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Infliximab Reduces Endoscopic, but not Clinical, Recurrence of Crohn's Disease Following Ileocolonic Resection

Short title: Infliximab for Post-Surgical CD Prevention

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Abbreviations used in this paper: 6-MP, 6-mercaptopurine; CI, confidence interval; ARR, absolute risk reduction; ATI, antibodies to infliximab; AZA, azathioprine; CDAI, Crohn's disease activity index; MTX, methotrexate; PREVENT, Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE® (infliximab) and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence; TNF, tumor necrosis factor.

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ABSTRACT

Background & Aims: Most patients with Crohn's disease (CD) eventually require an intestinal resection. However, CD frequently recurs following resection. We performed a randomized trial to compare the ability of infliximab vs placebo to prevent CD recurrence.

Methods: We evaluated the efficacy of infliximab in preventing post-operative recurrence of CD in 297 patients at 104 sites worldwide, from November 2010 through May 2012. All study patients had undergone ileocolonic resection within 45 days before randomization. Patients were randomly assigned (1:1) to groups given infliximab (5 mg/kg) or placebo every 8 weeks for 200 weeks. The primary endpoint was clinical recurrence a composite outcome consisting of a CD Activity Index score above 200 and a ≥70 point increase from baseline, and endoscopic recurrence (Rutgeerts score greater than or equal to i2, determined by a central reader), or development of a new or re-draining fistula or abscess, before or at week 76. Endoscopic recurrence was a major secondary endpoint.

Results: A smaller proportion of patients in the infliximab group had a clinical recurrence before or at week 76 compared with the placebo group, but this difference was not statistically significant (12.9% vs 20.0%; absolute risk reduction [ARR] with infliximab, 7.1%; 95% confidence interval [CI], –1.3% to 15.5%; P=.097). A significantly smaller proportion of patients in the infliximab group had endoscopic recurrence compared to the placebo group (30.6% vs 60.0%; ARR with infliximab, 29.4%; 95% CI, 18.6% to 40.2%; P<.001). Additionally, a significantly smaller proportion of patients in the infliximab group had endoscopic recurrence based only on Rutgeerts scores greater than or equal to i2 (22.4% vs 51.3%; ARR with infliximab, 28.9%; 95% CI, 18.4% to 39.4%; P<.001). Patients previously treated with anti-tumor necrosis factor agents or those with more than 1 resection were at greater risk for clinical recurrence. The safety profile of infliximab was similar to that from previous reports.

Conclusions: Infliximab is not superior to placebo in preventing clinical recurrence following CD-related resection. However, infliximab

does reduce endoscopic recurrence. ClinicalTrials.gov no: NCT01190839.

Key words: PREVENT; anti-TNF; inflammatory bowel disease; CDAI

INTRODUCTION

Crohn's disease (CD) often requires intestinal resection despite treatment with immunosuppressive and biologic therapies.[1,2] Historically, up to 70% of patients who undergo CD-related resection develop post-operative endoscopic recurrence at or proximal to the surgical anastomosis within one year.[3,4] Recent systematic reviews and meta-analyses have shown that approximately one-third of patients with CD who have a first resection require a second within 10 years, and the majority of these second intestinal resections occur within 5 years of the first. However, over the past few decades the risk of second resection has decreased.[5] Additionally, a decreasing trend has been found over the past 6 decades in the cumulative risk of resection 1, 5, and 10 years after CD diagnosis.[6]

Studies of probiotics, aminosalicylates, and budesonide[7-13] for prevention of post-operative recurrence have overall yielded negative results. Studies of nitroimidazole antibiotics have been positive for prevention of clinical recurrence. Studies of thiopurines have had mixed

results for the prevention of clinical recurrence. Neither nitroimidazole antibiotics nor thiopurines have consistently prevented endoscopic recurrence.[14-16] Initial studies,[17,18] a small placebo-controlled trial,[19] and subsequent observational studies[20-25] suggested that tumor necrosis factor (TNF) antagonists might be effective for prevention of post-operative recurrence. In recent studies of CD treatment strategies after intestinal resection, therapy adjusted according to 6-month colonoscopy findings led to effective disease control. [26-28] Overall, optimal post-operative management is unclear.

Given these considerations, we evaluated the efficacy and safety of infliximab for prevention of post-operative CD recurrence.

METHODS

Patients

The PREVENT study (NCT01190839) was a Phase 3, multicenter, placebo-controlled, double-blind, randomized study conducted at 104 sites globally between November 2010 and May 2012. The institutional

review board or ethics committee at each site approved the protocol, and patients provided written informed consent. All authors had access to the study data and had reviewed and approved the final manuscript.

Enrolled patients were at least 18 years old with a confirmed diagnosis of CD who had undergone ileocolonic resection with ileocolonic anastomosis. An end or loop ileostomy within one year was permitted if stoma closure and ileocolonic anastomosis occurred within 45 days of randomization. Patients had no evidence of macroscopic CD, no known active CD elsewhere in the gastrointestinal tract, and were eligible for randomization within 45 days of resection. Patients were ineligible if the qualifying surgery occurred more than 10 years after CD diagnosis and was performed for stricturing disease involving <10 cm of bowel. Patients were also required to have a baseline CD Activity Index (CDAI)[29] score <200 and at least one of the following risk factors for disease recurrence: 1) qualifying surgery that was their second intra-abdominal resection within 10 years, 2) third or more intra-abdominal resection, 3) resection for a penetrating CD complication (e.g., abscess

or fistula), 4) a history of perianal fistulizing CD provided the event had not occurred within 3 months, or 5) smoking 10 or more cigarettes per day for the past year. The prespecified risk factors of smoking, perforating disease, and previous resection had been identified from previous studies and utilized in a recent postoperative study.[26,30-36]

Patients receiving oral aminosalicylates or immunosuppressives (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]) pre-surgery could continue treatment with maintenance of stable doses after resection. Patients not receiving these agents pre-surgery could not receive them post-surgery. Rectal aminosalicylates were discontinued at least 2 weeks before randomization. Initiation of corticosteroids or antibiotics for CD treatment was prohibited.

Study Design

Patients were randomized equally to receive infliximab (REMICADE, Janssen Biotech, Inc.) 5 mg/kg or placebo every 8 weeks (q8w). Placebo and infliximab infusions were administered in a blinded manner. Randomization was stratified by the number of risk factors for

recurrence (1 or >1) and current use of an immunosuppressive (yes/no). Unlike dosing regimens used previously and that described in the prescribing information for patients with CD,[37] q8w dosing without the three-dose induction regimen was utilized in this study. This dosing regimen was chosen because patients in this study were in surgically-induced remission and did not have active CD at the time they entered the study; thus, q8w dosing for maintenance of remission was employed. Also, some patients may not have been naïve to infliximab, and data from an infliximab trial in patients with psoriasis showed a higher rate of serious infusion reactions at the week 2 infliximab infusion after a hiatus.[38]

CDAI scores were determined at each visit, and as required at interim assessments; baseline CDAI refers to the CDAI collected during the screening period (ie, no fewer than 10 days and no greater than 45 days before randomization) that qualified the patient for the study. Patients who met CDAI criteria (ie, ≥200 and an increase of ≥70 points from the baseline CDAI score) for clinical recurrence or reached week 76

underwent a video ileocolonoscopy. Patients who discontinued study agent prior to week 76 had a video ileocolonoscopy at the time of discontinuation. If clinical recurrence was observed, patients could receive blinded infliximab doses at an increase of 5mg/kg for each subsequent scheduled infusion visit, i.e., patients receiving placebo increased to 5mg/kg and patients receiving 5mg/kg to 10mg/kg.

Serum samples were collected at baseline and week 72 for measurement of infliximab and antibodies to infliximab (ATI).[39] Adverse events, concomitant medications, and CD-related hospitalizations and surgeries were recorded throughout.

Endpoints

The primary endpoint was clinical recurrence prior to or at week 76 defined by a ≥70-point increase from baseline with a total CDAI score ≥200, and evidence of endoscopic recurrence defined by a Rutgeerts score[3] of ≥i2 (i0, no lesions; i1, ≤5 aphthous lesions; i2, >5 aphthous lesions or anastomotic ulcer <1 cm; i3, diffuse aphthous ileitis with diffusely inflamed mucosa; i4, diffuse inflammation with large ulcers,

nodules, and/or narrowing) at the anastomotic site or its equivalent elsewhere in the gastrointestinal tract, or fistula/abscess development (ie., new draining external fistula, internal fistula, re-opening and draining of a previously existing external fistula, perianal abscess, or intra-abdominal abscess >3 months after the index surgery). Patients were considered to have clinical recurrence if they had a treatment failure (ie, initiated a prohibited CD medication, had a prohibited use of a CD medication, or had CD-related surgery).

The major secondary endpoint was endoscopic recurrence of CD prior to or at week 76 defined as a Rutgeerts score of ≥i2 either at the anastomosis or elsewhere in the GI tract, whether this occurred at the week 76 video ileocolonoscopy, or at a prior video ileocolonoscopy. Patients who developed a fistula or abscess, or had a treatment failure were considered to have endoscopic recurrence.

Endoscopic recurrence prior to or at week 76 defined by endoscopic score only (Rutgeerts score ≥i2) was also analyzed. Endoscopy

endpoints prior to or at week 76 including that for the primary endpoint were evaluated by a central reader (P.R.).

A secondary efficacy endpoint was clinical recurrence prior to or at week 104.

Study Duration

While treatment was planned for a maximum of 208 weeks, the study was terminated after week 104 because the primary outcome was not met.

Statistical analysis

All randomized patients were included in efficacy analyses according to assigned treatment regardless of actual treatment received. All patients who received at least one dose of study agent were included in safety and pharmacokinetic analyses based on actual treatment received.

For continuous outcomes, the last value before treatment failure was carried forward.

Seven sensitivity analyses were performed (5 pre-specified and 2 post hoc) on the primary endpoint.

Odds ratios for pre-specified subgroup analyses (eg, demographics, disease characteristics, concomitant medications) of clinical recurrence were summarized.

Categorical data (eg, clinical or endoscopic recurrence) were compared using the Cochran-Mantel-Haenszel $\chi 2$ test. Continuous measures were compared using analysis of variance on the van der Waerden normal scores. Time-to-event endpoints were analyzed using the log-rank test. A Cox model was used to evaluate predictors of clinical recurrence. Statistical testing was performed at $\alpha=0.05$ (two-sided) level of significance.

A fixed-sequence testing procedure controlled the overall Type I error rate at the 0.05 level. If the test for the primary endpoint was not positive, statistical tests for other endpoints were not considered

positive, even if the nominal p-value reached the 0.05 level of significance.

In a study conducted with a patient population similar to that proposed for this study, approximately 40% of patients in the placebo group experienced clinical recurrence by Week 52.[19] For calculation of sample size, 50% and 30% of placebo-and infliximab-treated patients respectively were expected to develop clinical recurrence by week 76. A sample size of 290 patients, 145 per treatment, provided 93% power to detect a 20% between-group difference in clinical recurrence prior to or at week 76.

RESULTS

PATIENTS

Demographics, qualifying characteristics, and risk factors of the 297 randomized patients (placebo, N=150; infliximab, N=147) were similar between treatment groups. The most common risk factor for intestinal resection was penetrating complication (Table 1, Supplementary Tables S2, S3). Approximately 20% of randomized patients received concomitant immunosuppressives (Table 1). Antibiotics were administered for CD to 6 patients in the placebo group and 2 patients in the infliximab 5 mg/kg group; these patients were considered treatment failures.

Patient disposition is shown in Figure 1. Approximately one-third of randomized patients discontinued study drug prior to week 76, most commonly for adverse events.

PRIMARY ENDPOINT

Clinical recurrence rates prior to or at week 76 were 12.9% and 20.0% for the infliximab and placebo groups, respectively (absolute risk reduction [ARR] with infliximab, 7.1%; 95% confidence interval [CI], -1.3% to 15.5%); these results were not statistically significant (*P*=.097) (Figure 2). Of note, clinical recurrence rates prior to or at week 76 among patients who met both CDAI and endoscopic criteria were 4.1% and 9.3% (*P*=.056) for the infliximab and placebo groups, respectively (Table 2).

In general, the results of the sensitivity analyses were consistent with the results of the primary endpoint analysis (Supplementary Table S1).

Time to clinical recurrence is summarized in Figure 3 for the infliximab and placebo groups (Log rank *P*=.141).

Results observed in pre-specified subgroups were generally consistent with the overall results with a few exceptions including CD duration, baseline CDAI score, prior TNF therapy, race, geographic location,

disease location in gastrointestinal tract, and patients undergoing their second intra-abdominal operation (Supplementary Figures S1A-D).

SECONDARY ENDPOINTS

Endoscopic recurrence

Endoscopic recurrence, as defined by Rutgeerts score ≥i2; or abscess, fistula recurrence or development; or treatment failure, prior to or at week 76 for the infliximab and placebo groups was 30.6% and 60.0%, respectively (ARR with infliximab, 29.4%; 95% CI, 18.6% to 40.2%; P<.001; Figure 4A).

Similarly, endoscopic recurrence defined only by Rutgeerts scores ≥i2 for the infliximab and placebo groups was 22.4% and 51.3%, respectively (ARR with infliximab, 28.9%; 95% CI, 18.4% to 39.4%; P<.001; Figure 4A).

Classification of patients by Rutgeerts score i1 (<5 aphthous ulcers) and i2 (≥5 aphthous ulcers or anastomotic ulcer <1 cm) endoscopic recurrence may be of negligible clinical significance and potentially

separated by only 1 aphthous ulcer. Classifying patients by normal mucosa (i0) or aggressive endoscopic recurrence (i3/i4) provides a more meaningful distinction.

Central endoscopic results prior to or at week 76 were presented in Figure 4B. Of 73 patients with an i0 Rutgeerts score prior to or at week 76, 54 (74.0%) and 19 (26.0%) patients were in infliximab and placebo groups, respectively (Supplementary Figure S2). Of 59 patients with an i3 or i4 Rutgeerts score prior to or at week 76, 11 (18.6%) and 48 (81.4%) patients were in the infliximab and placebo groups, respectively (Supplementary Figure S2).

Among patients with endoscopy results prior to or at week 76, the distribution of Rutgeerts scores are summarized in Figure 4B.

Clinical recurrence at Week 104

Clinical recurrence rates prior to or at week 104 were 17.7% and 25.3% for the infliximab and placebo groups, respectively (ARR with infliximab, 7.6%, 95% CI, -1.7%, to 17.0%; *P*=.098) (Figure 2).

CDAI scores at Week 104

The median changes from baseline in CDAI score at the last visit prior to or at week 104 were -15.0 and -22.0 for placebo and infliximab 5 mg/kg respectively (P=.058). Median CDAI scores through Week 104 are shown in Supplementary Figure S3.

HOSPITALIZATIONS AND SURGERIES

Hospitalizations and surgeries were uncommon with no statistically significant differences observed between groups through week 104 (Supplementary Table S4).

PREDICTORS OF CLINICAL RECURRENCE

Patients with more than one resection or who received anti-TNF therapy pre-surgery were more likely to have a clinical recurrence (Supplementary Table S5).

SAFETY

Among 297 randomized patients, 291 received at least 1 dose of study drug. The average duration of treatment before a dose increase was similar for infliximab and placebo (74.3 weeks and 75.9 weeks, respectively; Table 3).

Adverse and serious adverse event rates were similar between groups. Infection rates, including serious infections, were also similar. More patients in the infliximab than placebo group discontinued therapy because of an adverse event through the final visit, most commonly for adverse events related to the gastrointestinal or infection and infestation system organ class (Supplementary Table S6).

There were no deaths or malignancies (excluding nonmelanoma skin cancer) in infliximab-treated patients (Table 3).

Infusion reactions occurred in 8.2% of placebo-treated compared with 19.4% of infliximab-treated patients (Table 3).

PHARMACOKINETICS AND IMMUNOGENICITY

For patients in the infliximab 5 mg/kg group, median trough serum infliximab concentrations were 0.00 μg/mL and 2.18 μg/mL at week 0 and week 72, respectively.

At week 72, median serum infliximab concentration for patients receiving immunosuppressives was numerically greater than those not receiving immunosuppressives (4.89 μg/mL versus 1.83 μg/mL, respectively). The proportion of infliximab-treated patients with endoscopic recurrence prior to or at week 76 decreased with increasing serum infliximab concentration. This effect was not observed for clinical recurrence (Supplementary Figure S4).

Overall, ATIs were present in 16.2% of patients, none of whom were receiving immunosuppressives at baseline. This ATI incidence is based on an antigen-bridging enzyme immunoassay in which detectable levels of circulating infliximab may interfere with the ability to assess the presence of ATI. Endoscopic recurrence prior to or at week 76 was seen

in 64.7% (11 of 17), 46.7% (7 of 15), and 30.1% (22 of 73) of patients who were positive, negative, or inconclusive for ATI, respectively. This effect was not observed for clinical recurrence.

DISCUSSION

This study evaluating infliximab for prevention of post-surgical CD recurrence following ileocolonic resection did not meet the primary endpoint of clinical recurrence and was prematurely terminated at week 104. The endoscopic recurrence rate in infliximab-treated patients is consistent with those of small, randomized, controlled trials.[18,19]

We also found that patients with a prior resection and use of anti-TNF therapy pre-surgery were at a higher risk for postoperative CD recurrence. However, it is possible that these factors reflect disease severity and/or complicated disease course rather than independent risk factors for recurrence; however, these results should be interpreted with caution due to the small sample size.

The PREVENT trial is the first large, multicenter, placebo-controlled postoperative CD study with a biologic. Assumptions on postoperative clinical and endoscopic recurrence were extrapolated from the collective results of several smaller studies, including the trial by Regueiro.

Patients enrolled in that small study[19] may have had a higher risk of post-operative CD recurrence, most with penetrating disease and a high proportion having undergone at least two resections. The intent of the PREVENT study was to enroll a similar high-risk population; however, 69.6% had only one risk factor for recurrence, and 57.4% were undergoing their first intestinal resection. This may account for the difference in the placebo clinical recurrence rate prior to or at week 76 in PREVENT (20.0%) and the 12-month rate reported previously (38.5%).[19]

It should be noted that while the risk factors for postoperative recurrence, i.e., cigarette smoking, recurrent surgery, and penetrating disease, have been included in numerous previous studies,[26,30-36] these factors have never been formally validated or replicated. Likewise, the combination of factors would presume a higher risk of postoperative recurrence; this additive effect has also not been replicated. Therefore, the stratification of risk based on the small sample size of the Regueiro trial may have resulted in an overestimation of effect in PREVENT.

The low baseline median CDAI of 105.5 required many patients to double their CDAI score over the course of the study to meet the clinical recurrence criterion of CDAI ≥200. This possibly contributed to the small proportions of patients (infliximab, 4.1%; placebo, 9.3%) who met both CDAI and endoscopic criteria for clinical recurrence prior to or at week 76. Furthermore, only17.5% of patients received concomitant immunosuppressives compared with 45.8% of patients in the Regueiro trial.[19] Administration of immunosuppressives increases infliximab levels, reduces immunogenicity, and increases efficacy of infliximab.[40]

Patients in PREVENT underwent a video ileocolonoscopy at week 76, when CDAI criteria met the definition of clinical recurrence, or when they discontinued the study. Week 76, rather than 24 or 48 weeks was selected as the primary timepoint due to the combined clinical and endoscopic endpoint. Clinical recurrence within the first year after resection is low as endoscopic recurrence often occurs initially without clinical symptoms.[3,41-44]

We hypothesized that waiting 18 months after resection for primary composite endpoint assessment would be sufficient to detect clinical recurrence without endoscopic recurrence causing severe, irreversible bowel damage. Additionally, when the PREVENT study was designed (2009) only one small proof-of-concept study[19] and an open-label experience[18] in post-operative patients with CD treated with anti-TNF therapies were published to guide the timing and definition of clinical endpoints.

Our selection of a composite endpoint appeared to be supported by a subsequent publication by Walters, et al.[45] who explored the utility of the CDAI in determining symptomatic disease recurrence in patients having previously undergone ileocolonic resection for CD, and concluded that "a combination of symptom assessment plus endoscopic evidence of recurrence should remain the gold standard definition for assessing outcomes in postoperative CD trials." However, it must be acknowledged that the composite endpoint prospectively implemented here was not formally validated in this clinical setting.

Because early endoscopic recurrence appears to correlate with future clinical recurrence and the need for resection,[3] it is currently recommended that patients with CD undergo a surveillance ileocolonoscopy 6 to 12 months postoperatively to assess for endoscopic recurrence.[41-44] Recent studies have suggested anti-TNF therapy effectiveness in this setting based on therapy adjusted according to 6-month postoperative colonoscopy findings.[26-28]

There are limitations to the study. Infliximab may have been started as late as 45 days after resection by which time there could have been early endoscopic recurrence. This would mean that treatment was initiated in response to active inflammation rather than prevention of CD recurrence. The rationale for waiting 45 days was to ensure at least 14 to 21 days passed with no surgical resection complication, and to allow enough time for the CDAI collection and additional patient screening. The median time between resection and first study infusion was 36.5 days for placebo and 35 days for infliximab 5 mg/kg, and is unlikely to have significantly altered the results. While we designed the study as

q8w maintenance infusions after resection, it is possible that the three-dose induction and concomitant use of immunosuppressants could have led to even lower recurrence rates as described previously[40] and reduced immunogenicity.

While prevention of clinical recurrence was not achieved, infliximab-treated patients achieved a lower endoscopic recurrence rate than those assigned to placebo. Consistent with other studies using anti-TNF therapies,[17,18,25,46] infliximab-treated patients had lower recurrence defined by endoscopic criteria only.

The primary endpoint of clinical recurrence may be influenced by symptom-based CDAI score which consists of diarrhea, abdominal pain, and general well-being components that may be neither sensitive nor specific for mucosal inflammation, integral to disease recurrence.[47] Regueiro and colleagues also found no correlation between CDAI scores and endoscopic disease activity one year after ileocolonic resection with the majority of patients in clinical remission (CDAI<150) despite endoscopic recurrence.[48]

The severity of endoscopic recurrence has a high predictive value for the need for future resection.[3,49] If the goal of mucosal healing and maintenance of intestinal normalcy, rather than symptom control alone, are relevant IBD inflammatory bowel disease management targets, then a post-operative strategy for prevention of endoscopic recurrence may be clinically relevant, especially for high-risk patients.[50,51] Given the high rates of clinically silent, but endoscopically active CD within 2 years of resection, we suggest that future postoperative studies utilize objective rather than subjective criteria for active CD, and have the primary assessment no more than one year after resection.

A postoperative strategy of escalating treatment for endoscopic recurrence at 6 months was evaluated in POCER.[28] Patients were risk-stratified (high vs. low) for CD recurrence then randomized to have an initial colonoscopy at 6 months or no colonoscopy until 18 months. All patients received 3 months of metronidazole, if tolerated, and high-risk patients were treated with postoperative thiopurine, or if previously intolerant, adalimumab. Patients undergoing a 6-month colonoscopy

were started on or received additional treatment for endoscopic recurrence. The primary endpoint of the POCER study was postoperative endoscopic recurrence at 18 months. The 18-month endoscopic recurrence rate in patients previously undergoing a colonoscopy at 6 months was 49% compared to 67% in those who had not had a 6 month colonoscopy. The 6-month endoscopic recurrence rate in high-risk patients receiving thiopurine was 45% compared to 21% with anti-TNF therapy and is similar to the 18-month endoscopic recurrence rate in the PREVENT trial (51.3% in placebo and 22.4% in infliximab). Therefore, it may be reasonable to approach low risk patients undergoing their first resection for CD conservatively and initiate treatment only if there is endoscopic recurrence at 6 months. High-risk patients with recurrent intestinal resection for CD should be considered for postoperative anti-TNF therapy.

In conclusion, infliximab was not significantly superior for prevention of clinical recurrence following CD ileocolonic resection, but did reduce endoscopic recurrence.

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TABLE and FIGURE Legends

Table 1: Baseline demographics, disease characteristics, and concomitant CD medications; randomized patients

Table 2: Reasons for clinical recurrence prior to or at Week 76

Table 3: Key safety findings through week 104; treated patients

Figure 1: Study flow diagram

Figure 2: Clinical recurrence prior to or at week 76 and prior to or at week 104[a,b]

a. P-values based on the Cochran-Mantel-Haenszel χ^2test stratified by the number of risk factors for recurrence of active Crohn's disease (1 or >1) and baseline use (yes/no) of an immunosuppressives (ie, azathioprine, 6-mercaptopurine, or methotrexate).
b. denotes nominal P-value.

Figure 3: Time to first clinical recurrence prior to or at week 76; all randomized patients

Figure 4: Endoscopic recurrence prior to or at week 76; all randomized patients (A) and central endoscopic results prior to or at week 76 (Rutgeerts score i0, i1, i2, i3, i4) (B)[a,b,c]

a. P-values based on the Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active Crohn's disease (1 or >1) and baseline use (yes/no) of an immunosuppressives (ie, azathioprine, 6-mercaptopurine, or methotrexate).
b. † denotes nominal p-value.
c. i0, no lesions; i1, ≤5 aphthous lesions; i2, >5 aphthous lesions or anastomotic ulcer <1 cm; i3, diffuse aphthous ileitis with diffusely inflamed mucosa; i4, diffuse inflammation with large ulcers,nodules, and/or narrowing.

Table 1: Baseline demographics , disease characteristics, and concomitant cd medications; randomized patients

	Placebo (N=150)	Infliximab 5 mg/kg (N=147)	Total (N=297)
Sex, n (%)			
N	150	147	297
Male	81 (54.0)	77 (52.4)	158 (53.2)
Female	69 (46.0)	70 (47.6)	139 (46.8)
Race, n (%)			
N	150	147	297
White	138 (92.0)	138 (93.9)	276 (92.9)
Black or African American	4 (2.7)	3 (2.0)	7 (2.4)
Asian	2 (1.3)	1 (0.7)	3 (1.0)
Other	6 (4.0)	5 (3.4)	11 (3.7)
Age (yrs)			
N	150	147	297
Mean (SD)	35.4 (12.41)	37.1 (13.49)	36.3 (12.96)
Median	34.0	35.0	34.0
IQ range	(25.0; 44.0)	(26.0; 45.0)	(26.0; 44.0)
Range	(18; 69)	(18; 76)	(18; 76)
Weight (kg)			
N	150	147	297
Mean (SD)	69.70 (16.083)	69.64 (17.716)	69.67 (16.883)
Median	67.30	66.00	66.80
IQ range	(58.10; 78.10)	(57.20; 79.50)	(58.00; 78.30)
Range	(41.0; 127.0)	(40.0; 125.7)	(40.0; 127.0)
Disease duration (yrs)			
N	150	146	296
Mean (SD)	6.39 (7.457)	8.38 (8.651)	7.37 (8.115)
Median	3.32	6.49	5.17
IQ range	(0.74; 9.71)	(1.45; 11.07)	(0.80; 10.61)
Range	(0.1; 37.5)	(0.1; 45.9)	(0.1; 45.9)
CDAI score			
N	150	146	296
Mean (SD)	109.8 (54.75)	107.7 (52.75)	108.8 (53.69)
Median	109.5	102.5	105.5
IQ range	(66.0; 153.0)	(64.0; 148.0)	(65.0; 152.5)
Range	(4; 240)	(3; 202)	(3; 240)
Involved GI areas, n (%)			
N	150	146	296
Ileum	146 (97.3)	144 (98.6)	290 (98.0)
Colon	76 (50.7)	89 (61.0)	165 (55.7)
Proximal small intestine, stomach and/or esophagus	6 (4.0)	6 (4.1)	12 (4.1)
Perianal	13 (8.7)	17 (11.6)	30 (10.1)
Extra intestinal manifestations	15 (10.0)	21 (14.4)	36 (12.2)

Table 1: Baseline demographics , disease characteristics, and concomitant cd medications; randomized patients

	Placebo (N=150)	Infliximab 5 mg/kg (N=147)	Total (N=297)
Findings at surgery, n (%)			
N	150	146	296
Stricture	86 (57.3)	84 (57.5)	170 (57.4)
Abscess	41 (27.3)	47 (32.2)	88 (29.7)
Internal fistula	86 (57.3)	67 (45.9)	153 (51.7)
Sinus tracts	10 (6.7)	7 (4.8)	17 (5.7)
Perforation	12 (8.0)	19 (13.0)	31 (10.5)
Prior intra-abdominal surgeries, n (%)			
N	150	146	296
0	91 (60.7)	79 (54.1)	170 (57.4)
1-2	51 (34.0)	63 (43.2)	114 (38.5)
>2	8 (5.3)	4 (2.7)	12 (4.1)
CD medication history, n (%)			
N	150	146	296
Any CD medication	144 (96.0)	136 (93.2)	280 (94.6)
Anti-tumor necrosis factor	30 (20.0)	37 (25.3)	67 (22.6)
Adalimumab	17 (11.3)	21 (14.4)	38 (12.8)
Infliximab	15 (10.0)	18 (12.3)	33 (11.1)
Certolizumab	0	3 (2.1)	3 (1.0)
Corticosteroid (excluding budesonide)	96 (64.0)	104 (71.2)	200 (67.6)
Budesonide	67 (44.7)	63 (43.2)	130 (43.9)
Immunosuppressive drugs	88 (58.7)	85 (58.2)	173 (58.4)
6-MP	22 (14.7)	19 (13.0)	41 (13.9)
AZA	77 (51.3)	73 (50.0)	150 (50.7)
Methotrexate	7 (4.7)	11 (7.5)	18 (6.1)
Aminosalicylates	101 (67.3)	100 (68.5)	201 (67.9)
Antibiotics	88 (58.7)	94 (64.4)	182 (61.5)
Concomitant CD medications, n (%)			
N	150	147	297
Any CD medication	47 (31.3)	53 (36.1)	100 (33.7)
Corticosteroid (excluding budesonide)	4 (2.7)	10 (6.8)	14 (4.7)
≥20 mg/day P.Eq	0	1 (0.7)	1 (0.3)
< 20 mg/day P.Eq	4 (2.7)	9 (6.1)	13 (4.4)
Budesonide	2 (1.3)	2 (1.4)	4 (1.3)
Immunosuppressive drugs	27 (18.0)	25 (17.0)	52 (17.5)
6-MP/AZA	27 (18.0)	21 (14.3)	48 (16.2)
Methotrexate	0	4 (2.7)	4 (1.3)
Aminosalicylates	27 (18.0)	28 (19.0)	55 (18.5)

Key: CD, Crohn's disease; CDAI, Crohn's disease activity index; GI, gastrointestinal; P.Eq, prednisone equivalent; 6-MP, 6-mercaptopurine; AZA, azathioprine; SD, standard deviation.

Table 2: Reasons for clinical recurrence[a] prior to or at Week 76

Reasons	Placebo (N=150)	Infliximab 5 mg/kg (N=147)
Met CDAI and endoscopic criteria, n (%)	14 (9.3)	6 (4.1)
Met fistula/abscess criteria, n (%)	7 (4.7)	3 (2.0)
Developed a new draining external fistula	2 (1.3)	0
Re-opened and drained a previously existing external fistula	0	1 (0.7)
Developed a new internal fistula	3 (2.0)	2 (1.4)
Developed a new perianal abscess	6 (4.0)	1 (0.7)
Developed a new intra-abdominal abscess >3 months after the date of the index surgery	0	1 (0.7)
Had a treatment failure, n (%)	14 (9.3)	14 (9.5)
Initiated a prohibited CD medication	7 (4.7)	4 (2.7)
Had a prohibited use of a CD medication	12 (8.0)	12 (8.2)
Had a surgery for CD	2 (1.3)	2 (1.4)
Met at least 1 of the following 2 criteria, n (%)	1 (0.7)	0
Discontinued study agent due to recurrent symptoms of CD	0	0
Met CDAI criteria at the time of discontinuation of study agent	1 (0.7)	0
Did not have sufficient data to evaluate clinical recurrence status at both Week 72 and Week 76, n (%)	0	0

a. Patients could have more than one reason for clinical recurrence

Key: CD, Crohn's disease; CDAI, Crohn's disease activity index.

Table 3: Key safety findings through week 104; treated patients

			Infliximab (dose increase)		
	Placebo[a] (N=146)	Infliximab 5 mg/kg[a,b] (N=145)	Placebo/ Infliximab 5 mg/kg[c] (N=25)	Infliximab 5 mg/kg/ Infliximab 10 mg/kg[c] (N=9)	All Infliximab[d] (N=170)
Avg duration of follow-up (weeks)	85.4	85.7	50.6	39.4	82.6
Avg duration of treatment (weeks)	75.9	74.3	32.4	13.9	68.9
Patients with ≥1 adverse events, n (%)	132 (90.4)	133 (91.7)	19 (76.0)	7 (77.8)	152 (89.4)
Patients with ≥1 serious adverse events, n (%)	32 (21.9)	28 (19.3)	3 (12.0)	2 (22.2)	32 (18.8)
Patients who discontinued study agent because of ≥1 adverse events, n (%)	13 (8.9)	35 (24.1)	10 (40.0)	5 (55.6)	50 (29.4)
Patients who died, n (%)	1 (0.7)	0	0	0	0
Patients with 1 or more malignancies,[e] n (%)	2 (1.4)	0	0	0	0
Patients with ≥1 infections, n (%)	85 (58.2)	84 (57.9)	8 (32.0)	4 (44.4)	93 (54.7)
Patients with ≥1 serious infections, n (%)	9 (6.2)	7 (4.8)	1 (4.0)	1 (11.1)	9 (5.3)
Patients with ≥1 infusion reaction,[f] n (%)	12 (8.2)	26 (17.9)	7 (28.0)	1 (11.1)	33 (19.4)

a. Includes data up to the time of dose increase for those who increased dose. Six patients were randomized but not treated and analyzed for efficacy only, and 2 patients inadvertently received infliximab 5 mg/kg and analyzed for safety as infliximab-treated patients.

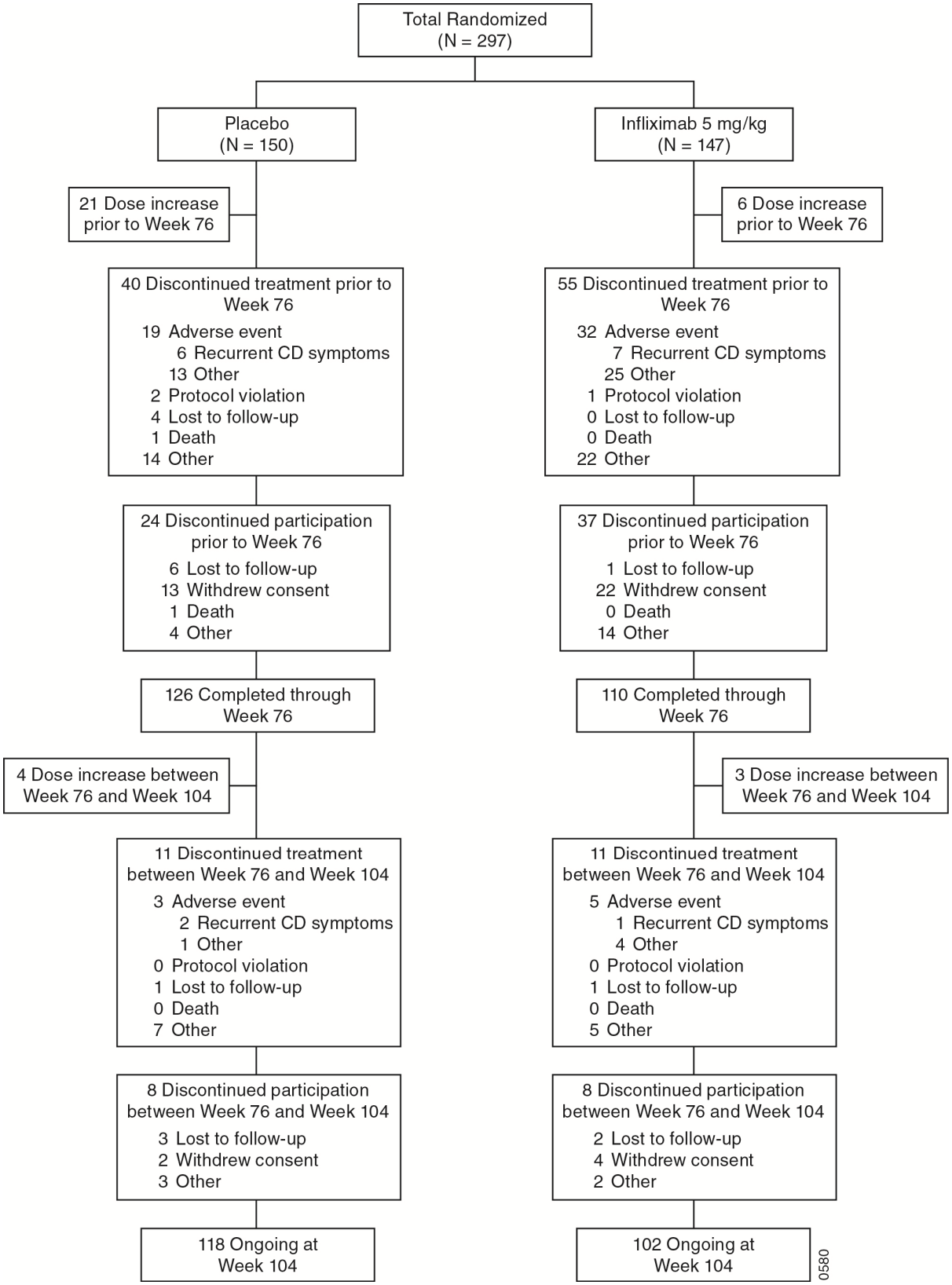
b. Two patients were randomized to the placebo group, but received one infusion of infliximab. These patients were analyzed in the infliximab 5 mg/kg group for safety.

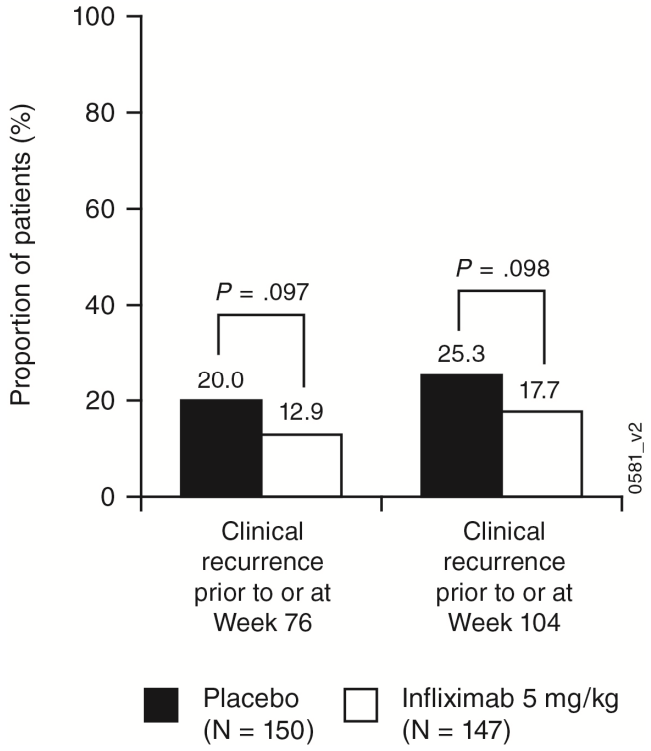
c. Includes data from the time of dose increase onward.

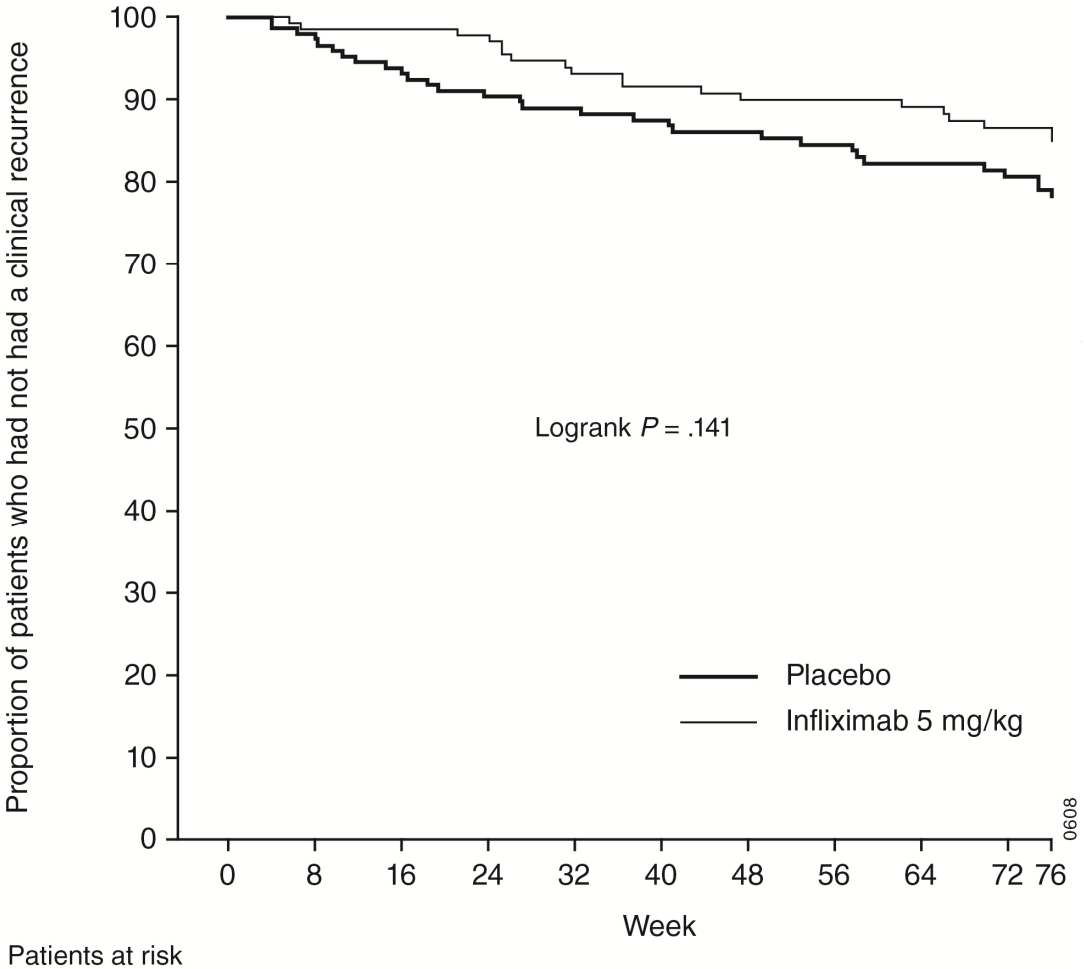
d. Includes data from the time of the first Infliximab dose onward.

e. Malignancies excluding Non-Melanoma Skin Cancers were defined by individual event terms in Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) System Organ Class.

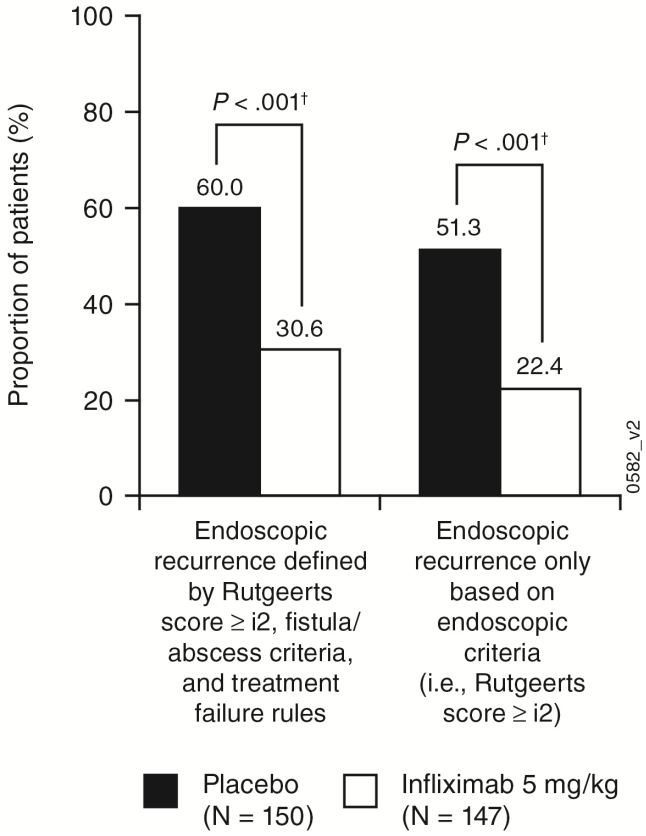
f. An infusion reaction was defined as any adverse event that occurred during or within 1 hour of the administration of the study agent infusion.







Patients at risk											
Placebo	150	144	136	129	125	122	115	111	107	102	96
Infliximab 5 mg/kg	147	138	134	129	118	115	112	110	107	99	97



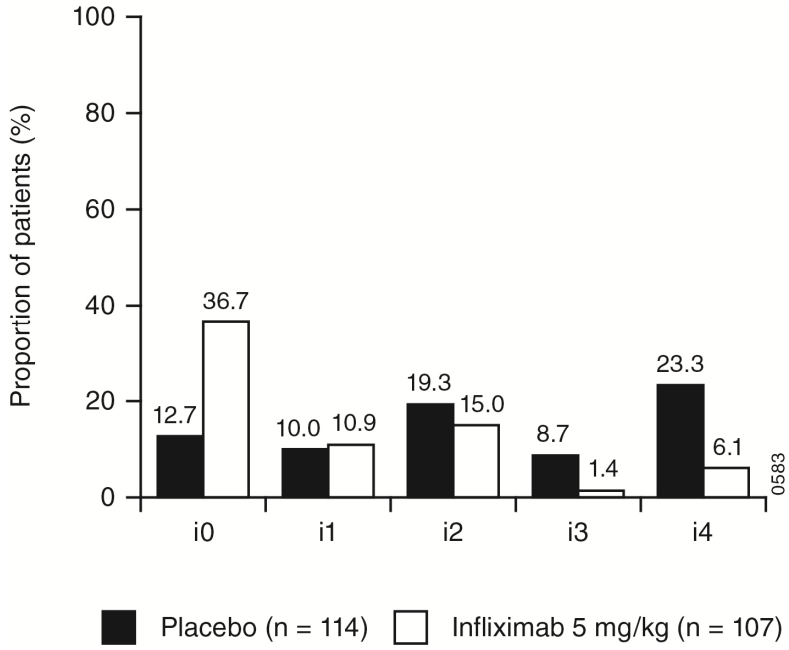


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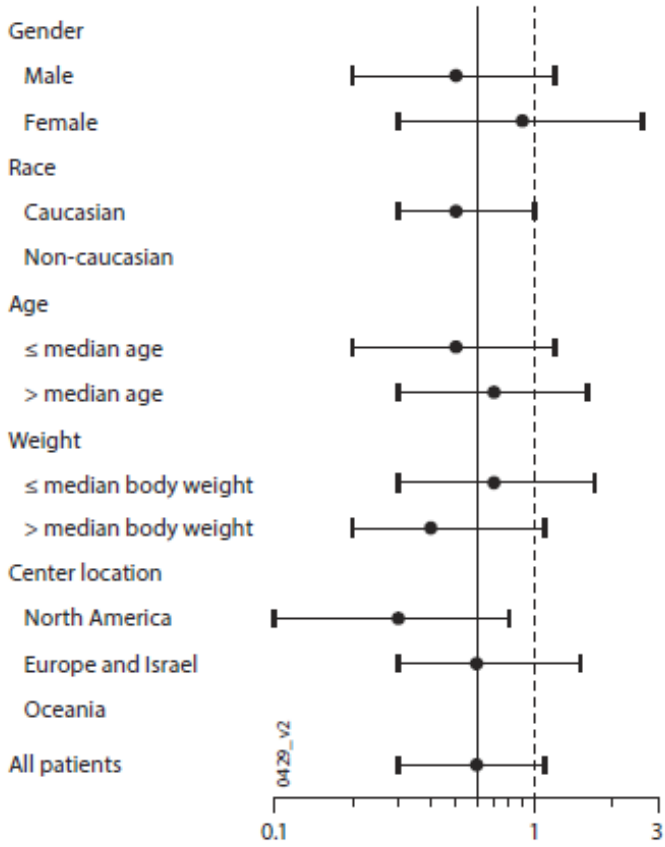
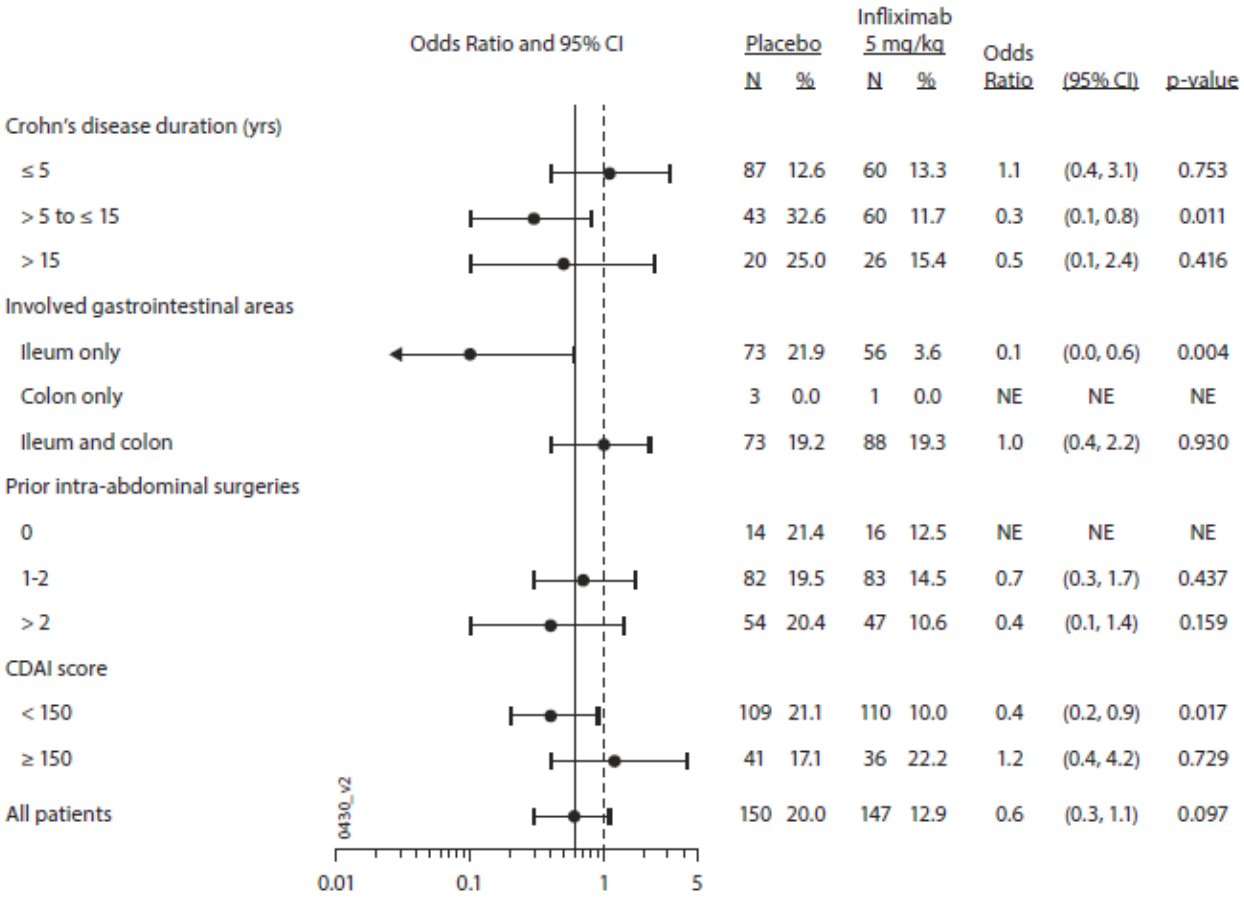
Figure S1A: Plot of odds ratio (vertical bars) and 95% confidence intervals (horizontal bars) for comparing the proportion of patients with clinical recurrence prior to or at week 76 in the infliximab group vs. the placebo group by demographic characteristics at baseline; randomized patients



	Placebo		Infliximab 5 mg/kg		Odds		
	N	%	N	%	Ratio	(95% CI)	p-value
Gender							
Male	81	25.9	77	14.3	0.5	(0.2, 1.2)	0.105
Female	69	13.0	70	11.4	0.9	(0.3, 2.6)	0.836
Race							
Caucasian	138	21.0	138	12.3	0.5	(0.3, 1.0)	0.052
Non-caucasian	12	8.3	9	22.2	NE	NE	NE
Age							
≤ median age	76	21.1	73	12.3	0.5	(0.2, 1.2)	0.126
> median age	74	18.9	74	13.5	0.7	(0.3, 1.6)	0.408
Weight							
≤ median body weight	72	19.4	78	15.4	0.7	(0.3, 1.7)	0.387
> median body weight	78	20.5	69	10.1	0.4	(0.2, 1.1)	0.075
Center location							
North America	36	36.1	42	14.3	0.3	(0.1, 0.8)	0.015
Europe and Israel	94	16.0	91	11.0	0.6	(0.3, 1.5)	0.317
Oceania	20	10.0	14	21.4	NE	NE	NE
All patients	150	20.0	147	12.9	0.6	(0.3, 1.1)	0.097

Key: CI, confidence interval; NE, not evaluable.

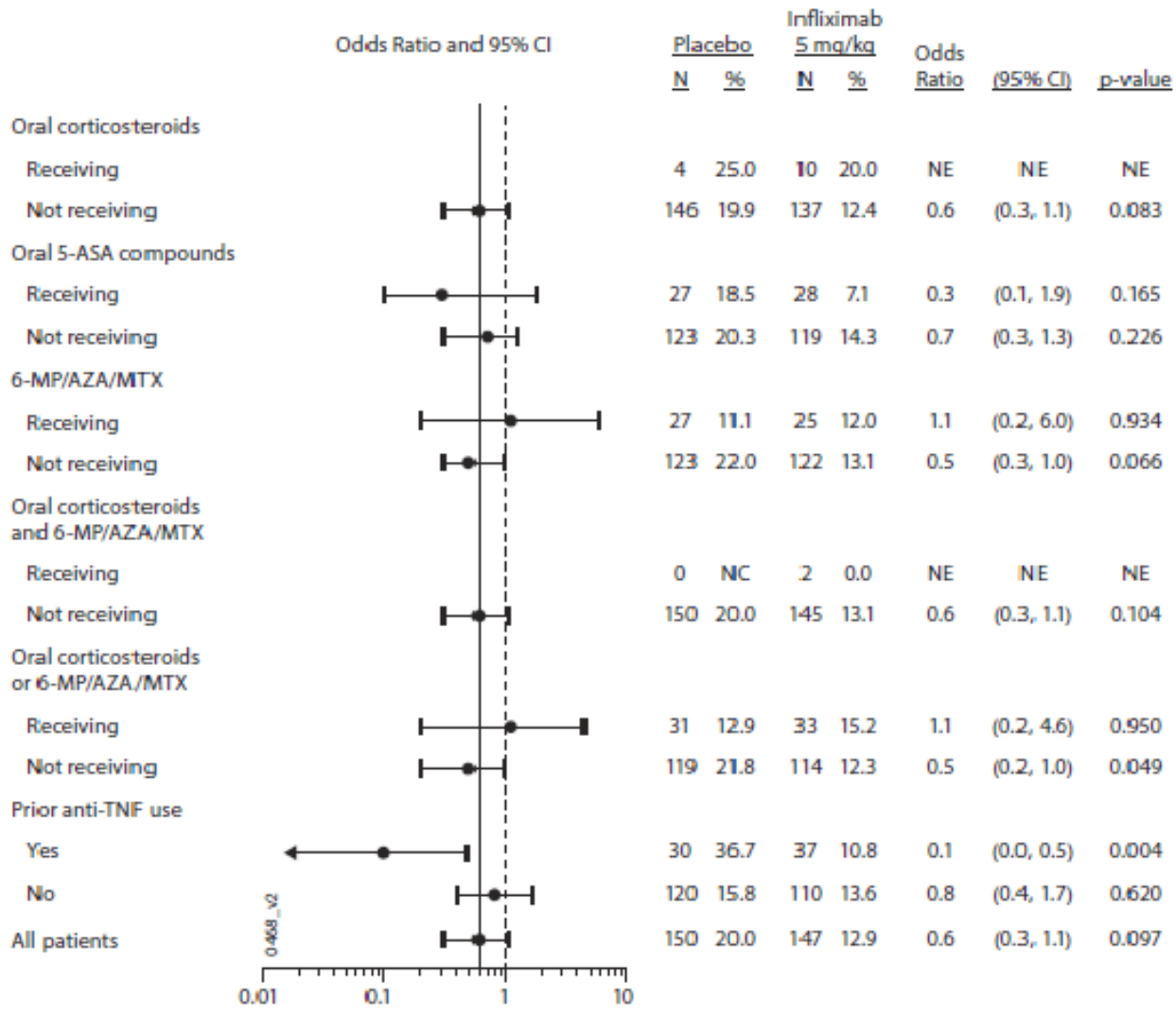
Figure S1B: Plot of odds ratio (vertical bars) and 95% confidence intervals (horizontal bars) for comparing the proportion of patients with clinical recurrence prior to or at week 76 in the infliximab group vs. the placebo group by Crohn's disease characteristics at baseline; randomized patients



	Placebo N	Placebo %	Infliximab 5 mg/kg N	Infliximab 5 mg/kg %	Odds Ratio	(95% CI)	p-value
Crohn's disease duration (yrs)							
≤ 5	87	12.6	60	13.3	1.1	(0.4, 3.1)	0.753
> 5 to ≤ 15	43	32.6	60	11.7	0.3	(0.1, 0.8)	0.011
> 15	20	25.0	26	15.4	0.5	(0.1, 2.4)	0.416
Involved gastrointestinal areas							
Ileum only	73	21.9	56	3.6	0.1	(0.0, 0.6)	0.004
Colon only	3	0.0	1	0.0	NE	NE	NE
Ileum and colon	73	19.2	88	19.3	1.0	(0.4, 2.2)	0.930
Prior intra-abdominal surgeries							
0	14	21.4	16	12.5	NE	NE	NE
1-2	82	19.5	83	14.5	0.7	(0.3, 1.7)	0.437
> 2	54	20.4	47	10.6	0.4	(0.1, 1.4)	0.159
CDAI score							
< 150	109	21.1	110	10.0	0.4	(0.2, 0.9)	0.017
≥ 150	41	17.1	36	22.2	1.2	(0.4, 4.2)	0.729
All patients	150	20.0	147	12.9	0.6	(0.3, 1.1)	0.097

Key: CI, confidence interval; yrs, years; NE, not evaluable; CDAI, Crohn's disease activity index

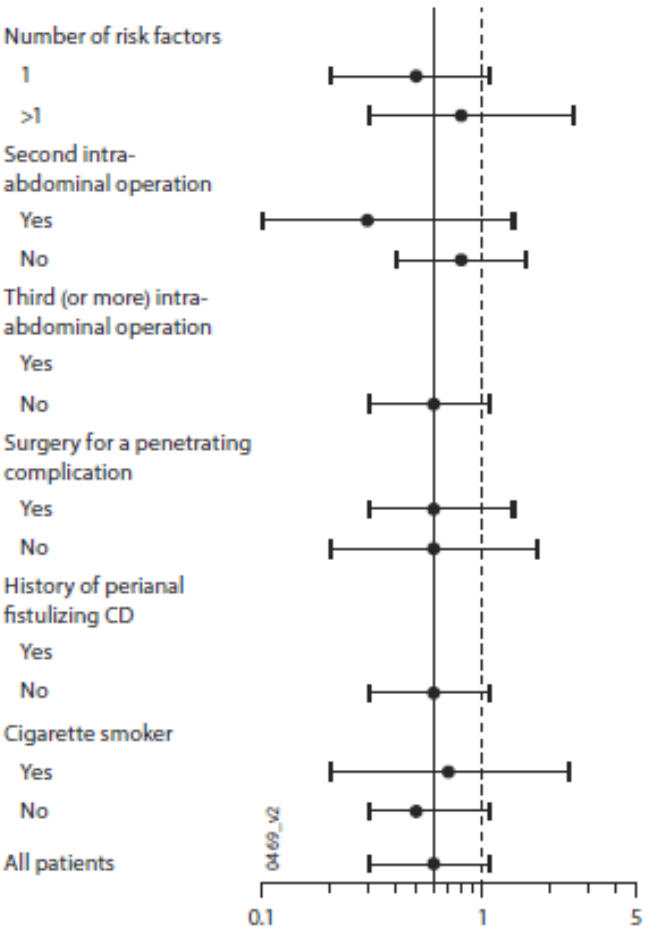
Figure S1C: Plot of odds ratio (vertical bars) and 95% confidence intervals (horizontal bars) for comparing the proportion of patients with clinical recurrence prior to or at week 76 in the infliximab group vs. the placebo group by baseline Crohn's disease-related concomitant medication use and anti-TNF history; randomized patients



	Placebo N	Placebo %	Infliximab 5 mg/kg N	Infliximab 5 mg/kg %	Odds Ratio	(95% CI)	p-value
Oral corticosteroids							
Receiving	4	25.0	10	20.0	NE	NE	NE
Not receiving	146	19.9	137	12.4	0.6	(0.3, 1.1)	0.083
Oral 5-ASA compounds							
Receiving	27	18.5	28	7.1	0.3	(0.1, 1.9)	0.165
Not receiving	123	20.3	119	14.3	0.7	(0.3, 1.3)	0.226
6-MP/AZA/MTX							
Receiving	27	11.1	25	12.0	1.1	(0.2, 6.0)	0.934
Not receiving	123	22.0	122	13.1	0.5	(0.3, 1.0)	0.066
Oral corticosteroids and 6-MP/AZA/MTX							
Receiving	0	NC	2	0.0	NE	NE	NE
Not receiving	150	20.0	145	13.1	0.6	(0.3, 1.1)	0.104
Oral corticosteroids or 6-MP/AZA/MTX							
Receiving	31	12.9	33	15.2	1.1	(0.2, 4.6)	0.950
Not receiving	119	21.8	114	12.3	0.5	(0.2, 1.0)	0.049
Prior anti-TNF use							
Yes	30	36.7	37	10.8	0.1	(0.0, 0.5)	0.004
No	120	15.8	110	13.6	0.8	(0.4, 1.7)	0.620
All patients	150	20.0	147	12.9	0.6	(0.3, 1.1)	0.097

Key: CI, confidence interval; NC, not calculable; NE, not evaluable; 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AZA, azathioprine; MTX, methotrexate; TNF, tumor necrosis factor.

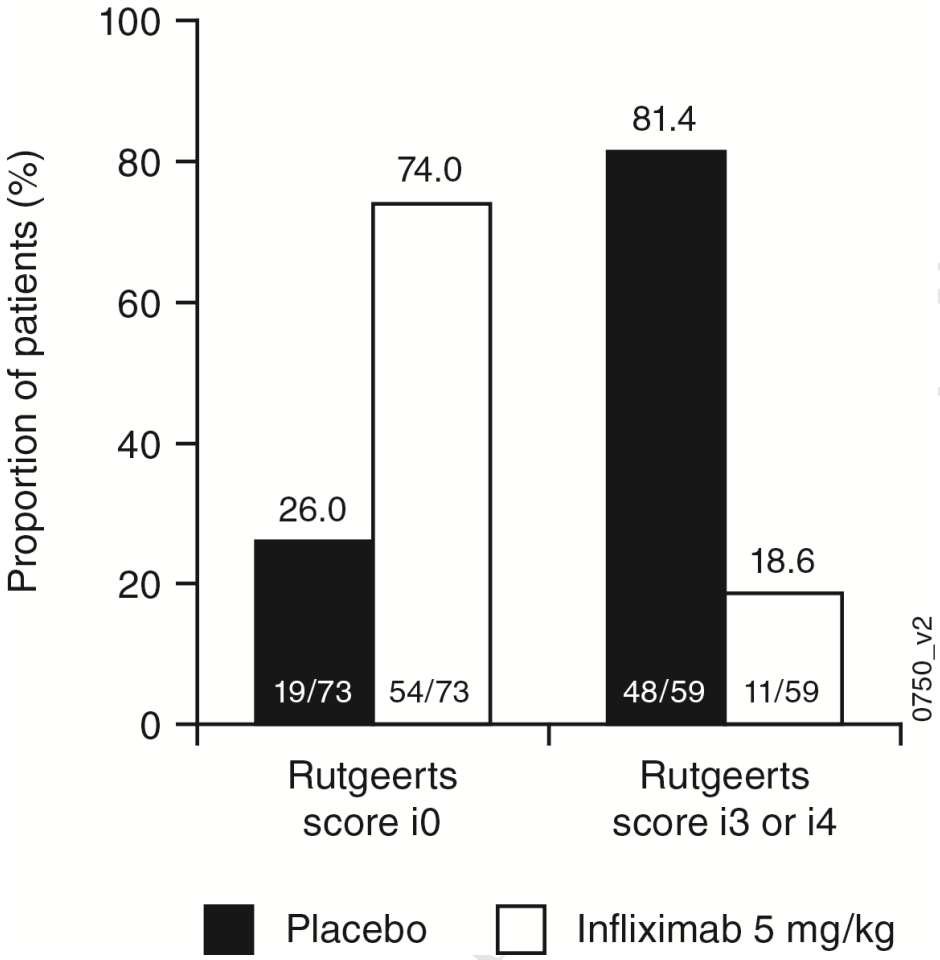
Figure S1D: Plot of odds ratio (vertical bars) and 95% confidence intervals (horizontal bars) for comparing the proportion of patients with clinical recurrence prior to or at week 76 in the infliximab group vs. the placebo group by risk factors for recurrence of active Crohn's disease at baseline; randomized patients



	Placebo N	Placebo %	Infliximab 5 mg/kg N	Infliximab 5 mg/kg %	Odds Ratio	(95% CI)	p-value
Number of risk factors							
1	107	20.6	99	12.1	0.5	(0.2, 1.1)	0.099
>1	43	18.6	47	14.9	0.8	(0.3, 2.6)	0.723
Second intra-abdominal operation							
Yes	30	36.7	31	12.9	0.3	(0.1, 1.4)	0.180
No	120	15.8	115	13.0	0.8	(0.4, 1.6)	0.501
Third (or more) intra-abdominal operation							
Yes	12	25.0	14	21.4	NE	NE	NE
No	138	19.6	132	12.1	0.6	(0.3, 1.1)	0.087
Surgery for a penetrating complication							
Yes	106	17.0	98	11.2	0.6	(0.3, 1.4)	0.231
No	44	27.3	48	16.7	0.6	(0.2, 1.8)	0.394
History of perianal fistulizing CD							
Yes	12	16.7	16	12.5	NE	NE	NE
No	138	20.3	130	13.1	0.6	(0.3, 1.1)	0.114
Cigarette smoker							
Yes	37	18.9	38	15.8	0.7	(0.2, 2.5)	0.651
No	113	20.4	108	12.0	0.5	(0.3, 1.1)	0.092
All patients	150	20.0	147	12.9	0.6	(0.3, 1.1)	0.097

Key: CD, Crohn's disease; CI, confidence interval; NE, not evaluable

Figure S2: Central endoscopic results prior to or at Week 76 by Rutgeerts score (i0 vs i3 or i4)[a]



a. i0, no lesions; i1, ≤5 aphthous lesions; i2, >5 aphthous lesions or anastomotic ulcer <1 cm; i3, diffuse aphthous ileitis with diffusely inflamed mucosa; i4, diffuse inflammation with large ulcers,nodules, and/or narrowing.

Figure S3: Median Crohn's Disease Activity Index (CDAI) scores through week 104; randomized patients

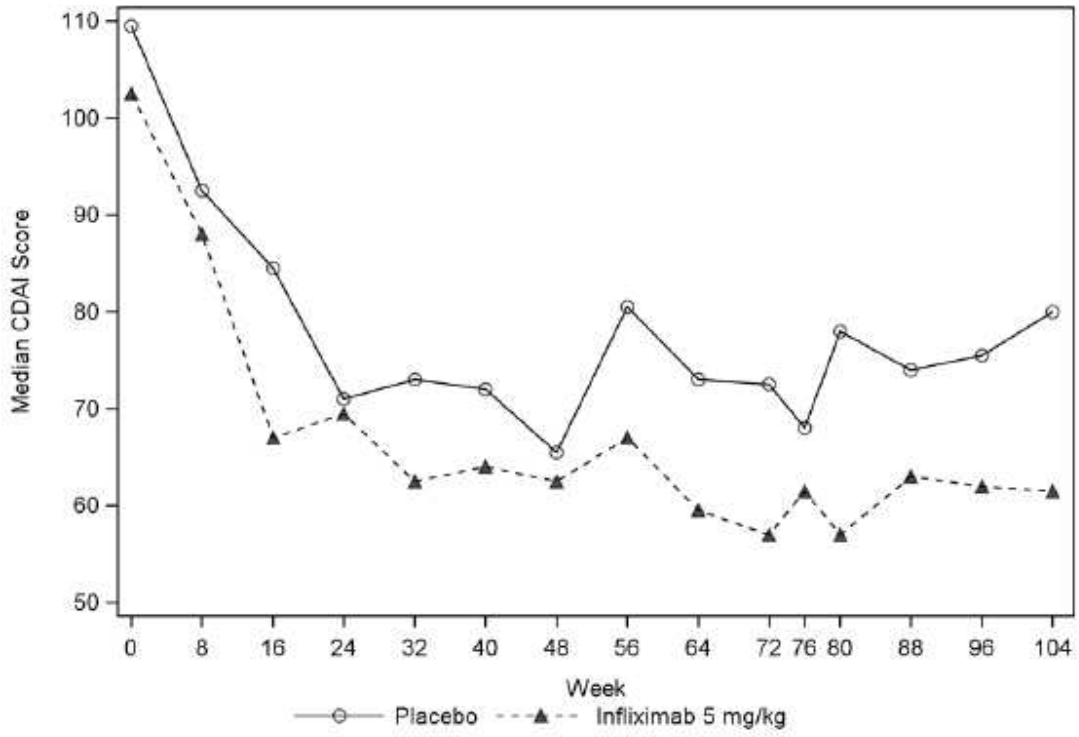
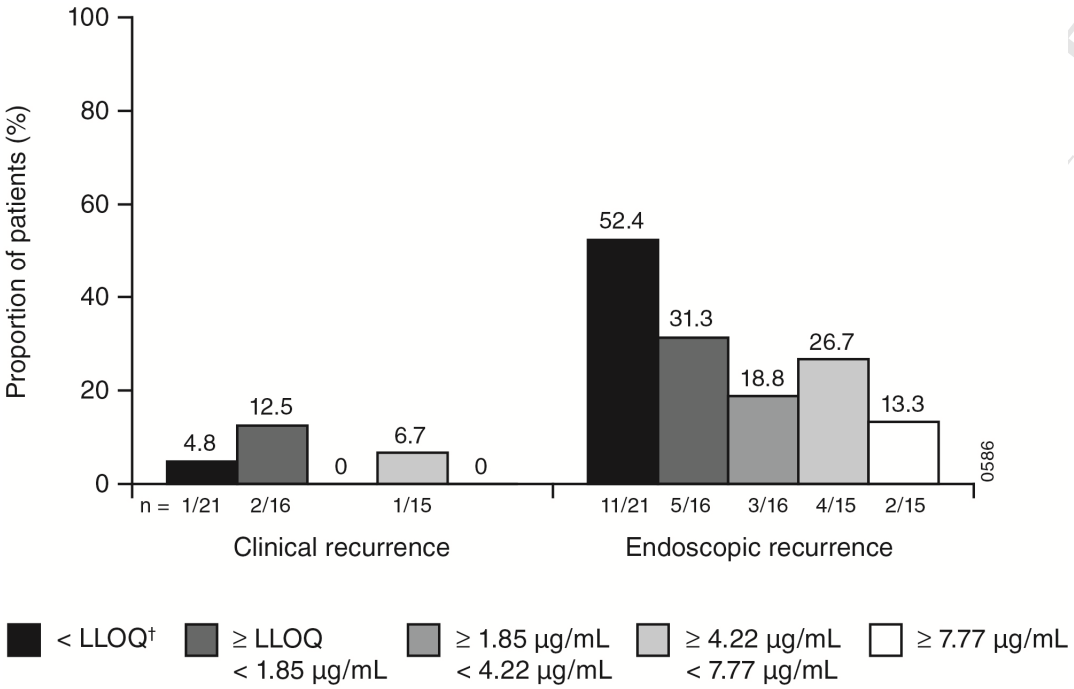


Figure S4: Clinical and endoscopic recurrence prior to or at week 76 by serum infliximab concentration at week 72; treated patients[a]



* Includes data up to the time of dose increase for those who increased dose.
† LLOQ = 0.1 µg/mL; Quartiles are based on patients with detectable concentration.

Key: LLOQ, lower limit of quantification

Table S1 Sensitivity analyses of the primary endpoint[a]

Method	Placebo (N=150)	Infliximab 5 mg/kg (N=147)	*P*-value
Sensitivity analysis #1, n[b]	122	103	
n (%)	29 (23.8)	19 (18.4)	.368
Sensitivity analysis #2, n[c]	148	143	
n (%)	30 (20.3)	19 (13.3)	.108
Sensitivity analysis #3, n[d]	147	145	
n (%)	29 (19.7)	18 (12.4)	.086
Sensitivity analysis #4, n[e]	133	134	
n (%)	28 (21.1)	17 (12.7)	.073
Sensitivity analysis #5, n[f]	150	147	
n (%)	31 (20.7)	19 (12.9)	.075
Sensitivity analysis #6, n[g]	150	147	
n (%)	57 (38.0)	62 (42.2)	.453
Sensitivity analysis #7, n[h]	150	147	
n (%)	31 (20.7)	19 (12.9)	.072

a. The same data handling rules that were used for the primary endpoint analysis were used for the sensitivity analyses.

b. The first sensitivity analysis excluded patients who discontinued study agent prior to Week 76 or who did not have sufficient data to evaluate clinical recurrence status at Week 76; patients who had already demonstrated clinical recurrence prior to or at Week 76 (other than meeting only the CDAI criteria at the time of discontinuation of study agent) were not excluded.

c. The second sensitivity analysis excluded patients who were not treated.

d. The third sensitivity analysis excluded patients where the local and central readers disagreed on whether the criteria for endoscopic recurrence were met.

e. The fourth sensitivity analysis was a "per-protocol" analysis that excluded patients with at least 1 pre-specified deviation.

f. The fifth sensitivity analysis used evidence of endoscopic recurrence based on the interpretation of the local reader.

g. The sixth sensitivity analysis (post hoc) considered patients who did not have sufficient data to evaluate clinical recurrence to have clinical recurrence.

h. The seventh sensitivity analysis (post hoc) used evidence of endoscopic recurrence based on the interpretation of the local reader if evaluable central reader results were not available.

P-values were based on the Cochran-Mantel-Haenszel χ-square test stratified by the number of risk factors for recurrence of active Crohn's disease and baseline use of an immunomodulator.

Table S2: Qualifying surgery characteristics; randomized patients

	Placebo (N=150)	Infliximab 5 mg/kg (N=147)	Total (N=297)
Length of small intestine resected (cm)			
N	140	141	281
Mean (SD)	22.58 (14.822)	22.12 (15.191)	22.35 (14.984)
Median	20.00	19.00	20.00
IQ range	(13.00; 28.50)	(12.00; 30.00)	(12.00; 29.00)
Range	(0.0; 85.0)	(0.0; 70.0)	(0.0; 85.0)
Length of colon resected (cm)			
N	132	134	266
Mean (SD)	9.59 (9.640)	10.15 (10.057)	9.87 (9.837)
Median	7.00	6.75	7.00
IQ range	(4.80; 11.00)	(4.00; 15.00)	(4.50; 12.50)
Range	(0.0; 73.0)	(0.0; 65.0)	(0.0; 73.0)
Type of anastomosis, n (%)			
N	150	145	295
End-to-end	35 (23.3)	45 (31.0)	80 (27.1)
End-to-side	16 (10.7)	10 (6.9)	26 (8.8)
Side-to-side	82 (54.7)	75 (51.7)	157 (53.2)
Unknown	17 (11.3)	15 (10.3)	32 (10.8)
Findings at surgery, n (%)			
N	150	146	296
Stricture	86 (57.3)	84 (57.5)	170 (57.4)
Abscess	41 (27.3)	47 (32.2)	88 (29.7)
Internal fistula	86 (57.3)	67 (45.9)	153 (51.7)
Sinus tracts	10 (6.7)	7 (4.8)	17 (5.7)
Perforation	12 (8.0)	19 (13.0)	31 (10.5)

Key: SD, standard deviation; IQ, interquartile.

Table S3: Risk factors for recurrence of active Crohn's disease at baseline; randomized patients

	Placebo (N=150)	Infliximab 5 mg/kg (N=147)	Total (N=297)
Risk factor, n (%)			
N	150	146	296
Second intra-abdominal operation for CD in the past 10 years	30 (20.0)	31 (21.2)	61 (20.6)
Qualifying surgery was the patient's ≥3 intra-abdominal operation for CD	12 (8.0)	14 (9.6)	26 (8.8)
Qualifying surgery was performed for a penetrating complication of CD	106 (70.7)	98 (67.1)	204 (68.9)
Any history of perianal fistulizing CD provided that this has not been active in the 3 months before study start	12 (8.0)	16 (11.0)	28 (9.5)
Cigarette smoker and has been unable or unwilling to quit smoking despite counseling to stop smoking	37 (24.7)	38 (26.0)	75 (25.3)
Number of risk factors, n (%)			
N	150	146	296
1	107 (71.3)	99 (67.8)	206 (69.6)
2	39 (26.0)	43 (29.5)	82 (27.7)
3	4 (2.7)	4 (2.7)	8 (2.7)
4	0	0	0
5	0	0	0

Key: CD, Crohn's disease

Table S4: Crohn's disease-related hospitalizations and surgeries through weeks 76 and 104

	Week 76			Week 104		
	Placebo (N=150)	Infliximab 5 mg/kg (N=147)	*P* value*	Placebo (N=150)	Infliximab 5 mg/kg (N=147)	*P* value*
Hospitalizations, n(%)	6 (4.0)	7 (4.8)	.878	10 (6.7)	7 (4.8)	.362
Surgeries, n (%)	2 (1.3)	2 (1.4)	.951	3 (2.0)	2 (1.4)	.626

* P value is based on the Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active Crohn's disease and baseline use of an immunomodulator.

Table S5: Predictors for clinical recurrence

Variables	Hazard Ratio (95% CI)
Placebo vs. Infliximab 5 mg/kg	1.735 (0.968, 3.110)
Prior anti-TNF use: no vs. yes	0.556 (0.301, 1.026)
Number of prior surgeries: 1 vs. >1	0.583 (0.331, 1.029)

CI, confidence interval; TNF, tumor necrosis factor

Table S6: Number of patients who discontinued study agent because of 1 or more treatment-emergent adverse events through the final visit by MedDRA system-organ class and preferred term; treated patients

			Infliximab (dose increase)		
	Placebo[a]	Infliximab 5 mg/kg[a]	Placebo → 5 mg/kg[b]	5 mg/kg → 10 mg/kg[b]	All Infliximab[c]
Patients treated	146	145	27	9	172
Avg duration of follow-up (weeks)	114.4	117.9	84.0	84.3	117.0
Avg duration of treatment (weeks)	94.7	96.9	50.3	34.2	91.3
Patients who discontinued study agent because of 1 or more adverse events, n (%)	19 (13.0)	37 (25.5)	12 (44.4)	5 (55.6)	54 (31.4)
System-Organ Class/Preferred Term					
Gastrointestinal Disorders, n (%)	8 (5.5)	10 (6.9)	6 (22.2)	4 (44.4)	20 (11.6)
Crohn's Disease	3 (2.1)	3 (2.1)	4 (14.8)	4 (44.4)	11 (6.4)
Anal Fistula	1 (0.7)	0	2 (7.4)	0	2 (1.2)
Small Intestinal Obstruction	0	2 (1.4)	0	0	2 (1.2)
Abdominal Pain	0	1 (0.7)	0	0	1 (0.6)
Diarrhoea	0	1 (0.7)	0	0	1 (0.6)
Enterocutaneous Fistula	0	1 (0.7)	0	0	1 (0.6)
Ileal Stenosis	0	1 (0.7)	0	0	1 (0.6)
Mouth Ulceration	0	1 (0.7)	0	0	1 (0.6)
Oesophageal Ulcer	0	1 (0.7)	0	0	1 (0.6)
Rectal Stenosis	0	1 (0.7)	0	0	1 (0.6)
Stomatitis	0	1 (0.7)	0	0	1 (0.6)
Vomiting	0	1 (0.7)	0	0	1 (0.6)

Table S6: Number of patients who discontinued study agent because of 1 or more treatment-emergent adverse events through the final visit by MedDRA system-organ class and preferred term; treated patients

			Infliximab (dose increase)		
	Placebo[a]	Infliximab 5 mg/kg[a]	Placebo → 5 mg/kg[b]	5 mg/kg → 10 mg/kg[b]	All Infliximab[c]
Abdominal Adhesions	1 (0.7)	0	0	0	0
Dysphagia	1 (0.7)	0	0	0	0
Ileal Fistula	1 (0.7)	0	0	0	0
Ileus	1 (0.7)	0	0	0	0
Infections and Infestations, n (%)	5 (3.4)	9 (6.2)	2 (7.4)	0	11 (6.4)
Anal Abscess	0	0	2 (7.4)	0	2 (1.2)
Abscess Intestinal	0	1 (0.7)	0	0	1 (0.6)
Clostridium Difficile Infection	0	1 (0.7)	0	0	1 (0.6)
Cytomegalovirus Infection	0	1 (0.7)	0	0	1 (0.6)
Oral Candidiasis	0	1 (0.7)	0	0	1 (0.6)
Oral Herpes	0	1 (0.7)	0	0	1 (0.6)
Pneumonia	0	1 (0.7)	0	0	1 (0.6)
Pneumonia Legionella	0	1 (0.7)	0	0	1 (0.6)
Rash Pustular	0	1 (0.7)	0	0	1 (0.6)
Tuberculosis	0	1 (0.7)	0	0	1 (0.6)
Abdominal Abscess	2 (1.4)	0	0	0	0
Bronchitis	1 (0.7)	0	0	0	0
Gastroenteritis	1 (0.7)	0	0	0	0
Vulvitis	1 (0.7)	0	0	0	0
Immune System Disorders, n (%)	0	5 (3.4)	3 (11.1)	0	8 (4.7)
Drug Hypersensitivity	0	1 (0.7)	2 (7.4)	0	3 (1.7)
Hypersensitivity	0	1 (0.7)	1 (3.7)	0	2 (1.2)
Anaphylactic Reaction	0	1 (0.7)	0	0	1 (0.6)
Anaphylactoid Reaction	0	1 (0.7)	0	0	1 (0.6)
Serum Sickness	0	1 (0.7)	0	0	1 (0.6)

Table S6: Number of patients who discontinued study agent because of 1 or more treatment-emergent adverse events through the final visit by MedDRA system-organ class and preferred term; treated patients

			Infliximab (dose increase)		
	Placebo[a]	Infliximab 5 mg/kg[a]	Placebo → 5 mg/kg[b]	5 mg/kg → 10 mg/kg[b]	All Infliximab[c]
Injury, Poisoning and Procedural Complications, n (%)	0	5 (3.4)	1 (3.7)	0	6 (3.5)
Infusion Related Reaction	0	5 (3.4)	1 (3.7)	0	6 (3.5)
Musculoskeletal and Connective Tissue Disorders, n (%)	4 (2.7)	4 (2.8)	1 (3.7)	0	5 (2.9)
Arthralgia	2 (1.4)	2 (1.4)	0	0	2 (1.2)
Myalgia	0	2 (1.4)	0	0	2 (1.2)
Lupus-Like Syndrome	0	0	1 (3.7)	0	1 (0.6)
Osteonecrosis	0	1 (0.7)	0	0	1 (0.6)
Polyarthritis	0	1 (0.7)	0	0	1 (0.6)
Neck Pain	1 (0.7)	0	0	0	0
Spondylitis	1 (0.7)	0	0	0	0
Skin and Subcutaneous Tissue Disorders, n (%)	1 (0.7)	4 (2.8)	0	0	4 (2.3)
Psoriasis	1 (0.7)	2 (1.4)	0	0	2 (1.2)
Alopecia	0	1 (0.7)	0	0	1 (0.6)
Erythema Nodosum	0	1 (0.7)	0	0	1 (0.6)
Nervous System Disorders, n (%)	0	3 (2.1)	0	0	3 (1.7)
Headache	0	1 (0.7)	0	0	1 (0.6)
Hypoaesthesia	0	1 (0.7)	0	0	1 (0.6)
Myelopathy	0	1 (0.7)	0	0	1 (0.6)
Syncope	0	1 (0.7)	0	0	1 (0.6)
General Disorders and Administration Site Conditions, n (%)	0	2 (1.4)	0	0	2 (1.2)
Pyrexia	0	2 (1.4)	0	0	2 (1.2)

Table S6: Number of patients who discontinued study agent because of 1 or more treatment-emergent adverse events through the final visit by MedDRA system-organ class and preferred term; treated patients

			Infliximab (dose increase)		
	Placebo[a]	Infliximab 5 mg/kg[a]	Placebo → 5 mg/kg[b]	5 mg/kg → 10 mg/kg[b]	All Infliximab[c]
Investigations, n (%)	0	2 (1.4)	0	0	2 (1.2)
Hepatic Enzyme Increased	0	1 (0.7)	0	0	1 (0.6)
Liver Function Test Abnormal	0	1 (0.7)	0	0	1 (0.6)
Pregnancy, Puerperium and Perinatal Conditions, n (%)	3 (2.1)	1 (0.7)	0	1 (11.1)	2 (1.2)
Pregnancy	3 (2.1)	1 (0.7)	0	1 (11.1)	2 (1.2)
Blood and Lymphatic System Disorders, n (%)	0	0	1 (3.7)	0	1 (0.6)
Pancytopenia	0	0	1 (3.7)	0	1 (0.6)
Respiratory, Thoracic and Mediastinal Disorders, n (%)	0	1 (0.7)	0	0	1 (0.6)
Respiratory Distress	0	1 (0.7)	0	0	1 (0.6)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) , n (%)	2 (1.4)	0	0	0	0
Renal Cancer	1 (0.7)	0	0	0	0
Thyroid Cancer	1 (0.7)	0	0	0	0
Surgical and Medical Procedures, n (%)	1 (0.7)	0	0	0	0
Intestinal Resection	1 (0.7)	0	0	0	0

[a] Includes data up to the time of dose increase for those who increased dose.
[b] Includes data from the time of dose increase onward.
[c] Includes data from the time of the first Infliximab dose onward.

Key: MeDRA, Medical dictionary for regulatory activities.