Efficacy and Safety of Biosimilar Infliximab in Bio-naïve Patients With Crohn's Disease

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Research Article

Keywords: infliximab, biosimilar, CT-P13, Crohn's disease

Posted Date: April 26th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-445258/v1

Abstract

The infliximab biosimilar CT-P13 was the first biosimilar drug targeting tumor necrosis factor-α. However, its efficacy and safety in real-world clinical situations have remained insufficient. Therefore, we aimed to verify the efficacy and safety of CT-P13 in bio-naïve patients with Crohn's disease. This retrospective multicenter study compared the remission rate at week 54 between patients with Crohn's disease treated with originator infliximab or CT-P13. Endoscopic and laboratory findings were assessed in both groups. A total of 184 (156 originator and 28 CT-P13) patients were analyzed. Of these, 138 originator users and 19 biosimilar users completed 54-week administration. The clinical remission rates in patients taking originator infliximab of CT-P13 at week 54 were 92.5% and 100%, respectively. The endoscopic scores of each group significantly decreased from baseline at week 54 in both groups, and the mucosal healing rate at week 54 was 53% and 64%, respectively. Laboratory data significantly improved from baseline to week 14 and 54 in both groups. Adverse events were observed more frequently in the CT-P13 group (25% vs. 4.5%, p = 0.0015). The efficacy of CT-P13 were comparable with those of originator infliximab in bio-naïve patients with Crohn's disease evaluated by clinical, endoscopic, and laboratory findings.

Introduction

Inflammatory bowel disease (IBD) is a chronic condition that causes serious complications and reduces quality of life. The emergence of anti-tumor necrosis factor (TNF)-α agents was an impactful event for the treatment of IBD.[1] Such biologic therapies have contributed to mucosal healing, prolonged remission, and improved fistula closure.[2–6] Infliximab (IFX), the first biologic drug for IBD, has significantly reduced the need for hospitalization and surgery.[7, 8] Although biologic agents help to improve outcomes such as remission rates and quality of life, they are less cost-effective than conventional therapies.[9] Thus, long-term use of these drugs can place a significant burden on the national health system.

Since the patent expiration of originator IFX, biosimilar products of IFX have been developed to overcome the high costs of originator IFX drugs. By definition, a biosimilar drug has the same quality, safety, and efficacy as the preceding biopharmaceutical. CT-P13 (Celltrion, Inc., Incheon, Republic of Korea) was the first infliximab biosynthetic and has been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). Based on randomized clinical trials for rheumatoid arthritis and ankylosing spondylitis,[10, 11] CT-P13 received marketing authorization from the EMA and FDA in 2013 and 2016, respectively.[12, 13] Therefore, for other indications including IBD, it has been approved as an extrapolated indication without a clinical trial.

Since its approval, the efficacy and safety of CT-P13 for IBD have mainly been validated by studies on switching from originator to biosynthetic IFX or vice-versa.[14–18] In January 2017, the European Crohn's and Colitis Organisation announced that no clinically meaningful difference existed in the efficacy and safety between CT-P13 and originator IFX and that switching products was acceptable.[19] In 2019, the first prospective randomized control trial, which included 220 active bio-naïve patients with Crohn's

disease (CD), indicated the non-inferiority of CT-P13 to originator IFX.[20] Although this study included almost 30% Asians, validation of the efficacy and safety of CT-P13 for CD patients in real-world clinical situations required more extensive evaluation in Asian patients with CD because of the rising prevalence of CD in the Asian population.[21]

This study aimed to verify the efficacy and safety of biosimilar anti-TNF-α agents compared with those of originator IFX through week 54 in patients with CD who were naïve to biological therapy in a Japanese hospital-based cohort.

Materials And Methods

Study design and participants

This was a retrospective multicenter study involving three hospitals to which experts of IBD have belonged in Chiba-city, Japan. We retrospectively reviewed the medical records of 443 patients who were diagnosed with CD between January 2004 and November 2019 at these hospitals. Patients who were treated with originator IFX or CT-P13 at least once were included, while those who were not treated by either agent and those who had treatment history of biologic agents were excluded. All available clinical data of eligible patients were obtained from medical records.

This study was approved by the Research Ethics Committee of Chiba University Hospital (No.3399). All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all subjects.

Treatment strategies of CD

CD diagnosis was based on the clinical, endoscopic, radiological, and pathological findings according to the Japanese guidelines.[22] Inflammatory diseases with granulomas other than CD were ruled out at the time of diagnosis. The treatment strategies of CD were also based on the Japanese guidelines stating that 5- aminosalicylates and budesonide are the first choice for mild to moderate active CD. Corticosteroids and/or immunomodulators (i.e. thiopurines; azathioprine/6-mercaptopurine) are considered for moderate-to-severe active CD. Nutritional therapy is concomitantly used as an optional treatment. Biologics including infliximab were chosen in cases of treatment failure of those conventional treatments. However, this strategy was a basic approach, and biologics were sometimes administered early after disease onset with a so-called top-down approach to achieve improved long-term outcomes with avoidance of bowel resection.

Infusion procedures of both IFX agents (originator and biosynthetic) were identified as follows: 5 mg/kg of IFX given as an intravenous infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion as remission induction therapy. Treatment was continued every 8 weeks to sustain remission as maintenance therapy. None of the patients received antihistamine, antiallergic agents, acetaminophen, or hydrocortisone before IFX infusion for infusion reaction management.

Outcomes and Assessments

Disease activity and endoscopic activity were evaluated by the Harvey–Bradshaw Index (HBI, Simple CDAI) and Simple Endoscopic Score Crohn Disease (SES-CD), respectively. Blood tests were performed before every infusion, and serum levels of C-reactive protein (CRP), serum albumin (ALB), and hemoglobin (Hb) were obtained. Efficacy was assessed based on the rate of remission status and laboratory data between originator IFX and CT-P13 groups, and safety was determined by investigating the occurrence of adverse events (AEs) in each group. Remission was defined as < 5 HBI regardless of the presence or absence of treatment intensification including an increase in infusion dose or shortened infusion interval. HBI was calculated at each infliximab infusion time point (0, 2, 6, 14, 22, 30, and 54 weeks). Mucosal healing was defined as SES-CD scores 0 – 3.[23–25] Laboratory findings (CRP, ALB and Hb) were compared between week 0, week 14, and week 54 in each IFX group. AEs were assessed according to the guidelines of the Common Terminology Criteria for Adverse Events, and severe AE was defined as Grade 3 or more. Efficacy and safety were analyzed using an intent-to-treat approach.

Statistical analysis

Demographic and clinical characteristics were compared using Fisher's exact test and Mann–Whitney U test. The comparison of efficacy and safety was performed with Fisher's exact test and the Wilcoxon signed-rank test. Additionally, multivariate analysis for baseline characteristics to remission rate by HBI at week 54 was performed. All statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA), and a p-value < 0.05 was considered to be statistically significant in two-sided tests.

Results

Study population

We identified 443 patients with CD who were treated in the three centers between January 2004 and November 2019. Of these, 195 patients who were not treated by biological medicinal product in that period were excluded. Additionally, 64 patients with a treatment history of biological medicinal products or who received biologics other than originator IFX or CT-P13 were excluded from this study. Finally, 184 bio-naïve patients were enrolled. Originator IFX was infused into 156 patients, and CT-P13 was infused to 28 patients. Of these, 138 patients treated by originator IFX and 19 treated by CT-P13 completed 54 weeks treatment, respectively (Fig. 1).

Baseline characteristics

The baseline characteristics of the patients and disease in this study are summarized in Table 1. The median age at diagnosis in originator IFX and CT-P13 was 22.0 (17.0–29.0) years and 24.0 (17.3–38.8) years, respectively. Median HBI in the originator IFX group was significantly higher than that in the CT-P3 group [3 (2–4) vs. 2 (1–3), p = 0.022], whereas median SES-CD was similar in both groups [10 (6.5–18)

vs. 12.5(6–21.5), p = 0.447]. The other factors of patient demographics and disease characteristics at baseline were similar between both groups.

Table 1
Baseline patient and disease characteristics

Baseline characteristics	Infliximab(n = 156)	CT-P13(n = 28)	p value
Age at diagnosis, median (IQR)(years)	22.0(17.0–29.0)	24.0(17.3–38.8)	0.0960
Disease duration, median (IQR)(months)	18.0(4.0–82.0)	12.5(4.8-34.08)	0.5170
Location of disease, n (%)			0.5530
Ileum	22(14.1%)	4(14.3%)	
Colon	26(16.7%)	7(25.0%)	
Ileum and colon	107(68.6%)	17(60.7%)	
unknown	1(0.6%)	0(0.0%)	
Anal lesion, n (%)	60(38.5%)	6(21.4%)	0.0915
History of segmental resection, n (%)	38(24.4%)	6(21.4%)	0.8140
HBI, median (IQR)	3(2–4)	2(1–3)	0.0221
SES-CD score, median (IQR)	10(6.5–18.0)	12.5(6.0-21.5)	0.4470
Sex			0.3300
Male, n (%)	124(79.5%)	20(71.4%)	
Female, n (%)	32(20.5%)	8(28.6%)	
Smoking status			0.4170
Current, n (%)	19(12.2%)	4(14.3%)	
Former, n (%)	23(14.7%)	7(25.0%)	
Non-Smoker, n (%)	95(60.9%)	15(53.6%)	
unknown, n (%)	19(12.2%)	2(7.1%)	
CRP, median (IQR) (mg/dl)	0.9(0.1–3.2)	0.61(0.1–1.66)	0.2000
Corticosteroid use			0.0498
Current, n (%)	43(27.6%)	6(21.4%)	
Former, n (%)	13(8.3%)	7(25.0%)	
Non-Corticosteroid user, n (%)	99(63.5%)	15(53.6%)	
unknown, n (%)	1(0.6%)	0(0.0%)	
Immunomodulators use			0.2260
Current, n (%)	19(12.1%)	7(25.0%)	

Baseline characteristics	Infliximab(n = 156)	CT-P13(n = 28)	p value
Former, n (%)	1(0.6%)	0(0.0.%)	
Non-immunomodulators user, n (%)	135(86.0%)	21(75.0%)	
unknown, n (%)	1(0.6%)	0(0.0.%)	

Data are n (%), median (IQR) in the intention-to-treat population.

SES-CD = Simplified Endoscopic Activity Score for Crohn's Disease.

CRP = C-reactive protein.

Immunomodulators include 6-mercaptopurine and azathioprine.

Efficacy assessed by HBI, SES-CD, and laboratory data

Remission rates in the originator IFX group and the CTP-13 group are shown in Fig. 2. Remission rates were > 90% in both groups at two weeks after the initial infusion through the entire 54 weeks in the analysis with exclusion of the dropped-out patients. No significant difference was observed in the remission rate between the two groups at all time points up to week 54. We confirmed that the baseline characteristics including the factors which differed between the two groups did not have any impact on the remission rate at week 54 by polytomous logistic regression analysis.

The remission rate at week 54 in the originator IFX group and in the CT-P13 group were 79.5% and 71.5%, respectively, on the assumption that dropped-out patients were deemed ineffective (Fig. 3). No significant difference in remission rate was observed between the two groups also in this analysis.

SES-CD was assessed at baseline and week 54. Median SES-CD scores at week 54 in the originator IFX group were significantly decreased compared with the baseline value of 10 to 3 ($p < 0.001$) and in the CTP-13 group from 12.5 to 3 ($p < 0.001$), respectively. Mucosal healing rates at week 54 were 53% and 64%, respectively (Fig. 4).

Laboratory data were assessed at baseline, week 14, and week 54. Serum CRP, ALB, and Hb levels were significantly improved from baseline to week 54 in both groups. Moreover, each index had already improved by week 14 (Fig. 5).

Adverse events

Seven (4.5%) of 156 patients showed adverse events in IFX group, whereas 7 (25%) of 28 patients represented adverse events in CT-P13 group ($p = 0.0015$). Among them, severe AE with Grade 3 or more occurred in three patients (1.9%) in the originator IFX group and one patient (3.5%) in the CT-P13 group. Originator IFX caused anaphylactic shock, liver damage, and anemia, while CT-P13 caused liver damage (Table 2). There were no significant differences in the rate of severe AE between the two groups.

Table 2
Adverse events

Total AE	Originator IFX(n = 156)	CT-P13(n = 28)
Skin reaction	1	2
Infusion reaction	3	1
Anaphylactic shock	1	
Liver injury	1	3
Thrombocytosis		1
Anemia	1	
Total	7(4.5%)	7(25%)
Severe AE (> Grade 3)	Originator IFX(n = 156)	CT-P13(n = 28)
Anaphylactic shock	1	
Liver injury	1	1
Anemia	1	
Total	3(1.9%)	1(3.5%)
AE = Adverse event, IFX = Infliximab		

Discussion

The present study demonstrates the efficacy and safety of CT-P13 compared with originator IFX in a real-world environment in Japan. Our data showed the remission rate at week 54 in bio-naïve patients with CD who were administered CT-P13 was equivalent to that of patients receiving originator IFX. Additionally, a significant improvement in endoscopic and laboratory findings was observed in both groups of patients. Our results also confirmed that the efficacy of CT-P13 was similar not only in clinical activity with HBI but also in endoscopic activity and laboratory findings.

Previous studies investigating the efficacy of CT-P13 in patients with CD reported remission rates of 53–88% at weeks 24–30.[26–28] A prospective Phase 3 trial showed a remission rate of 55% at week 30.[20] By contrast, our study showed higher remission rates compared with these previous studies. The higher remission rates could be attributable to higher remission rates at baseline. This phenomenon reflected that biologics were introduced to most of the patients with CD after induction of remission with corticosteroids or nutritional therapy. Although the evaluation in clinical activity appears to be ambiguous, we consider that this situation reflected that of real clinical practice of CD, at least in Japan.

By contrast, SES-CD was significantly decreased at week 54 from the baseline values in both the originator IFX and CT-P13 groups. These results confirmed that clinical activity alone was not sufficient to

assess the disease status and that endoscopic findings were rather important. To the best of our knowledge, very few clinical studies to date had focused on endoscopic findings to assess the efficacy of CT-P13. Jung et al. reported a mucosal healing rate of 66.8% at week 54 in five patients using CT-P13.[26] Our cohort included 20 patients using CT-P13 and showed similar rates of mucosal healing at week 54. Mucosal healing has been recently recognized as an important therapeutic target for CD and has been obtained at similar rates between patients with CT-P13 and those with originator IFX.[29] These results further support the equivalence of CT-P13 to originator IFX.

Similarly to endoscopic findings, all laboratory data in both CT-P13 and originator groups were significantly improved at week 54. These laboratory items may therefore be indicators for early assessment of CD. The strength of this study is the evaluation of the efficacy of CT-P13 for bio-naïve patients with CD from multifaceted viewpoints including clinical, endoscopic, and laboratory findings.

Previous reports have shown that the rate of severe AE of CT-P13 was approximately 0–2%,[20, 26] similar to the levels observed in the present study. Furthermore, no significant differences were observed in the rate of severe AE between the originator and CT-P13groups ($p = 0.49$). Thus, CT-P13 was assumed to be as safe for use as the originator IFX. However, when all AEs were included, the number of events were significantly higher in the CT-P13 group than in the originator IFX group. AEs in the CT-P13 users should be monitored continuously in the subsequent clinical experiences.

The advent of CT-P13 on the market has been a breakthrough in the pharmaco-economic system. Biosimilars are less costly primarily because they are not required to undergo the intensive clinical development process of approval and have a reduced cost of marketing. Several reports recommended the wide use of biosimilars for IBD to save on costs and for effectiveness.[30, 31] Such cost-saving potential of biosimilars was estimated to be $54 billion over ten years in the United States.[32] However, CT-P13 has not yet gained popularity in Japan largely due to the generous support for medical expenses by universal insurance and intractable disease system.[33] Indeed, the present study included fewer bio-naïve patients using CT-P13 compared with those using originator IFX. Although access to TNF-α inhibitors varies and is proportional to the socio-economic conditions of each country,[34, 35] wide use of biosimilars to reduce the cost of IBD treatment can potentially improve access to medication. We believe that this study will promote the use of biosimilar drugs not only in Japan but also in other countries.

Our study has some limitations. First, this was a retrospective study with a bias in patient selection an.d collected data. In fact, the number of patietns who dropped out was higher in the CT-P13 group. This result may be attributable to the fact that physicians were likely to discontinue the biosimilar due to the concern about the less clinincal evidence of the CT-P13. Second, the number of patients using CT-P13 was fewer compared with that of originator IFX. Despite these limitations, our results clearly showed the equivalence of CT-P13 to the originator IFX in the treatment of CD.

In conclusion, we confirmed that the efficacy and safety of CT-P13 are comparable to those of originator IFX in bio-naïve patients with CD as evaluated by clinical, endoscopic, and laboratory findings, although the number of CT-P13 users in this study was not large. The use of CT-P13 could be better promoted, but

further study with a larger cohort regarding the efficacy and safety of CT-P13 is required to develop a strategy for treatment with biologics to improve the quality of life in patients with CD.

Abbreviations

IBD, Inflammatory bowel disease; IFX, Infliximab; EMA, European Medicines Agency; FDA, Food and Drug Administration; CD, Crohn's disease; HBI, Harvey–Bradshaw Index; SES-CD, Simple Endoscopic Score Crohn Disease; CRP, C-reactive protein; ALB, serum albumin; Hb, hemoglobin; AEs, adverse events

Declarations

Author Contributions

Conceptualization: TO, NA, YO, SO, JK. Methodology: TO, NA, YO, SO, JK. Data curation: TO, NA, HK, MS, AN, TI, WS, TK, MT, HO, YY, YI, KK, TT, KO, KS, YF, YK. Formal analysis: TO, NA, SO, TM, TN, MA, TK, JK. Project administration: TO, NA, SO, JK. Visualization: TO, NA. Writing - original draft: TO, NA, SO, JK. Writing - review and editing: TO, NA, SO, JK, NK. Approval of final manuscript: all authors.

Statement of Ethics

This research complied with the guidelines for human studies and included evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the Research Ethics Committee of Chiba University Hospital (No.3399).

Competing interests

The authors declare no competing interests.

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Figures

Figure 1

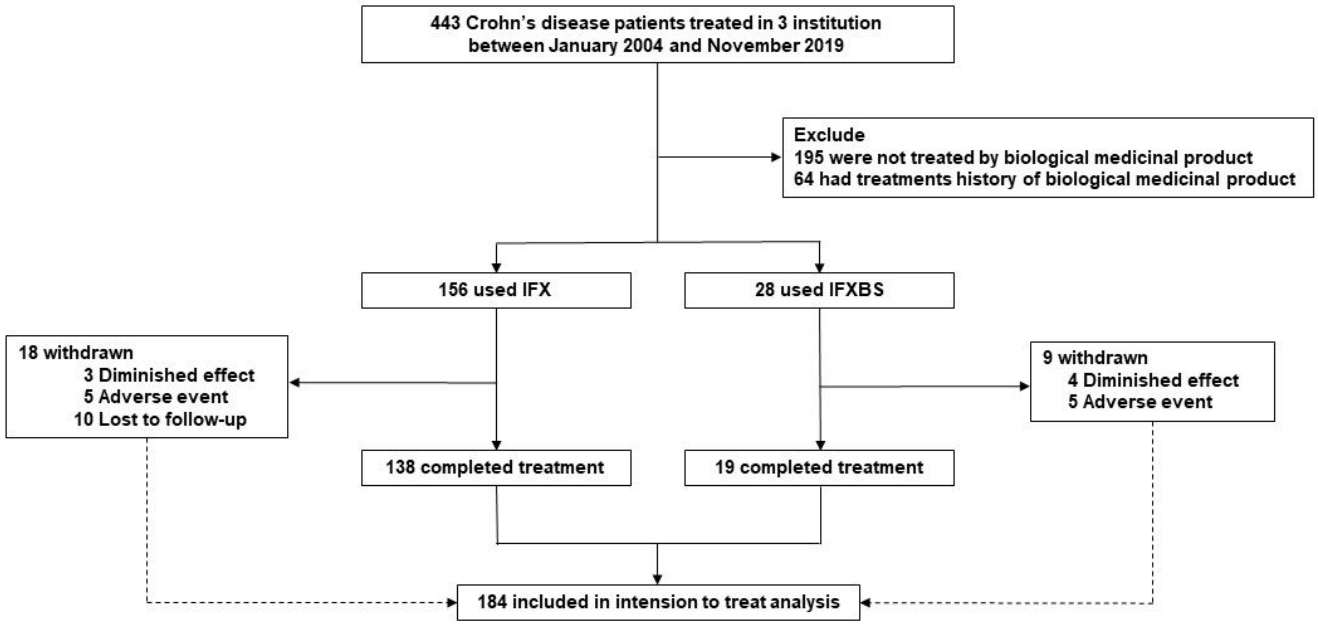

Figure 1

Flowcharts demonstrating the patient selection process of this retrospective study.

Figure 2

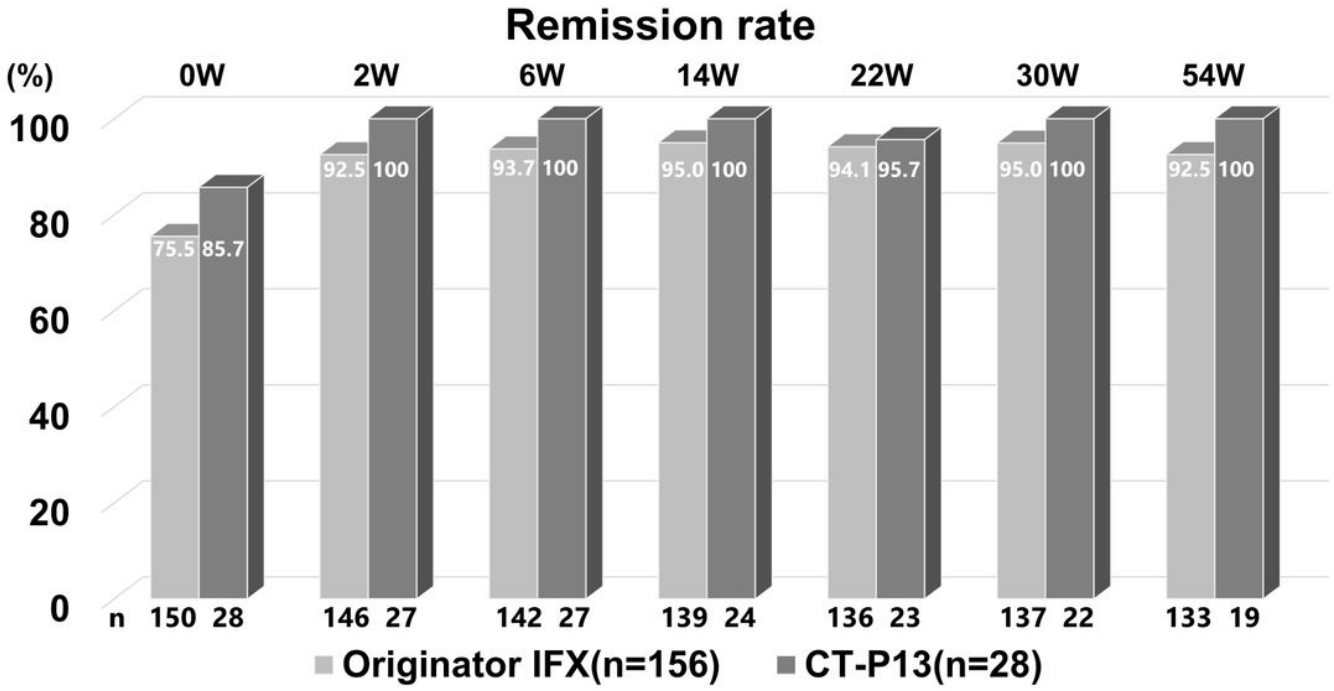

Figure 2

Clinical remission rate at baseline and weeks 2, 6, 14, 22, 30, and 54 in bio-naïve patients with Crohn's disease taking originator IFX or CT-P13 with exclusion of dropped-out patients. No significant difference in the remission rate was observed at any point in both groups. IFX, infliximab.

Figure 3

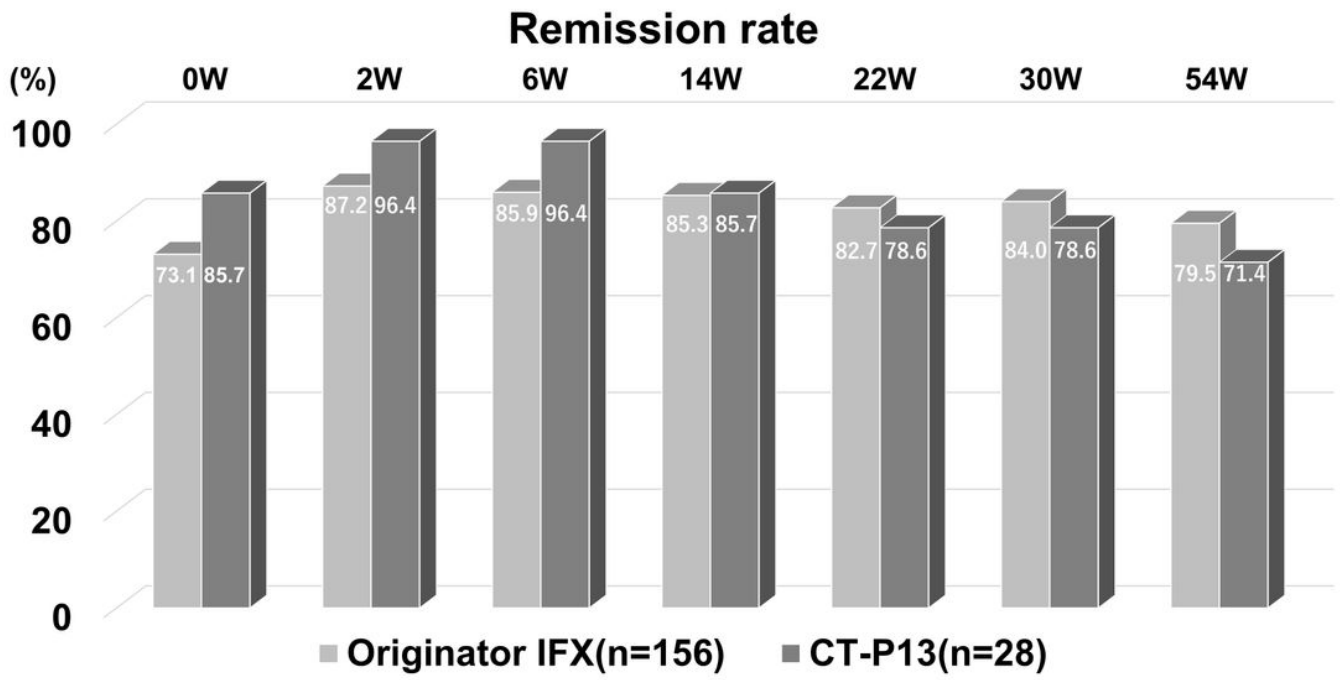

Figure 3

Clinical remission rate at baseline and weeks 2, 6, 14, 22, 30, and 54 in bio-naïve patients with Crohn's disease taking originator IFX or CT-P13 on the assumption that dropped-out patients were deemed ineffective. No significant difference in the remission rate was observed at any point in both groups. IFX, infliximab.

Figure 4

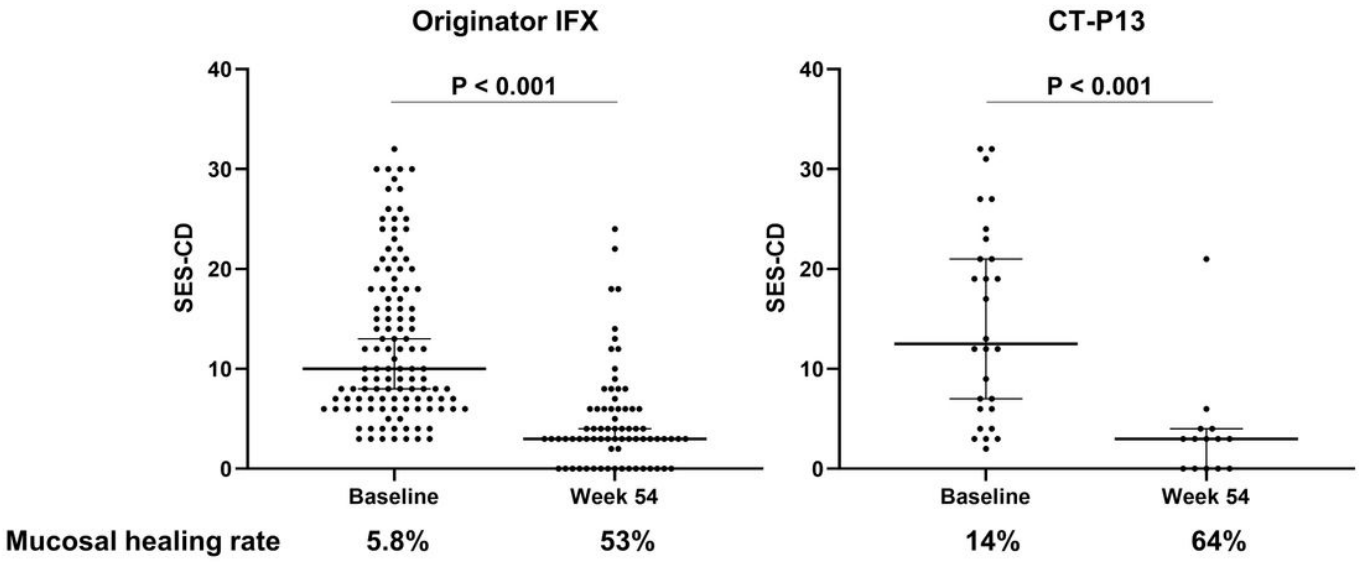

Figure 4

SES-CD and endoscopic remission rate in originator IFX and CT-P13 group at baseline and week 54. At week 54, SES-CD was significantly improved over baseline values. IFX, infliximab; SES-CD, Simple Endoscopic Score Crohn Disease.

Figure 5

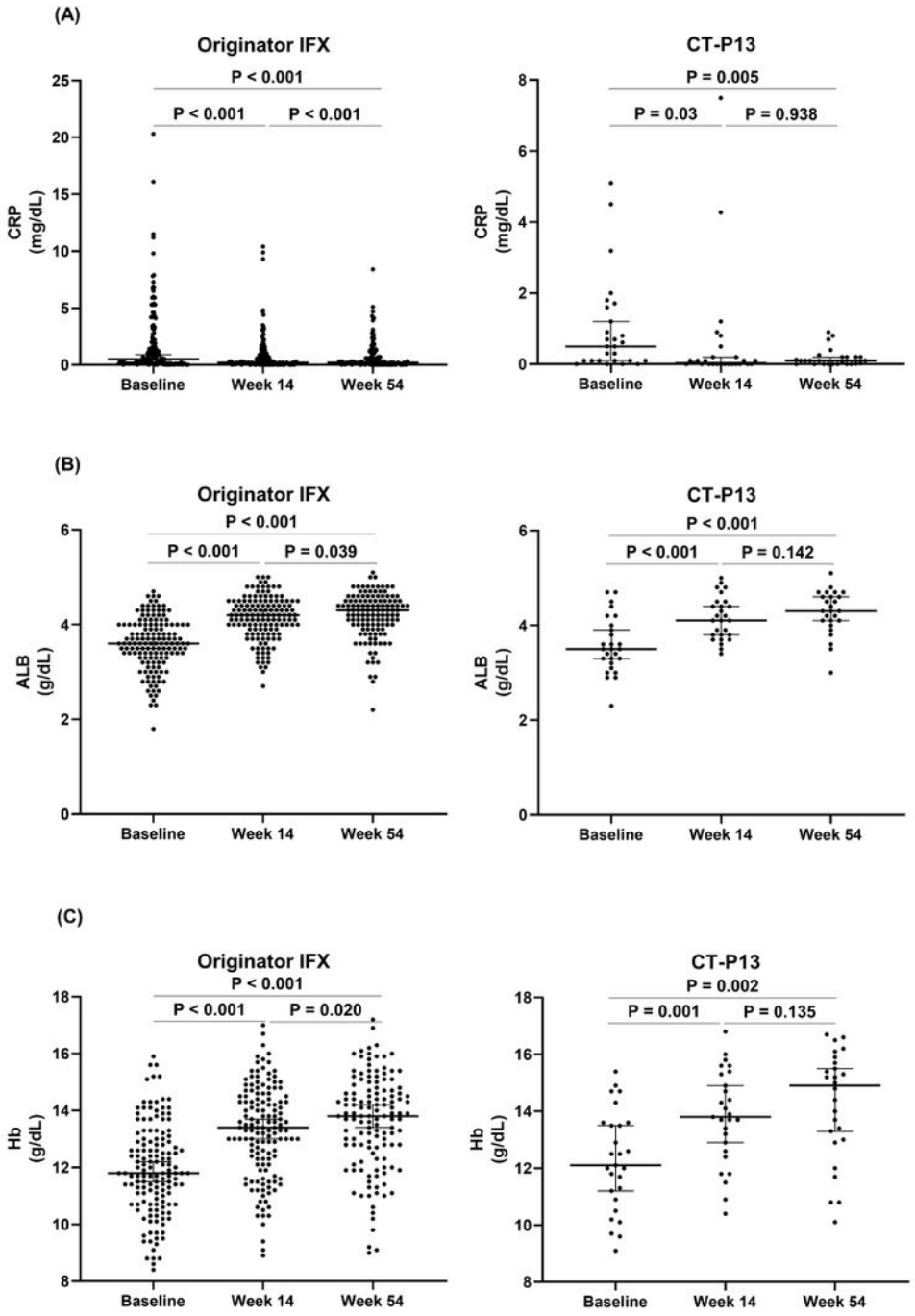

Figure 5

Laboratory findings from patients with Crohn's disease taking originator IFX or CT-P13 at baseline, week 14, and week 54. Each indicator (A: CRP, B: ALB, C: Hb) was significantly improved over baseline values at week 54. ALB, serum albumin; CRP, C-reactive protein, Hb, hemoglobin; IFX, infliximab.