SYNOPSIS

Name of Sponsor/Company	Janssen Biotech, Inc*
Name of Active Ingredient(s)	REMICADE® (infliximab)

* Janssen Pharmaceuticals, Inc is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen studies may vary, such as, but not limited to Janssen Biotech, Inc; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; or Janssen, Inc. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved
Date: 30 June 2015
Prepared by: Janssen Biotech, Inc

Protocol No.: REMICADECRD3001

Title of Study: 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

Study Name: PREVENT

EudraCT Number: 2010-018431-18

NCT No.: NCT01190839

Clinical Registry No.: CR017080

Coordinating Investigator(s): Miguel Regueiro, MD, AGAF, FACG, FACP - University of Pittsburgh School of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, [redacted] United States

Study Center(s): Australia (5 sites), Austria (2 sites), Belgium (4 sites), Canada (10 sites), Czech Republic (1 site), France (9 sites), Germany (11 sites), Hungary (4 sites), Israel (3 sites), Italy (10 sites), Netherlands (1 site), New Zealand (6 sites), Poland (3 sites), United Kingdom (4 sites), United States (31 sites)

Publication (Reference): None

Study Period: 19 October 2010 (informed consent for first potential subject) to 12 December 2014 (last observation for last subject); 9 February 2015 (final database lock)

Phase of Development: Phase 3b

Objectives: The primary objective of this study was to compare the efficacy of infliximab with that of placebo in the prevention of clinical recurrence of Crohn's disease (CD) prior to or at Week 76, defined as a composite endpoint that required endoscopic confirmation of recurrence, in subjects who were at an increased risk of active CD recurrence following ileocolonic resection.

The major secondary objective was to compare the efficacy of infliximab with that of placebo in the prevention of endoscopic recurrence of CD prior to or at Week 76, defined as a Rutgeerts score ≥i2 either at the anastomosis or elsewhere in the gastrointestinal (GI) tract, in subjects who were at an increased risk of active CD recurrence following ileocolonic resection.

Other objectives included an assessment of overall safety.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted to evaluate the therapeutic benefit (prevention of clinical and endoscopic recurrence) and safety of infliximab in the treatment of subjects who were at an increased risk of recurrence of active CD after ileocolonic resection. All subjects were randomized at Week 0 in a 1:1 ratio to receive intravenous (IV) infliximab 5 mg/kg or placebo. Randomization was stratified by the number of risk factors for recurrence of active CD (1 or >1) and the presence or absence of concurrent use of an immunomodulator (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]).

During the study, subjects who met the study definition of clinical recurrence were eligible to have a blinded infliximab dose increase (placebo → infliximab 5 mg/kg or infliximab 5 mg/kg → 10 mg/kg).

The primary endpoint, clinical recurrence, was assessed at Week 76. Treatment through Week 200 and a final safety visit at Week 208 were planned. The Week 76 database lock occurred on 11 February 2014 and the Week 104 database lock occurred on 22 July 2014. The study was discontinued by the sponsor following the Week 104 database lock because the primary endpoint at Week 76 and the subsequent criteria established for Week 104 were not met. None of the enrolled subjects completed study agent infusions and evaluations through Week 208. For this final report, the data were locked on 9 February 2015 after all subjects had completed 8 weeks of safety follow-up after receiving their last dose of study agent.

A Data Monitoring Committee was used to ensure the continuing safety of the subjects enrolled in this study. The committee met periodically to review interim safety data and make recommendations regarding the continuation of the study. The Data Monitoring Committee consisted of medical experts in the relevant therapeutic area and 1 statistician.

Number of Subjects (planned and analyzed): Approximately 290 subjects were planned to be enrolled. A total of 297 subjects were randomized (150 to the placebo group and 147 to the infliximab 5 mg/kg group). All randomized subjects were included in the efficacy data set. There were 291 subjects who received at least 1 administration of study agent (148 in the placebo group and 143 subjects in the infliximab 5 mg/kg group). Of these subjects, 2 who were randomized to the placebo group received 1 infusion of infliximab 5 mg/kg and were included in the infliximab 5 mg/kg group for safety. Therefore, the safety data set included 146 subjects who received placebo and 145 subjects who received infliximab 5 mg/kg.

At the time the study was stopped by the sponsor, 104 subjects in the placebo group and 85 subjects in the infliximab group were still in the study and 71 subjects in the placebo group and 68 subjects in the infliximab group were still receiving the study agent.

Diagnosis and Main Criteria for Inclusion: Subjects eligible for this study were men or women 18 years of age or older who had a documented diagnosis of CD confirmed by endoscopic, histologic, and/or radiologic studies prior to resection or by tissue obtained at resection and who underwent an ileocolonic surgical resection (ie, an intestinal resection with an ileocolonic anastomosis). Subjects who underwent an intestinal resection with an end or loop ileostomy (the "qualifying surgery") within the last year were also eligible if they had an operation to close the ileostomy and had intestinal continuity by construction of an ileocolonic anastomosis. In this case, the time parameters for eligibility referred to the time after the re-anastomosis surgery. Additionally, subjects must have had no evidence of macroscopic CD at the close of surgery according to the surgeon, no known active CD anywhere else in the GI tract, and were able to undergo randomization no later than 45 days after surgery.

Subjects must also have been at increased risk of recurrence of active CD, as defined by at least 1 of the following: the qualifying surgery was the subject's second intra-abdominal operation for CD in the past

10 years; the qualifying surgery was the subject's third (or more) intra-abdominal operation for CD; the qualifying surgery was performed for a penetrating complication of CD (ie, an intra-abdominal abscess, internal fistula, sinus tracts, or intestinal perforation; the subject had any history of perianal fistulizing CD provided that this had not been active in the 3 months prior to study start; or the subject was a cigarette smoker (defined as currently smoking and had smoked an average of at least 10 cigarettes a day for the past year or more) and had been unable or unwilling to quit smoking despite counseling to stop smoking.

Subjects must have been naïve to treatment with infliximab OR had received prior infliximab treatment (at any time) and had 3 successive well-tolerated infusions with the last of these 3 infusions ≤4 months before surgery, provided they had not received >1 year of consecutive infliximab infusions prior to surgery. Subjects must have had a baseline Crohn's Disease Activity Index (CDAI) score <200.

Test Product, Dose and Mode of Administration, Batch No.: Infliximab for IV administration was supplied in sterile, single-use 20 mL vials. Each vial contained 100 mg of infliximab. The infliximab batch number used in this study was 20001942. Subjects received a weight-based IV dose of 5 mg/kg.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo for IV administration was supplied in sterile, single-use 20 mL vials. The placebo batch number used in this study was 20001943.

Duration of Treatment: Infliximab or placebo was planned to be administered at Week 0 and every 8 weeks thereafter through Week 200.

After the sponsor made the decision to prematurely discontinue the study following the analysis of the Week 104 data, the study was unblinded on 1 August 2014 and the investigators were provided with the treatment assignment for subjects at their sites. The sponsor recommended that all subjects who were receiving placebo discontinue treatment immediately. Investigators were allowed to administer infliximab according to protocol for subjects who were receiving infliximab and elected to continue treatment; however, the last dose of infliximab for the study was to be administered no later than 17 October 2014. After study agent was discontinued, all subjects were requested to complete an 8-week safety follow-up period as per the protocol.

Criteria for Evaluation:

Pharmacokinetics: Blood samples were collected from all subjects prior to the infusion of the study agent at Week 0 and Week 72 to determine serum infliximab concentrations.

Immunogenicity (Antibodies to Infliximab): Blood samples were collected from all subjects prior to the infusion of the study agent at Week 0 and Week 72 for measuring antibodies to infliximab (ATI). Two different validated assays were performed for detection of ATI: 1) a bridging immunoassay in which infliximab was used to capture and then detect induced immune responses to infliximab (referred to as the original enzyme immunoassay [EIA] in this document); and 2) an electrochemiluminescence assay (ECLIA) which is 60-fold more sensitive than the original EIA (referred to as the drug-tolerant ECLIA in this document).

Efficacy: The CDAI score was to be calculated at Week 0 and every 8 weeks thereafter through Week 208 (also performed at Week 76) and at any time the subject had symptoms suggestive of a disease flare to capture clinical recurrence events. At any time during the study, a video ileocolonoscopy was performed for subjects who experienced a CDAI score ≥200 and an increase of ≥70 points from the baseline CDAI score, and who had a negative stool test for *Clostridium difficile* if their flare was predominantly diarrheal in the opinion of the investigator. All subjects were required to have a video ileocolonoscopy at Week 76, except subjects who met the study's definition of clinical recurrence prior to Week 76. Video ileocolonoscopies were also performed for subjects who discontinued study agent prior to or after Week 76 based on protocol specified criteria. Crohn's disease-related surgeries and

hospitalizations were to be recorded at Week 8 and every 8 weeks thereafter through Week 208 (also performed at Week 76). The Inflammatory Bowel Disease Questionnaire was to be completed by subjects at Weeks 8, 40, 76, 104, 152, and 208. The final efficacy assessment was to be performed at Week 208; however, the study was prematurely discontinued by the sponsor and all subjects had a final visit 8 weeks after receiving their last dose of study agent.

Safety: Safety evaluations for all subjects were to be performed at Week 0 and every 8 weeks through Week 208 (also performed at Week 76) and included measurement of vital signs, evaluation of signs and symptoms of tuberculosis (TB), the assessment of adverse events (AEs), and collection of samples for clinical laboratory tests. Serum samples were also to be collected for determination of the presence of antinuclear antibodies (ANA)/anti-double-stranded DNA (anti-dsDNA) antibodies at Weeks 0, 76, and 208. The final safety assessment was to be performed at Week 208; however, the study was prematurely discontinued by the sponsor and all subjects had a final visit 8 weeks after receiving their last dose of study agent.

Health Economics: The Work Productivity and Activity Impairment in Crohn's Disease (WPAI:CD) questionnaire was to be completed by subjects at Weeks 8, 40, 76, 104, 152, and 208. The study was prematurely discontinued by the sponsor and none of the enrolled subjects completed study agent infusions and evaluations through Week 208.

Statistical Methods: It was anticipated that the proportion of subjects with clinical recurrence prior to or at Week 76 would be 50% of subjects in the placebo group and 30% of subjects in the infliximab group. A sample size of 290 subjects, 145 per treatment group, would provide 93% power to detect the 20% difference in the proportion of subjects with clinical recurrence prior to or at Week 76 between the 2 treatment groups, with a 2-sided type I error (alpha) of 0.05.

The primary endpoint (clinical recurrence of CD prior to or at Week 76) analysis was performed using the intention-to-treat principle that included all randomized subjects. The Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active CD as defined in the inclusion criterion (1 or >1) and the presence or absence of concurrent use of an immunomodulator (AZA, 6-MP, or MTX) at Week 0, were used to compare the proportion of subjects with clinical recurrence prior to or at Week 76 between the infliximab group and the placebo group. This was a 2-sided test at the 0.05 significance level. The same methods used for the primary endpoint analysis were applied to the major secondary endpoint analysis to compare the proportion of subjects with endoscopic recurrence prior to or at Week 76 between the infliximab group and the placebo group.

Safety was assessed by summarizing AEs and laboratory tests (hematology, serum chemistry, ANA/ anti-dsDNA antibodies). Clinically significant vital sign changes were reported as AEs and were captured in the AE summary tables. Safety analyses were based on all subjects who received at least 1 infusion of study agent (including partial infusions).

RESULTS:

STUDY POPULATION:

A total of 297 subjects were randomized. The proportion of subjects who discontinued study agent prior to Week 76 was 26.7% for the placebo group and 37.4% for the infliximab 5 mg/kg group. The most common reason for discontinuation of study agent was AEs (12.7% in the placebo group, 21.8% in the infliximab 5 mg/kg group). The proportion of subjects who discontinued the study agent because the study was stopped by the sponsor was 47.3% in the placebo group and 46.3% in the infliximab 5 mg/kg group. While subjects who discontinued study agent were requested (per protocol) to remain in the study, 20.5% of randomized subjects terminated study participation prior to Week 76 (16.0% in the placebo group, 25.2% in the infliximab 5 mg/kg group). The most common reason for termination of study

participation prior to Week 76 was withdrawal of consent. At the end of the study, 63.6% of randomized subjects terminated study participation because the study was stopped by the sponsor (69.3% in placebo group, 57.8% in the infliximab 5 mg/kg group).

Demographics were generally well balanced between the 2 treatment groups. Among all randomized subjects, 53.2% were male, 92.9% were white, and the median age was 34.0 years. Baseline CD characteristics were generally similar between the 2 treatment groups with the exception of duration of disease (3.32 years for the placebo group, 6.49 years for the infliximab 5 mg/kg group) and colon involvement (50.7% for the placebo group, 61.0% for the infliximab 5 mg/kg group). For all randomized subjects, 98.0% had ileal involvement and the median CDAI score was 105.5 at baseline. The risk factors for recurrence of active CD were generally well balanced between the 2 treatment groups. The most common risk factor was that the qualifying surgery was for penetrating complications of CD (68.9% of randomized subjects who provided the risk factor information). Of randomized subjects, 69.6% had only 1 risk factor.

A total of 291 subjects were exposed to at least 1 scheduled infusion; 148 subjects randomized to placebo and 143 subjects randomized to infliximab 5 mg/kg. A total of 107 (72.3%) subjects in the placebo group and 88 (61.5%) subjects in the infliximab 5 mg/kg group were exposed to study agent through Week 72 (last infusion before Week 76 primary endpoint). Through Week 104, 95 (64.2%) subjects in the placebo group and 77 (53.8%) in the infliximab 5 mg/kg group were still exposed to study agent. Less than 5.0% of subjects in either treatment group received study agent after Week 176, 1 subject received study agent through Week 192, and no subjects completed study agent infusions through Week 200.

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

Pharmacokinetics

- Quantifiable serum infliximab concentrations were maintained over time in the majority of subjects in the infliximab 5 mg/kg group, with median trough serum infliximab concentration of 2.18 µg/mL at Week 72.
- Median serum infliximab concentration was higher in subjects in the infliximab 5 mg/kg group receiving immunomodulators (4.89 µg/mL) at baseline compared with subjects not receiving immunomodulators (1.83 µg/mL).

Immunogenicity (Antibodies to Infliximab)

- Of 105 subjects who received infliximab and had an evaluable sample at Week 72, 16.2% were positive for ATI with the original EIA. In comparison, 61.9% were positive for ATI with the drug-tolerant ECLIA. With both assay methods, the majority of subjects who were positive for ATI had antibody titers below 1:1000.
- All subjects who received infliximab and were positive for ATI with the original EIA were also positive with the drug-tolerant ECLIA, while 93.3% of subjects classified as negative for ATI with the original EIA were positive with the drug-tolerant ECLIA. In addition, 46.6% of those classified as inconclusive for ATI with the original EIA were positive with the drug-tolerant ECLIA.
- Among subjects who received infliximab and were positive for ATI with the drug-tolerant ECLIA, the median ATI titer was highest in subjects who were positive with the original EIA (1:12800), compared with those who were negative (1:1600), or inconclusive (1:200) with the original EIA.
- The use of immunomodulators appeared to be associated with a lower incidence of ATI with both assay methods.

- With the drug-tolerant ECLIA, the median serum infliximab concentration was lower in subjects in the infliximab 5 mg/kg group who were positive for ATI (0.58 µg/mL) compared with subjects who were negative for ATI (4.63 µg/mL); the impact of ATI on serum infliximab concentrations appeared to be more pronounced at higher antibody titers.

EFFICACY RESULTS:

Clinical Recurrence

- Primary efficacy endpoint
  - The proportion of subjects with clinical recurrence prior to or at Week 76 was observed to be higher in the placebo group (20.0%) compared with the infliximab 5 mg/kg group (12.9%), however the difference did not reach statistical significance (p=0.097).
    - Results of the sensitivity analyses were consistent with the results of the primary endpoint analysis.
    - The treatment effect for the proportion of subjects with clinical recurrence prior to or at Week 76 was generally similar across subgroups.
- Other analyses of clinical recurrence
  - When only considering the CDAI component of the primary endpoint, the proportion of subjects who had a ≥70-point increase from baseline in CDAI score and a CDAI score ≥200 prior to or at Week 76 was 22.7% for the placebo group and 17.7% for the infliximab 5 mg/kg group (p=0.233).
  - The proportion of subjects with clinical recurrence prior to or at Week 104 was observed to be higher in the placebo group (25.3%) compared with the infliximab 5 mg/kg group (17.7%), however the difference did not reach statistical significance (p=0.098)
  - Time to clinical recurrence in the infliximab 5 mg/kg group was longer through Week 76 and through Week 104, but not significantly different compared with the placebo group (Log rank p=0.141 and p=0.165, respectively).

Endoscopic Recurrence

- Major secondary efficacy endpoint
  - The proportion of subjects in the placebo group who met the criteria for endoscopic recurrence (60%) prior to or at Week 76 was observed to be higher compared with subjects in the infliximab 5 mg/kg group (30.6%). While the nominal p-value for this comparison was <0.001, per the prespecified testing procedure, statistical significance cannot be claimed for this endpoint because the primary endpoint was not significant.
    - Results of the sensitivity analyses of the major secondary endpoint were consistent with the results of the major secondary endpoint analysis
    - The results of a post hoc sensitivity analysis of subjects with an endoscopic recurrence based only on endoscopic criteria (ie, Rutgeerts score ≥i2) prior to or at Week 76 indicated that 51.3% of subjects in the placebo group and 22.4% of subjects in the infliximab 5 mg/kg group (p<0.001) had an endoscopic recurrence
- Other endoscopic recurrence analyses
  - The correlation between endoscopic recurrence prior to or at Week 76 and clinical recurrence prior to or at Week 104 was weak (Spearman correlation coefficient=0.272).

– In a post hoc analysis, the proportion of subjects with central endoscopic results for Rutgeerts scores of i2, i3, and i4 (ie, endoscopic recurrence) prior to or at Week 76 was observed to be higher in the placebo group (19.3%, 8.7%, and 23.3%, respectively) than in the infliximab 5 mg/kg group (15.0%, 1.4%, and 6.1%, respectively).

Crohn's Disease-related Hospitalizations and Surgeries

- Through Week 76, 6 (4.0%) subjects in the placebo group and 7 (4.8%) subjects in the infliximab 5 mg/kg group had 1 or more CD-related hospitalizations (p=0.878) and 2 (1.3%) subjects in the placebo group and 2 (1.4%) subjects in the infliximab 5 mg/kg group had 1 or more CD-related surgeries (p=0.951).
- Through the final visit, 11 (7.3%) subjects in the placebo group and 7 (4.8%) subjects in the infliximab 5 mg/kg group had 1 or more CD-related hospitalizations (p=0.292) and 4 (2.7%) subjects in the placebo group and 2 (1.4%) subjects in the infliximab 5 mg/kg group had 1 or more CD-related surgeries (p=0.406).

Efficacy and Pharmacokinetics

- No trend in clinical recurrence and serum infliximab concentration was observed; however, a higher serum infliximab concentration was associated with a lower incidence of endoscopic recurrence.

Efficacy and Immunogenicity (Antibodies to Infliximab)

- Subjects who were positive for ATI were more likely to experience endoscopic recurrence; however, the impact of ATI on endoscopic recurrence was more evident at higher ATI titers with the drug-tolerant ECLIA.

HEALTH ECONOMICS RESULTS: There was no difference between the 2 treatment groups in the median time lost from work due to CD or in the percentage of time lost from work due to CD during the past 7 days at Weeks 8, 40, 76, and 104 (at each time point the median time lost was 0.0). There was no difference between the 2 treatment groups in the median change from Week 8 in the productivity scale score or activity scale score at Weeks 40, 76, or 104 (at each time point the median change was 0.0).

SAFETY RESULTS: An overall summary of AEs through Week 76 is presented in the table below.

Subjects With Adverse Events Through Week 76

			Infliximab (dose increase)		
	Placebo[a] (N=146)	Infliximab 5 mg/kg[a] (N=145)	Placebo → 5 mg/kg[b] (N=21)	5 mg/kg → 10 mg/kg[b] (N=6)	All Infliximab[c] (N=166)
Subjects with 1 or more adverse events	127 (87.0%)	130 (89.7%)	17 (81.0%)	6 (100.0%)	147 (88.6%)
Subjects with 1 or more serious adverse events	30 (20.5%)	25 (17.2%)	3 (14.3%)	2 (33.3%)	29 (17.5%)
Subjects who discontinued study agent because of 1 or more adverse events	12 (8.2%)	27 (18.6%)	8 (38.1%)	5 (83.3%)	40 (24.1%)
Subjects who died	1 (0.7%)	0	0	0	0
Subjects with 1 or more malignancies[d] excluding non-melanoma skin cancers	2 (1.4%)	0	0	0	0
Subjects with 1 or more infections	77 (52.7%)	78 (53.8%)	8 (38.1%)	3 (50.0%)	87 (52.4%)
Subjects with 1 or more serious infections	8 (5.5%)	7 (4.8%)	1 (4.8%)	1 (16.7%)	9 (5.4%)
Subjects with 1 or more infusion reactions	11 (7.5%)	23 (15.9%)	6 (28.6%)	1 (16.7%)	29 (17.5%)

[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.
[d] 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.

The most frequent treatment-emergent AEs that occurred in infliximab-treated subjects through Week 76 are presented in the table below. Through the final visit, treatment-emergent AE data were similar.

Treatment-Emergent Adverse Events That Occurred in at Least 5% of All Infliximab-Treated Subjects Through Week 76

			Infliximab (dose increase)		
	Placebo[a] (N=146)	Infliximab 5 mg/kg[a] (N=145)	Placebo → 5 mg/kg[b] (N=21)	5 mg/kg → 10 mg/kg[b] (N=6)	All Infliximab[c] (N=166)
Subjects with 1 or more adverse events	127 (87.0%)	130 (89.7%)	17 (81.0%)	6 (100.0%)	147 (88.6%)
System organ class/preferred term					
Infections and Infestations	83 (56.8%)	82 (56.6%)	8 (38.1%)	3 (50.0%)	91 (54.8%)
Nasopharyngitis	27 (18.5%)	31 (21.4%)	1 (4.8%)	0	32 (19.3%)
Upper respiratory tract infection	17 (11.6%)	17 (11.7%)	3 (14.3%)	3 (50.0%)	23 (13.9%)
Gastrointestinal disorders	84 (57.5%)	77 (53.1%)	8 (38.1%)	4 (66.7%)	85 (51.2%)
Abdominal pain	27 (18.5%)	21 (14.5%)	2 (9.5%)	2 (33.3%)	25 (15.1%)
Diarrhoea	24 (16.4%)	19 (13.1%)	2 (9.5%)	1 (16.7%)	22 (13.3%)
Nausea	12 (8.2%)	15 (10.3%)	0	1 (16.7%)	16 (9.6%)
Crohn's disease	11 (7.5%)	5 (3.4%)	4 (19.0%)	3 (50.0%)	11 (6.6%)
Dyspepsia	4 (2.7%)	8 (5.5%)	1 (4.8%)	0	9 (5.4%)
Musculoskeletal and connective tissue disorders	46 (31.5%)	43 (29.7%)	4 (19.0%)	2 (33.3%)	48 (28.9%)
Arthralgia	31 (21.2%)	20 (13.8%)	4 (19.0%)	1 (16.7%)	25 (15.1%)
Back pain	8 (5.5%)	10 (6.9%)	0	2 (33.3%)	12 (7.2%)
General disorders and administration site conditions	38 (26.0%)	37 (25.5%)	3 (14.3%)	0	40 (24.1%)
Pyrexia	12 (8.2%)	15 (10.3%)	0	0	15 (9.0%)
Nervous system disorders	38 (26.0%)	37 (25.5%)	2 (9.5%)	2 (33.3%)	40 (24.1%)
Headache	25 (17.1%)	25 (17.2%)	1 (4.8%)	0	26 (15.7%)
Skin and subcutaneous tissue disorders	22 (15.1%)	36 (24.8%)	1 (4.8%)	2 (33.3%)	37 (22.3%)
Pruritus	4 (2.7%)	9 (6.2%)	0	1 (16.7%)	9 (5.4%)
Injury, poisoning and procedural complications	25 (17.1%)	29 (20.0%)	2 (9.5%)	1 (16.7%)	32 (19.3%)
Infusion related reaction	2 (1.4%)	8 (5.5%)	2 (9.5%)	0	10 (6.0%)
Investigations	8 (5.5%)	28 (19.3%)	3 (14.3%)	2 (33.3%)	32 (19.3%)
Respiratory, thoracic and mediastinal disorders	26 (17.8%)	23 (15.9%)	1 (4.8%)	2 (33.3%)	26 (15.7%)
Cough	11 (7.5%)	11 (7.6%)	0	0	11 (6.6%)
Psychiatric disorders	8 (5.5%)	15 (10.3%)	1 (4.8%)	1 (16.7%)	17 (10.2%)
Depression	3 (2.1%)	9 (6.2%)	0	0	9 (5.4%)
Blood and lymphatic system disorders	14 (9.6%)	11 (7.6%)	1 (4.8%)	0	12 (7.2%)
Eye disorders	3 (2.1%)	11 (7.6%)	0	0	11 (6.6%)
Reproductive system and breast disorders	10 (6.8%)	9 (6.2%)	0	1 (16.7%)	10 (6.0%)
Immune system disorders	6 (4.1%)	7 (4.8%)	2 (9.5%)	0	9 (5.4%)

[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.

Note: Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.

The overall safety evaluation of infliximab 5 mg/kg through Week 76 indicated that:

- Infliximab 5 mg/kg was well tolerated with a safety profile generally consistent with placebo.
- Overall rates of AEs and serious adverse events (SAEs) were similar between the placebo and infliximab 5 mg/kg groups.
- There were no deaths or malignancies (excluding non-melanoma skin cancer) in infliximab-treated subjects.

- More subjects discontinued study agent due to an AE in the infliximab 5 mg/kg group than in the placebo group. Common AEs leading to discontinuation in the infliximab 5 mg/kg group included infections, infusion-related reactions, and GI events associated with CD.
- More subjects in the infliximab 5 mg/kg group experienced an infusion reaction than in the placebo group.
  - There were 4 serious infusion reactions (1 in the placebo group and 3 in the infliximab 5 mg/kg group) through Week 76; one additional subject in the infliximab 5 mg/kg group experienced a serious infusion reaction through the final visit.
- Overall infection rates, including serious infections, were similar between the placebo and infliximab 5 mg/kg groups.
  - There were 4 serious infections considered opportunistic: 2 cytomegalovirus infections in subjects who received placebo, and *Legionella* pneumonia and miliary TB in subjects who received infliximab 5 mg/kg.
- Markedly abnormal changes in hematology and chemistry laboratory values were infrequently observed.
- Through Week 76, newly positive ANA (≥1:160) at any time was detected in 1 (0.9%) subject in the placebo group and 51 (40.8%) subjects in the infliximab group (including dose increase groups). Newly positive anti-dsDNA was not detected in any subjects in the placebo or infliximab groups (including dose increase groups).
- Infusion reactions were more frequent in subjects who were positive for ATI with either assay method. An apparent trend towards higher infusion reactions with higher ATI titers was observed with the drug-tolerant ECLIA.

Safety findings through the final visit were generally consistent with those observed through Week 76.

STUDY LIMITATIONS: One possible limitation of the study was that subjects were a lower-risk population than intended which may have resulted in a clinical recurrence rate that was lower than expected. A second potential limitation was the use of the largely symptom-based CDAI score as part of the primary composite endpoint for clinical recurrence. The CDAI is neither sensitive nor specific for mucosal inflammation which is integral to disease recurrence. Furthermore, the CDAI score has never been validated in a postoperative population.

CONCLUSIONS: The REMICADECRD3001 (PREVENT) study provides clinically important evidence on therapeutic benefit (prevention of clinical and endoscopic disease recurrence) and safety of infliximab 5 mg/kg in the treatment of subjects who were at an increased risk of recurrence of active CD after ileocolonic resection.

- Treatment with infliximab 5 mg/kg was not shown to be significantly better than placebo for prevention of clinical recurrence following CD surgery.
- The incidence of endoscopic recurrence was reduced following treatment with infliximab 5 mg/kg.
- The overall safety profile of infliximab in this study was generally similar to placebo and is consistent with that detailed in the infliximab prescribing information. No new safety issues were identified.
- The study was discontinued by the sponsor following the Week 104 database lock because the pre-defined stopping criteria were met.