to the originator compound [p < 0.05]. Until Week 30,
adverse events were experienced in 17.1% of all patients. Infusion reactions and infectious adverse events occurred in 6.6% and 5.7% of all patients, respectively.

**Conclusions:** This prospective multicentre cohort shows that CT-P13 is safe and effective in the induction of clinical remission and response in both CD and UC. Patients with previous infliximab exposure exhibited decreased response rates and were more likely to develop allergic reactions.

**Keywords:** Biosimilar; CT-P13; Crohn’s disease; efficacy; immunogenicity; inflammatory bowel diseases; infliximab; safety; ulcerative colitis

1. **Introduction**

Biosimilars are biological medicines that enter the market after the patent expiration of the original reference product. The first biosimilar monoclonal antibody, biosimilar infliximab CT-P13 [Remsima®, Celltrion, Republic of Korea and Inflectra®, Hospira, UK] received marketing authorisation from the European Medicine Agency [EMA] in June 2013 for all indications of the originator product. This includes the use of biosimilar infliximab in inflammatory bowel diseases [IBD], as an extrapolated indication based on comparative clinical studies in ankylosing spondylitis [PLANETAS] and rheumatoid arthritis [PLANETRA].

According to a European survey among gastroenterologists in 2013, there was a lack of confidence in using biosimilar infliximab in IBD. Concerns have also been raised by several national societies with regard to extrapolated indications. These concerns included the dosing of infliximab, which differs between indications, 5 mg/kg in IBD and 3 mg/kg in rheumatoid arthritis. The use of concomitant immunosuppressive medication is more common in rheumatological indications compared with IBD. Accordingly, in the PLANETRA study, all patients received combination treatment with methotrexate in addition to the originator or biosimilar infliximab. Additionally, there is no data on the downstream effects of anti-tumour necrosis factor-α [anti-TNF] medications in rheumatological conditions and in IBD.

In support of extrapolated indications, the European Medicines Agency [EMA] requires stringent analytical and pre-clinical comparability exercises as well as comparative clinical studies to demonstrate biosimilarity. Biosimilars may lead to significant cost savings and easier access to biologicals with sustained level of care.

As of May 2014, the Hungarian National Health Fund only reimburses the biosimilar infliximab [Inflectra®, Hospira, UK] for new induction treatment of IBD patients. New induction was defined as no infliximab treatment with the originator or the biosimilar compound in the previous 12 months. Switching from the originator compound to the biosimilar infliximab is not allowed according to current regulations.

Data on the use of the biosimilar infliximab CT-P13 in IBD are limited. Therefore, we designed a prospective, nationwide, multicentre, observational study to examine the efficacy, safety, and immunogenicity of CT-P13 infliximab biosimilar in induction and maintenance of remission in Crohn’s disease [CD] and ulcerative colitis [UC].

2. **Material and Methods**

2.1. **Patients**

The induction phase of this multicentre, nationwide prospective observational study was conducted between May 2014 and May 2015 at 12 sites in Hungary; the maintenance phase is still ongoing. Ethical approval was acquired from the National Ethical Committee 929772-2/2014/EKU [292/2014]). The study was registered at the EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENEP/SDPP9053]. All patients gave written informed consent to participation.

Consecutive IBD patients starting on infliximab biosimilar were prospectively enrolled in the study. Eligible patients were older than 18 years and were previously diagnosed either with CD or with UC based on clinical, biochemical, endoscopic, and histological findings. Patients with positive tuberculin skin tests and positive quantiferon assay [QuantiFERON®-TB Gold, Cellestis Limited, Carnegie, VIC, Australia] were ineligible. Standard chest radiographs were also obtained during screening. Eligible Crohn’s patients had moderate to severe therapy-refractory or steroid-dependent luminal disease, or therapy-refractory simple fistulising disease or complex fistulas. Eligible patients with ulcerative colitis had therapy-refractory, steroid-dependent or severe acute steroid-refractory colitis. None of the patients received infliximab treatment with the originator compound within 12 months before initiation of the biosimilar infliximab.

2.2. **Study design**

Eligible patients received intravenous infusions of the biosimilar infliximab CT-P13 [Inflectra®, Hospira, UK] at a dose of 5 mg/kg of body weight at Weeks 0, 2, and 6 and then every eight weeks. Patients only continued into the maintenance phase of the study if clinical remission or response was achieved at Week 14.

The primary endpoint of the study was early clinical remission in CD and UC at Week 14. Secondary endpoints were early clinical and biochemical response, immunogenicity, and safety, evaluated at Week 14, and clinical response, remission, and steroid-free remission, evaluated at Week 30. Further secondary endpoints of the maintenance phase included sustained clinical remission and response, biochemical response, mucosal healing, immunogenicity, and safety, evaluated at Week 54.

Clinical remission in CD was defined as a Crohn’s Disease Activity Index [CDAI] < 150 points or no fistula drainage as assessed by the Fistula Drainage Assessment. Clinical remission in UC was defined as a partial Mayo Score [pMayo] of less than 3 points. Clinical response in CD was defined as a decrease in CDAI with more than 70 points or at least 50% reduction in the number of draining fistulas. Clinical response in UC was defined as a decrease in the pMayo score with more than 3 points. At Week 14, response and remission were evaluated and defined whether patients were eligible for maintenance treatment. Biochemical activity was evaluated by measuring total blood count [TBC], serum C-reactive protein [CRP, normal cut-off: 5 mg/l], and albumin. The Simple Endoscopic Score for Crohn’s Disease [SES-CD] was used to assess mucosal healing in CD and the Mayo score was evaluated in UC.
The conventional and bridging enzyme-linked immunosorbent assay [ELISA] methods were used to measure infliximab biosimilar trough level [TL] and anti-drug antibody [ADA] [LISA TRACKER, Theradiag, France]. The ELISA kit was validated for accuracy and reproducibility of therapeutic drug level monitoring [TDM] of the biosimilar infliximab [Theradiag, France/Hospira, UK]. ELISA measurements were centralised and performed at the Department of Laboratory Medicine, Semmelweis University, Budapest.

2.3. Follow-up, safety, efficacy, and immunogenicity evaluations

A nationwide harmonised monitoring strategy was applied, as mandated by the National Health Fund. Demographical data collection, registration of previous and concomitant medication, monitoring clinical, biochemical and endoscopic responses, perianal imaging, and TDM were performed [Supplementary Table 1, available as Supplementary data at ECCO-JCC online]. Laboratory tests at additional time points were driven by individual patient needs and were left to the discretion of the treating physician.

2.4. Statistical analysis

Data were analysed with the use of SPSS 20.0 software. Descriptive statistics were used to characterise patients’ demographics, early clinical remission and response rates, and adverse events. Clinical response, remission rates, and antidrug antibody positivity rates were compared between infliximab-exposed and naive patients by chi² test or Fisher exact test. Biochemical response and infliximab trough levels were evaluated by t-test with separate variance estimates or one-way analysis of variance [ANOVA], using Scheffe post-hoc analysis, as appropriate; p < 0.05 was considered statistically significant.

3. Results

3.1. Patients and follow-up

In all, 210 consecutive eligible [126 CD and 84 UC] patients from 12 sites were enrolled in the study. By May 2015, 108 CD and 74 UC patients reached Week 6 and 97 CD and 58 UC patients reached the primary endpoint of Week 14. Week 30 secondary endpoint was reached by 58 CD and 25 UC patients. Patient follow-up is being continued until Week 54. Until Week 30, CT-P13 treatment was stopped in 19 patients due to adverse events [n = 17] or loss of response [n = 2; LOR] and 1 patient was lost to follow-up after Week 14 infusion [Figure 1].

The median disease duration in CD patients was 6 years; 42.1% of CD patients had ileocolonic disease, 33.3% exhibited perianal manifestation, and 26.2% had gone through previous surgery; 26.2% of patients had received previous anti-TNF treatment, 22.3% with the originator infliximab [Remicade®, Merck & Co.] and 3.9% with adalimumab [Humira®, AbbVie]. At baseline, 47.6% and 62.5% of CD patients received concomitant steroid and thiopurine therapy, respectively. The median disease duration in UC patients was 4 years; 57.1% of UC patients had extensive disease. At inclusion, 64.7% and 57.3% of patients were on concomitant steroid and thiopurine therapy, respectively. Detailed patient demographic data are presented in Table 1.

3.2. Early clinical remission and response

At Week 6, 77.8% [n = 84] of CD patients had clinical response to treatment with CT-P13 and 49.1% [n = 53] of CD patients were in clinical remission. Among UC patients, 77% [n = 57] and 67.6% [n = 50] had clinical response and remission, respectively [Figure 2a]. At Week 14, 81.4% of CD patients [n=79] had clinical response and 53.6% of CD patients [n=52] were in clinical remission; 77.6% [n = 45] of UC patients had clinical response by Week 14 and 58.6% [n = 34] were in clinical remission [Figure 2b].

Clinical response rates at Week 6 were significantly higher in both CD and UC infliximab-naïve patients compared with those previously exposed to the originator compound [87.3 vs. 51.7% in CD and 81.4 vs. 60% in UC, p < 0.05 and p < 0.05, respectively Figure 2c]. Clinical remission rates at Week 14 were significantly higher both in CD and UC patients without previous exposure to the originator infliximab compared with those previously exposed [60.9% vs. 35.7% in CD and 65.1% vs. 33.3% in UC, p < 0.05 and p < 0.05, respectively, Figure 2d].

3.3. Clinical response, remission, and steroid-free clinical remission at Week 30

At Week 30, 67.2% of Week 14 responder CD patients [n = 39] maintained clinical response to CT-P13 and 53.4% [n = 31] were in...

Figure 1. Patients and follow-up. LOR, loss of response; AE, adverse event; CD, Crohn’s disease; UC, ulcerative colitis. One CD patient was lost to follow-up after Week 14.
clinical remission [Figure 3]. Difference between naive patients and those with previous infliximab exposure did not reach significance either in terms of clinical remission or in clinical response [60% vs. 38.9%, \( p = 0.13 \) and 75% vs. 50%, \( p = 0.06 \), respectively]. Steroid-free clinical remission was reached in 50% of CD patients \( n = 29 \) by Week 30. Of note, patients in the anti-TNF exposed subgroup of patients had higher response and remission rates at Week 30 if they received concomitant azathioprine therapy [12.5% vs. 75%, \( p = 0.01 \) and 12.5% vs. 62.5%, \( p = 0.04 \)].

At Week 30, 80% of Week 14 responder UC patients \( n = 20 \) maintained clinical response to CT-P13 and 68% of the patients \( n = 17 \) were in clinical remission [Figure 3]. Clinical response and remission were reached in 84.2% and 78.9% of infliximab-naïve patients compared with 66.6% and 33.3% of previously exposed patients [not significant, \( p = 0.35 \) and \( p = 0.06 \), respectively]. Steroid-free clinical remission was achieved in 56% of UC patients \( n = 14 \) by Week 30.

### 3.4. Biochemical response

In CD patients the mean CRP level was 20.9 mg/l at baseline, which decreased to 10.6 mg/l at Week 14 [\( p = 0.02 \), Figure 4a]. Mean platelet count decreased from 370 G/l at baseline to 330 G/l at Week 14 [\( p < 0.001 \)]. Change in the mean serum albumin level between baseline and Week 14 was not significant [42.1 vs. 43.4 g/l].

In UC patients mean CRP level was 32.4 mg/l at baseline and decreased to 7.5 mg/l at Week 14 [\( p < 0.001 \), Figure 4b]. Mean platelet count decreased from 403 G/l at baseline to 329 G/l at Week 14 [\( p = 0.007 \)]. There was no significant change in the mean albumin level of the patients between baseline and Week 14 [41.2 vs. 43.3 g/l].

### 3.5. Therapeutic drug level monitoring

Mean trough levels [TL] of CD patients were 24.8 [\( n = 31 \), 18.4 [\( n = 31 \) and 4.8 μg/ml [\( n = 61 \), missing TL analysis \( n = 36 \)] at Weeks 2, 6, and 14. In UC patients, mean trough levels were 19.3 [\( n = 19 \), 6.2 [\( n = 14 \), and 3.3 μg/ml [\( n = 42 \), missing TL analysis \( n = 16 \)] at Weeks 2, 6, and 14, respectively. Difference between TLs of CD and UC patients was significant at Week 6 [\( p < 0.001 \)]. Patients with previous infliximab exposure had a tendency towards lower early mean TLs compared with patients without previous infliximab exposure [15.0 vs. 21.5 μg/ml at Week 2, 7.7 vs. 10.2 μg/ml at Week 6, and 4.8 vs. 3.2 μg/ml at Week 14, not significant].

Anti-drug antibodies [ADA] were detected in 9.1% [9/99 patients] of all CD patients at baseline and 21.3% [13/61 patients] at Week 14. In infliximab-naïve CD patients, ADA positivity was 4% [3/75 patients] and 16.7% [8/48 patients] at baseline and at Week 14, respectively. In CD patients with previous infliximab exposure, ADA positivity was 24.2% [6/24] and 38.5% [5/13] at baseline and at Week 14, respectively. Patients exposed to previous infliximab treatment had significantly higher baseline ADA positivity as compared with naive patients [\( p = 0.006 \)]. At Week 14, 38.5% of previously exposed patients had ADA positivity compared with 16.7% in infliximab-naïve patients [not significant].

ADA was detected in 8.8% [6/68 patients] of all UC patients at baseline and 23.8% [10/42 patients] at Week 14. In infliximab-naïve UC patients, ADA positivity was 3.6% [2/55 patients] and 21.9% [7/32 patients] at baseline and at Week 14, respectively. In UC patients with previous infliximab exposure, baseline ADA positivity was 30.8% [4/13 patients], and at Week 14 ADA positivity was 30% [3/10 patients]. Baseline ADA positivity was detected in a significantly higher number of patients who had received previous infliximab treatment as compared with infliximab-naïve patients [\( p = 0.02 \)]. There was no significant difference in ADA positivity at Week 14 between patient groups when stratified according to previous infliximab exposure.

### 3.6. Adverse events

Up to Week 30, adverse events had occurred in 17.1% of all patients. Infusion reactions occurred in 6.7% [\( n = 14 \)] of CT-P13 treated patients. Ten of the 14 patients experiencing infusion reaction of any severity had previously received the originator infliximab. Infusion reactions occurred in a significantly higher proportion of patients with previous infliximab exposure compared with naive patients [27% vs. 2.5%, \( p < 0.001 \)]. No infusion reactions occurred in patients with previous exposure to adalimumab. Possible delayed hypersensitivity occurred in one patient. Infectious adverse events occurred in 5.7% of all patients; one patient had invasive fungal sepsis, which resulted in her death [Table 2].

### 4. Discussion

Our results show that biosimilar infliximab CT-P13 induces and maintains high clinical remission and response rates in both CD and UC patients up to week 30. There was a significant difference in the early response and remission rates between patients previously exposed to the originator compound as compared with the infliximab-naïve patients. This was associated with significantly higher baseline ADA positivity in both CD and UC patients previously
exposed to the originator compound. Clinical improvement during induction was coupled with decreased biochemical activity in both CD and UC as compared with baseline.

The ACCENT I trial demonstrated that 39% of Week 2-responder CD patients exhibited clinical remission at Week 30 when treated with infliximab 5 mg/kg compared with 21% in placebo-treated responders. Additionally, real-life clinical data with the originator support high response and remission rates during induction in CD patients. In comparison, clinical response and remission in CD patients after the induction treatment with CT-P13 were 82% and 54%, respectively, and 67.2% of Week 14-responder CT-P13-treated CD patients maintained clinical response up to week 30. This is in line with an earlier retrospective national initiative, which demonstrated 86% response and 46% remission rates in CD from the same background population after induction treatment with the originator compound.

In the ACT 1 and ACT 2 trials, 69% and 64% of UC patients who received 5 mg/kg of infliximab had a clinical response at Week 8 and 49% and 41% of patients maintained response at Week 30, respectively. In comparison, in our real-life cohort with CT-P13, clinical response was 78% at Week 14. Additionally, 80% of Week-14 UC responders sustained clinical response at Week 30. This is comparable to a retrospective, multicentre analysis that showed 22% primary non-response to the originator compound in UC.

Our findings are also in line with the results of a retrospective study and a case series regarding the efficacy of CT-P13 in IBD. In the present cohort, drug-related adverse events were experienced in 17.1% of patients until Week 30. This is remarkably lower than adverse events reported in either the PLANETAS or the PLANETRA study. We did not detect any cases of latent tuberculosis during the study period in our BCG-vaccinated population.
Additionally, changes in the clinical laboratory parameters per se were not considered a safety endpoint. The rate of infusion-related reactions with CT-P13 in IBD was comparable to those reported in the rheumatological studies [6.7% vs. 6.6 and 3.9%]. Of note, IBD patients in the present cohort were not routinely premedicated with antihistamine, were not necessarily on concomitant immunosuppressives, and may have been previously exposed to the originator compound. In our study population, 22% of CD and 11% of UC patients had previously received the originator infliximab. Re-initiation of infliximab treatment has previously been shown to be an effective and safe therapeutic option.22,23 According to the results of the present study, a word of caution is needed, since the majority of early infusion reactions occurred in patients with a previous anti-TNF exposure by the originator molecule and a drug holiday beyond 1 year. Therefore a risk-benefit evaluation is recommended before initiating a long drug holiday in patients in remission, and further data are warranted.

Pharmacokinetic evaluation of CT-P13 in IBD has not been previously reported. In our present study, mean TLs were 24.8, 18.4, and 4.8 \(\mu\)g/ml in CD and 19.3, 36.2, and 3.3 \(\mu\)g/ml in UC at Weeks 2, 6, and 14, respectively. In comparison, a post-hoc analysis of the ACCENT I trial found that median Week 14 trough levels of patients with and without sustained response to infliximab induction with 5 mg/kg, were 4.0 and 1.9 \(\mu\)g/ml, respectively.24 Interestingly, in our cohort patients with previous infliximab exposure had a tendency towards lower early TLs compared with naïve patients. This was associated with significantly higher baseline ADA positivity [4% vs. 24%] and lower early response and remission rates in patients previously exposed to the originator compound. ADA positivity in the CT-P13-treated infliximab-naïve and previously exposed CD patients were 24.2% and 38.5% at Week 14, respectively. In comparison, ADA positivity was previously reported to range between 12.5% to 43% and 0.9% to 14% in infliximab-naïve patients with scheduled infliximab infusions of the originator compound, depending on the administration of concomitant immunosuppression.25 In comparison, in a head-to-head Japanese trial in rheumatoid arthritis, CT-P13 or infliximab was administered in combination with methotrexate and ADA were detected in 19.6% of patients in the CT-P13 group and 15.1% of patients in the infliximab group at Week 14.26 The development of antibodies has previously been associated with increased risk of infusion reactions and reduced response to treatment.27 Additionally, when re-initiating the infliximab therapy after a drug holiday, when antibodies to infliximab were detectable, the hazard ratio for infusion reaction was 7.7.23 This underlines our findings that 10 of 14 patients who experienced infusion reaction of any severity had previously received the originator infliximab. Furthermore, it has recently been demonstrated that anti-infliximab

<table>
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<th>Adverse event</th>
<th>Patient no. [%]</th>
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<tr>
<td>Infections</td>
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<tr>
<td>Upper respiratory tract infection</td>
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<tr>
<td>Pneumonia</td>
<td>1 [0.5%]</td>
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<tr>
<td>Tuberculosis</td>
<td>0 [0%]</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2 [1%]</td>
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<tr>
<td>Vaginitis</td>
<td>1 [0.5%]</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 [0.5%]</td>
</tr>
<tr>
<td>Viral infections [influenza, herpes, varicella]</td>
<td>0 [0%]</td>
</tr>
<tr>
<td>Invasive fungal infection</td>
<td>1 [0.5%]</td>
</tr>
<tr>
<td>Acute infusion reactions</td>
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<tr>
<td>Anaphylaxis</td>
<td>1 [0.5%]</td>
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<tr>
<td>Other</td>
<td>13 [6.2%]</td>
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<tr>
<td>Possible delayed hypersensitivity</td>
<td>1 [0.5%]</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 [4.3%]</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0 [0%]</td>
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Figure 3. Clinical response and remission at Week 30.

Figure 4. Early biochemical response. a. Mean CRP levels [± SEM] in CD during induction treatment. \(p = 0.02\), compared with baseline. b. Mean CRP levels [± SEM] in UC during induction treatment. \(p < 0.001\), compared with baseline. CRP, C-reactive protein; SEM, standard error of the mean; CD, Crohn’s disease; UC, ulcerative colitis.
antibodies in IBD patients recognise and cross-react with CT-P13 and neutralise each drug’s activity.\(^8\) In contrast, anti-adalimumab antibodies do not cross-react with CT-P13.\(^24\) Consistently, no infusion reactions occurred in patients with previous adalimumab exposure in our cohort. Consequently, ADA to infliximab that were detected at baseline in our previously exposed patient population could have been responsible for the reduced rate of early clinical response. The clinical importance of ADAs detected at baseline [five patients, transient in three patients] in the infliximab-naïve population needs further investigation.

This study is a nationwide, multicentre, prospective cohort with a harmonised monitoring strategy. However, there are limitations to acknowledge. During the induction phase, only clinical and biochemical endpoints were evaluated and therefore the study lacks an early endoscopic endpoint. Nevertheless, following the national monitoring strategy, endoscopic evaluation will be available at Week 54 both in CD and in UC patients. Our study did not aim to evaluate interchangeability, as switching from the originator compound to the biosimilar [or vice versa] was not allowed by the national health authorities. However, preliminary retrospective data are showing favourable outcome, and a randomised, double-blind, parallel-group study, the NOR-SWITCH study [ClinicalTrials.gov identifier: NCT02148640] is currently being pursued.\(^10,11,29\)

Despite the EMAs strict regulations to granting marketing authorisation to the first biosimilar monoclonal antibody, several concerns have been raised regarding its administration in IBD. So far only limited data from retrospective real-life experience have been available on the use of the biosimilar infliximab CT-P13 in IBD.\(^10,11\) Therefore, this nationwide cohort was designed to satisfy this unmet need and prospectively evaluate the efficacy and safety of CT-P13 in IBD.

To conclude, this prospective multicentre cohort shows that CT-P13 is effective and safe in the induction of clinical remission and response in both CD and UC. Efficacy and safety of CT-P13 reported herein is comparable to those of observational studies of the originator compound. Importantly, induction treatment with the biosimilar infliximab was less effective in patients previously exposed to the originator compound. Further data are warranted to evaluate the efficacy of CT-P13 in maintaining remission in IBD.

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**Conflict of Interest**
KBG conceived the study, performed data collection, and drafted the manuscript. BDL, KF, JB, LB, BG, PAG, TK, LL, AACS, MJ, FN, KP, MP, AP, LL, ÅS, TS, ZS, GTT, AV, and TM performed data collection. BzS carried out measurements for therapeutic drug level monitoring. PLL conceived the study and consulted the concept, performed data collection and validation, carried out statistical analysis, supervised the manuscript preparation. All authors read and approved the final manuscript.

**Supplementary Data**
Supplementary data are available at ECCO-JCC online.

**Conference Presentation**
Part of this work was presented as a poster at ECCO 2015, Barcelona, and at DDW 2015, Washington DC. Preliminary data on Week-8 outcomes have been published as a single-centre experience.\(^30\)

**References**