CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103772 / S-5113

Trade Name: Remicade

Generic Name: Infliximab

Sponsor: Centocor, Inc.

Approval Date: September 15, 2005

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APPLICATION NUMBER:

103772 / S-5113

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103772 / S-5113

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103772/5113

Centocor, Incorporated
Attention: Stella S. Jones, PhD
Vice President, Worldwide Regulatory Affairs
200 Great Valley Parkway
Malvern, PA 19355-1307

SEP 15 2005

Dear Dr. Jones:

Your request to supplement your biologics license application for Infliximab to include a new indication for the treatment of patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response to conventional therapy, has been approved.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies until June 30, 2009.

We acknowledge your written commitments to to conduct postmarketing studies as described in your letter of September 2, 2005, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 601.70. This commitment is listed below.

    a. Deferred pediatric study under PREA for the treatment of moderately to severely active ulcerative colitis in pediatric patients.

    b. Final protocol submitted to the IND: March 31, 2006

    c. First patient enrolled in study: June 30, 2006

    d. Last patient enrolled in study: December 31, 2007

    e. Last patient out: December 31, 2008

f. Final Report Submission: June 30, 2009

Submit final study reports to this BLA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "Required Pediatric Study Commitments".

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

Pursuant to 21 CFR 201.57(f)(2), patient labeling must be reprinted at the end of the package insert.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

This information will be included in your biologics license application file.

Sincerely,

Marc Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine
Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)

Summary Text: Clinical Supplmt. Efficacy - New/Expanded Indication
LETTER: Pediatric Deferral Granted (PDG)

REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:

- Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).

RIS Data Check:

- Verify short summary - Ltr. & Submission screen should match.
- Check Letter for PMCs (if PMCs - add "PMCs - Approved With" special characteristic code.)
- Check if Major Approval - if so - add code.
- Perform Review Completion Process
- Milestone: Confirm Approved Status

cc: Attached label is sent to everyone
HFD-109/C. Stark
HFD-109/K. Schneider
HFD-108/L. Liang
HFD-108/J. Siegel
HFD-108/E. Unger
HFD-108/M. Walton
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HFD-240/OTCOM/ B. Poole

HFI-20/Press/ L. Gelb
HFI-20/Press/ J. Brodsky
HFD-230/OTCOM/CDER WebMaster
HFD-001/B. Duvall-Miller (if PMC commitments)
HFD-109/C. O'Leary
HFD-42/DDMAC/M. Kiester
HFD-410/ODS/DSRCS/ Karen Young
CDER-OCTAP960PM (PEDs e-mail account)
HFD-322/IPCB/ E. Rivera-Martinez
HFM-555/DMA/ S. Kozlowski
HFM-535/DTP/ A. Rosenberg
HFM-570/DTBIMP/ M. Walton
HFM-570 C. Lee (if clinical PMC commitments)
HFD-328/TFRB Blue File/Mike Smedley
HFD-430/ODS/DDRE (hard copy)
HFD-410/CDER Medwatch Safety Labeling (hard copy)
DRMP BLA file (hard copy)

History: CLStark: 9.12.2005: 9.14.2005

File Name: S:\Stark\Centocor\STN 103772_5113\STN 103772_5113 AP.doc

Office	Name/Signature	Date
DRMP		9/14/05
DTBIMP		9/14/05
DRMP	Schneider	9-15-05
OTOTMP		9/15/05
ODSP/DDOP	Kelly Leonard	9/20/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103772 / S-5113

LABELING

REMICADE®
(infliximab)

for IV Injection

WARNING

RISK OF INFECTIONS

TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS). ANTI-TUBERCULOSIS TREATMENT OF PATIENTS WITH A REACTIVE TUBERCULIN SKIN TEST REDUCES THE RISK OF TB REACTIVATION IN PATIENTS RECEIVING TREATMENT WITH REMICADE. HOWEVER, ACTIVE TUBERCULOSIS HAS DEVELOPED IN PATIENTS RECEIVING REMICADE WHO WERE TUBERCULIN SKIN TEST NEGATIVE PRIOR TO RECEIVING REMICADE.

PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST.[1] TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE. PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING REMICADE FOR SIGNS AND SYMPTOMS OF ACTIVE TUBERCULOSIS, INCLUDING PATIENTS WHO ARE TUBERCULIN SKIN TEST NEGATIVE.

DESCRIPTION

REMICADE® is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of 10^{10} M^{-1}. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

CLINICAL PHARMACOLOGY

General

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.[2,3] Infliximab does not neutralize TNFβ (lymphotoxin α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro*[3] or *in vivo*.[4] Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

Pharmacodynamics

Elevated concentrations of TNFα have been found in involved tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis. In rheumatoid arthritis, treatment with REMICADE reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with REMICADE reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with REMICADE, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from REMICADE-treated patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with REMICADE resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin as well as a reduction of macrophages in the synovium. The relationship between these pharmacodynamic activities and the mechanism(s) by which REMICADE exerts its clinical effects is unknown.

Pharmacokinetics

Single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis and 5 mg/kg in Crohn's disease indicate that the median terminal half-life of infliximab is 8.0 to 9.5 days.

Following an initial dose of REMICADE, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of REMICADE, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

A pediatric Crohn's disease pharmacokinetic study was conducted in 21 patients aged 11 to 17 years old. No notable differences in single-dose pharmacokinetic parameters were observed between pediatric and adult Crohn's disease patients (see PRECAUTIONS, Pediatric Use).

CLINICAL STUDIES

Rheumatoid Arthritis

The safety and efficacy of REMICADE were assessed in two multicenter, randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs was permitted.

Study RA I was a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of REMICADE + MTX: 3 mg/kg or 10 mg/kg of REMICADE by IV infusion at weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX.

Study RA II was a placebo-controlled study of three active treatment arms in 1004 MTX naive patients of 3 or fewer years duration active rheumatoid arthritis. Patients enrolled had a median age of 51 years with a median disease duration of 0.6 years, median swollen and tender joint count of 19 and 31, respectively, and >80% of patients had baseline joint erosions. At randomization, all patients received MTX (optimized to 20 mg/wk by week 8) and either placebo, 3mg/kg or 6 mg/kg REMICADE at weeks 0, 2, and 6 and every 8 weeks thereafter.

Data on use of REMICADE without concurrent MTX are limited (see ADVERSE REACTIONS, Immunogenicity).[5,6]

Clinical response

In Study RA I, all doses/schedules of REMICADE + MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo + MTX (Table 1). This improvement was observed at week 2 and maintained through week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with REMICADE + MTX compared to placebo + MTX (Table 2). More patients treated with REMICADE reached a major clinical response than placebo-treated patients (Table 1).

In Study RA II, after 54 weeks of treatment, both doses of REMICADE + MTX resulted in statistically significantly greater response in signs and symptoms compared to MTX alone as measured by the proportion of patients achieving ACR 20, 50 and 70 responses (Table 1). More patients treated with REMICADE reached a major clinical response than placebo-treated patients (Table 1).

Table 1

ACR RESPONSE (PERCENT OF PATIENTS)

	Study RA I					Study RA II		
		REMICADE + MTX					REMICADE + MTX	
		3 mg/kg		10 mg/kg			3 mg/kg	6 mg/kg
Response	Placebo + MTX (n=88)	q 8 wks (n=86)	q 4 wks (n=86)	q 8 wks (n=87)	q 4 wks (n=81)	Placebo + MTX (n=274)	q 8 wks (n=351)	q 8 wks (n=355)
ACR 20								
Week 30	20%	50%[a]	50%[a]	52%[a]	58%[a]	N/A	N/A	N/A
Week 54	17%	42%[a]	48%[a]	59%[a]	59%[a]	54%	62%[c]	66%[a]
ACR 50								
Week 30	5%	27%[a]	29%[a]	31%[a]	26%[a]	N/A	N/A	N/A
Week 54	9%	21%[c]	34%[a]	40%[a]	38%[a]	32%	46%[a]	50%[a]
ACR 70								
Week 30	0%	8%[b]	11%[b]	18%[a]	11%[a]	N/A	N/A	N/A
Week 54	2%	11%[c]	18%[a]	26%[a]	19%[a]	21%	33%[b]	37%[a]
Major clinical response[#]	0%	7%[c]	8%[b]	15%[a]	6%[c]	8%	12%	17%[a]

A major clinical response was defined as a 70% ACR response for 6 consecutive months (consecutive visits spanning at least 26 weeks) through week 102 for Study RA I and week 54 for Study RA II.

[a] $p \leq 0.001$
[b] $p < 0.01$
[c] $p < 0.05$

Table 2
COMPONENTS OF ACR 20
AT BASELINE AND 54 WEEKS (Study RA I)

	Placebo + MTX (n=88)		REMICADE + MTX[a] (n=340)	
Parameter (medians)	Baseline	Week 54	Baseline	Week 54
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain[b]	6.7	6.1	6.8	3.3
Physician's Global Assessment[b]	6.5	5.2	6.2	2.1
Patient's Global Assessment[b]	6.2	6.2	6.3	3.2
Disability Index (HAQ-DI)[c]	1.8	1.5	1.8	1.3
CRP (mg/dL)	3.0	2.3	2.4	0.6

[a]All doses/schedules of REMICADE + MTX
[b]Visual Analog Scale (0=best, 10=worst)
[c]Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

Radiographic response

Structural damage in both hands and feet was assessed radiographically at week 54 by the change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.[7]

In Study RA I, approximately 80% of patients had paired x-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 3) and maintained through 102 weeks.

In Study RA II, >90% of patients had at least two evaluable x-rays. Inhibition of progression of structural damage was observed at weeks 30 and 54 (Table 3) in the REMICADE + MTX groups compared to MTX alone. In an exploratory analysis of Study RA II, patients treated with REMICADE + MTX demonstrated less progression of structural damage compared to MTX alone, whether baseline acute phase reactants (ESR and CRP) were normal or elevated: patients with elevated baseline acute phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 4.2 units compared to patients treated with REMICADE + MTX who demonstrated 0.5 units of progression; patients with normal baseline acute phase reactants

treated with MTX alone demonstrated a mean progression in vdH-S score of 1.8 units compared to REMICADE + MTX who demonstrated 0.2 units of progression. Of patients receiving REMICADE + MTX, 59% had no progression (vdH-S score ≤ 0 unit) of structural damage compared to 45% patients receiving MTX alone. In a subset of patients who began the study without erosions, REMICADE + MTX maintained an erosion free state at 1 year in a greater proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively ($p<0.01$). Fewer patients in the REMICADE + MTX groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).

Table 3
RADIOGRAPHIC CHANGE
FROM BASELINE TO WEEK 54

	Study RA I			Study RA II		
		REMICADE + MTX			REMICADE + MTX	
	Placebo + MTX (n=64)	3 mg/kg q 8 wks (n=71)	10 mg/kg q 8 wks (n=77)	Placebo + MTX (n=282)	3 mg/kg q 8 wks (n=359)	6 mg/kg q 8 wks (n=363)
Total Score						
Baseline						
Mean	79	78	65	11.3	11.6	11.2
Median	55	57	56	5.1	5.2	5.3
Change from baseline						
Mean	6.9	1.3[a]	0.2[a]	3.7	0.4[a]	0.5[a]
Median	4.0	0.5	0.5	0.4	0.0	0.0
Erosion Score						
Baseline						
Mean	44	44	33	8.3	8.8	8.3
Median	25	29	22	3.0	3.8	3.8
Change from baseline						
Mean	4.1	0.2[a]	0.2[a]	3.0	0.3[a]	0.1[a]
Median	2.0	0.0	0.5	0.3	0.0	0.0
JSN Score						
Baseline						
Mean	36	34	31	3.0	2.9	2.9
Median	26	29	24	1.0	1.0	1.0
Change from baseline						
Mean	2.9	1.1[a]	0.0[a]	0.6	0.1[a]	0.2
Median	1.5	0.0	0.0	0.0	0.0	0.0

[a] $P < 0.001$ for each outcome against placebo.

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Physical function response

Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ-DI) and the general health-related quality of life questionnaire SF-36.

In Study RA I, all doses/schedules of REMICADE + MTX showed significantly greater improvement from baseline in HAQ-DI and SF-36 physical component summary score averaged over time through week 54 compared to placebo + MTX, and no worsening in the SF-36 mental component summary score. The median (interquartile range) improvement from baseline to week 54 in HAQ-DI was 0.1 (-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for REMICADE + MTX ($p<0.001$). Both HAQ-DI and SF-36 effects were maintained through week 102. Approximately 80% of patients in all doses/schedules of REMICADE + MTX remained in the trial through 102 weeks.

In Study RA II, both REMICADE treatment groups showed greater improvement in HAQ-DI from baseline averaged over time through week 54 compared to MTX alone; 0.7 for REMICADE + MTX vs. 0.6 for MTX alone ($p\leq0.001$). No worsening in the SF-36 mental component summary score was observed.

Active Crohn's Disease

The safety and efficacy of single and multiple doses of REMICADE were assessed in two randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to severely active Crohn's disease [Crohn's Disease Activity Index (CDAI) ≥220 and ≤400] with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.

In the single-dose trial[8] of 108 patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at week 4 vs. 81% (22/27) of patients receiving 5 mg/kg REMICADE ($p<0.001$, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission (CDAI<150) at week 4.

In a multidose trial (ACCENT I [Study Crohn's I])[9], 545 patients received 5 mg/kg at week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at week 2 were randomized and analyzed separately from those not in response at week 2. Corticosteroid taper was permitted after week 6.

At week 2, 57% (311/545) of patients were in clinical response. At week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 4).

Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg REMICADE maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at week 54 (Table 4).

Table 4
CLINICAL REMISSION AND STEROID WITHDRAWAL

	Single 5 mg/kg Dose[a]	Three Dose Induction[b]	
		REMICADE Maintenance q 8 wks	
	Placebo Maintenance	5 mg/kg	10 mg/kg
Week 30	25/102	41/104	48/105
Clinical remission	25%	39%	46%
p-value[c]		0.022	0.001
Week 54			
Patients in remission able to discontinue corticosteroid use[d]	6/54 11%	14/56 25%	18/53 34%
p-value[c]		0.059	0.005

[a] REMICADE at week 0
[b] REMICADE 5 mg/kg administered at weeks 0, 2 and 6
[c] p-values represent pairwise comparisons to placebo
[d] Of those receiving corticosteroids at baseline

Patients in the REMICADE maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss of response than patients in the placebo maintenance group (Figure 1). At weeks 30 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg REMICADE-treated groups compared to the placebo group in the disease specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.

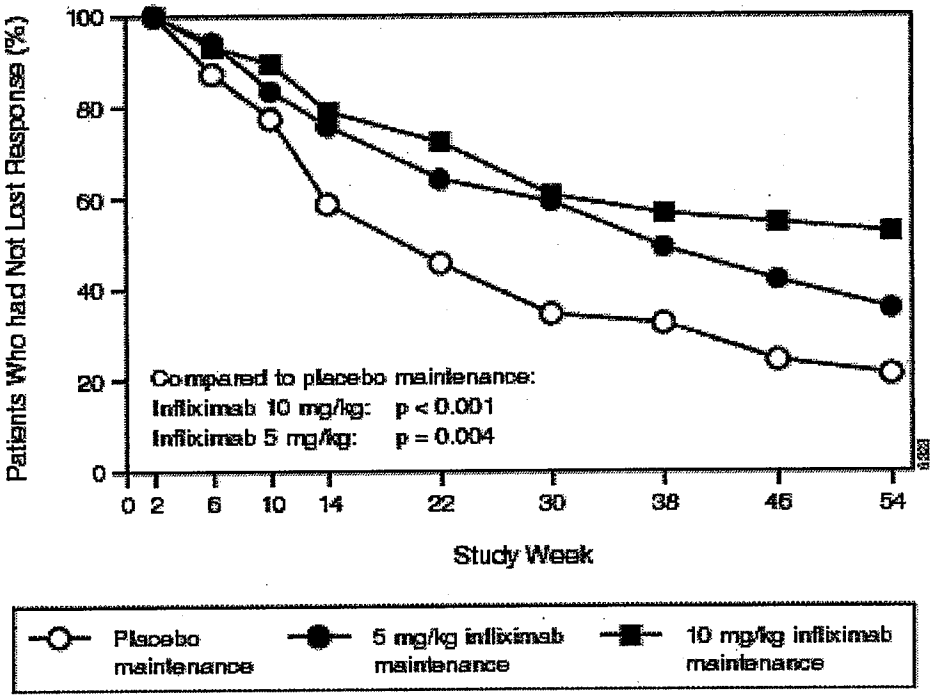

Figure 1
Kaplan-Meier estimate of the proportion of patients who had not lost response through week 54

In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 13 of 43 patients in the REMICADE maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at week 10. Of the REMICADE-treated patients showing mucosal healing at week 10, 9 of 12 patients also showed mucosal healing at week 54.

Patients who achieved a response and subsequently lost response were eligible to receive REMICADE on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at week 2, 59% (92/157) of REMICADE maintenance patients responded by week 14 compared to 51% (39/77) of placebo maintenance patients. Among patients who did not respond by week 14, additional therapy did not result in significantly more responses (see DOSAGE AND ADMINISTRATION).

Fistulizing Crohn's Disease

The safety and efficacy of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled studies in patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-aminosalicylates, antibiotics, MTX, 6-mercaptopurine (6-MP) and/or azathioprine (AZA) was permitted.

In the first trial,[10] 94 patients received three doses of either placebo or REMICADE at weeks 0, 2 and 6. Fistula response (≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least two consecutive visits without an increase in medication or surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE group (p=0.002) and 56% (18/32) of patients in the 10 mg/kg REMICADE group (p=0.021) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure of all fistula was achieved in 52% of REMICADE-treated patients compared with 13% of placebo-treated patients (p<0.001).

In the second trial (ACCENT II [Study Crohn's II]), patients who were enrolled had to have at least one draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg REMICADE at weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg REMICADE maintenance at week 14. Patients received maintenance doses at week 14 and then every eight weeks through week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.

Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the patients had received previous immunosuppressive and antibiotic therapy.

At week 14, 65% (177/273) of patients were in fistula response. Patients randomized to REMICADE maintenance had a longer time to loss of fistula response compared to the placebo maintenance group (Figure 2). At week 54, 38% (33/87) of REMICADE-treated patients had no draining fistulas compared with 22% (20/90) of placebo-treated patients (p=0.02). Compared to placebo maintenance, patients on REMICADE maintenance had a trend toward fewer hospitalizations.

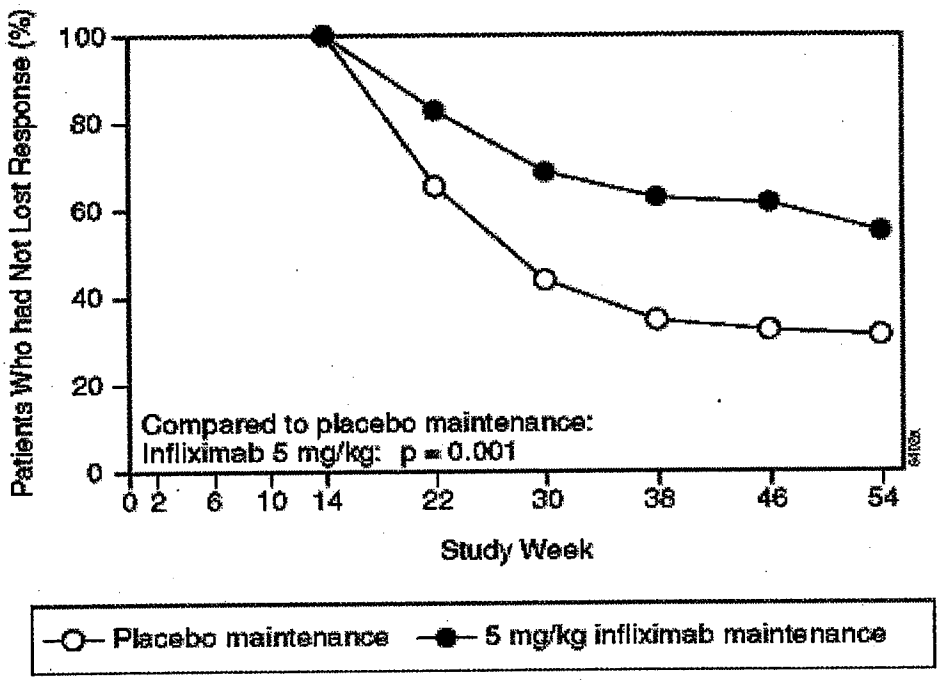

Figure 2
Life table estimates of the proportion of patients who had not lost fistula response through week 54

Patients who achieved a fistula response and subsequently lost response were eligible to receive REMICADE maintenance therapy at a dose that was 5 mg/kg higher than the dose to which they were randomized. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg REMICADE, and 57% (12/21) of REMICADE maintenance patients responded to 10 mg/kg.

Patients who had not achieved a response by week 14 were unlikely to respond to additional doses of REMICADE.

Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

Ankylosing Spondylitis

The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New York criteria for Ankylosing Spondylitis.[11] Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited.

Doses of REMICADE 5 mg/kg or placebo were administered intravenously at Weeks 0, 2, 6, 12 and 18.

At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20), was seen in 60% of patients in the REMICADE-treated group vs. 18% of patients in the placebo group ($p<0.001$). Improvement was observed at week 2 and maintained through week 24 (Figure 3 and Table 5).

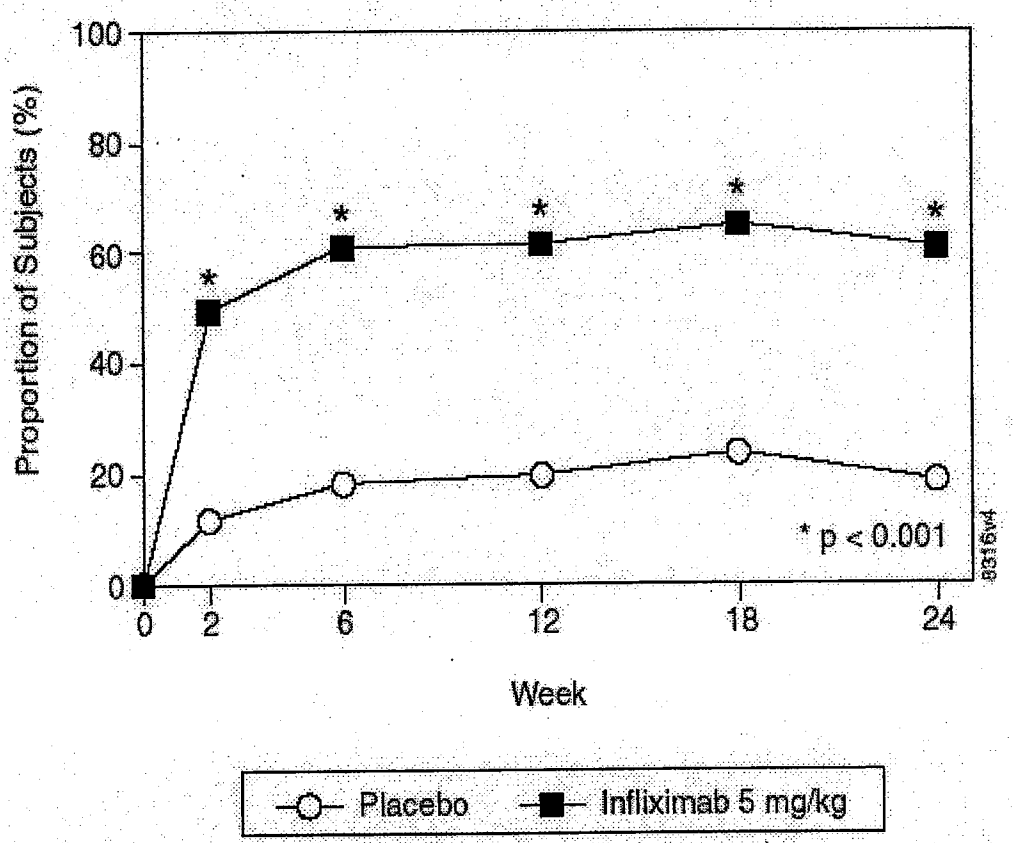

Figure 3
Proportion of patients achieving ASAS 20 response

At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving REMICADE, compared to 9% and 4%, respectively, for patients receiving placebo ($p<0.001$, REMICADE vs. placebo). A low level of disease activity (defined as a value <20 [on a scale of 0-100 mm] in

each of the four ASAS response parameters) was achieved in 22% of REMICADE-treated patients vs. 1% in placebo-treated patients (p<0.001).

Table 5
Components of Ankylosing Spondylitis Disease Activity

	Placebo (n=78)		REMICADE 5mg/kg (n=201)		
	Baseline	24 Weeks	Baseline	24 Weeks	p-value
ASAS 20 response Criteria (Mean)					
Patient global assessment[a]	6.6	6.0	6.8	3.8	<0.001
Spinal pain[a]	7.3	6.5	7.6	4.0	<0.001
BASFI[b]	5.8	5.6	5.7	3.6	<0.001
Inflammation[c]	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP[d] (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober's test[e]	4.0	5.0	4.3	4.4	0.75
Chest expansion[e]	3.6	3.7	3.3	3.9	0.04
Tragus to wall[e]	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion[e]	10.6	11.0	11.4	12.9	0.03

[a] measured on a VAS with 0="none" and 10="severe"
[b] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions
[c] Inflammation, average of last 2 questions on the 6 question BASDAI
[d] CRP normal range 0-1.0 mg/dL
[e] Spinal mobility normal values: modified Schober's test: >4 cm; chest expansion:>6 cm; tragus to wall: <15 cm; lateral spinal flexion: >10 cm

The median improvement from baseline in the general health-related quality of life questionnaire SF-36 physical component summary score at week 24 was 10.2 for the REMICADE group vs. 0.8 for the placebo group (p<0.001). There was no change in the SF-36 mental component summary score in either the REMICADE group or the placebo group.

Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled study of 70 patients with ankylosing spondylitis.

Psoriatic Arthritis

Safety and efficacy of REMICADE were assessed in a multicenter, double-blind, placebo-controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID therapy (≥ 5 swollen joints and ≥ 5 tender joints) with one or more of the following subtypes: arthritis involving DIP joints (n = 49), arthritis mutilans (n = 3), asymmetric peripheral arthritis (n = 40), polyarticular arthritis (n = 100), and spondylitis with peripheral arthritis (n = 8).

Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg REMICADE or placebo at weeks 0, 2, 6, 14, and 22 (100 patients in each group). At week 16, placebo patients with < 10% improvement from baseline in both swollen and tender joint counts were switched to REMICADE induction (early escape).

Treatment with REMICADE resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 58% of REMICADE-treated patients achieving ACR 20 at week 14, compared with 11% of placebo-treated patients ($p < 0.001$). The response was similar regardless of concomitant use of methotrexate. Improvement was observed as early as week 2. At 6 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients receiving REMICADE compared to 16%, 4%, and 2%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral arthritis subtypes.

Compared to placebo, treatment with REMICADE resulted in improvements in the components of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 6).

The results of this study were similar to those seen in an earlier multicenter, randomized, placebo-controlled study of 104 patients with psoriatic arthritis.

Table 6
COMPONENTS OF ACR 20 AND PERCENTAGE OF PATIENTS WITH 1 OR MORE JOINTS WITH DACTYLITIS AND PERCENTAGE OF PATIENTS WITH ENTHESOPATHY AT BASELINE and WEEK 24

	Placebo (n=100)		REMICADE 5mg/kg[a] (n=100)	
Parameter (medians)	Baseline	Week 24	Baseline	Week 24
No of Tender Joints[b]	24	20	20	6

No. of Swollen Joints[c]	12	9	12	3
Pain[d]	6.4	5.6	5.9	2.6
Physician's Global Assessment[d]	6.0	4.5	5.6	1.5
Patient's Global Assessment[d]	6.1	5.0	5.9	2.5
Disability Index (HAQ-DI)[e]	1.1	1.1	1.1	0.5
CRP (mg/dL)[f]	1.2	0.9	1.0	0.4
% Patients with 1 or more digits with dactylitis	41	33	40	15
% Patients with enthesopathy	35	36	42	22

[a] $p<0.001$ for percent change from baseline in all components of ACR 20 at week 24, $p<0.05$ for % of patients with dactylitis, and $p=0.004$ for % of patients with enthesopathy at week 24
[b] Scale 0-68
[c] Scale 0-66
[d] Visual Analog Scale (0=best, 10=worst)
[e] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)
[f] Normal range 0-0.6 mg/dL

Improvement in PASI in patients with baseline body surface area (BSA) ≥ 3% (n=87 placebo, n=83 REMICADE) was achieved at week 14, regardless of concomitant methotrexate use, with 64% of REMICADE-treated patients achieving at least 75% improvement from baseline vs. 2% of placebo-treated patients; improvement was observed as early as week 2. At 6 months, the PASI 75 and PASI 90 responses were achieved by 60% and 39%, respectively, of patients receiving REMICADE compared to 1% and 0%, respectively, of patients receiving placebo.

Ulcerative Colitis

The safety and efficacy of REMICADE were assessed in two randomized, double-blind, placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative colitis (UC) (Mayo score[12] 6 to 12 [of possible range 0-12], Endoscopy subscore ≥ 2) with an inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents was permitted. Corticosteroid taper was permitted after week 8. In both studies, patients were randomized to receive either placebo, 5 mg/kg REMICADE or 10 mg/kg REMICADE at weeks 0, 2, 6, 14 and 22.

Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-mercaptopurine (6-MP), or azathioprine (AZA). Patients in Study UC II had failed to respond or were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-MP/azathioprine (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%,

respectively). Clinical response was defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

In both studies, greater percentages of patients in both REMICADE groups achieved a clinical response, a sustained clinical response (response at both weeks 8 and 30), clinical remission and other assessed clinical outcomes than in the placebo group (Table 7). Of patients on corticosteroids at baseline, greater proportions of patients in the REMICADE treatment groups were in clinical remission and able to discontinue corticosteroids at week 30 compared with the patients in the placebo treatment groups (22% in REMICADE treatment groups vs. 10% in placebo group in Study UC I; 23% in REMICADE treatment groups vs. 3% in placebo group in Study UC II). The REMICADE-associated response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.

Table 7

Response, Remission and Mucosal Healing in Ulcerative Colitis Studies

	Study UC I			Study UC II		
	Placebo	5 mg/kg REMICADE	10 mg/kg REMICADE	Placebo	5 mg/kg REMICADE	10 mg/kg REMICADE
Patients randomized	121	121	122	123	121	120
Clinical Response[1]						
Week 8	37%	69%*	62%*	29%	65%*	69%*
Week 30	30%	52%*	51%**	26%	47%*	60%*
Sustained Response (both Week 8 and 30)	23%	49%*	46%*	15%	41%*	53%*
Clinical Remission[2]						
Week 8	15%	39%*	32%**	6%	34%*	28%*
Week 30	16%	34%*	37%*	11%	26%**	36%*
Sustained Remission (both Week 8 and 30)	8%	23%*	26%*	2%	15%*	23%*

Mucosal Healing[3]						
Week 8	34%	62%*	59%*	31%	60%*	62%*
Week 30	25%	50%*	49%*	30%	46%**	57%*

* $P < 0.001$, ** $P < 0.01$

[1] Defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1. (The Mayo score consists of the sum of four subscores: stool frequency, rectal bleeding, physician's global assessment and endoscopy findings.)

[2] Defined as a Mayo score ≤ 2 points, no individual subscore >1.

[3] Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.

The improvement with REMICADE was consistent across all Mayo subscores through week 30 (study UC I shown in Table 8; Study UC II was similar).

Table 8
Proportion of patients in Study UC I with Mayo subscores indicating inactive or mild disease through week 30

	Study UC I		
		REMICADE	
	Placebo (n=121)	**5 mg/kg** (n=121)	**10 mg/kg** (n=122)
Stool frequency			
Baseline	17%	17%	10%
Week 8	35%	60%	58%
Week 30	35%	51%	53%
Rectal Bleeding			
Baseline	54%	40%	48%
Week 8	74%	86%	80%
Week 30	65%	74%	71%
Physician's global assessment			
Baseline	4%	6%	3%
Week 8	44%	74%	64%
Week 30	36%	57%	55%
Endoscopy findings			
Baseline	0%	0%	0%
Week 8	34%	62%	59%
Week 30	26%	51%	52%

INDICATIONS AND USAGE

Rheumatoid Arthritis

REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

Crohn's Disease

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

REMICADE is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease.

Ankylosing Spondylitis

REMICADE is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Psoriatic Arthritis

REMICADE is indicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis.

Ulcerative Colitis

REMICADE is indicated for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

CONTRAINDICATIONS

REMICADE at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), REMICADE treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure (see WARNINGS and ADVERSE REACTIONS, Patients with Heart Failure).

REMICADE should not be administered to patients with known hypersensitivity to any murine proteins or other component of the product.

WARNINGS

RISK OF INFECTIONS
(See boxed WARNING)

SERIOUS INFECTIONS, INCLUDING SEPSIS AND PNEUMONIA, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS.

REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE THERAPY SHOULD BE DISCONTINUED (see ADVERSE REACTIONS, Infections).

CASES OF TUBERCULOSIS, HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS, PNEUMOCYSTOSIS, OTHER BACTERIAL, MYCOBACTERIAL AND FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.

SERIOUS INFECTIONS WERE SEEN IN CLINICAL STUDIES WITH CONCURRENT USE OF ANAKINRA AND ANOTHER TNFα-BLOCKING AGENT, ETANERCEPT, WITH NO ADDED CLINICAL BENEFIT COMPARED TO ETANERCEPT ALONE. BECAUSE OF THE NATURE OF THE ADVERSE EVENTS SEEN WITH COMBINATION OF ETANERCEPT AND ANAKINRA THERAPY, SIMILAR TOXICITIES MAY ALSO RESULT FROM THE COMBINATION OF ANAKINRA AND OTHER TNFα-BLOCKING AGENTS. THEREFORE, THE COMBINATION OF REMICADE AND ANAKINRA IS NOT RECOMMENDED.

Hepatotoxicity

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. As with other immunosuppressive drugs, use of REMICADE has been associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e., surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with REMICADE. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury (see ADVERSE REACTIONS, Hepatotoxicity).

Patients with Heart Failure

REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear. (See CONTRAINDICATIONS and ADVERSE REACTIONS, Patients with Heart Failure.)

Hematologic Events

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities.

Hypersensitivity

REMICADE has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's disease patients 3 to 12 days after REMICADE therapy was reinstituted following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction (see ADVERSE REACTIONS, Infusion-related Reactions).

Neurologic Events

REMICADE and other agents that inhibit TNF have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and CNS manifestation of systemic vasculitis. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders. Discontinuation of REMICADE should be considered in patients who develop significant central nervous system adverse reactions.

Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE, more malignancies have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, 14 patients were diagnosed with malignancies among 2897 REMICADE-treated patients vs. 1 among 1262 control patients (at a rate of 0.65/100 patient-years among REMICADE-treated patients vs. a rate of 0.13/100 patient-years among control patients), with median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of REMICADE clinical trials, 4 patients developed lymphomas among 4292 patients treated with REMICADE (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1265 control patients (median duration of follow-up 0.5 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per

100 patient-years of follow-up, which is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, 4 lymphomas were observed for a rate of 0.11 cases per 100 patient-years of follow-up, which is approximately 5-fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

The potential role of TNF-blocking therapy in the development of malignancies is not known (see ADVERSE REACTIONS, Malignancies). Rates in clinical trials for REMICADE cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving REMICADE.

PRECAUTIONS

Autoimmunity

Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE, treatment should be discontinued (see ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome).

Vaccinations

No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently.

Information for Patients

Patients should be provided the REMICADE Patient Information Sheet and provided an opportunity to read it prior to each treatment infusion session. Because caution should be exercised in administering REMICADE to patients with clinically important active infections, it is important that the patient's overall health be assessed at each treatment visit and any questions resulting from the patient's reading of the Patient Information Sheet be discussed.

Drug Interactions

Concurrent administration of etanercept (another TNFα-blocking agent) and anakinra (an interleukin-1 antagonist) has been associated with an increased risk of serious infections, and increased risk of neutropenia and no additional benefit compared to these medicinal products

alone. Other TNFα-blocking agents (including REMICADE) used in combination with anakinra may also result in similar toxicities (see WARNINGS, RISK OF INFECTIONS).

Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory agents, folic acid and corticosteroids.

Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants (see ADVERSE REACTIONS, Immunogenicity and Infusion-related Reactions). Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.

Carcinogenesis, Mutagenesis and Impairment of Fertility

A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. The significance of these findings for human risk is unknown. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

Pregnancy Category B

Since infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether REMICADE is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from REMICADE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and in pediatric patients with Crohn's disease or ulcerative colitis have not been established.

Geriatric Use

In rheumatoid arthritis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients aged 65 or older compared to younger patients although the incidence of serious adverse events in patients aged 65 or older was higher in both REMICADE and control groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (see ADVERSE REACTIONS, Infections).

ADVERSE REACTIONS

The data described herein reflect exposure to REMICADE in 3263 patients (1304 patients with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis, 150 with psoriatic arthritis, 484 with ulcerative colitis and 17 patients with other conditions), including 1484 patients exposed beyond 30 weeks and 296 exposed beyond one year. The most common reason for discontinuation of treatment was infusion-related reactions (e.g. dyspnea, flushing, headache and rash). Adverse events have been reported in a higher proportion of

rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in patients with Crohn's disease.

Infusion-related Reactions

Acute infusion reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated patients in all clinical studies experienced an infusion reaction compared to approximately 10% of placebo-treated patients. Among all REMICADE infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial infusion were not associated with a higher incidence of reactions.

Patients who became positive for antibodies to infliximab were more likely (approximately 2- to 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion reactions (see ADVERSE REACTIONS, Immunogenicity and PRECAUTIONS, Drug Interactions).

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with REMICADE administration.

Reactions following readministration

In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been

observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year.

Infections

In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE and may reflect recrudescence of latent disease (see WARNINGS, RISK OF INFECTIONS). In the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54 weeks Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess.

In REMICADE clinical studies in patients with ulcerative colitis, infections treated with antimicrobials were reported in 19% of REMICADE-treated patients (average of 27 weeks of follow-up) and in 14% of placebo-treated patients (average 22 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies.

In post-marketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving REMICADE alone or in combination with immunosuppressive agents.

Autoantibodies/Lupus-like Syndrome

Approximately half of REMICADE-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately one-fifth of REMICADE-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

Malignancies

In controlled trials, more REMICADE-treated patients developed malignancies than placebo-treated patients. (See WARNINGS, Malignancies.)

Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving REMICADE during post-approval use.

Patients with Heart Failure

In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. There were trends towards increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II). (See CONTRAINDICATIONS and WARNINGS, Patients with Heart Failure.)

Immunogenicity

Treatment with REMICADE can be associated with the development of antibodies to infliximab. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug free intervals >16 weeks. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see ADVERSE REACTIONS, Infusion-related Reactions) than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading.

Hepatotoxicity

Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving REMICADE (see WARNINGS, Hepatotoxicity). Reactivation of hepatitis B has occurred in patients receiving REMICADE who are chronic carriers of this virus (i.e., surface antigen positive) (see WARNINGS, Hepatotoxicity).

In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls (Table 9), both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications.

Table 9 Proportion of patients with elevated ALT in Clinical Trials

	Proportion of patients with elevated ALT					
	≥1 to <3 x ULN		≥3 x ULN		≥5 x ULN	
	Placebo	REMICADE	Placebo	REMICADE	Placebo	REMICADE
Rheumatoid arthritis[1]	24%	34%	3%	4%	<1%	<1%
Crohn's disease[2]	34%	39%	4%	5%	0%	2%
Ulcerative colitis[3]	12%	15%	1%	2%	<1%	<1%
Ankylosing spondylitis[4]	13%	40%	0%	6%	0%	2%
Psoriatic arthritis[5]	16%	42%	0%	5%	0%	2%

[1] Placebo patients received methotrexate while REMICADE patients received both REMICADE and methotrexate. Median follow-up was 58 weeks.
[2] Placebo patients in the 2 Phase III trials in Crohn's disease received an initial dose of 5 mg/kg REMICADE at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT analysis. Median follow-up was 54 weeks.
[3] Median follow-up was 30 weeks.
[4] Median follow-up was 24 weeks.
[5] Median follow-up was 24 weeks for REMICADE group and 18 weeks for placebo group.

Other Adverse Reactions

Safety data are available from 3263 REMICADE-treated patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 150 with psoriatic arthritis, and 17 with other conditions. Adverse events reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 10. The types and frequencies of adverse reactions observed were similar in REMICADE-treated

rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons.

Table 10

ADVERSE EVENTS OCCURRING IN 5% OR MORE OF PATIENTS RECEIVING 4 OR MORE INFUSIONS FOR RHEUMATOID ARTHRITIS

	Placebo (n=350)	REMICADE (n=1129)
Average weeks of follow-up	59	66
Gastrointestinal		
Nausea	20%	21%
Abdominal Pain	8%	12%
Diarrhea	12%	12%
Dyspepsia	7%	10%
Respiratory		
Upper respiratory tract infection	25%	32%
Sinusitis	8%	14%
Pharyngitis	8%	12%
Coughing	8%	12%
Bronchitis	9%	10%
Rhinitis	5%	8%
Skin and appendages disorders		
Rash	5%	10%
Pruritus	2%	7%
Body as a whole-general disorders		
Fatigue	7%	9%
Pain	7%	8%
Resistance mechanism disorders		
Fever	4%	7%
Moniliasis	3%	5%
Central and peripheral nervous system disorders		
Headache	14%	18%
Musculoskeletal system disorders		
Back pain	5%	8%
Arthralgia	7%	8%
Urinary system disorders		
Urinary tract infection	6%	8%
Cardiovascular disorders, general		
Hypertension	5%	7%

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice.

The most common serious adverse events observed in clinical trials were infections (see ADVERSE REACTIONS, Infections). Other serious, medically relevant adverse events ≥0.2% or clinically significant adverse events by body system were as follows:

Body as a whole: allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela
Blood: pancytopenia
Cardiovascular: circulatory failure, hypotension, syncope
Gastrointestinal: constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia
Central & Peripheral Nervous: meningitis, neuritis, peripheral neuropathy, dizziness
Heart Rate and Rhythm: arrhythmia, bradycardia, cardiac arrest, tachycardia
Liver and Biliary: biliary pain, cholecystitis, cholelithiasis, hepatitis
Metabolic and Nutritional: dehydration
Musculoskeletal: intervertebral disk herniation, tendon disorder
Myo-, Endo-, Pericardial and Coronary Valve: myocardial infarction
Platelet, Bleeding and Clotting: thrombocytopenia
Neoplasms: basal cell, breast, lymphoma
Psychiatric: confusion, suicide attempt
Red Blood Cell: anemia, hemolytic anemia
Reproductive: menstrual irregularity
Resistance Mechanism: cellulitis, sepsis, serum sickness
Respiratory: adult respiratory distress syndrome, lower respiratory tract infection (including pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency
Skin and Appendages: increased sweating, ulceration
Urinary: renal calculus, renal failure
Vascular (Extracardiac): brain infarction, pulmonary embolism, thrombophlebitis
White Cell and Reticuloendothelial: leukopenia, lymphadenopathy

The following adverse events have been reported during post-approval use of REMICADE: neutropenia (see WARNINGS, Hematologic Events), interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional neurologic events have also been observed, see WARNINGS, Neurologic Events). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure.

OVERDOSAGE

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis

The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. REMICADE should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at higher doses (see ADVERSE REACTIONS, Infections).

Crohn's Disease or Fistulizing Crohn's Disease

The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active Crohn's disease or fistulizing disease. For patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue REMICADE in these patients.

Ankylosing Spondylitis

The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion, then every 6 weeks thereafter.

Psoriatic Arthritis

The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. REMICADE can be used with or without methotrexate.

Ulcerative Colitis

The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active ulcerative colitis.

Preparation and Administration Instructions
Use aseptic technique.

REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after reconstitution should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE infusion should begin within 3 hours of preparation.

1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE solution required.

2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.

3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.

4. The infusion solution must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 μm or less). Any unused portion of the infusion solution should not be stored for reuse.

5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMICADE with other agents. REMICADE should not be infused concomitantly in the same intravenous line with other agents.

6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

Storage

Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the expiration date. This product contains no preservative.

HOW SUPPLIED

REMICADE lyophilized concentrate for IV injection is supplied in individually-boxed single-use vials in the following strength:

NDC 57894-030-01 100 mg infliximab in a 20 mL vial

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Rx Only

REMICADE® (infliximab)
Patient Information Sheet

You should read this information sheet before you start using REMICADE® (pronounced rem-eh-kaid) and before each time you are scheduled to receive REMICADE. This information sheet does not take the place of talking with your doctor. You and your doctor should talk about your health and how you are feeling before you start taking REMICADE, while you are taking it and at regular checkups. If you do not understand any of the information in this sheet, you should ask your doctor to explain what it means.

What is REMICADE?

REMICADE is a medicine that is used to treat adults with moderately to severely active rheumatoid arthritis, Crohn's disease and ulcerative colitis. In Crohn's disease and ulcerative colitis, REMICADE is for people who have not responded well enough to other medicines. REMICADE is also used to treat active ankylosing spondylitis and psoriatic arthritis.

How does REMICADE work?

The medicine REMICADE is a type of protein that recognizes, attaches to and blocks the action of a substance in your body called tumor necrosis factor. Tumor necrosis factor (TNF) is made by certain blood cells in your body. REMICADE will not cure rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis or psoriatic arthritis, but blocking TNF with REMICADE may reduce the inflammation caused by TNF in your body. You should also know that REMICADE may help you feel better but can also cause serious side effects and can reduce your body's ability to fight infections (see below).

What should I know about the immune system, and taking REMICADE for Rheumatoid Arthritis, Crohn's Disease, Ulcerative Colitis, Ankylosing Spondylitis or Psoriatic Arthritis?

The immune system protects the body by responding to "invaders" like bacteria, viruses and other foreign matter that enter your body by producing antibodies and putting them into action to fight off the "invaders." In diseases like rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis, TNF can cause your immune system to attack healthy tissues in your body and cause inflammation and damage. If these diseases are untreated, it can cause permanent damage to the body's bones, cartilage and tissue.

While taking REMICADE can block the TNF that causes inflammation, it can also lower your body's ability to fight infections. So, taking REMICADE can make you more prone to getting infections or it can make an infection that you already have worse. You should call your doctor right away if you think you have an infection.

What important information should I know about treatment with REMICADE?

REMICADE, like other medicines that affect your immune system, is a strong medicine that can cause serious side effects. Possible serious side effects include:

Serious Infections:

- Some patients have had serious infections while receiving REMICADE. Some of the patients have died from these infections. Serious infections include TB (tuberculosis), and infections caused by viruses, fungi or bacteria that have spread throughout the body. If you develop a fever, feel very tired, have a cough, or have flu-like symptoms, these could be signs that you may be getting an infection. If you have any of these symptoms while you are taking or after you have taken REMICADE, you should tell your doctor right away.

Heart Failure:

- If you have been told that you have a heart problem called congestive heart failure and you are currently being treated with REMICADE, you will need to be closely monitored by your doctor. If you develop new or worse symptoms that are related to your heart condition, such as shortness of breath or swelling of your ankles or feet, you must contact your doctor immediately.

Blood Problems:

- In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you stop bleeding. Some of the patients have died from this failure to produce blood cells. If you develop a fever that doesn't go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop your treatment.

Allergic Reactions:

- Some patients have had severe allergic reactions to REMICADE. These reactions can happen while you are getting your REMICADE infusion or shortly afterwards. The symptoms of an allergic reaction may include hives (red, raised, itchy patches of skin), difficulty breathing, chest pain and high or low blood pressure. Your doctor may decide to stop REMICADE treatment and give you medicines to treat the allergic reaction.
- Some patients who have been taking REMICADE for Crohn's disease have had allergic reactions 3 to 12 days after receiving their REMICADE treatment. The symptoms of this type of delayed reaction may include fever, rash, headache and muscle or joint pain. Call your doctor right away if you develop any of these symptoms or any other unusual symptoms such as difficulty swallowing.

Nervous System Disorders:

- There have been rare cases where people taking REMICADE or other TNF blockers have developed disorders that affected their nervous system. Signs that you could be having a problem include: changes in your vision, weakness in your arms and/or legs, and numbness or tingling in any part of your body.

Cancer:

- Reports of a type of blood cancer called lymphoma in patients on REMICADE or other TNF blockers are rare but occur more often than expected for people in general. People who have been treated for rheumatoid arthritis, Crohn's disease, ankylosing spondylitis or psoriatic arthritis for a long time, particularly those with highly active disease may be more prone to

develop lymphoma. Cancers, other than lymphoma, have also been reported. If you take REMICADE or other TNF blockers, your risk for developing lymphoma or other cancers may increase. You should also tell your doctor if you have had or develop lymphoma or other cancers while you are taking REMICADE.

Liver Injury:

- There have been rare cases where people taking REMICADE have developed serious liver problems, some fatal. Signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-colored urine, right sided abdominal pain, fever, and severe fatigue (tiredness). You should contact your doctor immediately if you develop any of these symptoms.

Other Important Information

Some patients have developed symptoms that can resemble a disease called lupus. Lupus-like symptoms may include chest discomfort or pain that doesn't go away, shortness of breath, joint pain, or a rash on the cheeks or arms that gets worse in the sun. If you develop any of these symptoms your doctor may decide to stop your treatment with REMICADE.

What are the more common side effects of REMICADE?

The more common side effects with REMICADE are respiratory infections (that may include sinus infections and sore throat), coughing and stomach pain.

Who should not take REMICADE?

YOU SHOULD NOT take REMICADE if you have:

- Heart failure, unless your doctor has talked to you and decided that you are able to take REMICADE.
- Had an allergic reaction to REMICADE or any other product that was made with murine (mouse) proteins.

What health concerns should I talk to my doctor about?

Before receiving your first treatment with REMICADE you should tell your doctor if you:

- Have or think you may have any kind of infection. The infection could be in only one place in your body (such as an open cut or sore), or an infection that affects your whole body (such as the flu). Having an infection could put you at risk for serious side effects from REMICADE.
- Have an infection that won't go away or a history of infection that keeps coming back.
- Have had TB (tuberculosis), or if you have recently been with anyone who might have TB. Your doctor will examine you for TB and perform a skin test. If your doctor feels that you are at risk for TB, he or she may start treating you for TB before you begin REMICADE therapy.
- Have lived in or visited an area of the country where an infection called histoplasmosis or coccidioidomycosis (an infection caused by a fungus that affects the lungs) is common. If you don't know if the area you live in is one where histoplasmosis or coccidioidomycosis is common, ask your doctor.

- Have or have previously had heart failure or other heart conditions.
- Have or have had a condition that affects your nervous system, like multiple sclerosis, or Guillain-Barré syndrome, or if you experience any numbness, or tingling, or have had a seizure.
- Are pregnant or nursing.
- Have recently received or are scheduled to receive a vaccine.

Can I take REMICADE while I am on other medicines?
Tell your doctor if you are taking any other medicines including over the counter medicines, supplements or herbal products before you are treated with REMICADE. If you start taking or plan to start taking any new medicine while you are taking REMICADE, tell your doctor.

REMICADE and KINERET should not be taken together.

How will REMICADE be given to me?
REMICADE will be given to you by a healthcare professional. REMICADE will be given to you by an IV. This means that the medicine will be given to you through a needle placed in a vein in your arm. It will take about 2 hours to give you the full dose of medicine. During that time and for a period after you receive REMICADE, you will be monitored by a healthcare professional. Your doctor may ask you to take other medicines along with REMICADE.

Only a health care professional should prepare the medicine and administer it to you.

How often will I receive REMICADE?
Rheumatoid Arthritis
If you are receiving REMICADE for rheumatoid arthritis you will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks. Your doctor will monitor your response to REMICADE and may change your dose or treat you more frequently (as often as every 4 weeks).

Crohn's Disease or Fistulizing Crohn's Disease
If you are receiving REMICADE for active Crohn's disease or fistulizing Crohn's disease, you will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks. Your doctor will monitor your response to REMICADE and may change your dose.

Ulcerative Colitis
If you are receiving REMICADE for ulcerative colitis, you will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks and your doctor will monitor your response to REMICADE.

Ankylosing Spondylitis
If you are receiving REMICADE for ankylosing spondylitis you will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 6 weeks.

Psoriatic Arthritis
If you are receiving REMICADE for psoriatic arthritis you will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks.

What if I still have questions?
If you have any questions, or problems, always talk first with your doctor. You can also visit the REMICADE internet site at www.remicade.com.

Product developed and manufactured by:
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355

Revised September 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103772 / S-5113

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Supplemental BLA
Submission Number	STN 103772.5113
Submission Code	sBLA
Submission Date	March 24, 2005
PDUFA Goal Date	September 23, 2005
Reviewer Name	Li-ching Liang, M.D. LL CDER/ODE VI/DTBIMP
Through	Jeff Siegel, M.D. JS CDER/ODE VI/DTBIMP and Marc Walton, M.D., Ph.D. CDER/ODE VI/DTBIMP
Review Completion Date	September 15, 2005
Established Name	Remicade®
Therapeutic Class	TNF Antagonist
Applicant	Centocor, Inc.
Priority Designation	Priority
Formulation	aqueous solution
Dosing Regimen	5 mg/kg IV at 0, 2, and 6 weeks followed by Q8 wk dosing
Indication	Ulcerative Colitis
Intended Population	Moderate to severely active ulcerative colitis patients

Table of Contents

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Recommend approving the efficacy supplement with revisions to the proposed label.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None are warranted at the present time.

1.2.2 Required Phase 4 Commitments

The Sponsor has committed to conduct a randomized, controlled, and adequately powered clinical trial to assess the safety and efficacy of infliximab in pediatric patients with moderately to severely active ulcerative colitis. The final protocol will be submitted to the IND by March 31, 2006 with an expected study start date of June 30, 2006. The sBLA submission to the FDA is expected by June 30, 2009.

1.2.3 Other Phase 4 Requests

No new Phase 4 commitments are required.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

REMICADE® is currently approved in the U.S. for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, and psoriatic arthritis. In rheumatoid arthritis, it is indicated for reducing the signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. It is indicated in Crohn's disease for reducing the signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. It is also indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closre in patients with fistulizing Crohn's disease. Lastly, REMICADE® is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

The primary objective of the two randomized, double-blind, placebo-controlled studies C0168T37 (ACT 1) and C0168T46 (ACT 2) was to determine the efficacy and safety of

infliximab 5 mg/kg and 10 mg/kg intravenously in active ulcerative colitis (UC) subjects who failed to tolerate or respond to currently available therapies at 8 and 30 weeks compared to placebo, when given at 0, 2, and 6 weeks followed by Q8 wk dosing. The current submission provides Week 30 clinical data from the two clinical studies and Week 54 data (for ACT 1 only). The primary endpoint for both studies was clinical response at Week 8. Other efficacy endpoints included clinical response at Week 30, clinical remission at Week 8 and Week 30, sustained response at Weeks 8 and 30, sustained remission at Weeks 8 and 30, mucosal healing at Week 8 and Week 30, corticosteroid use at Week 8 and Week 30, SF-36 and IBDQ response at Week 8 and Week 30.

1.3.2 Efficacy

The Week 30 data demonstrated that moderately to severely active ulcerative colitis subjects who failed to tolerate or respond to currently available UC therapies who received infliximab had a significant increase in the proportion of patients attaining clinical response and remission at Weeks 8 and 30 compared to placebo. For the combined infliximab groups, 65% of subjects attained clinical response at Week 8 in the ACT 1 trial and 69% in the ACT 2 trial, compared to 37% and 29% among placebo controls ($p < 0.001$ for both comparisons). At Week 30, 51% and 54% of infliximab-treated subjects were in response compared to 30% and 26% of placebo controls ($p < 0.001$ for both comparisons). Remission rates were also increased in the infliximab groups (35% at Weeks 8 and 30 for ACT 1 and 31% at both timepoints for ACT 2) compared to controls (15% and 16% in ACT 1 at Weeks 8 and 30; 6% and 11% in ACT 2 at Weeks 8 and 30; $p < 0.001$ for all comparisons). Week 54 data (collected in ACT 1 only) showed these benefits were sustained. Improvement was also observed with mucosal healing and in histologic scores.

1.3.3 Safety

The overall safety profile reported from the ACT 1 and ACT 2 studies was comparable to that already seen in other clinical trials and in the post-marketing use of TNF antagonists. Serious adverse events, including malignancies and lymphomas, and serious infectious events, including tuberculosis and opportunistic infections, continue to be an important concern in the use of TNF antagonists. Serious infectious AEs occurred in similar proportions of subjects (<3%) compared to other TNF clinical trials. Pooled data reviewed during this submission from the controlled trials of all the approved indications demonstrated a higher rate of malignancies in the infliximab-treated patients compared to controls (0.69 vs. 0.13 cases per 100 patient-years). The rate among infliximab-treated patients was similar to the expected rate in the general population while the rate among controls was lower.

1.3.4 Dosing Regimen and Administration

Both Studies C0168T37 and C0168T46 used the currently approved dosing regimen, which is 5 mg/kg IV at weeks 0, 2, and 6 followed by Q8 week dosing. The — ıg/kg dose was also studied at these administration times. b(4)

1.3.5 Drug-Drug Interactions

No drug-drug interactions were explored in this supplement.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Infliximab is a chimeric monoclonal antibody that binds with high affinity and specificity to human TNFα and neutralizes its biological activity.

2.2 Currently Available Treatment for Indications

Currently approved products for the treatment of ulcerative colitis include corticosteroids and aminisalicylates.

2.3 Availability of Proposed Active Ingredient in the United States

This product is currently licensed and marketed in the United States. There are no known availability issues with the proposed ingredient.

2.4 Important Issues With Pharmacologically Related Products

An increased risk of serious infections and lymphoma is associated with currently approved TNF-antagonists. A higher rate of lymphoma has been observed in RA and Crohn's disease patients receiving TNF-blockers compared to the general U.S. population.

2.5 Presubmission Regulatory Activity

Infliximab was initially approved in the U.S. for rheumatoid arthritis and has subsequently been approved for Crohn's disease (including the treatment of fistulizing Crohn's disease), ankylosing spondylitis, and psoriatic arthritis. The application was approved for Fast Track designation on June 8, 2004 for patients with active UC who were intolerant of, or unresponsive to corticosteroids, aminosalicylates, and/or immunosuppressive agents, for 1) reduction of signs and symptoms of UC, 2) induction and maintenance of remission, 3) mucosal healing, and 4) reduction in the need for a colectomy. This application was also granted priority review because a) current ulcerative colitis therapies are limited by their effectiveness and/or toxicity, b) moderate to severe ulcerative colitis meets the criterion of a serious or life-threatening condition, c) there are currently no approved therapies for the indications listed above, and d) this represents a significant unmet medical need.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of the clinical data for this review consisted of study reports and datasets of two Centocor-sponsored, randomized, controlled clinical trials in multinational sites (C0168T37 and C0168T46).

4.4 Data Quality and Integrity

Clinical investigator (CI) inspections were conduced at three sites that enrolled a large number of subjects. One of the three inspected sites had minor protocol deviations which consisted of discrepancies among study records related to unreported adverse events, but overall, data from this site and the other two inspected sites were deemed acceptable for use in support of the sBLA by the Division of Scientific Investigations.

4.6 Financial Disclosures

Two investigators from each of the ACT 1 and ACT 2 trials reported having a significant equity interest in [redacted] in their portfolios or their spouses', estimated to exceed $50,000 based upon the fair market value of [redacted] stock at the time of site initiation. b(6)

Investigator Name	Site Number	Study	Number of Subjects Enrolled
James Leavitt, M.D.	018	ACT 1	14
Alan Safdi, M.D.	014	ACT 1	12
Stephen Hanauer, M.D.	107	ACT 2	11
Joseph Spaar	163	ACT 2	3

These few investigative sites would not be expected to influence the overall study results, as there were a total of 62 investigative sites for ACT 1 and 55 sites for ACT 2, with 364 subjects enrolled in each study.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

For the ulcerative colitis indication, the Sponsor proposed the wording:

"Remicade is indicated for reducing signs and symptoms, [redacted] clinical remission, [redacted] mucosal healing, and [redacted] eliminating b(4)

corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy."

6.1.1 Methods

The clinical data from both randomized, double-blind studies were analyzed to determine whether a clinical benefit existed for active ulcerative colitis subjects who received Remicade® vs. placebo at Week 8 and Week 30. The FDA statistical reviewer confirmed the major efficacy analyses and performed sensitivity analyses to corroborate the findings of the Sponsor.

6.1.2 General Discussion of Endpoints

In both the ACT 1 and ACT 2 studies, the primary endpoint that was chosen was based on the Mayo score, used to assess disease activity in ulcerative colitis subjects. The Mayo score is a composite score consisting of four subscores (ie. stool frequency, rectal bleeding, endoscopy findings, and physician's global assessment) and is a reasonable scoring index for ulcerative colitis because it allows for an adequate overall assessment of a subject's disease status. Unlike the use of the Crohn's Disease Activity Index in Crohn's disease clinical trials, there is currently no universally accepted and validated measure of disease activity in UC patients. The Mayo score was agreed upon by the Agency as an acceptable scoring index to use in the ACT 1 and ACT 2 studies because it incorporates patient reporting, a physician's assessment, an endoscopic component, and an assessment of rectal bleeding, which is an important and accepted clinical measure of disease activity. The definitions of remission (a Mayo score of ≤ 2, with no individual subscore > 1) and of mucosal healing (an endoscopy findings subscore of 0 or 1) are consistent with quiescent or minimal disease activity.

6.1.3 Study Design

Both ACT 1 and ACT 2 were randomized, double-blind, placebo-controlled, multicenter, international, parallel-group studies, with identical primary and secondary endpoints. ACT 1 was conducted between March 2002 and September 2004 at 62 international sites, and ACT 2 was conducted between June 2002 to September 2004 at 55 international sites. Both studies required subjects to have moderately to severely active ulcerative colitis, defined as a Mayo score between 6 and 12 (minimum possible score – 0; maximum score – 12). In addition, subjects were also required to have endoscopically active colitis as well, indicated by an endoscopy findings subscore of ≥ 2 (maximum possible score 3). In addition, subjects must have met at least one of the following criteria: 1) had current treatment with at least 1 of the following: oral corticosteroids, 6-mercaptopurine (6-MP), azathioprine (AZA), 2) had failed to successfully taper, tolerate, or respond to oral corticosteroids within the past 18 months, or 3) had failed to tolerate or respond to 6-MP or AZA within the previous 5 years. The major difference between ACT 2 compared to ACT 1 was that subjects could have been enrolled into ACT 2 if they had moderate to severely active UC while solely on current treatment with 5-aminosalicylate (5-ASA) compounds. Thus, subjects in ACT 2 could have been randomized to receive infliximab therapy even before receiving a trial of corticosteroids. The goal of this

design strategy was to explore whether infliximab could be a worthwhile treatment before a trial of corticosteroids in a subject with active UC. The other main difference between both studies was that the length of ACT 1 was 54 weeks, whereas ACT 2 was 30 weeks long. The complete inclusion/exclusion criteria for the ACT 1 and ACT 2 studies are listed in Appendix 1.

In both studies, 364 subjects each were randomized to either placebo, infliximab 5 mg/kg, or infliximab 10 mg/kg, using adaptive randomization. Investigative site and corticosteroid refractory status were used as stratification variables. For those subjects who were on concomitant corticosteroids at the time of enrollment, investigators could begin to taper steroids as guided by the subject's condition. Investigators were advised to taper steroids according to protocol guidelines. For subjects whose corticosteroid dose was > 20 mg/day of prednisone or equivalent, the recommended taper was to lower the daily dose by 5 mg/week. For subjects whose corticosteroid dose was $\leq$ 20 mg/day of prednisone or equivalent, investigators were advised to decrease the daily dose by no more than 2.5 mg/week. Topical UC therapy was not allowed within 2 weeks of screening, and all other UC specific medications were maintained at baseline doses until Week 30.

The primary efficacy endpoint for both ACT 1 and ACT 2 was clinical response at Week 8. Clinical response was defined as a decrease in the Mayo Score of $\geq$ 30% and $\geq$ 3 points, accompanied by a decrease in the rectal bleeding subscore of $\geq$ 1 or a rectal bleeding subscore of 0 or 1. A positive study would be declared if the combined test and at least 1 of the pairwise comparisons of infliximab with placebo was significant at the 2-sided 0.05 level of significance, using a Cochran-Mantel-Haenszel chi-square test, stratified by corticiosteroid refractory status and center location. A summary of how the Mayo score is calculated is found in Appendix 2.

The major secondary endpoints of both studies were:

- the proportion of subjects in clinical remission at Week 8,
- the proportion of subjects in clinical remission at Week 30,
- the proportion of subjects in clinical response at Week 30, and
- the proportion of subjects with mucosal healing at Week 8.

Clinical remission was defined as a Mayo score of $\leq$ 2 points, with no individual subscore > 1, thus, subjects in remission must have had a rectal bleeding subscore of 0 or 1. Mucosal healing was defined as having an endoscopy findings subscore of 0 or 1. All secondary efficacy analyses were intended to support the primary efficacy analysis. No adjustments were made for multiple comparisons, and all p-values were considered nominal.

Other efficacy endpoints specified by the Sponsor included:

- the median daily corticosteroid dose among treatment arms,
- sustained response (defined as subjects in clinical response at both Week 8 and Week 30),
- sustained remission (defined as subjects in clinical remission at both Week 8 and Week 30),

- median total Mayo scores and median partial Mayo scores,
- maximum grade of histological assessment of inflammation (a substudy of ACT 1 only),
- change from baseline in CRP values through Week 30,
- the number of colectomies and ostomies per treatment group,
- health-related quality of life, measured by the IBDQ and SF-36, and
- number of UC-related hospitalizations/surgeries/procedures, and all ICU and TPN days through Week 30.

The study schedules of events and evaluations for both studies are listed in Appendix 3.

Study Inclusion/Exclusion Criteria

The complete inclusion/exclusion criteria for both the ACT 1 and ACT 2 studies can be found in Appendix 1.

Treatment Schema

The treatment schedules for both studies are represented in **Table 1** and **Table 2** for ACT 1 and ACT 2, respectively. ACT 1 was designed as a 54 week study. Subjects in ACT 2 were treated until Week 30, but had the option of having their study drug extended with continued Q8 wk dosing.

Table 1: Treatment Schedule – ACT 1

Group	Infusion	Wk 0	Wk 2	Wk 6	Wk 14	Wk 22	Wk 30	Wk 38	Wk 46	Wk 54
I	Placebo	P	P	P	P	P	P	P	P	P
II	5 mg/kg infliximab	5	5	5	5	5	5	5	5	5
III	10 mg/kg infliximab	10	10	10	10	10	10	10	10	10

Only data through Week 30 are presented by the Sponsor
Database lock for Week 54 data expected in June 2005

Table 2: Treatment Schedule – ACT 2

Group	Infusion	Wk 0	Wk 2	Wk 6	Wk 14	Wk 22	Wk 30
I	Placebo	P	P	P	P	P	P
II	5 mg/kg infliximab	5	5	5	5	5	5
III	10 mg/kg infliximab	10	10	10	10	10	10

Prior and Concomitant Therapy

For those subjects who were receiving medical treatment for UC at the time of enrollment, the regimen and doses must have been stable for a specified period before baseline. At the time of screening, subjects must have discontinued therapy before screening if they recently discontinued UC-specific medical therapy. All UC-specific therapies (i.e., immunomodulatory agents or aminosalicylates) must have been maintained at the baseline doses until the Week 54 visit (for ACT 1) or the Week 30 visit (for ACT 2), unless toxicity required earlier dose reduction. Topical corticosteroid therapy was not allowed within 2 weeks of screening and was also not allowed during the study. The concomitant medications that subjects were receiving at baseline for ACT 1 and ACT 2 are shown in **Table 3** and **Table 4**, respectively.

At the time of enrollment into ACT 1 (**Table 3**), the concomitant medications that subjects took at baseline were comparable across all treatment arms. 94% of all subjects were being treated with at least one UC medication. 61% were on concomitant steroids at baseline, 49% were on immunomodulatory drugs, and 70% were taking aminosalicylates. 40% of subjects were on ≥ 20 mg/day of corticosteroids.

ACT 1

Table 3: Summary of concomitant medications for ulcerative colitis at baseline

		Infliximab			
	Placebo	**5 mg/kg**	**10 mg/kg**	**Total**	**p-value**
Subjects randomized N, (%)	121	121	122	364	
Any UC medication	113 (93)	115 (95)	114 (93)	342 (94)	0.829
Corticosteroids	79 (65)	70 (58)	73 (60)	222 (61)	0.470
≥ 20 mg/day	54 (45)	45 (37)	46 (38)	145 (40)	
< 20 mg/day	25 (21)	25 (21)	27 (22)	77 (21)	
Immunomodulatory drugs	53 (44)	66 (55)	59 (48)	178 (49)	0.245
6-mercaptopurine	17 (14)	21 (17)	15 (12)	53 (15)	
Azathioprine	36 (30)	45 (37)	44 (36)	125 (34)	
Aminosalicylates	85 (70)	82 (68)	86 (71)	253 (70)	0.878
Olsalazine	5 (4)	4 (3)	2 (2)	11 (3)	
Balsalazide	14 (12)	16 (13)	11 (9)	41 (11)	
Sulfasalazine	10 (8)	7 (6)	15 (12)	32 (9)	
Mesalamine	58 (48)	57 (47)	60 (49)	175 (48)	
Other aminosalicylates	0	0	0	0	

Similarly in ACT 2 (**Table 4**), there were no significant differences across treatment groups with baseline concomitant medications. 95% of all subjects in ACT 2 were on at least one UC medication. 51% of subjects were on corticosteroids at baseline, 43% were taking immunomodulatory drugs, and 75% were being treated with aminosalicylates. 36% of subjects were taking ≥ 20 mg/day of corticosteroids.

ACT 2

Table 4: Summary of concomitant medications for ulcerative colitis at baseline

		Infliximab			
	Placebo	**5 mg/kg**	**10 mg/kg**	**Total**	**p-value**
Subjects randomized N, (%)	123	121	120	364	
Any UC medication	117 (95)	113 (93)	116 (97)	346 (95)	0.502
Corticosteroids	60 (49)	60 (50)	66 (55)	186 (51)	0.575
≥ 20 mg/day	43 (35)	40 (33)	47 (39)	130 (36)	
< 20 mg/day	17 (14)	20 (17)	19 (16)	56 (15)	
Immunomodulatory drugs	54 (44)	52 (43)	50 (42)	156 (43)	0.939
6-mercaptopurine	19 (15)	11 (9)	13 (11)	43 (12)	
Azathioprine	35 (29)	41 (34)	37 (31)	113 (31)	
Aminosalicylates	89 (72)	92 (76)	91 (76)	272 (75)	0.759
Olsalazine	0	2 (2)	1 (< 1)	3 (< 1)	
Balsalazide	14 (11)	14 (12)	12 (10)	40 (11)	
Sulfasalazine	8 (7)	8 (7)	9 (8)	25 (7)	
Mesalamine	68 (55)	70 (58)	72 (60)	210 (58)	
Other aminosalicylates	0	0	0	0	

Planned Methods of Analysis

For the primary analysis, the proportion of subjects in clinical response at Week 8 was compared among treatment groups in two stages. Using the Cochran-Mantel-Haenszel chi-square test, the combined infliximab treatment groups were compared with the placebo treatment group. If this test was statistically significant, then the second stage of analysis compared each infliximab treatment group with the placebo treatment group. A positive study would be declared if the combined test and at least 1 of the pairwise comparisons of infliximab with placebo was significant at the 2-sided 0.05 level of significance, stratified by corticosteroid refractory status and center location (North America, European Union, and the Southern Hemisphere).

If one but not all 4 of the Mayo subscores were missing at a specific timepoint, the last available value for each missing subscore was carried forward to compute a full Mayo score for that visit. If all 4 subscores were missing at a visit, the Mayo score was considered missing at that visit.

Treatment Failure and Missing Data Rules

Subjects who had 1) a colectomy or ostomy (defined as a colostomy, ileostomy, or other enterostomy, 2) discontinued study infusions due to lack of efficacy, 3) a protocol-prohibited medication change between Week 0 and Week 8, or 4) insufficient data at Week 8 visit were imputed to be nonresponders at Week 8.

Schedule of Study Events

The schedules of study events for both ACT 1 and ACT 2 are found in Appendix 3. Collection of adverse event data, concomitant medication review, determination of infliximab concentration and determination of antibodies to infliximab were performed out to Week 66 in ACT 1 and out to Week 42 in ACT 2.

6.1.4 Efficacy Findings

Subject Disposition

In both the ACT 1 and ACT 2 Studies, 364 subjects were randomized and treated. No subjects in either study were randomized and not treated.

In ACT 1, 38% of all randomized subjects discontinued study infusions (**Table 5**). A higher proportion of subjects randomized to placebo (55%) discontinued study infusions compared to subjects who received infliximab (30%). Across all treatment groups, the largest proportion of subjects who discontinued study infusions did so due to lack of efficacy. Twice as many placebo-treated subjects discontinued study infusions for lack of efficacy compared to the infliximab treatment groups (41% vs. 20%, respectively). Comparable proportions of subjects discontinued due to adverse events across all treatment groups. 26% of all subjects in ACT 1 terminated the study by Week 30 (**Table 6**). No deaths occurred and 1% of subjects were lost to follow up. A larger proportion of subjects in the placebo group terminated the study, due to withdrawal of consent or "other" causes (due to worsening of underlying disease), compared to the infliximab treatment groups.

ACT 1

Table 5: Number of subjects who permanently discontinued study infusions through week 30 by reason for discontinuation

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Total
Subjects randomized N, (%)	121	121	122	364
Subjects who discontinued study infusions	66 (55)	34 (28)	38 (31)	138 (38)
Reason for discontinuation				
Required by protocol due to total colectomy	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Adverse event	9 (7)	7 (6)	9 (7)	25 (7)
Lack of efficacy	50 (41)	25 (21)	24 (20)	99 (27)
Other	6 (5)	1 (<1)	4 (3)	11 (3)

Table 6: Number of subjects who terminated the study through week 30 by reason for termination

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Total
Subjects randomized N, (%)	121	121	122	364
Subjects who terminated study	46 (38)	23 (19)	26 (21)	95 (26)
Reason for termination				
Death	0	0	0	0
Lost to follow-up	1 (<1)	2 (2)	1 (<1)	4 (1)
Withdrawal of consent	24 (20)	8 (7)	11 (9)	43 (12)
Other	21 (17)	13 (11)	14 (12)	48 (13)

In ACT 2, 29% of all randomized subjects discontinued study infusions (**Table 7**). As in ACT 1, a higher proportion of subjects randomized to placebo (46%) discontinued study infusions compared to those who received infliximab (21%). Across all treatment groups, the most frequent cause of discontinuation of study infusions was due to lack of efficacy. Twice as many placebo-treated subjects discontinued study infusions due to lack of efficacy (33%) compared with 17% for both infliximab treatment groups. A smaller proportion of subjects in the infliximab treatment groups (3%) discontinued study infusions due to adverse events compared to those in the placebo group (10%). 27% of subjects in ACT 2 terminated the study by Week 30 (**Table 8**), with placebo-treated subjects terminating in a higher percentage (41%) than either of the two infliximab dose groups (20% each). Withdrawal of consent and termination due to "other" causes (worsening of underlying colitis) accounted for the higher proportion of terminated subjects in the placebo group. No deaths occurred and 3% of all subjects were lost to follow up.

ACT 2

Table 7: Number of subjects who permanently discontinued study infusions through week 30 by reason for discontinuation

		Infliximab		
	Placebo	**5 mg/kg**	**10 mg/kg**	**Total**
Subjects randomized N, (%)	123	121	120	364
Subjects who discontinued study infusions	56 (46)	24 (20)	26 (22)	106 (29)
Reason for discontinuation				
Required by protocol due to total colectomy	0	0	0	0
Adverse event	12 (10)	2 (2)	5 (4)	19 (5)
Lack of efficacy	40 (33)	20 (17)	20 (17)	80 (22)
Other	4 (3)	2 (2)	1 (<1)	7 (2)

Table 8: Number of subjects who terminated the study through week 30 by reason for termination

		Infliximab		
	Placebo	**5 mg/kg**	**10 mg/kg**	**Total**
Subjects randomized N, (%)	123	121	120	364
Subjects who terminated study	50 (41)	24 (20)	24 (20)	98 (27)
Reason for termination				
Death	0	0	0	0
Lost to follow-up	5 (4)	5 (4)	1 (<1)	11 (3)
Withdrawal of consent	20 (16)	7 (6)	13 (11)	40 (11)
Other	25 (20)	12 (10)	10 (8)	47 (13)

Subject Disposition Schema

The subject disposition schemas for both ACT 1 and ACT 2 are displayed in **Figure 1** and **Figure** 2, respectively.

Figure 1: ACT 1 Study Disposition Schema

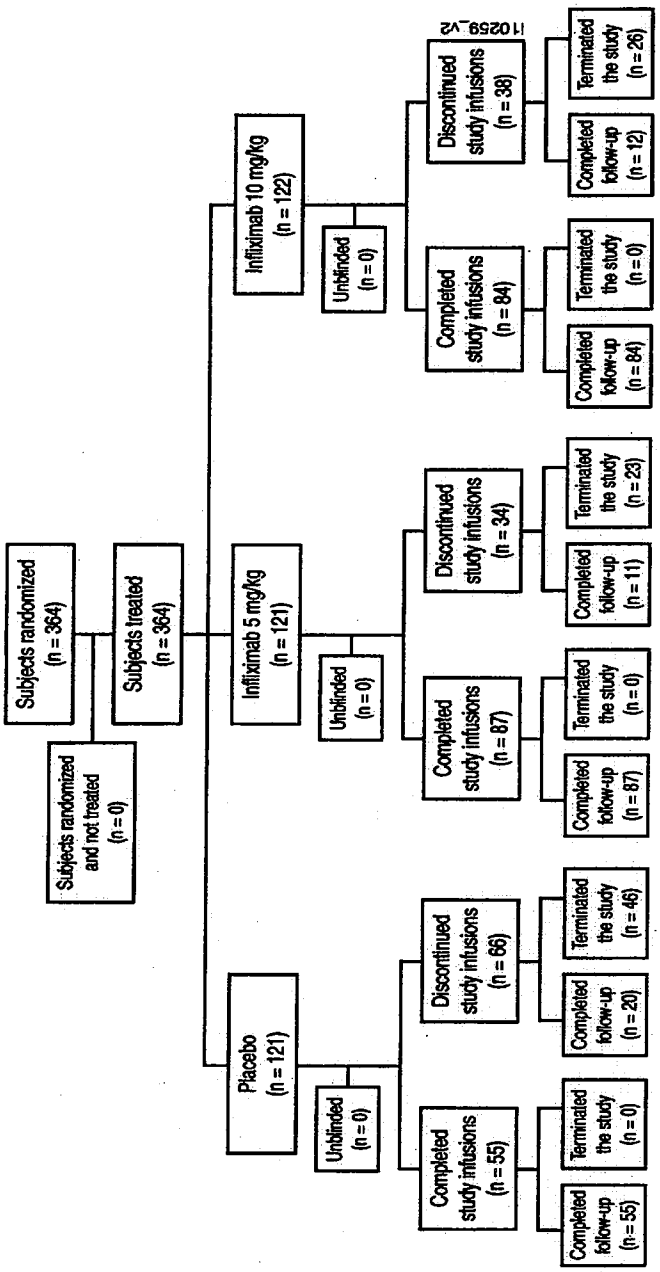
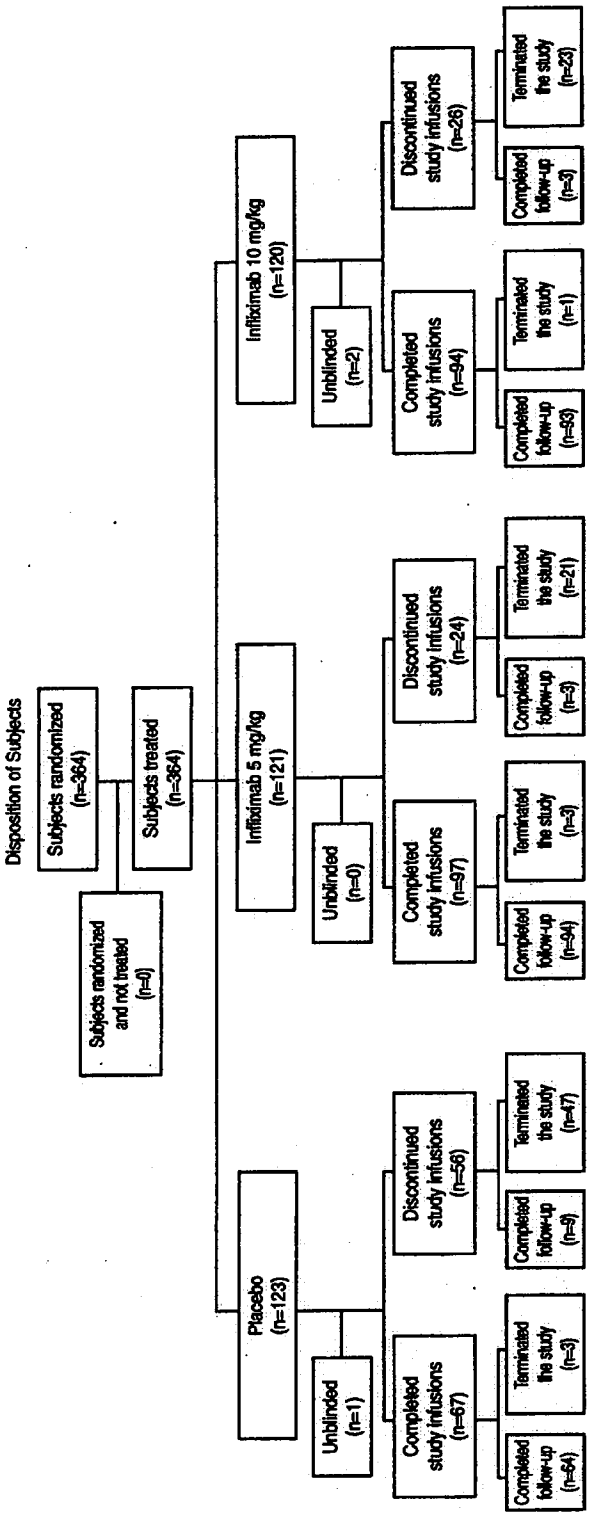


Figure 2: ACT 2 Subject Disposition Schema



Demographics

Baseline Demographics

The baseline demographics and disease characteristics for subjects enrolled in ACT 1 (**Table 9**) and ACT 2 (**Table 10**) are presented below. 61% of ACT 1 subjects were male, and 93% were Caucasian, with a median age of 40 years and median weight of 77 kg. Similar demographics were seen in ACT 2: 59% of subjects were male, 95% were Caucasian, with a median age of 38 years and median weight of 75 kg. For both studies, no baseline demographic imbalances were seen among treatment arms.

Table 9: Baseline demographics – ACT 1

		Infliximab		
	Placebo	**5 mg/kg**	**10 mg/kg**	**Total**
Subjects randomized	121	121	122	364
Sex				
Male	72 (60)	78 (65)	72 (59)	222 (61)
Race				
Caucasian	111 (92)	116 (96)	113 (93)	340 (93)
Black	2 (2)	1 (<1)	3 (3)	6 (2)
Asian	1 (<1)	2 (2)	1 (<1)	4 (1)
Other	7 (6)	2 (2)	5 (4)	14 (4)
Age (yrs)				
Median	40.0	42.0	39.0	40.0
Weight (kg)				
Median	75.0	79.0	76.1	76.5

Table 10: Baseline demographics – ACT 2

		Infliximab		
	Placebo	**5 mg/kg**	**10 mg/kg**	**Total**
Subjects randomized	123	121	120	364
Sex				
Male	71 (58)	76 (63)	68 (57)	215 (59)
Race				
Caucasian	117 (95)	116 (96)	111 (93)	344 (95)
Black	5 (4)	2 (2)	1 (<1)	8 (2)
Asian	0	0	5 (4)	5 (1)
Other	1 (<1)	3 (3)	3 (3)	7 (2)
Age (yrs)				
Median	37.0	40.0	39.0	38.0
Weight (kg)				
Median	74.7	77.0	75.0	75.0

Baseline Disease Characteristics

Baseline disease characteristics for ACT 1 (**Table 11**) and ACT 2 (**Table 12**) are shown below. For all subjects enrolled in ACT 1, the median duration of UC was 4.7 years, the median CRP level was 0.8 mg/dL, 46% had extensive disease, and 31% were refractory to corticosteroids. Similar baseline disease characteristics were seen in ACT 2, with a median duration of UC of 5.5 years, CRP level of 0.7 mg/dL, 40% of subjects having extensive disease, and 29% being refractory to corticosteroids. No imbalances were seen among treatment arms for each study.

Table 11: Baseline disease characteristics – ACT 1

		Infliximab		
	Placebo	**5 mg/kg**	**10 mg/kg**	**Total**
Subjects randomized	121	121	122	364
UC duration (yrs)				
N	121	121	122	364
Median	4.4	4.1	5.9	4.7
UC symptoms duration (yrs)				
N	121	121	122	364
Median	5.0	5.0	6.5	6.0
CRP (mg/dL)				
N	119	120	121	360
Median	0.8	0.9	1.0	0.8
Extent of disease				
N	120	119	121	360
Limited to left side of colon	66 (55)	63 (53)	67 (55)	196 (54)
Extensive	54 (45)	56 (47)	54 (45)	164 (46)
Refractory to corticosteroids				
N	121	121	122	364
Yes	38 (31)	36 (30)	38 (31)	112 (31)
Previous segmental resection(s)				
N	121	121	122	364
Yes	0	1 (<1)	1 (<1)	2 (<1)
Other UC-related GI surgical procedures				
N	121	121	122	364
Yes	3 (3)	2 (2)	2 (1)	7 (2)

Table 12: Baseline disease characteristics – ACT 2

		Infliximab		
	Placebo	**5 mg/kg**	**10 mg/kg**	**Total**
Subjects randomized	123	121	120	364
UC duration (yrs)				
N	123	121	120	364
Median	3.7	5.2	4.7	4.9
UC symptoms duration (yrs)				
N	123	120	120	363
Median	4.5	6.4	5.3	5.5
CRP (mg/dL)				
N	121	120	119	360
Median	0.6	0.8	0.6	0.7
Extent of disease				
N	120	118	120	358
Limited to left side of colon	70 (58)	70 (59)	75 (63)	215 (60)
Extensive	50 (42)	48 (41)	45 (38)	143 (40)
Refractory to corticosteroids				
N	123	121	120	364
Yes	36 (29)	35 (29)	34 (28)	105 (29)
Previous segmental resection(s)				
N	123	121	120	364
Yes	1 (<1)	2 (2)	0	3 (<1)
Other UC-related GI surgical procedures				
N	123	121	120	364
Yes	2 (2)	3 (3)	2 (2)	7 (2)

Baseline Mayo scores

The baseline Mayo scores for ACT 1 and ACT 2 are presented in **Table 13** and **Table 14**, respectively. Within both studies, Mayo subscores were well matched between treatment groups. Less than 1% of subjects in ACT 1 had a normal number of stools, with the majority (61%) having a Stool Frequency subscore of 3, representing 5 or more stools above the normal daily number. 82% of all subjects in ACT 1 had some form of daily rectal bleeding, with 13% of all subjects passing blood alone, rectally. No subjects had an Endoscopy subscore of 0 or 1, indicating that all subjects had endoscopic evidence of either moderate or severe UC. 96% of subjects had a Physician's Global Assessment subscore which was consistent with moderate to severe disease activity.

Table 13: ACT 1 Baseline Mayo scores

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Total
Subjects randomized	121	121	122	364
Mayo score (0-12), Median	8.0	9.0	8.5	8.0
Stool Frequency subscore				
Normal number of stools	0	2 (2)	0	2 (<1)
1-2 stools above normal	20 (17)	18 (15)	12 (10)	50 (14)
3-4 stools above normal	28 (23)	29 (24)	32 (26)	89 (25)
5 or more stools above normal	73 (60)	72 (60)	78 (64)	223 (61)
Rectal Bleeding subscore				
No blood seen	28 (23)	15 (12)	21 (17)	64 (18)
Streaks of blood with stool less than half the time	37 (31)	33 (27)	37 (30)	107 (29)
Obvious blood with stool most of the time	37 (31)	57 (47)	52 (43)	146 (40)
Blood alone passed	19 (16)	16 (13)	12 (10)	47 (13)
Endoscopy subscore				
Normal or inactive disease	0	0	0	0
Mild disease	0	0	0	0
Moderate disease	74 (61)	73 (60)	88 (72)	235 (65)
Severe disease	47 (39)	48 (40)	34 (28)	129 (35)
Physician's global assessment subscore				
Normal	0	0	0	0
Mild disease	5 (4)	7 (6)	3 (3)	15 (4)
Moderate disease	87 (72)	93 (77)	100 (82)	280 (77)
Severe disease	29 (24)	21 (17)	19 (16)	69 (19)

The profile of Mayo scores for subjects in ACT 2 (**Table 14**) was similar to that in ACT 1. Less than 1% of all subjects had a normal number of stools, 57% of subjects had 5 or more stools above normal, 11% passed blood alone, 99% had Endoscopy subscores indicating moderate to severe disease, and 96% had a Physician's Global Assessment subscore indicating high disease activity.

Table 14: ACT 2 Baseline Mayo scores

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Total
Subjects randomized	123	121	120	364
Mayo score (0-12), Median	9.0	8.0	8.0	8.0
Stool Frequency subscore				
Normal number of stools	0	0	1 (<1)	1 (<1)
1-2 stools above normal	16 (13)	19 (16)	19 (16)	54 (15)
3-4 stools above normal	34 (28)	31 (26)	37 (31)	102 (28)
5 or more stools above normal	73 (59)	71 (59)	63 (53)	207 (57)
Rectal Bleeding subscore				
No blood seen	19 (15)	18 (15)	18 (15)	55 (15)
Streaks of blood with stool less than half the time	34 (28)	51 (42)	37 (31)	122 (34)
Obvious blood with stool most of the time	56 (56)	41 (34)	49 (41)	146 (40)
Blood alone passed	14 (11)	11 (9)	16 (13)	41 (11)
Endoscopy subscore				
Normal or inactive disease	0	0	0	0
Mild disease	1 (<1)	0	2 (2)	3 (<1)
Moderate disease	72 (59)	72 (60)	76 (63)	220 (60)
Severe disease	50 (41)	49 (41)	42 (35)	141 (39)
Physician's global assessment subscore				
Normal	1 (<1)	0	0	1 (<1)
Mild disease	3 (2)	6 (5)	4 (3)	13 (4)
Moderate disease	97 (79)	95 (79)	96 (80)	288 (79)
Severe disease	22 (18)	20 (17)	20 (17)	62 (17)

Efficacy Analyses

Primary Endpoint: Clinical Response at Week 8

The proportion of subjects in clinical response at Week 8 for ACT 1 and ACT 2 are presented in **Table 15** and **Table 16**, respectively. In ACT 1, 69% of subjects randomized to infliximab 5 mg/kg and 62% who were given infliximab 10 mg/kg were in clinical response at Week 8, compared to 37% of placebo subjects. In ACT 2, 65% and 69% of subjects who received infliximab 5 mg/kg and 10 mg/kg, respectively, were in clinical response at Week 8 compared to 29% of those that received placebo. All comparisons of infliximab-treated subjects to controls were statistically significant.

ACT 1

Table 15: Number of subjects in clinical response at week 8[a,b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Subjects in clinical response	45 (37)	84 (69)	75 (62)	159 (65)
p-value		< 0.001	< 0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical response.
[b] Analysis is stratified by corticosteroid refractory status and center location.

ACT 2

Table 16: Number of subjects in clinical response at week 8[a,b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Subjects in clinical response	36 (29)	78 (65)	83 (69)	161 (69)
p-value		< 0.001	< 0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical response.
[b] Analysis is stratified by corticosteroid refractory status and center location.

Major Secondary Endpoints:

The major secondary endpoints assessed durability of responses, attaining low levels of disease activity (i.e. remission), and endoscopic changes. Specifically, the major prespecified secondary endpoints for both ACT 1 and ACT 2 were 1) clinical response at Week 30, 2) clinical remission at Week 8 and Week 30, and 3) mucosal healing. In ACT 1 and ACT 2, respectively, greater proportions of infliximab-treated subjects achieved these secondary endpoints compared to placebo-treated subjects. Clinical response at Week 30 for the infliximab-treated groups was seen in 51% and 54% of subjects compared to 30% and 26% of the placebo-treated subjects in ACT 1 (**Table 17**) and ACT 2 (**Table 18**), respectively.

Clinical Response at Week 30

ACT 1

Table 17: Number of subjects in clinical response at week 30[a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Subjects evaluated	121	121	122	243
Subjects in clinical response	36 (30)	63 (52)	62 (51)	125 (51)
p-value		< 0.001	0.002	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical response.
[b] Analysis is stratified by corticosteroid refractory status and center location.

ACT 2

Table 18: Number of subjects in clinical response at week 30[a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Subjects evaluated	123	121	120	241
Subjects in clinical response	32 (26)	57 (47)	72 (60)	129 (54)
p-value		< 0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical response.
[b] Analysis is stratified by corticosteroid refractory status and center location.

Clinical Remission at Week 8 and Week 30

Clinical remission in the ACT studies was defined as a Mayo score of ≤ 2 and no individual subscore greater than 1. This endpoint, measured at Week 8 and Week 30, was an important goal for subjects to achieve because by having no individual subscore > 1, this represented quiescent or minimal disease activity according to the Mayo scoring scale. The proportions of subjects in clinical remission at Week 8 and Week 30 for ACT 1 (**Table 19**) and ACT 2 (**Table 20**) are presented below. In both studies, greater proportions of infliximab-treated subjects achieved clinical remission compared to placebo-treated subjects. In ACT 1, 35% of subjects in the combined infliximab treatment group were in clinical remission compared to 15% of placebo subjects at Week 8. Similar responses were seen at Week 30, where 35% of the subjects in the combined infliximab treatment group were in remission compared to 16% of the placebo subjects. In ACT 2, 31% of the infliximab-treated subjects were in clinical remission at Weeks 8 and 30 compared to 6% and 11%, of the placebo subjects, respectively. It should be noted that the subjects in clinical remission at Weeks 8 and 30 may not have been the same subjects at both visits. Subjects who had clinical remission at both Weeks 8 and 30 are presented further along in the review under the section of "sustained remission".

ACT 1

Table 19: Number of subjects in clinical remission through week 30[a,b,c]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Week 8				
N	121	121	122	243
Subjects in clinical remission	18 (15)	47 (39)	39 (32)	86 (35)
p-value		<0.001	0.002	<0.001
Week 30				
N	121	121	122	243
Subjects in clinical remission	19 (16)	41 (34)	45 (37)	86 (35)
p-value		0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical remission from the time of the event onward.
[b] Subjects who had insufficient data at a timepoint are considered to not be in clinical remission at that timepoint.
[c] Analysis is stratified by corticosteroid refractory status and center location.

ACT 2

Table 20: Number of subjects in clinical remission through week 30[a,b,c]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Week 8				
N	123	121	120	241
Subjects in clinical remission	7 (6)	41 (34)	33 (28)	74 (31)
p-value		<0.001	<0.001	<0.001
Week 30				
N	123	121	120	241
Subjects in clinical remission	13 (11)	31 (26)	43 (36)	74 (31)
p-value		0.003	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical remission from the time of the event onward.
[b] Subjects who had insufficient data at a timepoint are considered to not be in clinical remission at that timepoint.
[c] Analysis is stratified by corticosteroid refractory status and center location.

Mucosal Healing

In ACT 1 and ACT 2, mucosal healing was defined as having an endoscopy subscore of 0 or 1 indicating minimal or no endoscopic evidence of erythema/bleeding. The proportions of subjects who had mucosal healing through Week 30 are presented in **Table 21** for ACT 1 and **Table 22** for ACT 2. As was previously presented, all subjects in ACT 1 had either moderately or severely active disease endoscopically (represented by a Mayo score of either 2 or 3). 60% of the combined infliximab group subjects in ACT 1 had mucosal healing at Week 8 compared to 34% of placebo subjects. At Week 30, 50% of the combined infliximab group had mucosal healing compared to 25% of placebo subjects. The proportion of subjects with mucosal healing were comparable between the 5 mg/kg and 10 mg/kg infliximab groups. A greater proportion of infliximab-treated subjects achieved mucosal healing in ACT 1, at Week 8 and at Week 30 than those treated with placebo.

ACT 1

Table 21: Number of subjects with mucosal healing through week 30[a, b, c]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Week 8				
Subjects with mucosal healing	41 (34)	75 (62)	72 (59)	147 (60)
p-value		< 0.001	< 0.001	<0.001
Week 30				
Subjects with mucosal healing	30 (25)	61 (50)	60 (49)	121 (50)
p-value		< 0.001	< 0.001	<0.001

[c] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not have mucosal healing from the time of the event onward.
[b] Subjects with insufficient data at a timepoint are considered to not have mucosal healing at that timepoint.
[c] Analysis is stratified by corticosteroid refractory status and center location.

In ACT 2, 61% of the combined infliximab group had mucosal healing at Week 8 compared to 31% in the placebo group. At Week 30, 52% of the combined infliximab group had mucosal healing compared to 30% in the placebo group. As in ACT 1, a greater proportion of infliximab-treated subjects achieved mucosal healing in ACT 2 compared to placebo-treated subjects. The point estimates were similar in both trials, with 61% achieving mucosal healing at Week 8 and approximately 51% at Week 30 for combined infliximab groups.

ACT 2

Table 22: Number of subjects with mucosal healing through week 30[a, b, c]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Week 8				
Subjects with mucosal healing	38 (31)	73 (60)	74 (62)	147 (61)
p-value		< 0.001	< 0.001	<0.001
Week 30				
Subjects with mucosal healing	37 (30)	56 (46)	68 (57)	124 (52)
p-value		0.009	< 0.001	<0.001

[c] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not have mucosal healing from the time of the event onward.
[b] Subjects with insufficient data at a timepoint are considered to not have mucosal healing at that timepoint.
[c] Analysis is stratified by corticosteroid refractory status and center location.

Sensitivity Analyses (FDA)

Completer Analyses of Responders vs. Nonresponders

In order to better assess the robustness of the primary endpoint, FDA conducted a sensitivity analysis of the proportion of subjects in response for those who actually completed the study. In ACT 1 (**Table 23**), at Week 8, 79% (96 of 121) of subjects randomized to placebo were still in the study compared to 94% (114 of 121) and 92% (112 of 122) of subjects randomized to infliximab 5 mg/kg and 10 mg/kg, respectively. At Week 30, 62% of the placebo subjects, 79% of the infliximab 5 mg/kg subjects, and 77% of the infliximab 10 mg/kg subjects were still in the study. Subjects randomized to placebo treatment were less likely to remain in the study at Week 8 and Week 30. Among subjects continuing in the study, those receiving infliximab were more likely to have a clinical response or remission at Weeks 8 and 30.

Among subjects who completed at least the first 8 weeks of the trial, 74% of the subjects receiving infliximab 5 mg/kg and 67% of the subjects receiving 10 mg/kg had a clinical response at Week 8, compared to 47% of placebo-treated subjects. In this completer group, 41% of the infliximab 5 mg/kg group and 35% of the 10 mg/kg group achieved a clinical response at Week 8, compared to 19% in the placebo group. For Week 30, a higher proportion of subjects in the infliximab 5 mg/kg and 10 mg/kg groups (79% and 77%, respectively) completed the Week 30 evaluation compared to 62% of the placebo-treated subjects. As with the Week 8 data, subjects who completed Week 30 evaluations had higher proportions of subjects achieving clinical response or remission if they were initially randomized to either infliximab group compared to subjects randomized to placebo. Completers of the Week 30 evaluations were also more likely to have had a sustained response or sustained remission if they were randomized to either infliximab treatment group than if they were randomized to placebo. Similar results were seen in ACT 2 (**Table 24**).

Table 23: Completer Analysis at Week 8 and Week 30 (ACT 1)

Description of response and endpoint	Placebo	Infliximab	
		5mg/kg*	10 mg/kg*
Subjects who completed at least the first 8 weeks. Clinical response at Week 8	45/96 (47)	84/114 (74)	75/112 (67)
Subjects who completed at least the first 8 weeks. Clinical remission at Week 8	18/96 (19)	47/114 (41)	39/112 (35)
Subjects who completed 30 weeks[a] Clinical response at Week 30	36/75 (48)	63/96 (66)	62/94 (66)
Subjects who completed 30 weeks[a] Clinical remission at Week 30	19/75 (25)	41/96 (43)	45/94 (48)
Subjects who completed 30 weeks[a] Sustained response at Week 8 and Week 30	28/75 (37)	59/96 (62)	56/94 (60)
Subjects who completed 30 weeks[a] Sustained remission at Week 8 and Week 30	10/75 (13)	28/96 (29)	32/94 (34)

* $p < 0.05$, pairwise comparison, infliximab dose group compared with placebo
[a] Totals do not correspond with the totals reported by Centocor: 2 subjects each, in 5mg/kg and 10mg/kg group, were coded as "completer" but these four subjects did not appear to have Week 30 clinic visits.

Table 24: Completer Analysis at Week 8 and Week 30 (ACT 2)

Description of response and endpoint	Placebo	Infliximab	
		5mg/kg*	10 mg/kg*
Subjects who completed at least the first 8 weeks. Clinical response at Week 8	36/102 (35)	78/118 (66)	83/111 (75)
Subjects who completed at least the first 8 weeks. Clinical remission at Week 8	7/102 (7)	41/118 (35)	33/111 (30)
Subjects who completed 30 weeks. Clinical response at Week 30	32/73 (44)	57/97 (59)	72/96 (75)
Subjects who completed 30 weeks. Clinical remission at Week 30	13/73 (18)	31/97 (32)	43/96 (45)
Subjects who completed 30 weeks. Sustained response at Week 8 and Week 30	19/73 (26)	50/97 (52)	64/96 (67)
Subjects who completed 30 weeks. Sustained remission at Week 8 and Week 30	3/73 (4)	18/97 (19)	27/96 (28)

* $p < 0.05$, pairwise comparison, infliximab dose group compared with placebo

Taken together, these data from both studies support the primary analysis and indicate that for subjects who stayed in the trial until the end, clinical responses and clinical remissions were seen more frequently in the infliximab groups.

Worst-Case Scenario Analyses

In order to assess whether missing data contributed to the differences in efficacy outcomes, FDA performed "worst-case scenario" analyses. Using this approach, placebo subjects in ACT 1 (**Table 25**) who had insufficient Mayo score data at Week 8 were considered to be in clinical response, whereas subjects in the infliximab treatment groups who had insufficient data were considered to not be in clinical response. In this sensitivity analysis, 65% of the combined infliximab treatment groups were in clinical response at Week 8 compared to 46% in the placebo-treated group ($p < 0.001$). Similar results were seen in ACT 2 (**Table 26**). Even in this worst-case scenario, a greater number of infliximab-treated groups achieved the primary endpoint compared to the placebo group (65% vs. 46% in ACT 1, and 67% vs. 34% in ACT 2).

Clinical Response at Week 8

ACT 1

Table 25: Number of subjects in clinical response at week 8 (worst-case scenario)[a,b,c]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Subjects evaluated	121	121	122	243
Subjects in clinical response	55 (46)	84 (69)	75 (62)	159 (65)
p-value		< 0.001	0.016	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy were considered to not be in clinical response.
[b] Subjects in the placebo treatment group who had insufficient data were considered to be in clinical response. Subjects in the infliximab treatment groups who had insuifficient data were considered to not be in clinical response.
[c] Analysis is stratified by corticosteroid refractory status and center location.

ACT 2

Table 26: Number of subjects in clinical response at week 8 (worst-case scenario)[a,b,c]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Subjects evaluated	123	121	120	241
Subjects in clinical response	42 (34)	78 (65)	83 (69)	161 (67)
p-value		< 0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy were considered to not be in clinical response.
[b] Subjects in the placebo treatment group who had insufficient data were considered to be in clinical response. Subjects in the infliximab treatment groups who had insuifficient data were considered to not be in clinical response.
[c] Analysis is stratified by corticosteroid refractory status and center location.

Analyses of Mayo Scores by Drop Out Status

In order to better understand the clinical status of those subjects who prematurely discontinued ACT 1 and ACT 2 and any potential bias attributable to dropouts, FDA analyzed the Mayo scores of subjects who had discontinued by Week 8 and Week 30 vs. those who remained in the studies at those evaluations. In this sensitivity analysis, subjects who discontinued the study before Week 8 and Week 30 had their last Mayo score value carried forward. In ACT 1 (**Table 27**), those subjects who dropped out by Week 8 and by Week 30 had median Mayo scores between 8 and 10, indicating ongoing moderate to severe disease activity. Mayo scores among infliximab-treated subjects who dropped out were not lower than placebo-treated subjects who dropped out. Subjects who remained in ACT 1 at both Weeks 8 and 30 had lower median Mayo

scores (between 3 and 6) compared to those that had discontinued. The combined infliximab treatment groups had median Mayo scores of 3 at both Week 8 and Week 30 compared to the placebo group which had median Mayo scores of 5 and 6. Similar results were seen in ACT 2 (**Table 28**). This sensitivity analysis showed that subjects who dropped out were indeed those who were not improving clinically as indicated by the Mayo score and the number of clinical responders seen in previous tables.

ACT 1

Table 27: Summary of the Mayo score at weeks 8 and 30 by drop out status[a,b]

	Subjects Who Dropped Out				Subjects Who Did Not Drop Out			
		Infliximab				Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined	Placebo	5 mg/kg	10 mg/kg	Combined
Week 8								
N[c]	29	9	10	19	92	112	112	224
Mean ± SD	8.5 ± 2.0	9.4 ± 1.8	10.0 ± 1.2	9.7 ± 1.5	5.4 ± 3.1	3.7 ± 2.9	4.2 ± 3.0	3.9 ± 3.0
Median	8.0	9.0	10.0	10.0	5.0	3.0	4.0	3.0
Week 30								
N[c]	17	14	16	30	75	98	96	194
Mean ± SD	8.1 ± 2.7	9.6 ± 1.5	8.0 ± 1.2	8.8 ± 1.5	5.5 ± 3.4	3.8 ± 3.3	3.8 ± 3.5	3.8 ± 3.4
Median	8.0	10.0	8.0	9.0	6.0	3.0	3.0	3.0

[a] Subjects with insufficient data had their last value carried forward.
[b] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[c] The quantity "N" is the number of subjects that dropped out/did not drop out from the previous timepoint up to and including the timepoint of interest.

ACT 2

Table 28: Summary of the Mayo score at weeks 8 and 30 by drop out status[a,b]

	Subjects Who Dropped Out				Subjects Who Did Not Drop Out			
		Infliximab				Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined	Placebo	5 mg/kg	10 mg/kg	Combined
Week 8								
N[c]	34	9	14	23	89	112	106	218
Mean ± SD	8.9 ± 1.8	9.2 ± 1.1	8.6 ± 1.3	8.8 ± 1.2	5.9 ± 2.5	3.8 ± 2.9	3.9 ± 2.5	3.9 ± 2.7
Median	9.0	9.0	8.0	9.0	6.0	4.0	3.0	3.0
Week 30								
N[c]	15	14	10	24	74	98	96	194
Mean ± SD	8.9 ± 1.6	8.6 ± 1.8	7.5 ± 3.8	8.2 ± 2.8	5.6 ± 3.1	4.3 ± 3.1	3.5 ± 3.0	3.9 ± 3.1
Median	9.0	9.0	7.5	9.0	5.5	3.0	3.0	3.0

[a] Subjects with insufficient data had their last value carried forward.
[b] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[c] The quantity "N" is the number of subjects that dropped out/did not drop out from the previous timepoint up to and including the timepoint of interest.

Taken together, these data are consistent and indicate that, overall, with respect to subjects choosing to remain in or discontinue from the studies, subjects who dropped out were those subjects with higher Mayo scores, compared to those that stayed in. These data validate the choice of using the non-responder imputation technique in the primary analysis.

Subgroup Analyses

Corticosteroid Refractory Status

We performed subset analyses to see if clinical responses were different in corticosteroid refractory and non-corticosteroid refractory subjects. The number of subjects who achieved the primary endpoint based on corticosteroid refractory status is displayed in **Table 29** and **Table 30**, for ACT 1 and ACT 2, respectively. In ACT 1, among subjects who enrolled in the study who were refractory to corticosteroids, 73% of those in the combined infliximab group were in clinical response at Week 8 compared to 35% in the placebo group ($p < 0.001$). For those subjects who were not refractory to corticosteroids, 63% in the combined infliximab group were in clinical response at Week 8 compared with 38% in the placebo group ($p < 0.001$).

ACT 1:

Table 29: Number of subjects in clinical response at week 8 by corticosteroid refractory status[a]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Corticosteroid refractory subjects[b], n	34	31	31	62
Subjects in clinical response	12 (35)	24 (77)	21 (68)	45 (73)
p-value		< 0.001	0.010	<0.001
Noncorticosteroid refractory subjects[b], n	87	90	91	181
Subjects in clinical response	33 (38)	60 (67)	54 (59)	114 (63)
p-value		<0.001	0.005	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical response.
[b] Analysis is stratified by center location.

In ACT 2 (**Table 30**), of subjects refractory to corticosteroids, 64% of the combined infliximab group achieved a clinical response at Week 8 vs. 38% in the placebo group ($p = 0.013$). Similarly, of subjects who were not refractory to corticosteroids, 68% of the combined infliximab group met the primary endpoint compared to 26% of the placebo group ($p < 0.001$).

ACT 2:

Table 30: Number of subjects in clinical response at week 8 by corticosteroid refractory status[a]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Corticosteroid refractory subjects[b], n	32	30	29	59
Subjects in clinical response	12 (38)	19 (63)	19 (66)	38 (64)
p-value		0.053	0.011	0.013
Noncorticosteroid refractory subjects[b], n	91	91	91	182
Subjects in clinical response	24 (26)	59 (65)	64 (70)	123 (68)
p-value		<0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical response.
[b] Analysis is stratified by center location.

Overall, irrespective of corticosteroid refractory status, there were significantly greater numbers of subjects in the combined infliximab groups for both studies that were in clinical response at Week 8 compared with subjects in the placebo treatment group.

Other Subgroups

To determine whether clinical responses varied depending on baseline demographics or on baseline disease activity characteristics, we performed subset analyses of the primary endpoint (**Figure 3** through **Figure 10**). Subgroup analyses of the Week 8 clinical response by baseline demographics are presented in **Figure 3** for ACT 1 and **Figure 4** for ACT 2. Considering baseline demographic characteristics, all subgroups had a greater clinical response if they were randomized to infliximab than if they were randomized to placebo. In ACT 1, infliximab-treated subjects who weighed < 60 kg had an odds ratio that was considerably less than heavier patients (1.2 vs. 2.4 and 4.9 in the heavier weight categories). However, this same subgroup in ACT 2 had an odds ratio of 3.3 in favor of infliximab in ACT 2. The low odds ratio in ACT 1 likely reflects the smaller number of subjects represented in this weight range.

Subgroup analyses of clinical response at Week 8 by baseline clinical disease characteristics are shown in **Figure 5** for ACT 1 and **Figure 6** for ACT 2. All subgroups demonstrated higher proportions of subjects in clinical response at Week 8 for infliximab treatment vs. placebo irrespective of their baseline clinical disease characteristics. Subjects with baseline CRP levels < 0.6 mg/dL in ACT 1 had an odds ratio for clinical response close to 1 (1.3), which could suggest less benefit in this subgroup. However, this finding is likely not significant, as the same subgroup in ACT 2 had an odds ratio of 7.1.

We next explored whether previous drug therapy for UC influenced responses to infliximab. When clinical response at Week 8 by drug history was examined (**Figure 7** for ACT 1 and **Figure 8** for ACT 2), all subgroups benefited more from receiving infliximab vs. placebo. The only exception to this was in ACT 2 for those subjects who previously received cyclosporine and/or tacrolimus, and/or mycophenolate mofetil for UC prior to enrolling in the study.

However, it is not possible to reach firm conclusions as the study was not powered to detect meaningful differences in this subgroup and the number of subjects who previously received these treatments was small.

Subgroup analyses of clinical response by baseline concomitant medications are shown in **Figure 9** for ACT 1 and **Figure 10** for ACT 2. All subgroups benefited more from receiving infliximab than placebo for both studies regardless of baseline concomitant medication.

In summary, subgroup analyses did not identify any category of active UC subjects who would not benefit from infliximab therapy.

Clinical Response at Week 8 by Baseline Demographic Characteristics

ACT 1

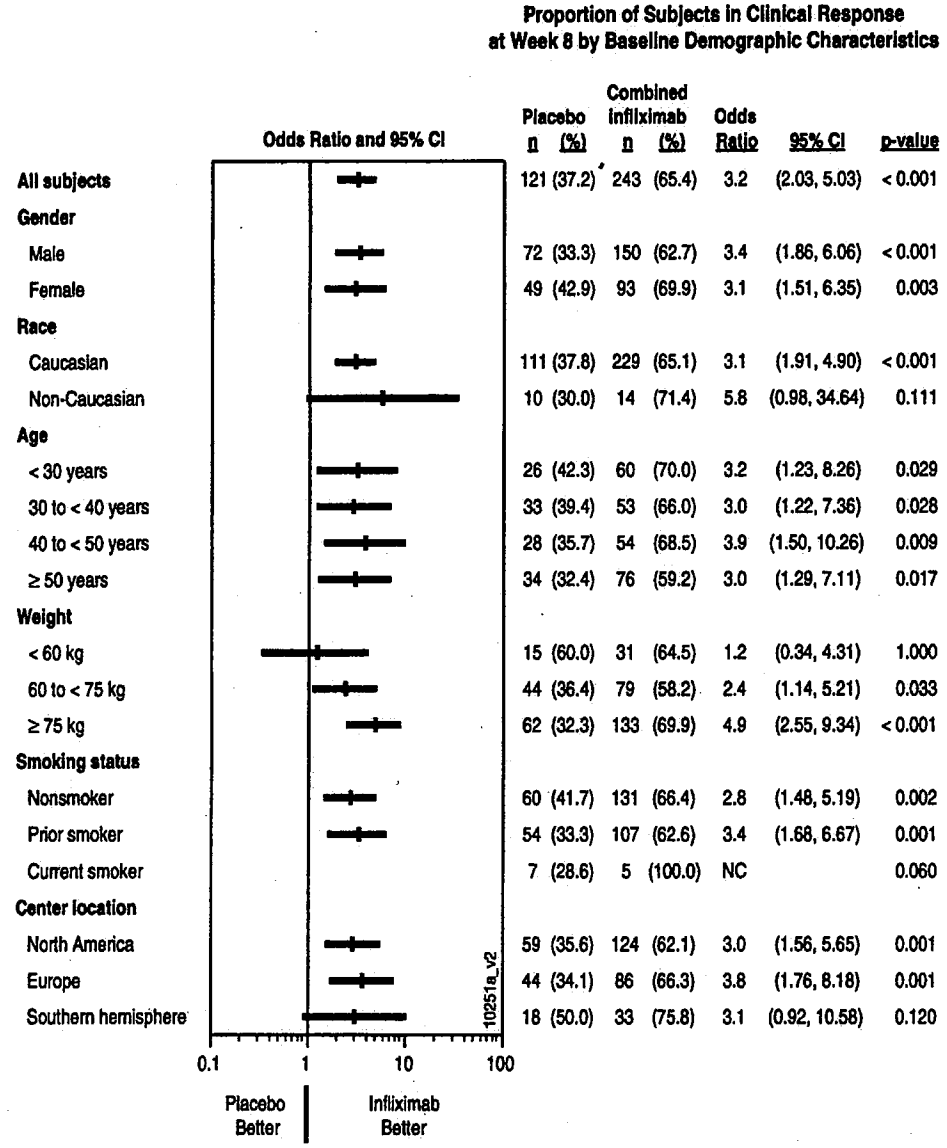


Figure 3: Plot of odds ratios and 95% confidence intervals for comparing the proportion of subjects in clinical response at Week 8 in the infliximab group (combined) vs. placebo group by baseline demographic characteristics.

ACT 2

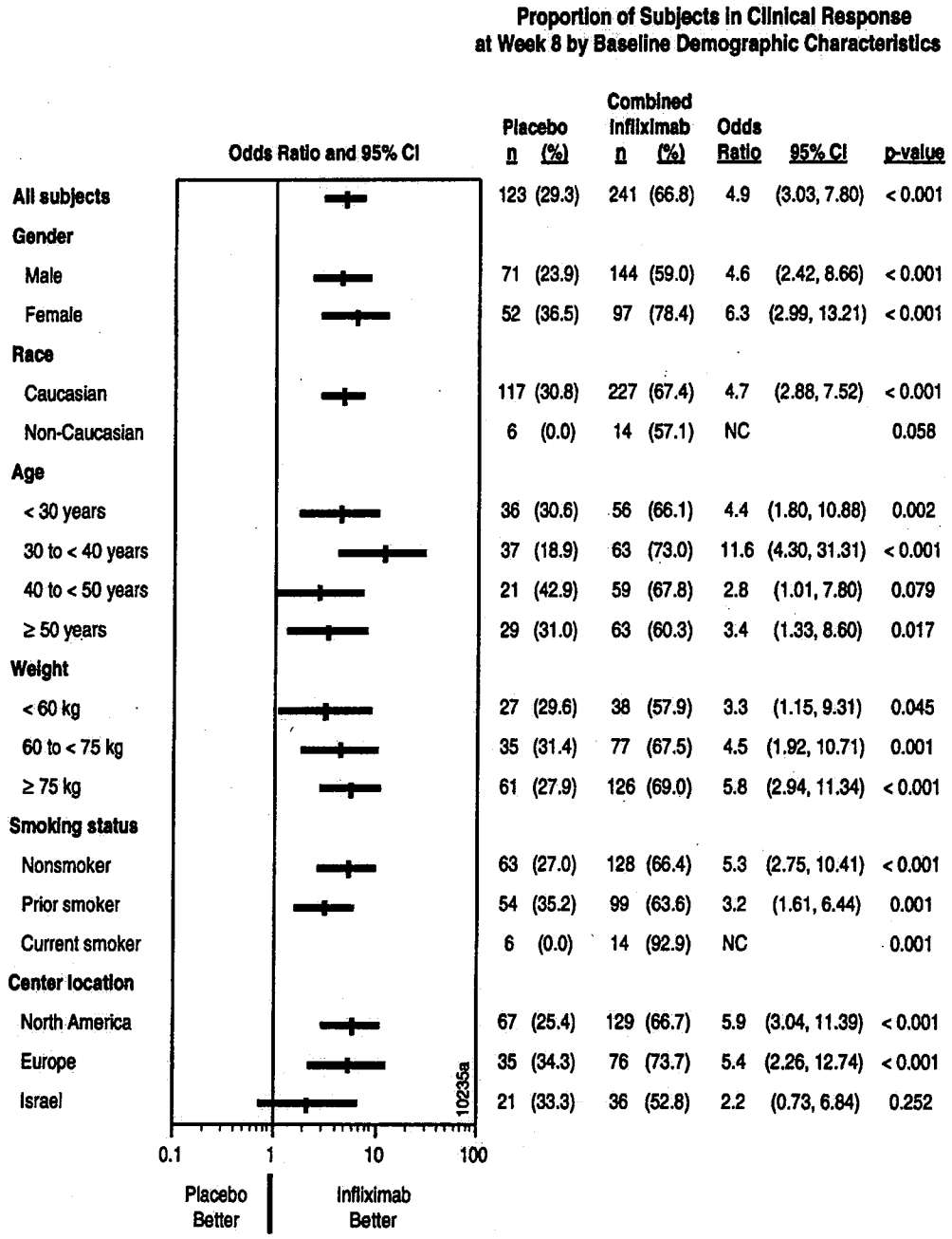


Figure 4: Plot of odds ratios and 95% confidence intervals for comparing the proportion of subjects in clinical response at Week 8 in the infliximab group (combined) vs. placebo group by baseline demographic characteristics.

Clinical Response by Baseline Clinical Disease Characteristics

ACT 1

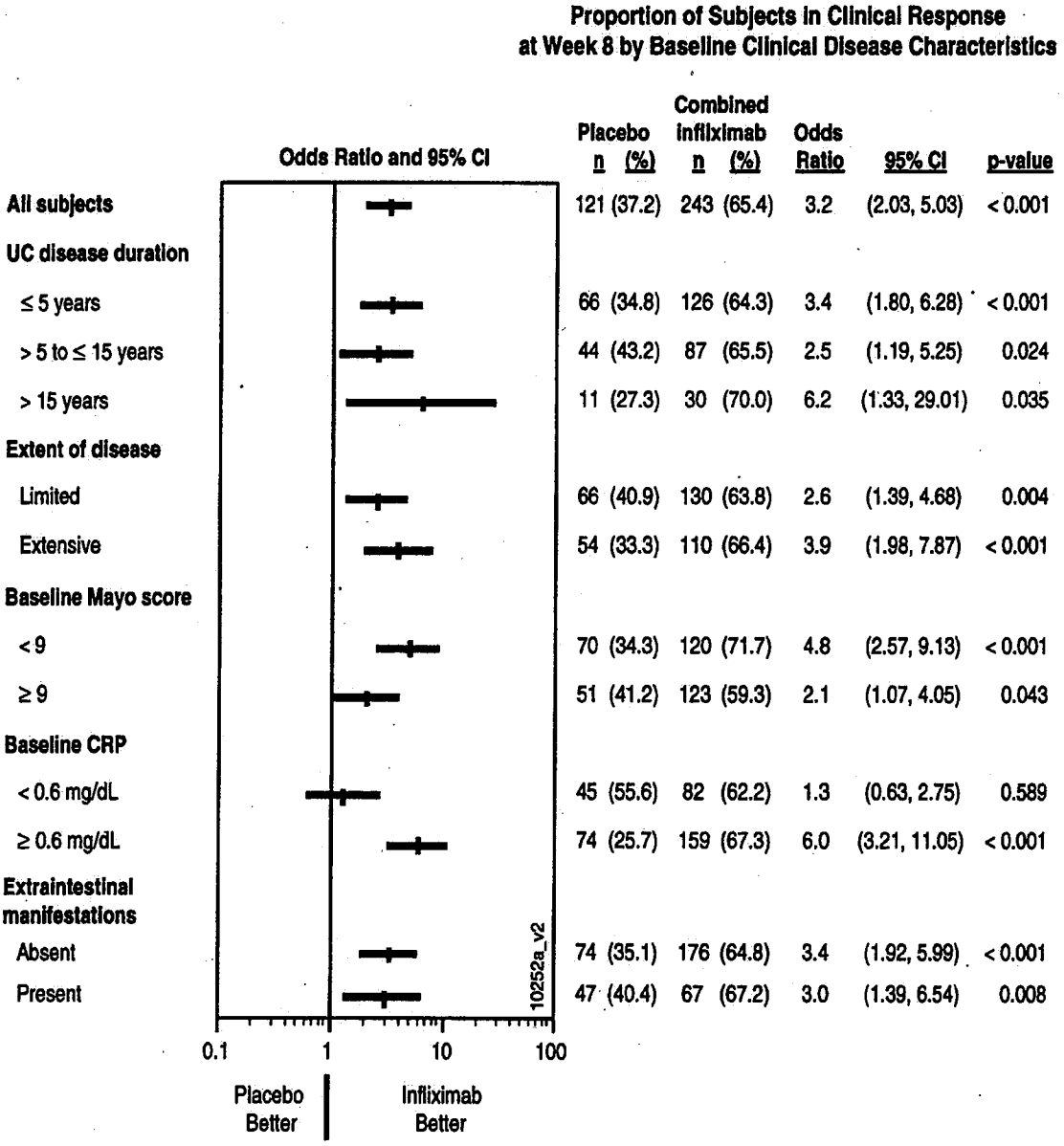


Figure 5: Plot of odds ratios and 95% confidence intervals for comparing the proportion of subjects in clinical response at Week 8 in the infliximab group (combined) vs. the placebo group by baseline clinical disease characteristics.

ACT 2

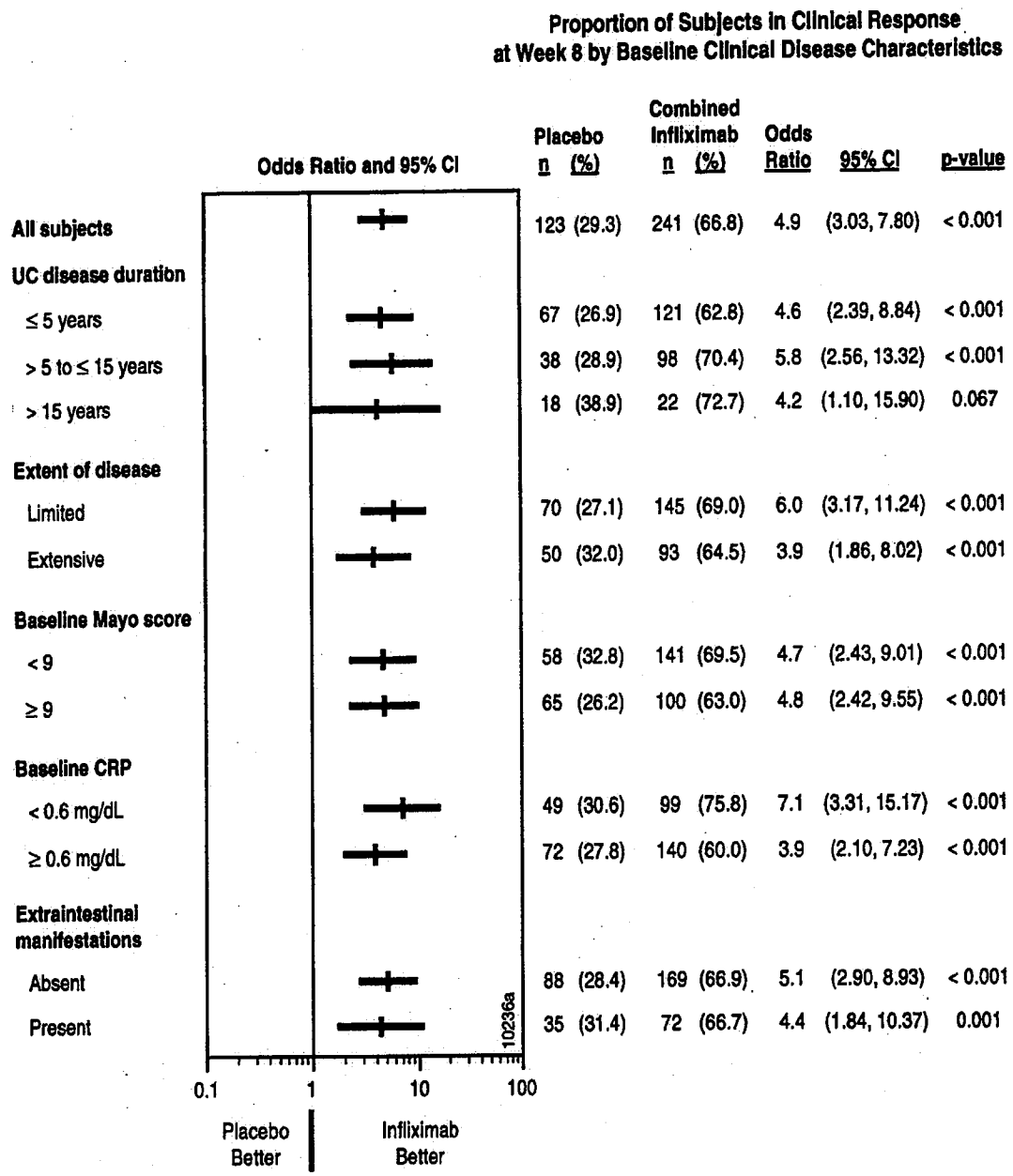


Figure 6: Plot of odds ratios and 95% confidence intervals for comparing the proportion of subjects in clinical response at Week 8 in the infliximab group (combined) vs. the placebo group by baseline clinical disease characteristics.

Clinical Response by Drug History

ACT 1

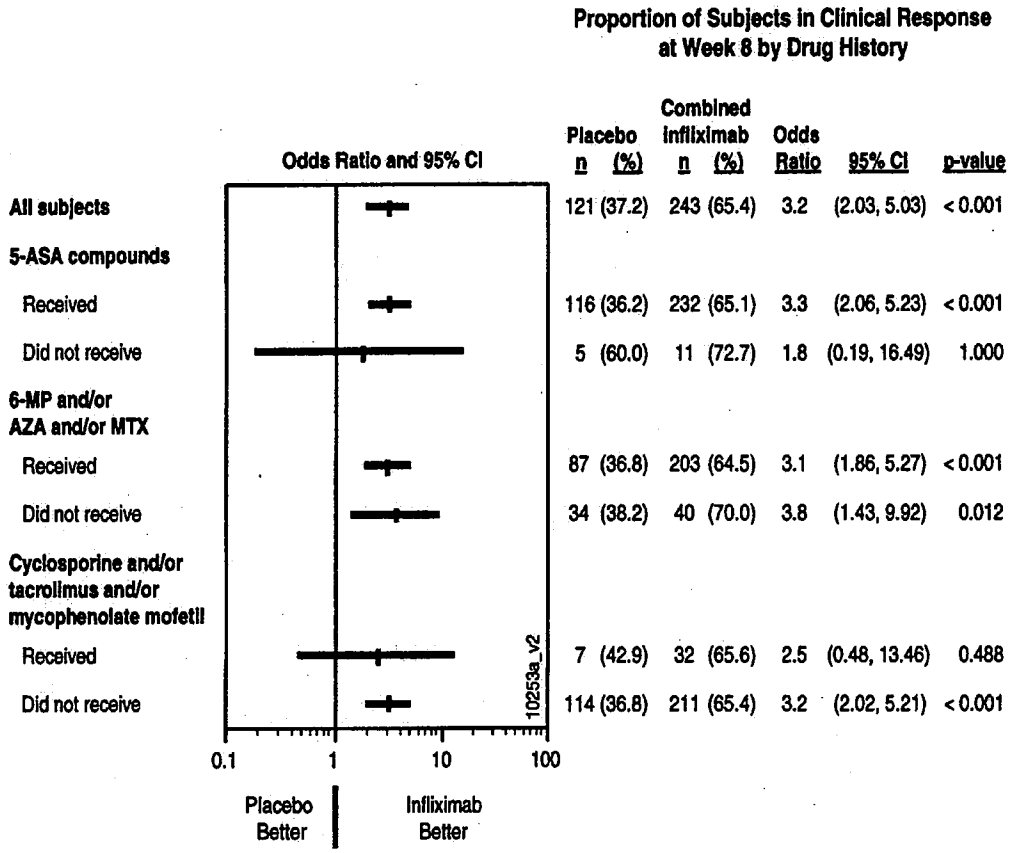


Figure 7: Plot of odds ratios and 95% confidence intervals for comparing the proportion of patients in clinical response at Week 8 in the infliximab group (combined) vs. the placebo group by drug history

ACT 2

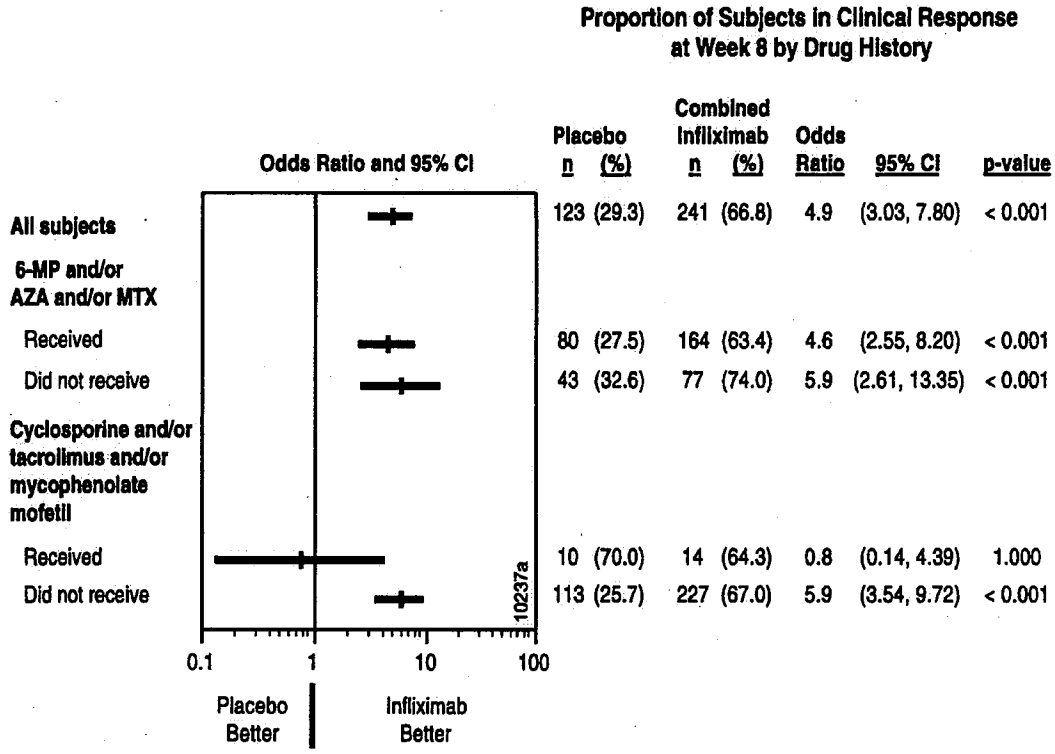


Figure 8: Plot of odds ratios and 95% confidence intervals for comparing the proportion of patients in clinical response at Week 8 in the infliximab group (combined) vs. the placebo group by drug history

Clinical Response by Baseline Concomitant Medications

ACT 1

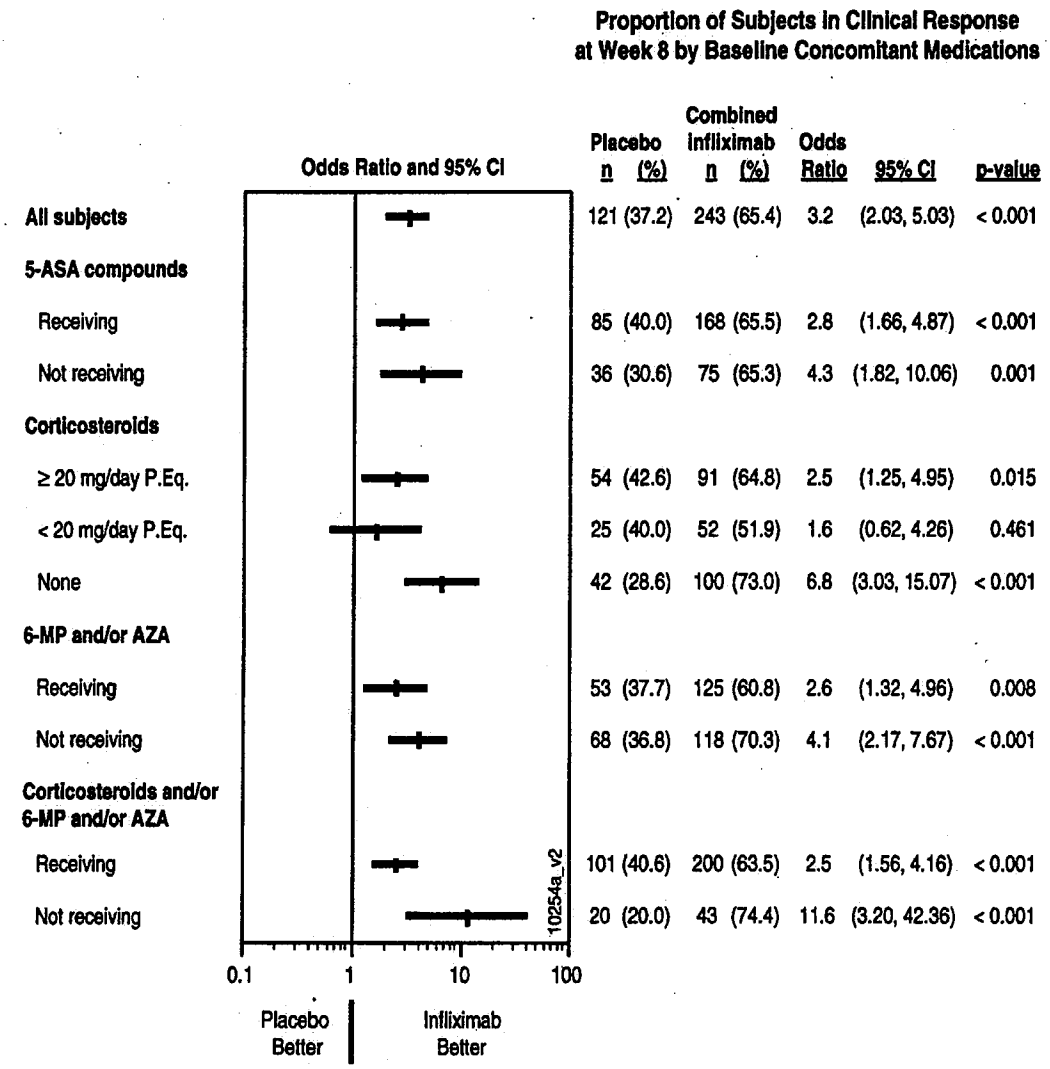


Figure 9: Plot of odds ratios and 95% confidence intervals for comparing the proportion of patients in clinical response at Week 8 in the infliximab group (combined) vs. the placebo group by baseline concomitant medications

ACT 2

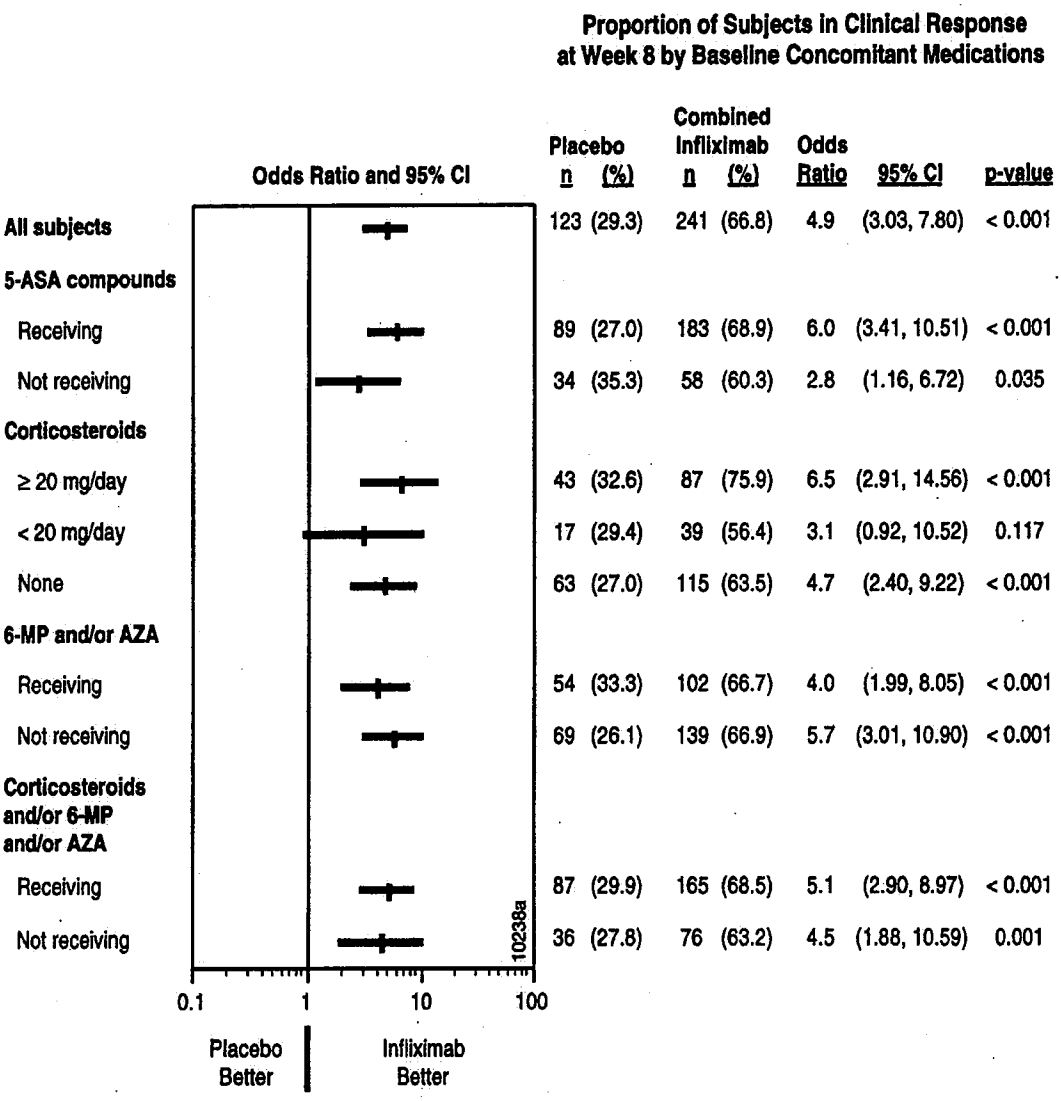


Figure 10: Plot of odds ratios and 95% confidence intervals for comparing the proportion of patients in clinical response at Week 8 in the infliximab group (combined) vs. the placebo group by baseline concomitant medications

Other Efficacy Endpoints

Other prespecified endpoints that the Sponsor evaluated were 1) sustained response, 2) sustained remission, 3) corticosteroid endpoints, 4) the Mayo Score, 5) C-reactive protein levels, 6) rates of colectomies and ostomies, 7) patient reported health-related outcomes, 8) a histological assessment (as a substudy of ACT 1 only), and 9) health economics.

Sustained Response

The proportions of subjects in sustained response are presented in **Table 31** for ACT 1 and **Table 32** for ACT 2. Sustained response was defined as the proportion of subjects who had a clinical response at both Weeks 8 and 30. In ACT 1, the combined infliximab group had 47% of subjects in sustained response through Week 30, compared to 23% of placebo subjects ($p < 0.001$). In ACT 2, the number of subjects in sustained response was similar to those in ACT 1, with 47% of the combined infliximab group achieving this endpoint compared to 15% in the placebo group.

ACT 1

Table 31: Number of subjects in sustained response (clinical response at both week 8 and week 30) through week 30[a,b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Subjects in sustained response	28 (23)	59 (49)	56 (46)	115 (47)
p-value		<0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in sustained response.
[b] Analysis is stratified by corticosteroid refractory status and center location.

ACT 2

Table 32: Number of subjects in sustained response (clinical response at both week 8 and week 30) through week 30[a,b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Subjects in sustained response	19 (15)	50 (41)	64 (53)	114 (47)
p-value		<0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in sustained response.
[b] Analysis is stratified by corticosteroid refractory status and center location.

Sustained Remission

The proportions of subjects in sustained remission (remission at both Week 8 and Week 30) are presented in **Table 33** (ACT 1), and **Table 34** (ACT 2). In both studies, the combined infliximab treatment groups had greater numbers of subjects in sustained remission compared to placebo-treated subjects. In ACT 1, 25% of the combined infliximab treatment group achieved sustained remission compared to 8% of the placebo arm ($p < 0.001$). Similarly in ACT 2, a greater proportion of infliximab-treated subjects (19%) were in sustained remission through Week 30 than in the placebo-treated group (2%).

ACT 1

Table 33: Number of subjects in sustained remission (remission at both week 8 and week 30) through week 30[a,b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Subjects in sustained remission	10 (8)	28 (23)	32 (26)	60 (25)
p-value		0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in sustained remission.
[b] Analysis is stratified by corticosteroid refractory status and center location.

ACT 2

Table 34: Number of subjects in sustained remission (remission at both week 8 and week 30) through week 30[a,b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Subjects in sustained remission	3 (2)	18 (15)	27 (23)	45 (19)
p-value		<0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in sustained remission.
[b] Analysis is stratified by corticosteroid refractory status and center location.

Corticosteroid Endpoints

Given the considerable toxicities associated with the use of corticosteroids, it is important to determine whether use of infliximab allowed the tapering of corticosteroids. Corticosteroid use in the infliximab and placebo groups is presented in **Table 35** through **Table 42.** Median daily corticosteroid doses (in mg. of prednisone or prednisone equivalence) for each treatment group are presented in **Table 35** (ACT 1) and **Table 36** (ACT 2). Because the protocol specified that tapering of corticosteroids could begin only after Week 8, median daily corticosteroid doses were unchanged at Week 8 compared to baseline (daily median of 20.0 mg/day for all three treatment groups). Beginning at Week 14 for ACT 1 (**Table 35**), the median daily dose for the combined infliximab group (10.0 mg/day) was lower than the median dose in the placebo group (12.5 mg/day) at every 8 week interval until Week 30. By Week 30, the median daily corticosteroid dose in the combined infliximab group was 7.5 mg/day compared to 10.0 mg/day in the placebo group. Subjects in the infliximab 5 mg/kg group appeared to tolerate a greater decrease in median daily corticosteroid dose, with a median dose of 5.6 mg/day of corticosteroids compared to 10.0 mg/day in the infliximab 10 mg/kg treatment group at Week 30 (**Figure 11**).

ACT 1

Table 35: Summary of the median daily corticosteroid dose (Prednisone Equivalent in mg, P.Eq) through Week 30 (randomized subjects with corticosteroids at baseline) [a, b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Randomized subjects with corticosteroids at baseline	79	70	73	143
Baseline	20.0	20.0	20.0	20.0
Week 8	20.0	20.0	20.0	20.0
Week 14	12.5	10.0	10.0	10.0
Week 22	10.0	5.0	7.5	6.3
Week 30	10.0	5.6	10.0	7.5

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects who discontinued the study had their last value carried forward.

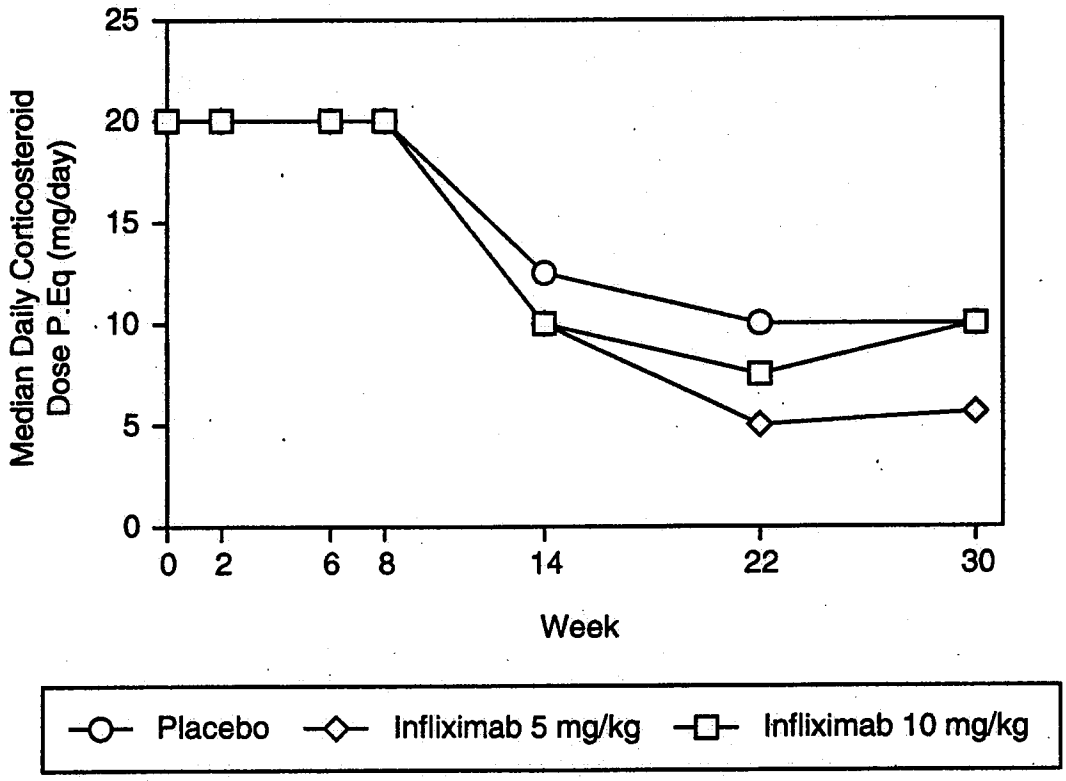


Figure 11: Median daily corticosteroid dose (P.Eq, mg) through Week 30; subjects with corticosteroids at baseline (ACT 1): Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward. Subjects who discontinued the study had their last value carried forward.

In similar fashion, ACT 2 subjects in the infliximab treatment groups tolerated a greater decrease in their daily corticosteroid doses compared to those in the placebo group (**Table 36**), with median daily corticosteroid doses which were less than half the median daily dose in placebo-treated subjects. At Week 14, the median daily corticosteroid dose among infliximab-treated subjects was 10.0 mg/day compared to 20.0 mg/day for placebo-treated subjects. By Week 30, the infliximab-treated group had a median daily dose of 6.9 mg/day vs. an unchanged 20.0 mg/day for the placebo subjects (**Figure 12**). The effects of infliximab on the ability to taper corticosteroids appear greater in ACT 2 compared to ACT 1, but this is because the placebo-treated subjects were unable to have their corticosteroid use tapered, with median daily corticosteroid dose remaining at 20 mg/day. The actual median daily corticosteroid dose for the combined infliximab groups at Week 30 was in fact quite comparable between ACT 1 and ACT 2 (7.5 mg/day and 6.9 mg/day, respectively). This shows that infliximab was able to effectively lower daily corticosteroid dose despite being used in two patient populations that varied from one another.

ACT 2

Table 36: Summary of the median daily corticosteroid dose (P.Eq, mg) through Week 30 (randomized subjects with corticosteroids at baseline) [a, b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Randomized subjects with corticosteroids at baseline	60	60	66	126
Baseline	20.0	20.0	20.0	20.0
Week 8	20.0	20.0	20.0	20.0
Week 14	20.0	10.0	10.0	10.0
Week 22	17.5	5.0	5.0	5.0
Week 30	20.0	7.5	5.0	6.9

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects who discontinued the study had their last value carried forward.

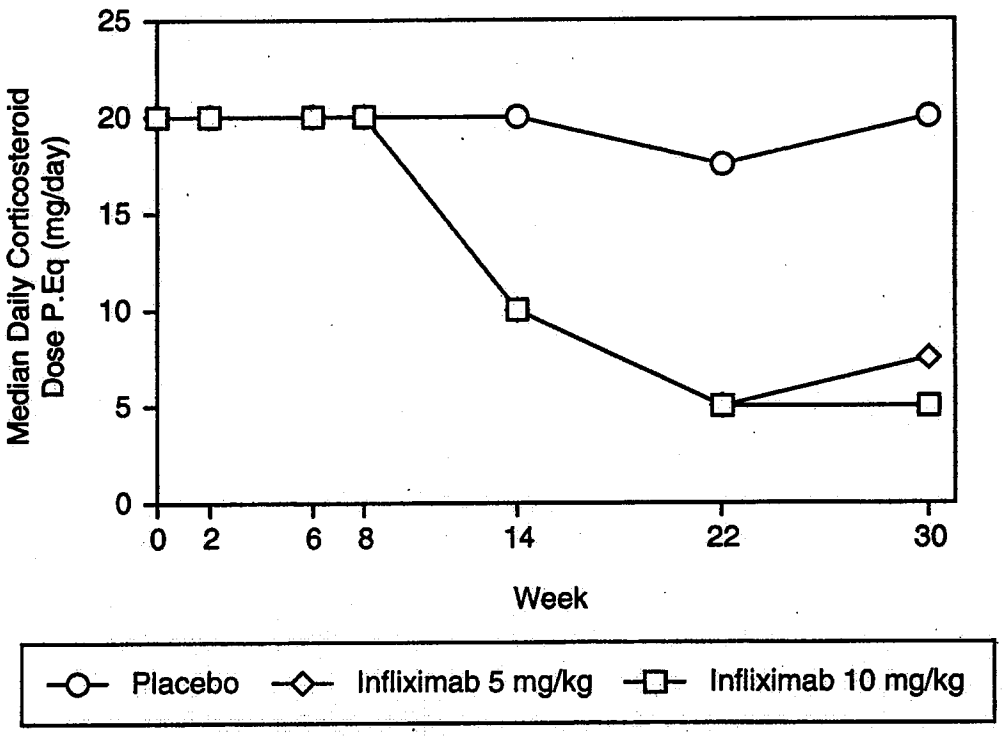


Figure 12: Median daily corticosteroid dose (P.Eq, mg) through Week 30; subjects with corticosteroids at baseline (ACT 2): Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward. Subjects who discontinued the study had their last value carried forward.

Additional Corticosteroid Analyses

Tapering corticosteroids would not represent as large a benefit if it occurred in the setting of active disease. Therefore, we also assessed whether infliximab treatment increased the proportion of subjects in clinical remission off corticosteroids. In ACT 1, the proportion of subjects on corticosteroids at baseline were comparable among the three treatment arms. Of 364 subjects randomized, 143 or 61% were on baseline corticosteroid treatment. The proportions of subjects in clinical remission without corticosteroids at Week 30 in ACT 1 are displayed in **Table 37**. Of these subjects on corticosteroids at baseline, 22% of infliximab-treated subjects achieved clinical remission without being on corticosteroids at Week 30 compared to 10% of placebo-treated subjects ($p = 0.039$). The data for the more stringent analysis of subjects who were on corticosteroids at baseline and achieved clinical remission off corticosteroids for ≥ 1 month at Week 30 are presented in
Table 38. 20% of the combined infliximab-treatment group achieved this endpoint compared to 9% of placebo-treated subjects ($p = 0.033$).

40% (145 of 364) of subjects randomized in ACT 1 were on daily doses of corticosteroids ≥ 20 mg/day of prednisone or equivalent. **Table 39** lists the proportion of subjects in ACT 1 who were in clinical remission at Week 30 and had been on a daily corticosteroid dose of < 10 mg/day for greater than 3 months. The combined infliximab treatment group had 23% of subjects achieve remission at Week 30 while being on < 10 mg/day of corticosteroids compared to 9% of placebo-treated subjects.

ACT 1

Table 37: Number of subjects in clinical remission without corticosteroids at Week 30 (randomized subjects with corticosteroids at baseline) [a,b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Randomized subjects with corticosteroids at baseline	79	70	73	143
Subjects evaluated	79	70	73	143
Subjects without corticosteroids and in clinical remission at Week 30	8 (10)	17 (24)	14 (19)	31 (22)
p-value		0.030	0.125	0.039

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical remission.
[b] Analysis is stratified by center location.

Table 38: Number of subjects in clinical remission without corticosteroids for ≥ 1 month at Week 30 (randomized subjects with corticosteroids at baseline) [a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Randomized subjects with corticosteroids at baseline	79	70	73	143
Subjects evaluated	79	70	73	143
Subjects without corticosteroids for ≥ 1 month and in clinical remission at Week 30	7 (9)	16 (23)	13 (18)	29 (20)
p-value		0.024	0.110	0.033

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical remission.
[b] Analysis is stratified by center location.

Table 39: Number of subjects in clinical remission with < 10 mg/day P.Eq for > 3 months at Week 30 (randomized subjects with > 20 mg/day P.Eq at baseline) [a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Randomized subjects with ≥ 20 mg/day P.Eq at baseline	54	45	46	91
Subjects evaluated	54	45	46	91
Subjects with ≤ 10 mg/day P.Eq for ≥ 3 months and in clinical remission at Week 30	5 (9)	9 (20)	12 (26)	21 (23)
p-value		0.140	0.031	0.042

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical remission.
[b] Analysis is stratified by center location.

In ACT 2, 51% of subjects were on corticosteroids at baseline, with comparable proportions of subjects per treatment arm. Infliximab-treated subjects were more likely to be in clinical remission without corticosteroids at Week 30 (23% for the combined infliximab group vs. 3% for placebo, **Table 40**). Similar numbers of subjects were in clinical remission without corticosteroids for ≥ 1 month at Week 30 (22% in combined infliximab groups compared to 3% of placebo (**Table 41**).

We also examined corticosteroid tapering in subjects on higher doses of corticosteroids at baseline. 36% (130 of 364) of the randomized subjects in ACT 2 were on ≥ 20 mg/day of prednisone or equivalent at baseline. Of these subjects (**Table 42**), 22% of subjects in the combined infliximab-treated group were in clinical remission on ≤ 10 mg/day for at least 3 months at Week 30 compared to 0 subjects in the placebo group (p = 0.001).

ACT 2

Table 40: Number of subjects in clinical remission without corticosteroids at Week 30 (randomized subjects with corticosteroids at baseline) [a, b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Randomized subjects with corticosteroids at baseline	60	60	66	126
Subjects evaluated	60	60	66	126
Subjects without corticosteroids and in clinical remission at Week 30	2 (3)	11 (18)	18 (27)	29 (23)
p-value		0.010	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical remission.
[b] Analysis is stratified by center location.

Table 41: Number of subjects in clinical remission without corticosteroids for ≥ 1 month at Week 30 (randomized subjects with corticosteroids at baseline) [a, b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Randomized subjects with corticosteroids at baseline	60	60	66	126
Subjects evaluated	60	60	66	126
Subjects without corticosteroids for ≥ 1 month and in clinical remission at Week 30	2 (3)	11 (18)	17 (26)	28 (22)
p-value		0.010	<0.001	0.001

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical remission.
[b] Analysis is stratified by center location.

Table 42: Number of subjects in clinical remission with ≤ 10 mg/day P.Eq for ≥ 3 months at Week 30 (randomized subjects with ≥ 20 mg/day P.Eq at baseline) [a, b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Randomized subjects with ≥ 20 mg/day P.Eq at baseline	43	40	47	87
Subjects evaluated	43	40	47	87
Subjects with ≤ 10 mg/day P.Eq for ≥ 3 months and in clinical remission at Week 30	0	9 (23)	10 (21)	19 (22)
p-value		0.003	0.001	0.001

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical remission.
[b] Analysis is stratified by center location.

These analyses of corticosteroid dose and disease activity support the use of infliximab in UC patients to reduce or eliminate the daily dose of corticosteroids. No consistent difference was seen between the infliximab 5 mg/kg and 10 mg/kg groups.

Mayo Score

Mayo scores were examined in detail for all treatment groups in studies ACT 1 and ACT 2. In ACT 1, the median baseline Mayo scores for the placebo group and combined infliximab treatment groups were 8.0 and 9.0, respectively, consistent with moderately to severely active ulcerative colitis based on a theoretical range of Mayo scores between a minimum of 0 and maximum of 12 (**Table 43**). By Week 8, the median change from baseline in Mayo score was -2.0 in the placebo group and -4.0 in the combined infliximab treatment groups ($p < 0.001$), indicating a greater reduction in disease activity for subjects receiving infliximab compared to placebo. By Week 30, both infliximab groups had median changes in the Mayo score of -3.0 compared to a median change of 0.0 from baseline in the placebo group.

The number of subjects with individual Mayo subscores of 0 or 1 at Week 8 or 30 is presented in **Table 44**. At the Week 8 and Week 30 visits, a greater proportion of subjects in each infliximab treatment group had scores of 0 or 1 for each of the individual Mayo subscores compared to those in the placebo group. This indicates that the improvements in the overall total Mayo scores for the combined infliximab group seen in **Table 43** were not due to selective effects of infliximab on particular Mayo subscores, but instead were the result of a collective reduction of all subscores.

The time course of change in Mayo scores for ACT 1 is shown in **Figure 13**. Since endoscopy was performed only at selected time points, the complete Mayo score is only available at baseline, Week 8, and Week 30 (upper graph). To further charazterize changes over time a partial Mayo score, which excludes the endoscopy component, is plotted in the lower graph. Differences between infliximab and placebo groups are observed as early as Week 2 and are maintained out to Week 30.

ACT 1

Table 43: Summary of change from baseline in the Mayo score through Week 30 [a,b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Randomized subjects	121	121	122	243
Baseline, n				
Median	8.0	9.0	8.5	9.0
Change from baseline, Week 8				
Median	-2.0	-5.0	-4.0	-4.0
p-value		<0.001	<0.001	<0.001
Change from baseline, Week 30				
Median	0.0	-3.0	-3.0	-3.0
p-value		<0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects who discontinued the study had their last value carried forward. Theoretical Mayo score minimum = 0, max. = 12

Table 44: Number of subjects with a score of 0 or 1 for the individual Mayo subscores through Week 30 [a, b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Subjects with a stool frequency subscore of 0 or 1				
Baseline	20 (17)	20 (17)	12 (10)	32 (13)
Week 8	42 (35)	72 (60)	71 (58)	143 (59)
Week 30	42 (35)	62 (51)	64 (53)	126 (52)
Subjects with a rectal bleeding subscore of 0 or 1				
Baseline	65 (54)	48 (40)	58 (48)	106 (44)
Week 8	89 (74)	104 (86)	98 (80)	202 (83)
Week 30	79 (65)	89 (74)	87 (71)	176 (72)
Subjects with an endoscopy subscore of 0 or 1				
Baseline	0	0	0	0
Week 8	41 (34)	75 (62)	72 (59)	147 (61)
Week 30	31 (26)	62 (51)	63 (52)	125 (51)
Subjects w/ physician's global assessment subscore of 0 or 1				
Baseline	5 (4)	7 (6)	3 (3)	10 (4)
Week 8	53 (44)	89 (74)	78 (64)	167 (69)
Week 30	43 (36)	69 (57)	67 (55)	136 (56)

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects who discontinued the study had their last value carried forward.

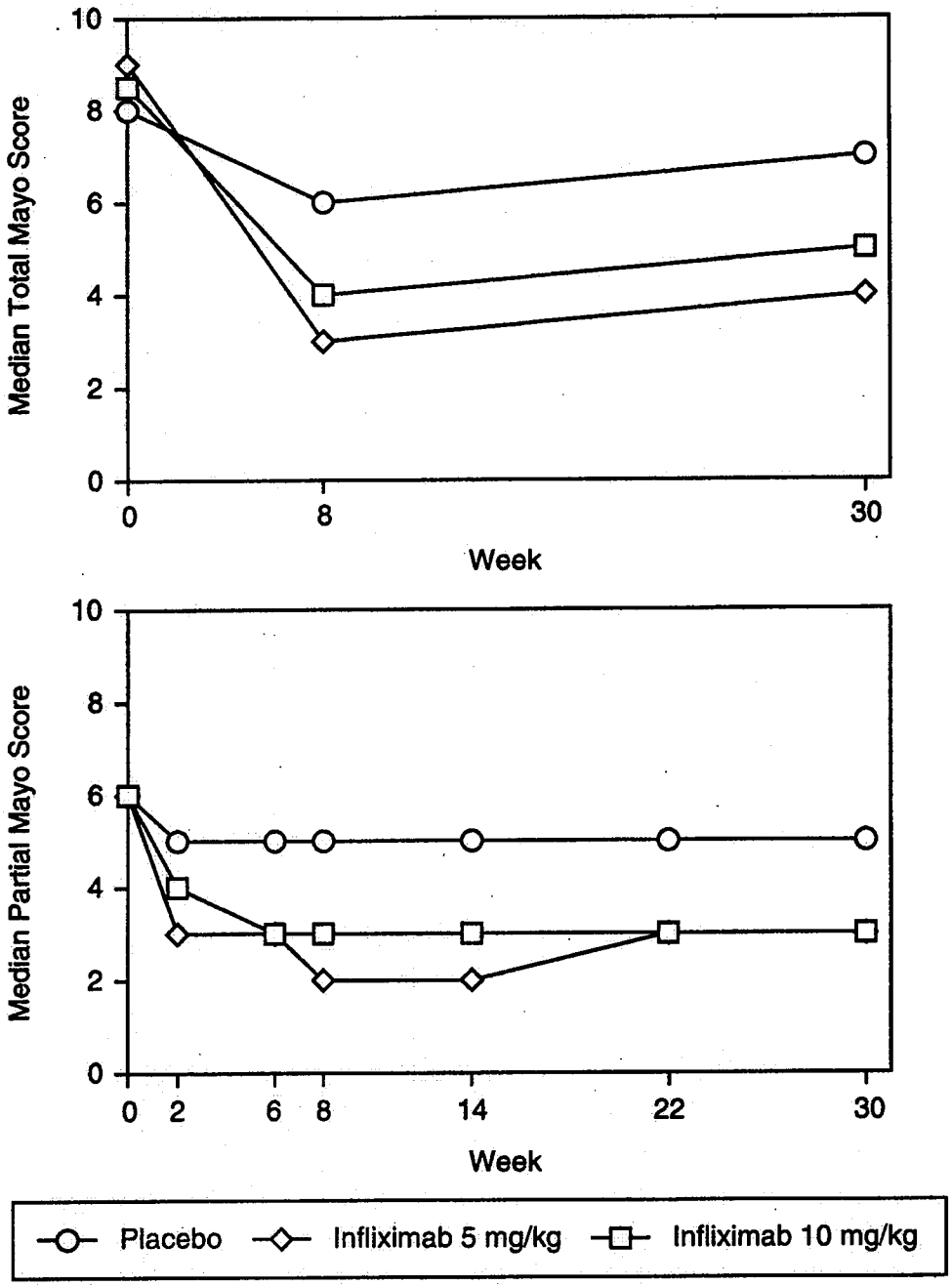


Figure 13: Median Partial and Total Mayo Score over time through Week 30

(ACT 1) Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward. Subjects who discontinued the study had their last value carried forward.

Similarly, in ACT 2, the median changes in the total Mayo scores for both infliximab treatment groups were greater than that seen for the placebo group (**Table 45**), (median changes -4.0 at both Weeks 8 and 30 for the combined infliximab group vs. a median change of -1.0 at Week 8 and 0.0 at Week 30 for the placebo group). Again, there was greater improvement of all individual Mayo subscores (**Table 46**) for both the infliximab 5 mg/kg and 10 mg/kg treatment groups at both Weeks 8 and 30 compared to the placebo group. The time course is depicted graphically in **Figure 14**.

ACT 2

Table 45: Summary of change from baseline in the Mayo score through Week 30 [a, b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Randomized subjects	123	121	120	241
Baseline				
Median	9.0	8.0	8.0	8.0
Change from baseline, Week 8				
Median	-1.0	-4.0	-4.0	-4.0
p-value		<0.001	<0.001	<0.001
Change from baseline, Week 30				
Median	0.0	-3.0	-4.0	-4.0
p-value		<0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects who discontinued the study had their last value carried forward.

Table 46: Number of subjects with a score of 0 or 1 for the individual Mayo subscores through Week 30 [a, b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Subjects with a stool frequency subscore of 0 or 1				
Baseline	16 (13)	19 (16)	20 (17)	39 (16)
Week 8	39 (32)	76 (63)	71 (59)	147 (61)
Week 30	38 (31)	61 (50)	64 (53)	125 (52)
Subjects with a rectal bleeding subscore of 0 or 1				
Baseline	53 (43)	69 (57)	55 (46)	124 (52)
Week 8	78 (63)	99 (82)	102 (85)	201 (83)
Week 30	70 (57)	91 (75)	96 (80)	187 (78)
Subjects with an endoscopy subscore of 0 or 1				
Baseline	1 (<1)	0	2 (2)	2 (<1)
Week 8	39 (32)	73 (60)	75 (63)	148 (61)
Week 30	40 (33)	61 (50)	71 (59)	132 (55)
Subjects w/ physician's global assessment subscore of 0 or 1				
Baseline	4 (3)	6 (5)	4 (3)	10 (4)
Week 8	43 (35)	83 (69)	79 (66)	162 (67)
Week 30	43 (35)	66 (55)	75 (63)	141 (59)

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects who discontinued the study had their last value carried forward.

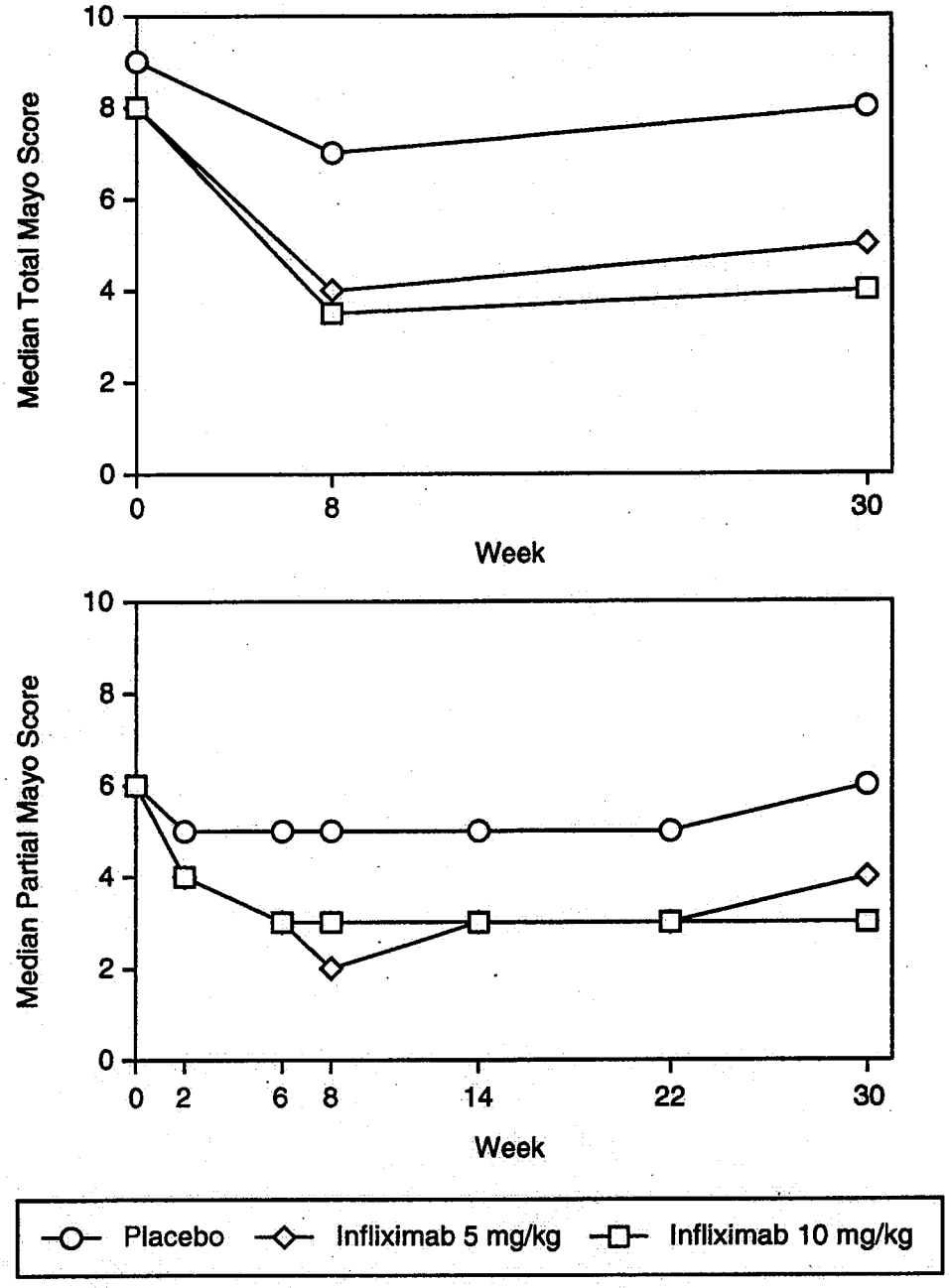


Figure 14: Median Partial and Total Mayo Score over time through Week 30 (ACT 2)
Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward. Subjects who discontinued the study had their last value carried forward.

C-reactive Protein (CRP)

CRP concentrations were followed for each subject as part of scheduled events. In ACT 1, baseline CRP concentrations were comparable between the combined infliximab group and placebo group. The summary of the change in CRP concentration from baseline through Week 30 is presented in **Table 47**. At every visit where the CRP concentration was measured, the mean decrease in CRP concentration was greater in the combined infliximab group vs. the placebo group.

ACT 1

Table 47: Summary of change from baseline in CRP concentration (mg/dL) through week 30[a,b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Baseline				
Mean ± SD	1.70 ± 2.65	1.41 ± 1.91	1.57 ± 2.28	1.49 ± 2.10
Median	0.80	0.85	1.00	0.90
Change from Baseline				
Week 2				
Mean ± SD	-0.25 ± 2.21	-0.65 ± 1.78	-0.92 ± 1.79	-0.79 ± 1.78
Median	0.00	-0.35	-0.40	-0.40
Week 6				
Mean ± SD	-0.15 ± 2.57	-0.55 ± 2.02	-0.41 ± 2.31	-0.48 ± 2.17
Median	0.00	-0.20	-0.30	-0.20
Week 8				
Mean ± SD	-0.22 2.06	-0.62 1.73	-0.59 1.44	-0.60 1.59
Median	0.00	-0.30	-0.20	-0.30
p-value		0.009	0.018	0.004
Week 14				
Mean ± SD	-0.29 ± 2.19	-0.62 ± 1.83	-0.50 ± 1.41	-0.56 ± 1.63
Median	0.00	-0.10	0.00	-0.10
Week 30				
Mean ± SD	-0.31 ± 2.59	-0.53 ± 1.77	-0.27 ± 1.68	-0.40 ± 1.73
Median	0.00	0.00	0.00	0.00
p-value		0.046	0.136	0.044

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects who discontinued the study had their last value carried forward.

Decreases in CRP levels were also seen in ACT 2 (**Table 48**), with a greater mean decrease in CRP for the combined infliximab group at every visit compared to the placebo group.

Being a strictly objective outcome measure makes CRP levels particularly valuable. As such, it is notable that infliximab use is associated with improvement in CRP concentrations in ACT 1 and ACT 2 as well as improvement in Mayo scores.

ACT 2

Table 48: Summary of change from baseline in CRP concentration (mg/dL) through week 30[a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Baseline				
Mean ± SD	1.63 ± 2.88	1.25 ± 2.26	1.38 ± 2.24	1.32 ± 2.24
Median	0.60	0.80	0.60	0.70
Change from Baseline				
Week 2				
Mean ± SD	-0.02 ± 1.38	-0.61 ± 2.22	-0.74 ± 1.95	-0.68 ± 2.08
Median	0.00	-0.30	-0.20	-0.30
Week 6				
Mean ± SD	0.14 ± 2.03	-0.36 ± 2.66	-0.60 ± 2.21	-0.48 ± 2.44
Median	0.00	-0.20	0.00	-0.10
Week 8				
Mean ± SD	-0.16 1.15	-0.53 2.24	-0.69 2.09	-0.61 2.16
Median	0.00	-0.15	0.00	0.00
p-value		<0.001	0.001	<0.001
Week 14				
Mean ± SD	-0.11 ± 1.58	-0.21 ± 2.81	-0.57 ± 2.18	-0.39 ± 2.52
Median	0.00	0.00	0.00	0.00
Week 30				
Mean ± SD	-0.07 ± 1.21	-0.16 ± 1.03	-0.42 ± 2.15	-0.29 ± 1.68
Median	0.00	0.00	0.00	0.00
p-value		0.084	0.080	0.045

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects who discontinued the study had their last value carried forward.

Colectomies and Ostomies

The number of colectomies and ostomies (defined as a colostomy, ileostomy, or other enterostomy) due to progression of disease in ACT 1 and ACT 2 are presented in **Table 49** and **Table 50**. In ACT 1, a total of 5 of 364 (1%) subjects underwent colectomy (4 in the combined infliximab group vs. 1 in the placebo group) and 3 of 364 (< 1%) subjects underwent an ostomy. In ACT 2, one subject had a colectomy and another underwent an ostomy for progression of disease, both from the placebo group. Taken together, there are too few numbers of subjects to conclude that any treatment arm reduced colectomy or ostomy rates.

ACT 1

Table 49: Number of subjects with a colectomy or ostomy through Week 30[a]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Randomized subjects	121	121	122	243
Subjects who had a colectomy	1 (<1)	3 (3)	1 (<1)	4 (2)
Subjects who had an ostomy [a]	1 (<1)	2 (2)	0	2 (<1)

[a] An ostomy is defined as colostomy, ileostomy, or other enterostomy.

ACT 2

Table 50: Number of subjects with a colectomy or ostomy through Week 30[a]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Randomized subjects	123	121	120	241
Subjects who had a colectomy	1 (<1)	0	0	0
Subjects who had an ostomy [a]	1 (<1)	0	0	0

[a] An ostomy is defined as colostomy, ileostomy, or other enterostomy.

Patient Reported Health-Related Outcomes

Patient reported health-related outcomes were measured using the 32-item inflammatory bowel disease questionnaire (IBDQ) and the 36-item short form health survey (SF-36). Both questionnaires were administered at baseline and at Weeks 8, 30, and 54. The IBDQ is a questionnaire designed specifically for inflammatory bowel disease subjects and the SF-36 is a generic health-related outcome questionnaire.

A. IBDQ Scores

The IBDQ is a 32-item questionnaire that is completed in approximately 15 minutes and consists of four "dimensional scores" under the headings of bowel (loose stools, pain), systemic (fatigue, altered sleep pattern), social (work attendance, need to cancel social events), and emotional (anger, depression, irritability). Patient responses are graded on a 7-point Likert scale with a score of "7" denoting "no problem at all" and "1" denoting a very severe problem. Scores range from 32 to 224 with higher scores indicating a better outcome. Median baseline total IBDQ scores were comparable for the combined infliximab group and the placebo group. At Weeks 8 and 30 for ACT 1 (**Table 51**), both infliximab groups had higher median changes in the total IBDQ score compared to placebo indicating improvement in health-related outcome (median

change of 36 for combined infliximab group vs. 16 for placebo group at Week 8, $p < 0.001$, and median change of 27 for the combined infliximab group vs. 0 for the placebo group at Week 30, also $p < 0.001$).

ACT 1

Table 51: Summary of baseline and change from baseline in IBDQ (total score) and IBDQ dimensions through Week 30 [a, b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Baseline, median	121	122	131	127
Change from baseline, median				
Week 8	16	39	33	36
p-value		<0.001	0.001	<0.001
Week 30	0	27	31	27
p-value		0.002	0.004	<0.001
Bowel dimension (baseline)	39	40	40	40
Change from baseline, median				
Week 8	5	16	13	14
p-value		<0.001	0.005	<0.001
Week 30	0	7	10	8
p-value		0.004	0.004	0.001
Emotional dimension (baseline)	49	48	51	50
Change from baseline, median				
Week 8	2	11	11	11
p-value		<0.001	0.004	<0.001
Week 30	0	7	7	7
p-value		<0.001	0.002	<0.001
Systemic dimension (baseline)	17	17	18	17
Change from baseline, median				
Week 8	2	5	5	5
p-value		<0.001	0.006	<0.001
Week 30	0	4	4	4
p-value		0.007	0.014	0.003
Social dimension (baseline)	18	18	21	20
Change from baseline, median				
Week 8	1	6	6	6
p-value		<0.001	0.002	<0.001
Week 30	0	3	4	4
p-value		0.039	0.031	0.015

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects who discontinued the study had their last value carried forward.

In ACT 2 (**Table 52**), starting with comparable median baseline IBDQ scores, the combined infliximab group had a median improvement of 34 points in the total IBDQ score compared to 7

points for the placebo group ($p < 0.001$) at Week 8. At Week 30, the median total IBDQ score improvement was 29 in the combined infliximab group vs. 0 in the placebo group ($p < 0.001$). In similar fashion to the ACT 1 study, the combined infliximab group in ACT 2 had statistically significant improvement in each of the four "dimensional" scores of the IBDQ at both Weeks 8 and 30 compared to the placebo group. Thus, the improvement in IBDQ scores for both studies did not depend on one or a few of the dimensional scores but rather was a consistent benefit indicated by improvement in all of the IBDQ subscores. No differences in IBDQ improvement were seen between the infliximab 5 mg/kg and 10 mg/kg groups.

ACT 2

Table 52: Summary of baseline and change from baseline in IBDQ dimensions through Week 30 [a, b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Baseline, median	127	121	131	127
Change from baseline, median				
Week 8	7	38	33	34
p-value		<0.001	<0.001	<0.001
Week 30	0	20	32	29
p-value		0.005	<0.001	<0.001
Bowel dimension (baseline)	38	38	38	38
Change from baseline, median				
Week 8	5	12	13	13
p-value		<0.001	<0.001	<0.001
Week 30	0	8	13	10
p-value		0.005	<0.001	<0.001
Emotional dimension (baseline)	50	50	53	51
Change from baseline, median				
Week 8	0	10	10	10
p-value		<0.001	<0.001	<0.001
Week 30	0	7	9	8
p-value		0.003	<0.001	<0.001
Systemic dimension (baseline)	18	18	19	18
Change from baseline, median				
Week 8	0	5	4	4
p-value		<0.001	<0.001	<0.001
Week 30	0	2	5	4
p-value		0.117	0.001	0.005
Social dimension (baseline)	20	20	22	21
Change from baseline, median				
Week 8	0	5	5	5
p-value		<0.001	0.013	<0.001
Week 30	0	3	5	4
p-value		0.005	0.003	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy, or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects who discontinued the study had their last value carried forward.

IBDQ Scores of > 16 Change from Baseline

A literature search was performed in order to determine what a clinically meaningful improvement in the IBDQ score was. IBDQ cut-offs of 16 and 32 were identified as low and high thresholds, respectively, for changes in the IBDQ which would each represent meaningful values. The proportion of subjects in each treatment arm that had an IBDQ change of ≥ 16 points is listed in **Table 53** for ACT 1, **Table 54** for ACT 2, and **Table 55** for the combined studies. Greater proportions of subjects who received 5 mg/kg and 10 mg/kg of infliximab had an IBDQ change of ≥ 16 at Week 8 compared to placebo (75% and 67% vs. 52%, respectively).

Table 53: Number of subjects with change in IBDQ ≥ 16 at Week 8 (ACT 1[a, b])

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Subjects evaluated	119	120	122	242
Subjects with change in IBDQ ≥ 16	62 (52)	90 (75)	82 (67)	172 (71)
p-value		< 0.001	0.017	< 0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.

Table 54: Number of subjects with change in IBDQ ≥ 16 at Week 8 (ACT 2[a, b])

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Subjects evaluated	123	121	120	241
Subjects with change in IBDQ ≥ 16	58 (47)	78 (65)	82 (68)	160 (66)
p-value		0.006	< 0.001	< 0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.

Table 55: Number of subjects with change in IBDQ ≥ 16 at Week 8 (ACT 1 and ACT 2 combined[a, b, c])

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	244	242	242	484
Subjects evaluated	242	241	242	483
Subjects with change in IBDQ ≥ 16	120 (50)	168 (70)	164 (68)	332 (69)
p-value		< 0.001	< 0.001	< 0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.
[c] Analysis is stratified by study.

IBDQ Scores of > 32 Change from Baseline

Using 32 points or greater as a cut-off value for improvement in IBDQ score, infliximab-treated groups in ACT 1 (**Table 56**) and ACT 2 (**Table 57**) had greater proportions of subjects (56% and 53%) who reached this threshold compared to placebo-treated subjects (32% and 33%), respectively. The improvement in IBDQ ≥ 32 points in the combined studies is shown in **Table 58**.

Table 56: Number of subjects with change in IBDQ ≥ 32 at Week 8 (ACT 1[a, b])

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Subjects evaluated	119	120	122	242
Subjects with change in IBDQ ≥ 32	38 (32)	72 (60)	64 (53)	136 (56)
p-value		< 0.001	0.001	< 0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.

Table 57: Number of subjects with change in IBDQ ≥ 32 at Week 8 (ACT 2[a, b])

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Subjects evaluated	123	121	120	241
Subjects with change in IBDQ ≥ 32	41 (33)	65 (54)	63 (53)	128 (53)
p-value		0.001	0.003	< 0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.

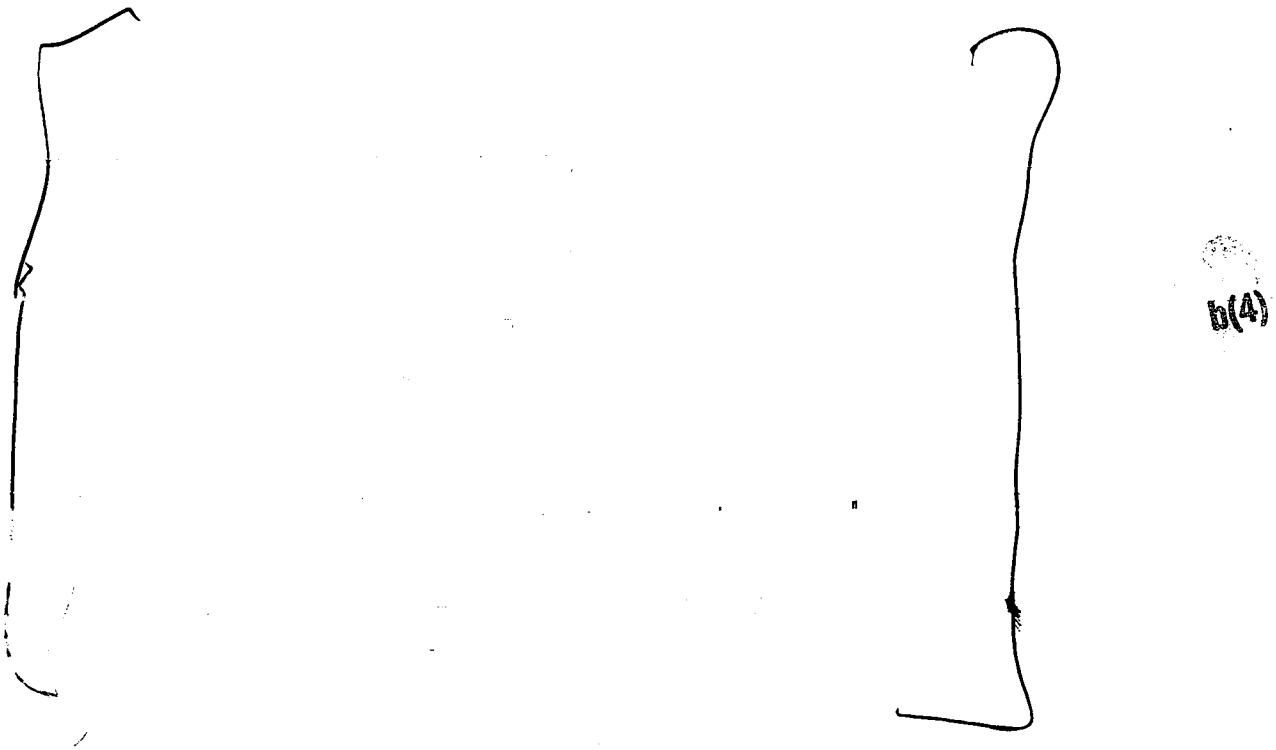
Table 58: Number of subjects with change in IBDQ ≥ 32 at Week 8 (ACT 1 and ACT 2 combined[a, b, c])

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	244	242	242	484
Subjects evaluated	242	241	242	483
Subjects with change in IBDQ ≥ 32	79 (33)	137 (57)	127 (53)	264 (55)
p-value		< 0.001	< 0.001	< 0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.
[c] Analysis is stratified by study.

It is important to note, however, that no analytical method was prespecified by the Sponsor and the IBDQ was not a major secondary endpoint, but was rather one endpoint in a list of "other efficacy endpoints". Because there are issues of multiplicity with the post hoc nature of these analyses, FDA cannot judge these data as being substantial evidence of efficacy.

B. SF-36 Scores



Histological Assessment (substudy of ACT 1 only)

A total of 104 out of 364 (29%) subjects in ACT 1, only, were enrolled in a substudy of histological inflammation, where assessment was based on the following classification system according to Geboes et al, Gut 2000; 47:404-409: Grade 0 - structural change only; Grade 1 - chronic inflammatory infiltrate; Grade 2A - lamina propria eosinophils; Grade 2B - lamina propria neutrophils; Grade 3- neutrophils in the epithelium; Grade 4- crypt destruction; Grade 5- erosions and ulcers. An increasing Grade indicated worsening level of disease activity and the worst histological features per biopsy specimen were recorded by a single, blinded pathologist (K. Geboes). Subjects had their severity of histology assessed at baseline, at Week 8, and at Week 30. Colonic biopsies were collected in a standard fashion at 15 to 20 cm from the anal verge during endoscopy of this particular group of subjects who consented to participate in the substudy. At baseline, the distribution of histological inflammation was comparable across treatment groups (**Table 61**). By Week 8, and onto Week 30, histological inflammation scores of Grade 3 and higher decreased in the combined infliximab treatment group, with subjects in the placebo group having smaller decreases and some increases in scores of Grade 5 inflammation by Week 30.

Table 61: Summary of histological assessment of inflammation based on maximum grade through week 30 (randomized subjects in histological substudy) [a,b]

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Randomized subjects in the Histological substudy[c]	34	35	35	70
Subjects evaluated	33	33	35	68
Baseline				
Grade 0	5 (15)	4 (12)	3 (9)	7 (10)
Grade 1	2 (6)	0	2 (6)	2 (3)
Grade 2A	3 (9)	2 (6)	5 (14)	7 (10)
Grade 2B	2 (6)	0	0	0
Grade 3	7 (21)	8 (24)	8 (23)	16 (24)
Grade 4	4 (12)	6 (18)	7 (20)	13 (19)
Grade 5	10 (30)	13 (39)	10 (29)	23 (34)
Week 8				
Grade 0	8 (24)	12 (36)	12 (34)	24 (35)
Grade 1	5 (15)	1 (3)	5 (14)	6 (9)
Grade 2A	0	6 (18)	2 (6)	8 (12)
Grade 2B	1 (3)	0	0	0
Grade 3	4 (12)	3 (9)	4 (11)	7 (10)
Grade 4	5 (15)	1 (3)	1 (3)	2 (3)
Grade 5	10 (30)	10 (30)	11 (31)	21 (31)
Week 30				
Grade 0	8 (24)	11 (33)	13 (37)	24 (35)
Grade 1	2 (6)	3 (9)	1 (3)	4 (6)
Grade 2A	2 (6)	4 (12)	1 (3)	5 (7)
Grade 2B	2 (6)	0	0	0
Grade 3	5 (15)	4 (12)	6 (17)	10 (5)
Grade 4	3 (9)	4 (12)	3 (9)	7 (10)
Grade 5	11 (33)	7 (21)	11 (31)	18 (27)

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.
[c] Subjects without a baseline result were excluded.

FDA analyzed these findings in greater detail since, clinically, endoscopic findings do not necessarily correlate with symptomatic responses and can sometimes lag behind clinical improvement. Therefore, it is unclear whether a decrease in histological inflammation would directly correlate with clinical response as well. To investigate this, the Agency evaluated the distribution of histological scores at baseline, Week 8, and Week 30 for subjects in clinical response at Week 8 (**Table 62**), subjects in clinical remission at Week 8 (**Table 63**), and subjects not in clinical response at Week 8 (**Table 64**).

Of the 104 subjects who consented to the endoscopy substudy, 53% (55 of 104) were in clinical response at Week 8 (**Table 62**). Of evaluated subjects, at baseline, 73% of the combined infliximab treatment group who had a clinical response at Week 8 had Grade 3 or higher histological scores compared to 44% of subjects in the placebo group. By Week 8, the proportion of the combined infliximab treatment group with Grade 3 or higher histological

scores decreased to 26% and to 40% at Week 30. In the placebo group, the proportion of subjects with Grade 3 or higher histological score at Week 30 remained unchanged, at 44%. Limited conclusions can be made about the data for the placebo arm because the number of clinical responders at Week 8 in that group was small. However, the data do indicate that infliximab-treated subjects with a clinical response had improved histological scores at both Weeks 8 and 30.

Table 62: Summary of histological assessment of inflammation based on maximum grade through week 30; subjects randomized in the histological substudy who were in clinical response at week 8[a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Randomized subjects in the histological substudy who were in clinical response at week 8[c]	10	26	19	45
Subjects evaluated[D]	9	24	19	43
Baseline				
Grade 0	3 (33)	3 (13)	3 (16)	6 (14)
Grade 1	0	0	0	0
Grade 2A	1 (11)	2 (8)	4 (21)	6 (14)
Grade 2B	1 (11)	0	0	0
Grade 3	1 (11)	6 (25)	2 (11)	8 (19)
Grade 4	2 (22)	5 (21)	7 (37)	12 (28)
Grade 5	1 (11)	8 (33)	3 (16)	11 (26)
Week 8				
Grade 0	4 (44)	10 (42)	10 (53)	20 (47)
Grade 1	3 (33)	0	4 (21)	4 (9)
Grade 2A	0	6 (25)	2 (11)	8 (19)
Grade 2B	0	0	0	0
Grade 3	0	1 (4)	1 (5)	2 (5)
Grade 4	2 (22)	1 (4)	1 (5)	2 (5)
Grade 5	0	6 (25)	1 (5)	7 (16)
Week 30				
Grade 0	4 (44)	10 (42)	11 (58)	21 (49)
Grade 1	0	2 (8)	0	2 (5)
Grade 2A	0	3 (13)	0	3 (7)
Grade 2B	1 (11)	0	0	0
Grade 3	1 (11)	3 (13)	2 (11)	5 (12)
Grade 4	1 (11)	3 (13)	3 (16)	6 (14)
Grade 5	2 (22)	3 (13)	3 (16)	6 (14)

[a] For histology assessment, subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.
[c] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data were considered to not be in clinical response.
[d] Subjects without a baseline result were excluded.

Histologic scores for subjects who were in clinical remission at Week 8 are shown in **Table 63**. At baseline, the combined infliximab group had 64% of subjects with a Grade 3 or higher

histological score. At Week 8, the percentage with Grade 3 or higher scores decreased to 0% and at Week 30, to 18%. Again, limited conclusions can be made about the placebo group because a small number of subjects in the placebo group had a remission at Week 8.

Table 63: Summary of histological assessment of inflammation based on maximum grade through week 30; subjects randomized in the histological substudy who were in clinical remission at week 8[a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Randomized subjects in the histological substudy who were in clinical remission at week 8	5	12	10	22
Subjects evaluated [c]	4	11	10	21
Baseline				
Grade 0	2 (50)	1 (9)	3 (30)	4 (19)
Grade 1	0	0	0	0
Grade 2A	1 (25)	2 (18)	1 (10)	3 (14)
Grade 2B	0	0	0	0
Grade 3	1 (25)	2 (18)	1 (10)	3 (14)
Grade 4	0	2 (18)	4 (40)	6 (29)
Grade 5	0	4 (36)	1 (10)	5 (24)
Week 8				
Grade 0	3 (75)	7 (64)	6 (60)	13 (62)
Grade 1	1 (25)	0	2 (20)	2 (10)
Grade 2A	0	4 (36)	2 (20)	6 (29)
Grade 2B	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Week 30				
Grade 0	3 (75)	7 (64)	7 (70)	14 (67)
Grade 1	0	0	0	0
Grade 2A	0	2 (18)	0	2 (10)
Grade 2B	0	0	0	0
Grade 3	0	1 (9)	0	1 (5)
Grade 4	0	1 (9)	2 (20)	3 (14)
Grade 5	1 (25)	0	1 (10)	1 (5)

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.
[c] Subjects without a baseline result were excluded.

49 of 104 (47%) subjects enrolled in the endoscopy substudy did not have a clinical response at Week 8 (**Table 64**). At baseline, 84% of the combined infliximab group in this subgroup had histological scores of Grade 3 or higher. By Week 8, this figure was 76%, and by Week 30, 72%. Placebo subjects who did not have a clinical response at Week 8 had 71% of subjects with Grade 3 or higher histological scores at baseline, 71% at Week 8, and 63% at Week 30.

Table 64: Summary of histological assessment of inflammation based on maximum grade through week 30; subjects randomized in the histological substudy who were not in clinical response at week 8[a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Randomized subjects in the histological substudy who were not in clinical response at week 8[c]	24	9	16	25
Subjects evaluated[d]	24	9	16	25
Baseline				
Grade 0	2 (8)	1 (11)	0	1 (4)
Grade 1	2 (8)	0	2 (13)	2 (8)
Grade 2A	2 (8)	0	1 (6)	1 (4)
Grade 2B	1 (4)	0	0	0
Grade 3	6 (25)	2 (22)	6 (38)	8 (32)
Grade 4	2 (8)	1 (11)	0	1 (4)
Grade 5	9 (38)	5 (56)	7 (44)	12 (48)
Week 8				
Grade 0	4 (17)	2 (22)	2 (13)	4 (16)
Grade 1	2 (8)	1 (11)	1 (6)	2 (8)
Grade 2A	0	0	0	0
Grade 2B	1 (4)	0	0	0
Grade 3	4 (17)	2 (22)	3 (19)	5 (20)
Grade 4	3 (13)	0	0	0
Grade 5	10 (42)	4 (44)	10 (63)	14 (56)
Week 30				
Grade 0	4 (17)	1 (11)	2 (13)	3 (12)
Grade 1	2 (8)	1 (11)	1 (6)	2 (8)
Grade 2A	2 (8)	1 (11)	1 (6)	2 (8)
Grade 2B	1 (4)	0	0	0
Grade 3	4 (17)	1 (11)	4 (25)	5 (20)
Grade 4	2 (8)	1 (11)	0	1 (4)
Grade 5	9 (38)	4 (44)	8 (50)	12 (48)

[a] For histology assessment, subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.
[c] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data were considered to not be in clinical response.
[d] Subjects without a baseline result were excluded.

The endoscopy substudy was conducted in less than a third of subjects enrolled into the ACT 1 study so limited conclusions can be made concerning histological inflammation scores correlating directly with clinical improvement. In clinical practice, an improvement in histological findings often does not correlate directly with an improvement in clinical symptoms and can be delayed in its time course. But in general, more histological improvement was seen with infliximab-treated subjects from baseline to Week 30, whereas the distribution of Grade 3 or higher histological inflammation scores remained comparable at baseline and at Week 30 for placebo subjects. Among infliximab-treated subjects, histologic improvement correlated with clinical improvement as histologic improvement was observed in clinical responders and those in remission but not in those without a clinical response.

Health Economics

The number of hospitalizations and surgeries for all subjects in ACT 1 (**Table 65**) and ACT 2 (**Table 66**) are summarized through Week 30. In ACT 1, there were no differences between the combined infliximab treatment and placebo groups pertaining to the mean number of intensive care unit (ICU)-related hospitalizations, UC-related surgeries or procedures, and number of days on total parenteral nutrition (TPN). It is not possible to draw conclusions about the effect of infliximab on the rates of these events because so few events occurred in the control arm.

ACT 1

Table 65: Summary of hospitalizations and surgeries through Week 30

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Average weeks of follow-up	22.4	26.9	26.6	26.7
Number of ICU-related hospitalizations				
Mean ± SD	0.12 ± 0.37	0.08 ± 0.28	0.10 ± 0.30	0.09 ± 0.29
Median	0	0	0	0
p-value		0.522	0.813	0.613
Number of ICU days				
Mean ± SD	0 ± 0	0.02 ± 0.27	0 ± 0	0.01 ± 0.19
Median	0	0	0	0
p-value		0.221	1.000	0.479
Number of UC-related surgeries/procedures				
Mean ± SD	0.07 ± 0.43	0.12 ± 0.52	0.07 ± 0.37	0.09 ± 0.45
Median	0	0	0	0
p-value		0.397	0.840	0.545
Number of UC-related inpatient surgeries/procedures				
Mean ± SD	0.06 ± 0.35	0.11 ± 0.51	0.07 ± 0.36	0.09 ± 0.44
Median	0	0	0	0
p-value		0.333	0.790	0.476
Number of UC-related outpatient surgeries/procedures				
Mean ± SD	0.02 ± 0.13	0.01 ± 0.09	0.01 ± 0.09	0.01 ± 0.09
Median	0	0	0	0
p-value		0.539	0.535	0.476
Number of days of TPN				
Mean ± SD	0.08 ± 0.91	0.15 ± 1.26	0.07 ± 0.72	0.11 ± 1.03
Median	0	0	0	0
p-value		0.537	0.968	0.738

In ACT 2, the combined infliximab group had fewer mean ICU-related hospitalizations compared to the placebo group (p = 0.024). Otherwise, no differences between the infliximab group and placebo group were seen regarding the number of ICU days, number of UC-related surgeries or procedures, and number of days on TPN. It is difficult to make conclusions about the effects of infliximab on these events because of the low event rates in the placebo arm and because of different results for the different outcome measures.

ACT 2

Table 66: Summary of hospitalizations and surgeries through Week 30

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomized	123	121	120	241
Average weeks of follow-up	21.9	27.5	26.6	27.1
Number of ICU-related hospitalizations				
Mean ± SD	0.15 ± 0.43	0.07 ± 0.29	0.08 ± 0.32	0.07 ± 0.31
Median	0	0	0	0
p-value		0.057	0.044	0.024
Number of ICU days				
Mean ± SD	0 ± 0	0.03 ± 0.36	0.01± 0.09	0.02 ± 0.27
Median	0	0	0	0
p-value		0.365	0.403	0.314
Number of UC-related surgeries/procedures				
Mean ± SD	0.02 ± 0.44	0.06 ± 0.39	0.04 ± 0.27	0.05 ± 0.34
Median	0	0	0	0
p-value		0.352	0.221	0.213
Number of UC-related inpatient surgeries/procedures				
Mean ± SD	0.06 ± 0.39	0.06 ± 0.39	0.03 ± 0.22	0.05 ± 0.32
Median	0	0	0	0
p-value		0.981	0.720	0.846
Number of UC-related outpatient surgeries/procedures				
Mean ± SD	0.03 ± 0.22	0 ± 0	0.01 ± 0.09	0 ± 0.06
Median	0	0	0	0
p-value		0.066	0.215	0.075
Number of days of TPN				
Mean ± SD	0.02 ± 0.18	0.31 ± 3.45	0.05 ± 0.55	0.18 ± 2.48
Median	0	0	0	0
p-value		0.909	0.955	0.922

Number of Hospitalizations

The total number of hospitalizations for both ACT 1 and ACT 2 are presented in **Table 67**. Some subjects had more than one event, but each hospitalization event is counted. The majority of hospitalizations involved subjects having exacerbations of ulcerative colitis and/or surgeries related to UC.

Table 67: Number of Hospitalizations: ACT 1 and ACT 2

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg
ACT 1	18	10	13
ACT 2	26	9	10

The hospitalization data represent pooled data from both ACT 1 and ACT 2 through Week 30. The mean number of hospitalizations for the combined infliximab treatment group was 9 hospitalizations per 100 subjects compared with 18 hospitalizations per 100 subjects in the placebo group ($p = 0.005$, unadjusted for multiple comparisons). As with the IBDQ data, the number of hospitalizations was examined in a post-hoc meta analysis, had no prespecified analytic method, and was not a major secondary endpoint. Thus, the number of hospitalizations should not be a substantiated claim.

Topline Results for Week 54 Data (ACT 1 only)

At the time of this review, initial "topline" efficacy and safety results through Week 54 (for ACT 1 only) were submitted by the sponsor and are presented in **Table 68** through **Table 73**. The Agency has not confirmed these results since Centocor has not yet submitted the data. The number of subjects in clinical response through Week 54 in ACT 1 is shown in **Table 68**. Using the intent-to-treat population and nonresponder imputation, 45% of the combined infliximab treatment group vs. 20% of the placebo subjects were in clinical response ($p < 0.001$), with no difference between the 5 mg/kg and 10 mg/kg infliximab groups.

Table 68: Number of subjects in clinical response through Week 54[a,b,c]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Week 8				
Subjects in clinical response	45 (37)	84 (69)	75 (62)	159 (65)
p-value		<0.001	<0.001	<0.001
Week 30				
Subjects in clinical response	36 (30)	63 (52)	62 (51)	125 (51)
p-value		<0.001	0.002	<0.001
Week 54				
Subjects in clinical response	24 (20)	55 (46)	54 (44)	109 (45)
p-value		<0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy were considered to not be in clinical response from the time of the event onward.
[b] Subjects who had in sufficient data at a timepoint were considered to not be in clinical response from the time of the event onward.
[c] Analysis is stratified by corticosteroid-refractory status and center location.

38% of the combined infliximab treatment group were in sustained response (**Table 69**, defined as being in response for the Week 8, 30, and 54 combined), compared with 14% of the placebo group ($p < 0.001$).

Table 69: Number of subjects in sustained response through Week 54 [a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Subjects in sustained response at both week 8 and week 30	28 (23)	59 (49)	56 (46)	115 (47)
p-value		<0.001	<0.001	<0.001
Subjects in sustained response at week 8, week 30, and week 54	17 (14)	47 (39)	45 (37)	92 (38)
p-value		<0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data were considered to not be in sustained response.
[b] Analysis is stratified by corticosteroid-refractory status and center location.

Those subjects who were in clinical remission at Week 54 are shown in **Table 70**. 35% of the combined infliximab group achieved a clinical remission at Week 54 compared to 17% in the placebo group ($p < 0.001$). Again, no differences were seen between the 5 mg/kg and 10 mg/kg infliximab groups.

Table 70: Number of subjects in clinical remission through Week 54[a,b,c]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Week 8				
Subjects in clinical remission	18 (15)	47 (39)	39 (32)	86 (35)
p-value		<0.001	0.002	<0.001
Week 30				
Subjects in clinical remission	19 (16)	41 (34)	45 (37)	86 (35)
p-value		0.001	<0.001	<0.001
Week 54				
Subjects in clinical remission	20 (17)	42 (35)	42 (34)	84 (35)
p-value		0.001	0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy were considered to not be in clinical remission from the time of the event onward.
[b] Subjects who had insufficient data at a timepoint were considered to not be in clinical remission at that timepoint.
[c] Analysis is stratified by corticosteroid-refractory status and center location.

The numbers of subjects able to achieve sustained remission (remission at Weeks 8, 30, and 54 combined) are seen in **Table 71**. 20% of the combined infliximab group achieved sustained remission through Week 54 vs. 7% for the placebo group ($p < 0.001$).

Table 71: Number of subjects in sustained remission through Week 54[a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Subjects in sustained remission at both week 8 and week 30	10 (8)	28 (23)	32 (26)	60 (25)
p-value		0.001	<0.001	<0.001
Subjects in sustained remission at week 8, week 30, and week 54	8 (7)	24 (20)	25 (21)	49 (20)
p-value		0.002	0.002	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data were considered to not be in sustained remission.
[c] Analysis is stratified by corticosteroid-refractory status and center location.

Mucosal Healing

Through Week 54, the number of subjects with a value of 0 or 1 for the endoscopy subscore was 46% for the combined infliximab group and 18% for the placebo group (**Table 72**). The infliximab 5 mg/kg group and 10 mg/kg groups appeared equally beneficial.

Table 72: Number of subjects with mucosal healing through Week 54[a,b,c]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	121	121	122	243
Week 8				
Subjects with mucosal healing	41 (34)	75 (62)	72 (59)	147 (61)
p-value		<0.001	<0.001	<0.001
Week 30				
Subjects with mucosal healing	30 (25)	61 (50)	60 (49)	121 (50)
p-value		<0.001	<0.001	<0.001
Week 54				
Subjects with mucosal healing	22 (18)	55 (46)	57 (47)	112 (46)
p-value		<0.001	<0.001	<0.001

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy were considered to not have mucosal healing from the time of the event onward.
[b] Subjects who had in sufficient data at a timepoint were considered to not be in clinical response from the time of the event onward.
[c] Analysis is stratified by corticosteroid-refractory status and center location.

The median Mayo scores through Week 54 for all treatment arms are shown in **Table 73.** The median Mayo score for the combined infliximab group remained at 5.0 at Week 54 from Week 30, whereas the median score in the placebo group increased from 7.0 at Week 30 to 8.0 at Week 54.

Table 73: Summary of the Mayo score through week 54[a,b]

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Randomized subjects	121	121	122	243
Baseline				
Median	8.0	9.0	8.5	9.0
Week 8				
Median	6.0	3.0	4.0	4.0
Week 30				
Median	7.0	4.0	5.0	5.0
Week 54				
Median	8.0	5.0	6.0	5.0

[a] Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward.
[b] Subjects with insufficient data had their last value carried forward.

Corticosteroids

Of those subjects on corticosteroids at baseline who received infliximab, the median daily corticosteroid dose decreased from 20 mg/day to 7.5 mg/day at Week 30 and 8.5 mg/day at Week 54 (**Table 74**). For placebo subjects, the median daily corticosteroid dose decreased from 20 mg/day at baseline to 10 mg/day at Week 30, but increased back to 20 mg/day at Week 54.

Table 74: Median daily corticosteroid dose for ACT 1 subjects through Week 54, mg/day

	Placebo Group	Combined Infliximab Group
Baseline	20	20
Week 30	10	7.5
Week 54	20	8.5

The proportion of subjects on corticosteroids at baseline who achieved a remission and were off corticosteroids at Week 30 and Week 54 are shown in **Table 75**. 22% of the combined infliximab group achieved clinical remission on no corticosteroids at Week 30 compared to 10% of the placebo group. At Week 54, the proportions were 21% of the combined infliximab group vs. 9% of the placebo group.

Table 75: Proportion of subjects in clinical remission and on no corticosteroids through Week 54, ACT 1 only

	Placebo Group	Combined Infliximab Group	p-value
Week 30	10%	22%	0.039
Week 54	9%	21%	0.022

Health-related Quality of Life Measures

Median total IBDQ scores at baseline were 123 and 127 for the placebo group and combined infliximab treatment group, respectively. By Weeks 8 and 30, median improvements in total IBDQ scores were greater than that seen in the placebo group ($p < 0.001$ at both Weeks 8 and 30). By Week 54, the infliximab 5 mg/kg group had a median improvement of 26 points and the infliximab 10 mg/kg group had an improvement of 19 points, while no change was seen in the placebo group ($p < 0.001$ for all comparisons).

For the SF-36 scores, both the physical and mental components of the SF-36 were improved at both Weeks 30 and 54 (unadjusted $p < 0.05$ for all comparisons).

6.1.6 Efficacy Conclusions

The primary objective of both the ACT 1 and ACT 2 studies was to evaluate the efficacy and safety of infliximab in subjects with moderately to severely active ulcerative colitis who were refractory to conventional therapy. To this end, the primary endpoint in both studies was prespecified to be the proportion of subjects who achieved a clinical response at Week 8. Using

the intent-to-treat population and the nonresponder imputation technique, 65% (ACT 1) and 69% (ACT 2) of the combined infliximab groups met the primary endpoint compared to 37% and 29% for the placebo groups, respectively. Comparisons of individual infliximab groups and the combined infliximab group to placebo were statistically significant. Results for the major secondary endpoint, clinical response at Week 30, demonstrated the durability of response at Week 30. The clinical benefit of infliximab was also determined by more stringent endpoints which included the proportion of subjects in clinical remission at Week 8 and at Week 30. In addition, the number of infliximab-treated subjects who achieved a sustained response (clinical response at both Week 8 and Week 30) and sustained remission (clinical remission at both Week 8 and Week 30) were also shown to be superior to placebo in both trials.

Sensitivity analyses conducted by both the Sponsor and FDA were consistent with the primary analysis and support the overall benefit of infliximab in this patient population. Subset analyses revealed a clinical benefit from infliximab in all subgroups studied. Other clinically important UC endpoints included the proportion of subjects who achieved mucosal healing at Week 8 and Week 30, and the proportion of subjects who achieved remission without the use of corticosteroids at Week 30. Higher proportions of infliximab-treated subjects achieved these endpoints compared to placebo-treated subjects in both ACT 1 and ACT 2. For both studies, no notable efficacy differences were seen between the infliximab 5 mg/kg and 10 mg/kg groups.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Three deaths occurred in subjects who participated in ACT 1 and ACT 2. These deaths all occurred after the Week 30 visits in both trials. One subject in ACT 1 (randomized to placebo) committed suicide 2 months after completing the main part of the ACT 1 trial. This death occurred 4 months after the last study infusion. The second death occurred in ACT 2 in a subject who received infliximab 5 mg/kg. This subject developed pulmonary histoplasmosis one week after the third infusion in the ACT 2 study extension and later died due to acute respiratory distress syndrome and renal failure. The third death associated with the ACT trials occurred in ACT 2 in a subject given placebo who died 7 months after completing ACT 2 due to a cerebrovascular accident who had been receiving commercially available infliximab for the treatment of concurrent rheumatoid arthritis.

Although of concern, these three deaths out of 728 randomized subjects do not suggest a major new safety signal for infliximab given the number of patients involved and the causes of death involved. The suicide occurred after completion of the study and this subject received placebo. Histoplasmosis and other opportunistic infections including fatal cases have been seen

previously and this risk is described in the REMICADE® package insert. Cardiovascular events are common in the older rheumatoid arthritis population.

7.1.2 Other Serious Adverse Events

Malignancies

A total of three malignancies were diagnosed during the ACT 1 and ACT 2 trials. One ACT 1 subject randomized to infliximab 5 mg/kg was diagnosed with prostate adenocarcinoma after the Week 8 visit and underwent radical prostatectomy. He had had an elevated PSA test prior to enrollment in ACT 1. In ACT 2, one subject randomized to placebo was diagnosed with a basal cell carcinoma. Another ACT 2 subject randomized to infliximab 5 mg/kg was diagnosed with rectal adenocarcinoma after the Week 14 infusion and underwent proctocolectomy, gamma radiation, and chemotherapy. This subject had a 15 year-long history of ulcerative colitis. Thus, excluding non-melanoma skin cancer, there were two malignancies in the UC trials, both in the infliximab arms.

Malignancies from all REMICADE® trials

The numbers of malignancies in the ulcerative colitis trials are too few to reach conclusions. To further explore whether there might be a relationship between infliximab use and malignancies, we examined the rate of malignancies across all the indications explored in clinical trials with infliximab. Previously, a higher number of malignancies has been observed in the infliximab arm of individual randomized trials but not in others. However, the rate of malignancies in the entire clinical trial database of infliximab was found to be comparable to the expected rate in the general population, based on the SEER database (March 4, 2003 Arthritis Advisory Committee meeting, http://www.fda.gov/ohrms/dockets/ac/cder03.html#Arthritis). We therefore examined an updated analysis of pooled data from all the controlled trials (**Table 76**). In controlled portions of infliximab trials in subjects with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and UC, 22 malignancies (excluding lymphomas) were diagnosed in 4292 infliximab-treated subjects vs. 1 malignancy among 1265 control patients. The median duration of follow-up was 0.5 years for infliximab-treated subjects vs. 0.4 years for placebo-treated subjects. Of these malignancies, the most common were breast, colorectal, and melanoma. The rate of malignancy was approximately 5-fold higher for infliximab as for placebo (0.69 cases per 100 pt-years vs. 0.13 cases per 100 pt-years for placebo). The rate of malignancies among infliximab-treated subjects was similar to the rate expected in the general population based on the SEER 2002 database, whereas the rate in control subjects was lower than expected.

In the controlled and open-label portions of these clinical trials of infliximab, 4 subjects (2 among RA subjects and 2 among Crohn's disease subjects) developed lymphomas among 4292 subjects given infliximab (median duration of follow up 1.0 years). Among 1265 placebo-treated subjects, no lymphomas were diagnosed (median duration of follow up 0.5 years).

Table 76: Number of subjects with 1 or more malignancies during study compared with the expected number of malignancies from the general US population according to the SEER database[a,b]

	UC Studies		RA Studies		All Studies	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Subjects treated	248	492	788	2363	1265	4292
Type of Malignancy						
Lymphoma						
Total subject-years of follow-up	105	252	584	2428	776	3787
Median subj.-yrs of follow-up	0.6	0.6	0.4	1.0	0.5	1.0
Observed number of subjects	0	0	0	2	0	4
Expected number of subjects[c]	0.02	0.05	0.14	0.62	0.18	0.84
SIR[d]	0.00	0.00	0.00	3.21	0.00	4.76
SIR 95% confidence interval[e]	(0,155.54)	(0,61.49)	(0,20.70)	(0,11.60)	(0,16.65)	(1.30,12.18)
Other Malignancies						
Total subj.-yrs of follow-up	105	251	583	2426	775	3783
Median subj.-yrs of follow-up	0.6	0.6	0.4	1.0	0.5	1.0
Observed number of subjects	0	2	1	16	1	22
Expected number of subjects[c]	0.42	1.07	4.20	18.04	4.92	22.57
SIR[d]	0.00	1.87	0.24	0.89	0.20	0.97
SIR 95% confidence interval[e]	(0,7.14)	(0.23,6.74)	(0.01,1.33)	(0.51,1.44)	(0.01,1.13)	(0.61,1.48)
All Malignancies						
Total subj.-yrs of follow-up	105	251	583	2425	775	3782
Median subj.-yrs of follow-up	0.6	0.6	0.4	1.0	0.5	1.0
Observed number of subjects	0	2	1	18	1	26
Expected number of subjects[c]	0.44	1.12	4.34	18.64	5.10	23.38
SIR[d]	0.00	1.79	0.23	0.97	0.20	1.11
SIR 95% confidence interval[e]	(0,6.82)	(0.22,6.45)	(0.01,1.28)	(0.57,1.53)	(0,1.09)	(0.73,1.63)

[a] Includes subjects with malignancies (excluding nonmelanoma skin cancers, which are not included in the SEER database) during study.
[b] UC Studies includes C0168T12, C0168T37, and C0168T46. RA Studies includes C0168T07, C0168T09, C0168T14, C0168T15/17, C0168T18, C0168T22, C0168T29, and C0168T41. All Studies includes C0168T08, C0168T11, C0168T16, C0168T20, C0168T21, C0168T26, C0168T50, and C0168T51 in addition to UC and RA studies.
[c] The expected number of subjects with malignancies is based on the SEER Database (2002), adjusted for age, gender, and race.
[d] SIR = Standardized Incidence Ratio (observed number of subjects with malignancy divided by expected number of subjects with malignancy)
[e] Confidence intervals based on an exact method.

Serious Adverse Events

The numbers of subjects with serious adverse events (SAEs) for both ACT 1 and ACT 2, combined, are presented in **Table 77**. The combined infliximab treatment groups from ACT 1 and ACT 2 had 13% of subjects who had 1 or more SAEs compared to 20% in the placebo groups from both studies. By system-organ class, the greatest number of SAEs occurred in the GI systems disorders class, due to worsening of colitis. The system-organ class of those SAEs that occurred in greater numbers in the combined infliximab group vs. placebo were: respiratory system (3 pneumonias in infliximab groups vs. 1 URI in placebo group); body as a whole-general (2 chest pain, fatigue, pain each, 1 abdominal hernia, enlarged abdomen each, in infliximab groups vs. 1 chest pain in placebo); central nervous and peripheral nervous systems (1 carpal tunnel syndrome, 1 headache, and 1 optic neuritis in infliximab groups vs. 0 in placebo group); resistance mechanism (4 fever in infliximab vs. 1 placebo; 3 abscesses in infliximab vs. 1 in placebo; 1 TB, 1 unspecified infection and 1 serum sickness in infliximab groups vs. 1

bacterial infection in placebo group); cardiovascular disorders (1 arteriosclerosis and 1 hypertension in infliximab groups vs. 0 in placebo group); and neoplasms (1 prostate adenocarcinoma and 1 rectal adenocarcinoma in infliximab groups vs. 0 in placebo group). Except for SAEs associated with the system-organ classes of GI system disorders, body as a whole-general, and resistance mechanism, all SAEs in other system-organ classes were reported in < 1% of subjects treated with infliximab. The profile of SAEs seen in the ACT 1 and ACT 2 trials is consistent with the known safety profile of infliximab.

Table 77: Number of subjects with 1 or more SAEs through week 30 by WHOART system organ class (ACT 1 and ACT 2 studies combined).

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects treated	244	242	242	484
Avg. wks of follow up	22.2	27.2	26.6	26.9
Avg. weeks of treatment	16.1	21.9	21.0	21.5
Subjects with 1 or more SAEs	48 (20)	30 (12)	34 (14)	64 (13)
WHOART system-organ class				
GI system disorders	33 (14)	23 (10)	20 (8)	43 (9)
Respiratory system[a]	1 (<1)	1 (<1)	3 (1)	4 (<1)
Body as a whole-general[b]	1 (<1)	5 (2)	6 (3)	11 (2)
CNS & PNS disorders[c]	0	1 (<1)	2 (<1)	3 (<1)
Skin & Appendages	1 (<1)	0	0	0
Resistance mechanism[d]	3 (1)	2 (<1)	7 (3)	9 (2)
Musculoskeletal	1 (<1)	1 (<1)	2 (<1)	3 (<1)
Psychiatric disorders	2 (<1)	0	0	0
Vascular (extracardiac)	4 (2)	1 (<1)	1 (<1)	2 (<1)
Cardiovascular disorders[e]	0	1 (<1)	1 (<1)	2 (<1)
Red blood cell disorders	4 (2)	2 (<1)	2 (<1)	4 (<1)
Neoplasms[f]	0	2 (<1)	0	2 (<1)
Ear and hearing disorders	0	1 (<1)	0	1 (<1)
Liver and biliary system	0	0	1 (<1)	1 (<1)
Metabolic & Nutritional	0	0	1 (<1)	1 (<1)
Myo-,endo-,pericardial, coronary and valve disorders	1 (<1)	0	1 (<1)	1 (<1)
Reproductive disorders	1 (<1)	0	1 (<1)	1 (<1)
White cell disorders	0	1 (<1)	0	1 (<1)
Blood disorders	1 (<1)	0	0	0
Urinary system disorders	2 (<1)	0	0	0

[a] 3 pneumonias in infliximab groups vs. 1 URI in placebo
[b] 2 chest pain, fatigue, pain (general) each, 1 abd hernia, enlarged abd each, in infliximab groups vs. 1 chest pain in placebo
[c] 1 carpal tunnel synd, 1 headache (infliximab 10mg/kg) and 1 optic neuritis (infliximab 5mg/kg) vs. 0 in placebo
[d] 4 fever in infliximab vs. 1 placebo; 3 abscess (infliximab 10mg/kg) vs. 1 placebo; 1 TB, 1 unspec. infection and 1 serum sickness (infliximab 10mg/kg) vs. 1 bacterial infection
[e] 1 arteriosclerosis and 1 hypertension in infliximab groups vs. 0 placebo
[f] 1 prostate adenoCA and 1 rectal adenoCA in infliximab groups

Serious Infectious Adverse Events

Serious infectious adverse events that occurred in ACT 1 and ACT 2 are listed in **Table 78** and **Table 79**, respectively. In ACT 1, 3% of subjects in the combined infliximab group vs. 2% of placebo subjects had one or more serious infections through Week 30. The only serious infectious adverse event occurring more than once was pneumonia, which occurred in two subjects who received infliximab 10 mg/kg. One case of tuberculosis was diagnosed in a subject who received infliximab 10 mg/kg.

ACT 1

Table 78: Number of subjects with 1 or more serious infections through week 30 by WHOART preferred term

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects treated	121	121	122	243
Avg. wks of follow up	22.4	26.9	26.6	26.7
Avg. weeks of treatment	17.8	24.5	23.4	24.0
Subjects with 1 or more serious infections	2 (2)	1 (<1)	5 (4)	6 (3)
WHOART preferred term				
Pneumonia	0	0	2 (2)	2 (<1)
Abscess	0	0	1 (<1)	1 (<1)
Fever	0	0	1 (<1)	1 (<1)
Gastroenteritis	0	0	1 (<1)	1 (<1)
Infection (TB)	0	0	1 (<1)	1 (<1)
Pancreatitis	0	1 (<1)	0	1 (<1)
Pharyngitis	0	0	1 (<1)	1 (<1)
Infection (bacterial)	1 (<1)	0	0	0
URI infection	1 (<1)	0	0	0

In ACT 2 (**Table 79**), 2% of subjects in the combined infliximab group had one or more serious infectious AEs compared to < 1% in the placebo group. No serious infectious AE occurred more than once in ACT 2 through Week 30. In summary, the infectious AEs observed in these two clinical trials are similar to those that have been observed previously among patients receiving infliximab.

ACT 2

Table 79: Number of subjects with 1 or more serious infections through week 30 by WHOART preferred term

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects treated	123	121	120	241
Avg. wks of follow up	21.9	27.5	26.6	27.1
Avg. weeks of treatment	14.4	19.3	18.6	18.9
Subjects with 1 or more serious infections	1 (<1)	2 (2)	3 (3)	5 (2)
WHOART preferred term				
Abscess	1 (<1)	0	1 (<1)	1 (<1)
Earache	0	1 (<1)	0	1 (<1)
Fever	0	1 (<1)	0	1 (<1)
Gastroenteritis	0	1 (<1)	0	1 (<1)
Infection	0	0	1 (<1)	1 (<1)
Vaginitis	0	0	1 (<1)	1 (<1)

Tuberculosis and Opportunistic Infections

In ACT 1, one subject given infliximab 10 mg/kg developed tuberculosis despite being PPD negative and having a normal chest x-ray during screening. One subject developed pulmonary histoplasmosis in ACT 2 during an extension period after a 3-dose re-induction with infliximab 5 mg/kg 22 weeks after the Week 30 visit. Herpes zoster infection was diagnosed in a total of 8 subjects in ACT 1 and ACT 2 combined. There were three subjects in ACT 1 (two subjects given infliximab 5 mg/kg and one subject given infliximab 10 mg/kg) and five subjects in ACT 2 diagnosed with Herpes zoster (three subjects in the infliximab 5 mg/kg group, two in the infliximab 10 mg/kg group, and one in the placebo group). These infectious AEs are similar to those seen in other infliximab clinical trials.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The number of subjects who discontinued study infusions in ACT 1 through Week 30 is shown in **Table 80**. 38% of subjects discontinued study infusions, with the majority of these doing so due to lack of efficacy. Adverse events resulted in 7% of all subjects discontinuing study infusions in ACT 1. Of these subjects, most discontinued due to worsening of their underlying ulcerative colitis (**Table 81**). The other AE's occurred in less than 1% of subjects.

ACT 1

Table 80: Number of subjects who permanently discontinued study infusions through week 30 by reason for discontinuation

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Total
Subjects randomized N, (%)	121	121	122	364
Subjects who discontinued study infusions	66 (55)	34 (28)	38 (31)	138 (38)
Reason for discontinuation				
Required by protocol due to total colectomy	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Adverse event	9 (7)	7 (6)	9 (7)	25 (7)
Lack of efficacy	50 (41)	25 (21)	24 (20)	99 (27)
Other	6 (5)	1 (<1)	4 (3)	11 (3)

Table 81: Number of subjects who permanently discontinued study infusions because of 1 or more adverse events through Week 30 by WHOART preferred term

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects treated	121	121	122	243
Avg. weeks follow-up	22.4	26.9	26.6	26.7
Avg. weeks of treatment	17.8	24.5	23.4	24.0
Subjects who permanently discontinued study infusions because of an adverse event	9 (7)	7 (6)	9 (7)	16 (7)
WHOART preferred term				
Colitis ulcerative	6 (5)	4 (3)	3 (3)	7 (3)
Adenocarcinoma nos	0	1 (<1)	0	1 (<1)
Allergic reaction	0	1 (<1)	0	1 (<1)
Anemia	0	0	1 (<1)	1 (<1)
Arthralgia	0	0	1 (<1)	1 (<1)
Brain neoplasm benign	0	0	1 (<1)	1 (<1)
Colitis	0	0	1 (<1)	1 (<1)
Diarrhea	1 (<1)	0	1 (<1)	1 (<1)
Eosinophilia	0	1 (<1)	0	1 (<1)
Infection tbc	0	0	1 (<1)	1 (<1)
Osteoarthritis	0	0	1 (<1)	1 (<1)
Serum Sickness	1 (<1)	1 (<1)	0	1 (<1)
Syncope	0	0	1 (<1)	1 (<1)
Chest pain	1 (<1)	0	0	0
Embolism pulmonary	1 (<1)	0	0	0
Upper respiratory tract infection	1 (<1)	0	0	0

In ACT 2, 5% of subjects discontinued infusions due to adverse events, with the majority of these discontinuations due to lack of efficacy (**Table 82**). Again, as in ACT 1, the principle AE resulting in discontinuation of study infusions was exacerbation of ulcerative colitis. Excluding

exacerbation of UC, of all the AE's listed in **Table 83** as a cause for discontinuation, no AE occurred more than once in either infliximab study arm.

ACT 2

Table 82: Number of subjects who permanently discontinued study infusions through week 30 by reason for discontinuation

		Infliximab		
	Placebo	**5 mg/kg**	**10 mg/kg**	**Total**
Subjects randomized N, (%)	123	121	120	364
Subjects who discontinued study infusions	56 (46)	24 (20)	26 (22)	106 (29)
Reason for discontinuation				
Required by protocol due to total colectomy	0	0	0	0
Adverse event	12 (10)	2 (2)	5 (4)	19 (5)
Lack of efficacy	40 (33)	20 (17)	20 (17)	80 (22)
Other	4 (3)	2 (2)	1 (<1)	7 (2)

Table 83: Number of subjects who permanently discontinued study infusions because of 1 or more adverse events through Week 30 by WHOART preferred term

		Infliximab		
	Placebo	**5 mg/kg**	**10 mg/kg**	**Combined**
Subjects treated	123	121	120	241
Avg. weeks follow-up	21.9	27.5	26.6	27.1
Avg. weeks of treatment	14.4	19.3	18.6	18.9
Subjects who permanently discontinued study infusions because of an adverse event	12 (10)	2 (2)	5 (4)	7 (3)
WHOART preferred term				
Colitis ulcerative	9 (7)	1 (<1)	5 (4)	7 (3)
Alopecia	0	0	1 (<1)	1 (<1)
Asthma	0	0	1 (<1)	1 (<1)
Dyspnea	0	0	1 (<1)	1 (<1)
Edema peripheral	0	0	1 (<1)	1 (<1)
Intestinal ulceration	0	1 (<1)	0	1 (<1)
Anemia	2 (2)	0	0	0
Arthralgia	1 (<1)	0	0	0
Colitis	1 (<1)	0	0	0
Hemorrhage rectum	1 (<1)	0	0	0
Hypocalcemia	1 (<1)	0	0	0
Hypoproteinemia	1 (<1)	0	0	0
Pain	1 (<1)	0	0	0

7.1.3.2 Adverse events associated with dropouts

The narratives for subjects who prematurely terminated from the study were reviewed and are summarized in the tables below. The adverse events associated with premature terminations from ACT 1 and ACT 2 are presented in **Table 84** and, **Table 85** respectively. In both studies, the majority of terminations from study were as a result of withdrawal of consent or lack of efficacy. In ACT 1 (**Table 84**), 4 subjects terminated from the study due to an adverse event. Two of these four subjects terminated the study due to the worsening of their underlying UC, which was classified as an AE. One subject was diagnosed with prostate adenocarcinoma and one developed multiple pulmonary emboli. In ACT 2 (**Table 85**), three subjects terminated the study due to adverse events. Two subjects terminated from the study due to worsening of their underlying disease, and one subject terminated due to dyspnea on exertion.

ACT 1

Table 84: Subjects with treatment-emergent adverse events resulting in termination from study

Age	Sex	Adverse Event WHOART Term	Treatment Arm	Week of Occurrence of AE on study
61	Male	Pulmonary embolism	Placebo	Week 0
41	Female	Worsening diarrhea	Placebo	Week 0
18	Female	Exacerbation of UC	Infliximab 5 mg/kg	Week 0
63	Male	Prostate adenocarcinoma	Infliximab 5 mg/kg	Week 6

ACT 2

Table 85: Subjects with treatment-emergent adverse events resulting in termination from study

Age	Sex	Adverse Event WHOART Term	Treatment Arm	Week of Occurrence of AE on study
22	Female	Hypoproteinemia, Hypocalcemia and anemia	Placebo	Week 2
34	Male	Severe diarrhea and Abdominal pain	Placebo	Week 0
26	Male	Dyspnea on exertion	Infliximab 10 mg/kg	Week 14

No pattern was observed in the adverse events leading to termination that differs from what is already known about the safety profile of infliximab.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse event data in the development program

Subjects had adverse events elicited during the screening period in the month preceding the Week 0 study drug dose. After randomization, subjects had AE evaluations at every dosing visit (Weeks 0, 2, 6, then every 8 weeks until the end of the respective study). For ACT 1, which was conducted to Week 54, subjects had evaluations up to Week 66. Vital signs, Mayo score, routine laboratories, and antibodies to infliximab were done until Week 54. For ACT 2, which was a 30 week study, the presence of AEs was evaluated out to Week 42. Vital signs, Mayo score, routine laboratories and antibodies to infliximab were performed until Week 30.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms were deemed to be appropriate. Treatment emergent adverse events were reported using the WHOART system-organ/preferred term classification. Individual AEs for both ACT 1 and ACT 2 were summarized by system-organ, preferred term, and relationship to study drug as determined by the Investigators.

7.1.5.3 Incidence of common adverse events

The incidence and profile of common adverse events in both ACT 1 and ACT 2 were comparable to those seen in other infliximab trials.

7.1.5.4 Common adverse event tables

The most frequently reported treatment-emergent AEs, defined as those occurring in $\geq$ 5% of infliximab-treated subjects in both ACT 1 and ACT 2 (combined), are presented in **Table 86**. The combined infliximab groups from both studies had 84% of subjects with one or more AEs compared to 77% of the combined placebo group. The system-organ class with the greatest number of AEs reported was GI system disorders in 40% of the combined infliximab groups vs. 45% of the placebo groups. This group was predominantly comprised of subjects who, not unexpectedly, reported the symptoms of worsening ulcerative colitis and abdominal pain. Under respiratory system, more infliximab-treated subjects reported an AE (36%) vs. placebo-treated subjects (27%). A higher number of pharyngitis and sinusitis cases accounted for this difference between study groups. AEs from other system-organ classes were reported in comparable numbers between the combined infliximab groups vs. the placebo groups from both studies.

Table 86: Number of subjects with 1 or more adverse events (in at least 5% of all infliximab-treated subjects) through week 30 by WHOART system organ class and preferred term (ACT 1 and ACT 2 studies combined)

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects treated	244	242	242	484
Avg. wks of follow up	22.2	27.2	26.6	26.9
Avg. weeks of treatment	16.1	21.9	21.0	21.5
Subjects with 1 or more AEs	188 (77)	202 (84)	202 (84)	404 (84)
WHOART system-organ class/ preferred term				
GI system disorders	109 (45)	94 (39)	97 (40)	191 (40)
Colitis ulcerative	46 (19)	32 (13)	29 (12)	61 (13)
Abdominal pain	29 (12)	21 (9)	30 (12)	51 (11)
Nausea	21 (9)	20 (8)	23 (10)	43 (9)
Vomiting	16 (7)	14 (6)	12 (5)	26 (5)
Respiratory system	66 (27)	79 (33)	95 (39)	174 (36)
URI infection	37 (15)	29 (12)	34 (14)	63 (13)
Pharyngitis	11 (5)	17 (7)	20 (8)	37 (8)
Sinusitis	10 (4)	14 (6)	18 (7)	32 (7)
Body as a whole-general	56 (23)	61 (25)	69 (29)	130 (27)
Pain	23 (10	19 (8)	24 (10)	43 (9)
Fatigue	14 (6)	17 (7)	25 (10)	42 (9)
CNS & PNS disorders	59 (24)	64 (26)	65 (27)	129 (27)
Headaches	44 (18)	41 (17)	43 (18)	84 (17)
Dizziness	9 (4)	14 (6)	12 (5)	26 (5)
Skin & Appendages	63 (26)	67 (28)	53 (22)	120 (25)
Rash	17 (7)	13 (5)	12 (5)	25 (5)
Resistance mechanism	52 (21)	56 (23)	57 (24)	113 (23)
Fever	20 (8)	25 (10)	20 (8)	45 (9)
Musculoskeletal	53 (22)	61 (25)	49 (20)	110 (23)
Arthralgias	22 (9)	33 (14)	25 (10)	58 (12)
Myalgia	12 (5)	15 (6)	11 (5)	26 (5)
Psychiatric disorders	20 (8)	18 (7)	15 (6)	33 (7)
Vascular (extracardiac)	17 (7)	13 (5)	12 (5)	25 (5)
Cardiovascular disorders	4 (2)	13 (5)	11 (5)	24 (5)

7.1.5.5 Identifying common and drug-related adverse events

The event rates of AE categories do not indicate that receiving infliximab treatment increased the rate of common AEs compared to placebo. No new adverse events by group classification or by preferred term were identified.

7.1.6 Less Common Adverse Events

Less common but clinically significant adverse events are discussed in section 7.1.2 of this review.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

General laboratory testing was performed according to the schedule outlined in section 7.1.5.1.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Both ACT 1 and ACT 2 were randomized, blinded, placebo-controlled trials which allowed for direct comparison of drug vs. control in subjects with active ulcerative colitis.

7.1.7.3 Standard analyses and explorations of laboratory data

The numbers of subjects with markedly abnormal postbaseline lab values were examined in both studies. In ACT 1, no noticeable differences were observed between the combined infliximab and placebo treatment groups in the number of subjects with markedly abnormal hematology values with the exception of hematocrit and lymphocytes. Placebo-treated subjects had a decreased hematocrit (defined as a value < 27%) in 7% of subjects compared to 3% of the combined infliximab group. 40% of placebo-treated subjects had decreased lymphocyte counts (defined as a value < 1.5 x $10^3/\mu L$) compared to 26% of the combined infliximab group. The distribution of chemistry laboratory values was similar across all treatment groups at baseline. Minor fluctuations of all chemistry values between the baseline and final visit were observed with no clinical sequelae in both the combined infliximab and placebo treatment groups.

Notable differences occurred for ALT and AST values between the combined infliximab and placebo treatment groups. In ACT 1, all markedly elevated ALT and AST values (defined as values that were both > 150 IU/L and an increase from baseline of $\geq$ 100%) occurred in subjects receiving infliximab. Markedly elevated ALT values occurred in 1 subject (<1%) receiving 5 mg/kg infliximab and in 2 subjects (2%) in the 10 mg/kg treatment group. Markedly elevated AST values occurred in 2 subjects (2%) in the 5 mg/kg infliximab treatment group. These elevations were transient and no subject had an SAE or discontinued study infusions due to an

elevated ALT or AST. All abnormal aminotransferase elevations resolved on follow-up despite continuation of study infusions.

In ACT 2, notable differences were observed between the combined infliximab and placebo treatment groups in the number with markedly abnormal hematology values (decreased hematocrit and decreased lymphocytes). As in ACT 1, more subjects in the placebo treatment group had a markedly abnormal decrease in hematocrit (10%) compared with subjects in the combined infliximab treatment group (3%). More placebo-treated subjects had a decrease in lymphocytes (32%) compared with subjects in the combined infliximab treatment group (20%).

The only notable difference between the combined infliximab and placebo treatment groups was for subjects with markedly elevated ALT values. Of the 5 subjects with markedly elevated ALT, 2 received 5 mg/kg infliximab and 2 received 10 mg/kg infliximab. One subject received placebo. No subjects discontinued study infusions due to elevated liver enzyme tests. Taken together, these data are consistent with information in the current Remicade® package insert indicating a higher proportion of elevated ALT in infliximab-treated subjects compared to controls, in previous Remicade® clinical trials for other indications.

7.1.7.5 Special assessments

No special laboratory assessments were performed in the ACT 1 and ACT 2 trials.

7.1.8 Vital Signs

Vital signs were collected according to the schedule outlined in section 7.1.5.1. No pattern of abnormal vital signs was observed.

7.1.8.4 Additional analyses and explorations

N/A. Infliximab is an approved product and its safety has previously been well characterized.

7.1.9 Electrocardiograms (ECGs)

ECGs were not formally collected in ACT 1 and ACT 2. Infliximab is an approved product with no known effects on ECG findings.

7.1.10 Immunogenicity

Information at the time of initial licensure of infliximab indicated that approximately 10% of subjects developed antibodies to infliximab. Antibody formation to infliximab through Week 30 of both the ACT 1 and ACT 2 trials is displayed in **Table 87**. In the combined ulcerative colitis trials, there were 5% of subjects who had positive antibodies to infliximab at any time through

Week 30. No increase in immunogenicity rates were seen in the UC studies compared to that currently stated in the package insert.

Table 87: Summary of antibody to infliximab status through week 30 (ACT 1 and ACT 2 combined data)

	Infliximab		
	5 mg/kg	10 mg/kg	Combined
Subjects treated	242	242	484
Subjects with appropriate samples[a]	189	185	374
Subjects positive for antibodies to infliximab at any time[b, c]	12 (6)	5 (3)	17 (5)
Titers			
1:10	3	0	3
1:20	4	0	4
1:40	1	4	5
1:80	1	1	2
1:160	1	0	1
1:320	1	0	1
1:640	1	0	1
Subjects negative for antibodies to infliximab at their last evaluation[b,d]	40 (21)	22 (12)	62 (17)
Subjects with inconclusive status at their last evaluation[b,e]	137 (73)	158 (85)	295 (79)

[a] Subjects with appropriate samples either had antibodies to infliximab at some timepoint following their first infusion or had 1 or more samples obtained at their last evaluation.
[b] Denominator is subjects with appropriate samples.
[c] Includes all subjects who had at least 1 positive sample at any time.
[d] Includes all subjects who had at least 1 negative sample at their last evaluation and excludes subjects who were positive.
[e] Includes subjects whose samples at their last evaluation were all inconclusive and excludes subjects who were positive.

7.1.11 Human Carcinogenicity

The potential role of TNF-blocker therapy in the development of malignancies is not known. The malignancies occurring in the ACT 1 and ACT 2 studies and in all Remicade® trials was previously discussed in section 7.1.2 of this review.

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no withdrawal phenomena and/or abuse potential issues identified with this product to date.

7.1.14 Human Reproduction and Pregnancy Data

No formal studies with infliximab have been conducted in pregnant women.

7.1.15 Assessment of Effect on Growth

No data are available to adequately assess the product's effect on growth.

7.1.16 Overdose Experience

The maximum tolerated dose of Remicade® has not been established in humans. Single doses up to 20 mg/kg have been administered without any direct toxic effect. There are no known signs or symptoms of adverse reactions or effects resulting from overdosage.

7.1.17 Postmarketing Experience

There is no new information from spontaneous AE reports that would require modification of the **Adverse Reaction Information from Spontaneous Reports** section.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

N/A. The Sponsor provided primary source data with data collected from studies under the Sponsor's IND. No secondary data sources were used.

7.2.3 Adequacy of Overall Clinical Experience

The Sponsor has a large safety database that exists for 4292 subjects in controlled trials for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease. The Sponsor had an adequate number of moderately to severely active ulcerative colitis subjects in the ACT 1 and ACT 2 trials. These subjects had pertinent risk factors to adequately assess the Sponsor's objectives of evaluating the effectiveness of infliximab in improving symptoms related to ulcerative colitis.

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing provided to subjects was adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

No new potential AEs were identified and there are no new recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

The primary source data provided was complete and of good quality.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Based on extensive prior experience, the use of infliximab is associated with a number of adverse events that appear drug related which are fully described in the current package insert. In this submission, the one category of adverse event associated with infliximab that was not previously appreciated is malignancies. Two malignancies were observed in the ulcerative colitis trials, both in the infliximab arms. However, it is difficult to draw conclusions from these data alone because of the small number of events and the greater number of patients (2:1) exposed to infliximab compared to placebo. Analysis of data from infliximab controlled trials of all indications combined revealed that malignancies were seen at a rate of 0.69 cases/100 pt-years compared to a rate of 0.13/100 pt-years with controls, a 5-fold higher rate. The malignancies observed were typical of common malignancies in the general population, including breast, colorectal, and melanoma.

While the 5-fold higher overall rate of malignancies in the pooled controlled trials suggests that infliximab may increase the risk of malignancy, the rate was not higher than the expected rate for the general U.S. population (SEER database). Instead, the rate for controls was lower than expected. Is there any other information that would support an association between infliximab and a risk of malignancy? Yes, three types of information support such an association:

- First, in a recent trial of infliximab in COPD, a larger number of malignancies was seen in the infliximab arm than with placebo (IND 10736)
- Second, in a trial of another TNF-blocker, etanercept, concomitant use with cyclophosphamide or MTX in Wegener's granulomatosus, a larger number of solid tumors were observed in the etanercept arm than with control (see Enbrel® package insert).
- Finally, there is biologic plausibility in that TNF-α is an important component of the immune system and immune surveillance plays a role in preventing malignancies.

8 ADDITIONAL CLINICAL ISSUES

8.4 Pediatrics

As per the Pediatric Research Equity Act of 2003 (PREA), the Sponsor is currently committed to conduct a randomized, controlled, and adequately powered clinical trial to assess the safety and efficacy in pediatric patients with moderately to severely active ulcerative colitis. The timelines are as follows: 3/31/2006: final protocol to be submitted to the IND. 6/30/2006: first patient enrolled in study. 12/31/2007: last patient enrolled in study. sBLA submission to FDA 6/30/2009.

9 OVERALL ASSESSMENT

9.1 Conclusions

In two large Phase 3 trials with similar design, the Sponsor met the primary efficacy endpoint by providing data to support the use of infliximab in patients with moderately to severely active ulcerative colitis. The primary efficacy analysis, subgroup analyses, sensitivity analyses, and analyses of major secondary endpoints were consistent with a clinical benefit of infliximab in this disease population. The overall safety profile of infliximab in these trials was consistent with the prior experience of infliximab in other clinical trials. Overall, the benefits of infliximab in this patient population outweigh the potential risks.

9.2 Recommendation on Regulatory Action

Recommend approval of the efficacy supplement with revisions to the label.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management plan is required.

9.3.2 Required Phase 4 Commitments

The Sponsor is currently committed to conduct a randomized, controlled, and adequately powered clinical trial to assess the safety and efficacy in pediatric patients with moderately to severely active ulcerative colitis. The timelines are as follows: 3/31/2006: final protocol to be

submitted to the IND. 6/30/2006: first patient enrolled in study. 12/31/2007: last patient enrolled in study. sBLA submission to FDA 6/30/2009.

9.3.3 Other Phase 4 Requests

No other Phase 4 requests are necessary.

9.5 Comments to Applicant

There are no comments to convey to the applicant.

10 APPENDICES

Appendix 1: Study Criteria for ACT 1 and ACT 2

Inclusion Criteria for ACT 1

1. Men or women ≥ 18 years of age at screening.
2. Have had ulcerative colitis of at least 3 months' duration at screening, confirmed by the biopsy taken at screening.
3. Have active colitis confirmed during the screening sigmoidoscopy by a score of ≥ 2 on the endoscopy subscore of the Mayo score.
4. Have active disease, as defined as a baseline Mayo score of 6 to 12 inclusive.
5. **Either** have concurrent treatment with **at least 1** of the following therapies:
    a. oral corticosteroids at a dose equivalent to or greater than 20 mg of prednisone per day for at least 6 weeks prior to baseline, with a stable dose ≤ 30 mg for at least 4 weeks prior to baseline.
    b. 6-MP at a dose equivalent to or greater than 1 mg/kg/day for at least 3 months prior to baseline, with a stable dose for at least 4 weeks prior to baseline.
    c. Azathioprine at a dose equivalent to or greater than 2 mg/kg/day for at lest 3 months prior to baseline, with a stable dose for at least 4 weeks prior to baseline.

    OR

    d. Have failed to tolerate or respond to corticosteroids (equivalent to prednisone ≥ 20 mg/day) within the previous 3 months and have failed to tolerate or respond to 6-MP or azathioprine.
6. Concomitant medications:
    a. If oral aminosalicylates or corticosteroids have been recently discontinued, they must have been stopped at least 4 weeks prior to baseline. If patient is on oral aminosalicylates or corticosteroids, the dose must have been stable for at least 4 weeks prior to baseline.
    b. If 6-MP or azathioprine has been recently discontinued, they must have been stopped at least 4 weeks prior to baseline. If patient is on 6-MP or azathioprine,

they must have been on it for at least 3 months prior to baseline, with a stable dose for at least 4 weeks prior to baseline.

c. If using bulking agents or stool softening agents chronically, the dose must have been stable for at least 2 weeks prior to screening and a stable dose should be maintained throughout the trial.

7. Patients at risk for colon cancer as defined below must have a screening colonoscopy:
   a. Within 5 years of the screening visit, if the patient is $\geq$ 45 years of age, to exclude adenomatous polyps. If adenomatous polyps were present, patients will not be eligible for participation in the trial until they are free of polyps.

   OR

   b. Within 1 year of the screening visit if the patient, regardless of age, has extensive colitis for $\geq$ 8 years or disease limited to the left side of colon for $\geq$ 10 years to screen for dysplasia.

   Duration of colitis for each patient should be determined from the date of onset of the patient's first symptom thought by their physician to be due to their ulcerative colitis. An adequate screening colonoscopy should include four quadrant biopsies taken every 10 cm with a minimum total number of 32 biopsies.

8. Men and women of childbearing potential must use adequate birth control measures (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) during the study and for 6 months after receiving the last infusion of study medication.
9. Antibiotics for the treatment of ulcerative colitis (e.g., ciprofloxacin and metronidazole) must have been discontinued at least weeks prior to baseline.
10. Screening laboratory tests must meet the following criteria:
    a. Hemoglobin ≥ 8.5 g/dL
    b. WBC count $\geq 3.5 \times 10^9$/L
    c. Neutrophils $\geq 1.5 \times 10^9$/L
    d. Platelets $\geq 100 \times 10^9$/L
    e. Lymphocyte count $\geq 0.5 \times 10^9$/L
    f. AST, ALT, alk phos levels must be within 3 times the upper limits of normal range for the laboratory conducting the test.
11. Have normal chest radiograph (P/A and lateral) results within 3 months prior to baseline.
12. Have a documented negative reaction to a PPD skin test performed within 3 months prior to baseline, unless skin testing is not indicated by published local guidelines or the patient is under treatment for latent TB.
13. Are willing and able to adhere to the study visit schedule and other protocol requirements.
14. Are capable of providing written informed consent, and the consent must be obtained prior to conducting any protocol-specified procedures.

Exclusion Criteria for ACT 1

1. Have severe extensive colitis as evidenced by:
   a. Physician judgment that the patient is likely to require colectomy within 12 weeks of baseline.

   OR

   b. Patient symptom complex at screening or baseline visits, including at least 4 of the following:
      - Diarrhea with $\geq$ 6 bowel movements/day with macroscopic blood in stool,
      - Focal severe or rebound abdominal tenderness,
      - Persistent fever ($\geq$ 37.5°C)
      - Tachycardia (> 90 beats/minute),
      - Anemia (< 8.5 g/dL).

2. Require, or required within the 2 months prior to screening, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage or other conditions possibly confounding the evaluation of benefit from infliximab treatment.

3. Have severe, fixed symptomatic stenosis of the large or small intestine.

4. Have current evidence of colonic obstruction or history within the 6 months prior to baseline, confirmed with objective radiographic or endoscopic evidence of a stricture with resulting obstruction (dilation of the colon proximal to the stricture on barium radiograph or an inability to traverse the stricture at endoscopy).

5. Have a history of colonic mucosal dysplasia.

6. Presence on baseline endoscopy of adenomatous colonic polyps, if not removed prior to study entry, or history of adenomatous colonic polyps that were not removed.

7. Presence of a stoma.

8. Have a history of extensive colonic resection that would prevent adequate evaluation of clinical disease activity to infliximab (eg, less than 30 cm of colon remaining).

9. Have a positive stool culture for enteric pathogens, pathogenic ova or parasites, or *Clostridium difficile* toxin within 4 months prior to baseline.

10. Are pregnant, nursing, or planning pregnancy (both men and women) within 18 months after screening (ie, approximately 6 months following last study infusion).

11. Have had treatment with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 8 weeks of screening.

12. Have received parenteral corticosteroids within 2 weeks prior to baseline.

13. Have received methotrexate within 8 weeks prior to baseline.

14. Have had topical (ie, via foam or enema) therapy with corticosteroids or 5-ASA compounds (eg, mesalamine) of the rectum or sigmoid within 2 weeks of screening.

15. Have had treatment with total parenteral nutrition (TPN) within 3 weeks of screening.

16. Have used any investigational drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer.

17. Had received previous treatment with monoclonal antibodies or receptor constructs that bind to TNFα (eg etanercept, CDP571, D2E7).

18. Had previous administration of infliximab.

19. Had a history of receiving murine recombinant products or a known allergy to murine proteins.

20. Had serious infections (eg, active hepatitis, pneumonia, or pyelonephritis) within 2 months of screening. Less serious infections (such as acute upper respiratory tract infection [colds] or a simple urinary tract infection) need not be considered as an exclusion at the discretion of the investigator.

21. Had or have had an opportunistic infection (eg, herpes zoster [shingles], cytomegalovirus, *Pneumocystic carinii*, aspergillosis, histoplasmosis, or mycobacteria other than TB) within 6 months prior to screening.

22. Had a known infection with human immunodeficiency virus (HIV) and/or hepatitis B or hepatitis C.

23. Had current signs and symptoms of systemic lupus erythematosus, or severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, or cerebral diseases.

24. Presence of a transplanted organ (with the exception of a corneal transplant > 3 months prior to screening).

25. Had any current known malignancy or malignancy within 5 years prior to screening (except for squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence).

26. Had a history of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (eg, nodes in the posterior triangle of the neck, infra-clavicular, epitrochlear, or periaortic areas), or splenomegaly.

27. Had a known substance abuse or dependency (drug or alcohol [than caffeine and/or nicotine]) within 3 years of screening.

28. Had poor tolerability of venipuncture or lack of adequate venous access for required blood sampling and infusion of study drug during the study period.

29. Had a known history of demyelinating disease such as multiple sclerosis or optic neuritis.

30. Had or have had a fistula.

31. Had a concomitant diagnosis of congestive heart failure (CHF), including medically controlled asymptomatic patients.

32. Required chronic and frequent use of antimotility agents for control of diarrhea (ie, diphenoxylate hydrochloride with atropine sulfate or loperamide).

33. Subjects on whom a baseline Mayo score could not be calculated due to frequent use of antimotility agents for control of diarrhea (ie, diphenoxylate hydrochloride with atropine sulfate or loperamide) within the 2 weeks prior to baseline.

34. Had used laxatives, except for preparation for endoscopy or other procedures, within I week prior to screening procedures required for assessment of the baseline Mayo score (eg, screening endoscopy or Mayo diary cards).

35. Chronic and frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) except low-dose aspirin for prevention of heart attacks, unstable angina, or transient ischemic attacks.

36. Had ulcerative colitis limited to only the rectum or to less than 20 cm of the colon.

37. Were considered ineligible to the TB eligibility assessment, screening, and early detection of reactivation rules defined in the protocol.

38. Had a chest radiograph within 3 months prior to baseline that showed a clinically significant abnormality, such as a malignancy or infection, or any abnormalities suggestive of TB as described in the protocol.

Inclusion Criteria for ACT 2

1. Were men or women $\geq$ 18 years of age at screening.

2. Had ulcerative colitis of at least 3 months' duration at screening, confirmed by the biopsy taken at screening. If the screening biopsy result was not yet available, a previous biopsy result confirming ulcerative colitis must be available in the subject's medical records and reviewed prior to receiving study agent.

3. Had active colitis confirmed during the screening sigmoidoscopy by a score of ≥ 2 on the endoscopy subscore of the Mayo score.

4. Had active disease, as defined as a baseline Mayo score of 6 to 12 inclusive.

5. **Either** had concurrent treatment with at least 1 of the following therapies (see also inclusion criterion 6, below):

   a. Oral corticosteroids at a stable dose equivalent to or greater than 20 mg of prednisone per day for at least 3 weeks prior to screening procedures required for assessment of the baseline Mayo score (eg, screening endoscopy or Mayo diary cards).

   b. 6-MP at a dose of 1 mg/kg/day (dose adjusted to commercially available tablet size), or a dose confirmed as therapeutic for the subject (eg, whole blood 6-thioguanine nucleotide [6-TGN] level $\geq$ 200 or a dose that is the highest tolerated dose [due to leukopenia, increased liver enzymes, nausea, etc]) for at least 3 months prior to baseline, with a stable dose for at least 4 weeks prior to baseline.

   c. Azathioprine at a dose of 2 mg/kg/day (dose adjusted to commercially available tablet size), or a dose confirmed as therapeutic for the subject (eg, whole blood 6-TGN level $\geq$ 200 or a dose that is the highest tolerated dose [due to leukopenia, increased liver enzymes, nausea, etc]) for at least 3 months prior to baseline, with a stable dose for at least 4 weeks prior to baseline.

   d. Oral aminosalicylates at a dose equivalent to or greater than 2.4 g of mesalamine per day, or a dose that is the highest tolerated dose (due to headache, fever, rash, nausea, etc), for at least 6 weeks prior to screening, with a stable dose for at least 3 weeks prior to screening.

OR

e. **Within the past 5 years:**

- Had failed to respond to a dose of 6-MP of I mg/kg/day (dose adjusted to commercially available tablet size), or a dose of azathioprine of 2 mg/kg/day (dose adjusted to commercially available tablet size), or a dose of 6-MP or azathioprine confirmed as therapeutic for the subject (eg, whole blood 6-TGN level:2: 200, or a dose that was the highest tolerated dose [due to leukopenia, increased liver enzymes, nausea, etc]) taken for 3 months, or

- Had medical complications and/or adverse events (AEs) from 6-MP or azathioprine that, in the judgment of their physician, precludes the use of these medications to treat ulcerative colitis (ie, pancreatitis, allergic reaction [high fever and/or rash and arthritis], . persistent elevated liver enzymes, or leukopenia unresponsive to dose reduction)

OR

f. **Within the past 18 months:**

- Had failed to successfully taper (ie, had a flare of disease on tapering to < 10 mg of prednisone on 2 separate occasions) or respond to corticosteroids (failed to respond to corticosteroids at a dose of at least 40 mg when administered orally for 2 weeks or intravenously for 1 week), or

- Had medical complications and/or AEs from corticosteroids, that in the judgment of their physician, precludes their use (ie, osteonecrosis, osteoporosis, psychosis, uncontrolled diabetes mellitus), or

- Had failed to respond to oral aminosalicylates at a dose equivalent to or greater than 2.4 g of mesalamine per day, or a dose that was the highest tolerated dose (due to headaches, fever, rash, nausea, etc), for at least 6 weeks, or

- Had medical complications and/or AEs from aminosalicylates, that in the judgment of their physician, precludes their use (ie, hypersensitivity reactions [pneumonitis, pancreatitis, etc], interstitial nephritis).

6. Concomitant medications:

a. If oral aminosalicylates or corticosteroids had been recently discontinued, they must have been stopped at least 4 weeks prior to baseline. If the subject was on oral aminosalicylates or corticosteroids, the dose must have been stable for at least 3 weeks prior to the screening procedures required for assessment of the baseline Mayo score (eg, screening endoscopy or Mayo diary cards). Subjects must have remained on this stable screening dose (through baseline) until after the Week-8 evaluation for corticosteroids and until the end of the study for aminosalicylates.

b. If 6-MP or azathioprine had been recently discontinued, they must have been stopped at least 4 weeks prior to baseline. If subjects were on 6-MP or azathioprine, they must have been on it for at least 3 months prior to baseline, with a stable dose for at least 4 weeks prior to baseline.

c. If using bulking or stool softening agents chronically, the dose must have been stable for at least 2 weeks prior to screening procedures required for assessment of the baseline

Mayo score (eg, screening endoscopy or Mayo diary cards) and a stable dose should have been maintained throughout the trial (see the protocol in Appendix 1).

7. Subjects at risk for colon cancer as defined below must have had a screening colonoscopy:

   a. Within 5 years of the screening visit, if the subject was ≥ 45 years of age, to exclude adenomatous polyps. If adenomatous polyps were present, subjects were not eligible for participation in the trial until they were free of polyps.

   OR

   b. Within 1 year of the screening visit, if the subject, regardless of age, had extensive colitis for ≥ 8 years or disease limited to the left side of colon for ≥ 10 years, to screen for dysplasia.

   Duration of colitis for each subject should have been determined from the date of onset of the subject's first symptom thought by their physician to be due to their ulcerative colitis.

   An adequate screening colonoscopy should have included 4 quadrant biopsies taken every 10 cm with a minimum total number of 32 biopsies. If an investigator planned to perform less than 32 biopsies, medical justification must have been discussed with and approved by the Centocor medical monitor or designee prior to the endoscopy.

8. Men and women of childbearing potential must have used adequate birth control measures (eg, abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) during the study and for 6 months after receiving the last infusion of study medication.

9. Antibiotics for the treatment of ulcerative colitis (eg, ciprofloxacin and metronidazole) must have been discontinued at least 3 weeks prior to baseline.

10. Screening laboratory tests must have met the following criteria:

    a. Hemoglobin ≥ 8.0 g/dL
    b. WBC count $\geq 3.5 \times 10^9$/L
    c. Neutrophils $\geq 1.5 \times 10^9$/L
    d. Platelets $\geq 100 \times 10^9$/L
    e. Lymphocyte count $\geq 0.5 \times 10^9$/L
    f. AST, ALT and alkaline phosphatase levels must be within 3 times the upper limit of normal range for the laboratory conducting the test.

11. Were willing and able to adhere to the study visit schedule and other protocol requirements.

12. Were capable of providing written informed consent, and the consent must have been obtained prior to conducting any protocol-specified procedures.

13. Were considered eligible according to the tuberculosis (TB) eligibility assessment, screening, and early detection of reactivation rules defined in the protocol.

Exclusion Criteria – ACT 2

1. Had severe extensive colitis as evidenced by:

   a. Investigator judgment that the subject was likely to require colectomy within 12 weeks of baseline.

OR

   b. Subject symptom complex at screening or baseline visits, including at least 4 of the following:

   - diarrhea with $\geq$ 6 bowel movements/day with macroscopic blood ins tool,
   - focal severe or rebound abdominal tenderness,
   - persistent fever ($\geq$ 37.5°C),
   - tachycardia (> 90 beats/minute),
   - anemia (< 8.5 g/dL).

2. Required, or required within the 2 months prior to screening, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage or other conditions possibly confounding the evaluation of benefit from infliximab treatment.

3. Had severe, fixed symptomatic stenosis of the large or small intestine.

4. Had current evidence of colonic obstruction or history within the 6 months prior to baseline, confirmed with objective radiographic or endoscopic evidence of a stricture with resulting obstruction (dilation of the colon proximal to the stricture on barium radiograph or an inability to traverse the stricture at endoscopy).

5. Had a history of colonic mucosal dysplasia.

6. Presence on screening endoscopy of adenomatous colonic polyps, if not removed prior to study entry, or history of adenomatous colonic polyps that were not removed.

7. Presence of a stoma.

8. Had a history of extensive colonic resection that would prevent adequate evaluation of

clinical disease activity to infliximab (eg, less than 30 cm of colon remaining).

9. Had a positive stool culture for enteric pathogens, pathogenic ova or parasites, or *Clostridium difficile* toxin within 4 months prior to baseline unless subject had received treatment and had a negative stool examination 1 week or longer after the end of treatment.

10. Were pregnant, nursing, or planning pregnancy (both men and women) within 12 months after screening (ie, approximately 7 to 8 months following last study infusion).

11. Had treatment with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 8 weeks of screening.

12. Had received parenteral corticosteroids within 2 weeks prior to baseline.

13. Had received methotrexate within 8 weeks prior to baseline.

14. Had topical (ie, via foam, enema, or suppository) therapy with corticosteroids or 5-ASA compounds (eg, mesalamine) of the rectum or sigmoid within 2 weeks of screening procedures required for assessment of the baseline Mayo score (eg, screening endoscopy or Mayo diary cards).

15. Have had treatment with total parenteral nutrition within 3 weeks of baseline.

16. Had used any investigational drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever was longer.

17. Had received previous treatment with monoclonal antibodies or receptor constructs that bind to TNFα (eg, etanercept, CDP571, D2E7).

18. Had received previous administration of infliximab.

19. Had a history of receiving murine recombinant products or a known allergy to murine proteins.

20. Had serious infections (eg, active hepatitis, pneumonia, or pyelonephritis) within 2 months of screening. Less serious infections (such as acute upper respiratory tract infection [colds] or a simple urinary tract infection) need not be considered as an exclusion at the discretion of the investigator.

21. Had or have had an opportunistic infection (eg, herpes zoster [shingles], cytomegalovirus, *Pneumocystis carinii*, aspergillosis, histoplasmosis, or mycobacteria other than TB) within 6 months prior to screening.

22. Had a known infection with human immunodeficiency virus (HIV) and/or hepatitis B or

hepatitis C.

23. Had current signs and symptoms of systemic lupus erythematosus, or severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, or cerebral diseases.

24. Presence of a transplanted organ (with the exception of a corneal transplant > 3 months prior to screening).

25. Had any current known malignancy or malignancy within 5 years prior to screening (except for squamous or basal cell carcinoma of the skin that had been treated with no evidence of recurrence).

26. Had a history of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (eg, nodes in the posterior triangle of the neck, infra-clavicular, epitrochlear, or periaortic areas), or splenomegaly.

27. Had a known substance abuse or dependency (drug or alcohol [other than caffeine and/or nicotine]) within 3 years of screening.

28. Had poor tolerability of venipuncture or lack of adequate venous access for required blood sampling and infusion of study drug during the study period.

29. Had a known history of demyelinating disease such as multiple sclerosis or optic neuritis.

30. Had or have had a fistula.

31. Had a concomitant diagnosis of congestive heart failure (CHF), including medically controlled asymptomatic subjects.

32. Required chronic and frequent use of anti motility agents for control of diarrhea (ie, diphenoxylate hydrochloride with atropine sulfate or loperamide).

33. Subjects on whom a baseline Mayo score could not be calculated due to frequent use of antimotility agents for control of diarrhea (ie, diphenoxylate hydrochloride with atropine sulfate or loperamide) within the 2 weeks prior to baseline.

34. Had used laxatives, except for preparation for endoscopy or other procedures, within 1 week prior to screening procedures required for assessment of the baseline Mayo score (eg, screening endoscopy or Mayo diary cards).

35. Chronic and frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) except low-dose aspirin for prevention of heart attacks, unstable angina, or transient ischemic attacks.

36. Had ulcerative colitis limited to only the rectum or to less than 20 cm of the colon.

37. Were considered ineligible according to the TB eligibility assessment, screening, and early detection of reactivation rules defined in the protocol.

38. Had a chest radiograph within 3 months prior to baseline that showed a clinically significant abnormality, such as a malignancy or infection, or any abnormalities suggestive of TB as described in the protocol.

Appendix 2: Calculation of Mayo score

Scoring System for Assessment of Ulcerative Colitis Activity (from Schroeder et al. N Engl J Med 1987;317:1625-9).

Stool frequency[a]
0 = Normal no. of stools for this patient
1 = 1-2 stools more than normal
2 = 3-4 stools more than normal
3 = 5 or more stools more than normal
Rectal bleeding[b]
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passed
Findings of flexible proctosigmoidoscopy
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment[c]
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease

[a] Each patient served as his or her own control to establish the degree of abnormality of stool frequency.
[b] The daily bleeding score represented the most severe bleeding of the day.
[c] The physician's global assessment acknowledged the three other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physician findings and the patient's performance status.

The possible range of scores is from 0 to 12.

Appendix 3: Study Schedules of Events for ACT 1 and ACT 2

Table 88: Study Schedule of Events – ACT 1

	TREATMENT											
ASSESSMENTS	Screen (-28 to 0 days)	Baseline (WkO)	Wk 2	Wk 6	Wk 8	Wk 14	Wk 22	Wk 30	Wk 38	Wk 46	Wk 54	Wk 66
Informed consent	X											
Chest radiograph	X[a]			X[a]								
Tuberculin skin test	X[o]											
Stool culture	X											
Randomization		X										
Infusion		X	X	X		X	X	X	X	X		
Demography/ medical history	X											
Inclusion/ exclusion criteria	X	X										
Physical exam	X										X	
Adverse event/con med review	X[b]	X[b]	X	X	X	X	X	X	X	X	X	X[p,q]
Vital signs		X[c]	X[c]	X[c]	X	X[c]	X[c]	X[c]	X[c]	X[C]	X	
Weight		X	X	X	X	X	X	X	X	X		
Mayo score	X[d]	X[e]	X[d]	X[d]	X	X[d]	X[d]	X	X[d]	X[d]	X	
Sigmoidoscopy	X[f]				X			X			X	
Health economics		X		X		X	X	X	X	X	X	
Quality-of-life assessments[g]		X			X			X			X	
CRP		X	X	X	X	X		X			X	
Hematology	X		X	X	X			X			X	
Chemistry	X		X	X	X			X			X	
Serum pregnancy test	X	X[h]										
Urine pregnancy test[i]		X	X	X		X	X	X	X	X		
ANA/anti-dsDNA		X						X			X	
Serum infliximab concentration		X[j]	X[j]	X[j]	X	X[j]		X[k]	X[k]	X[j]	X	X[p]
Antibodies to Infliximab[l]		X						X			X	X[p]
Inflammatory Markers[m]		X	X		X			X				
Biopsy confirmation of Ulcerative Colitis	X[n]											

Note: All items in study flow chart performed/obtained on infusion day must be completed prior to infusion.

[a] Chest x-ray must be performed at screening if none performed within 3 months prior to the first administration of study agent. A

repeat chest x-ray must be performed within 6 to 10 weeks after the first administration of study agent, except for patients in North America.
[b] Only the concomitant medication review to occur at screening and baseline.
[c] Vital signs obtained prior to infusion, approximately every 30 minutes during infusion, and 1 hour after the completion of the infusion.
[d] Partial Mayo score will be determined (ie, Mayo score without sigmoidoscopy).
[e] Endoscopy subscore taken during the screening sigmoidoscopy (or colonoscopy) will be used for baseline Mayo.
[f] Screening (prior to infusion) sigmoidoscopy must be performed within 2 weeks prior to week-0 visit. At least 72 hours must elapse between a colonoscopy with polypectomy or multiple biopsies and the baseline (week-0) visit. A colonoscopy will replace a sigmoidoscopy if screening for dysplasia or polypectomy is required.
[g] Quality-of-life assessments: IBDQ, [redacted] b(4)
[h] If 2 weeks or greater have elapsed between the screening visit and the baseline (week-0) visit, a repeat serum pregnancy test is required at baseline for all women of childbearing potential.
[i] Taken prior to study infusion for all women of childbearing potential.
[j] Blood for serum infliximab concentration to be obtained prior to infusion and 1 hour after the end of the infusion.
[k] Blood for serum infliximab concentration to be obtained prior to the infusion.
[l] Patients who develop a delayed hypersensitivity reaction, an infusion reaction resulting in discontinuation of study infusions, an infusion reaction considered by the investigator to be of severe intensity, or an infusion reaction classified as a serious adverse event, will have a 7 mL tube of blood drawn for the determination of antibodies to intliximab at the time of the reaction.
[m] If discontinuation occurs prior to week 30, blood for the measurement of inflammatory markers will only be drawn at the time of study discontinuation.
[n] Documentation of previous biopsy confirming the diagnosis of ulcerative colitis will be acceptable, if results from the screening biopsy are not yet available.
[o] A tuberculin skin test must be performed within 1 month prior to the first administration of study agent. In countries outside the United States and Canada, all subjects (except those who received previous BCG vaccination) who have a negative initial tuberculin skin test must undergo a second test, prior to the first administration of study agent, 1 to 3 weeks after the initial test.
[p] Will not be performed for patients who enter the study extension prior to the week-66 visit.
[q] Study site personnel will contact patients following this visit to collect adverse events occurring within 3 days after the week-66 blood draw.

Table 89: Study Schedule of Events – ACT 2

	TREATMENT								
ASSESSMENTS	Screen (-28 to 0 days)	Baseline (Wk 0)	Wk 2	Wk 6	Wk 8	Wk 14	Wk 22	Wk 30	Wk 42
Informed consent	X								
Chest radiograph	X[a]			X[a]					
Tuberculin skin test	X[n]								
Stool culture	X								
Randomization		X							
Infusion		X	X	X		X	X		
Demography/ medical history	X								
Inclusion/ exclusion criteria	X	X							
Physical exam	X							X	
Adverse event/con med review	X[b]	X[b]	X	X	X	X	X	X	X[o,p]
Vital signs		X[c]	X[c]	X[c]	X	X[c]	X[c]	X	
Weight		X	X	X		X	X		
Mayo score	X[d]	X[e]	X[d]	X[d]	X	X[d]	X[d]	X	
Sigmoidoscopy	X[f]				X			X	
Health economics		X		X		X	X	X	
Quality-of-life assessments[g]		X			X			X	
CRP		X	X	X	X	X		X	
Hematology	X		X		X			X	
Chemistry	X		X		X			X	
Serum pregnancy test	X	X[h]							
Urine pregnancy test[i]		X	X	X		X	X		
ANA/anti-dsDNA		X						X	
Serum infliximab concentration		X[j]	X[j]	X[m]	X	X[m]		X	X
Antibodies to infliximab[k]		X						X	X
Biopsy confirmation of ulcerative colitis	X[l]								

Note: All items in study flow chart performed/obtained on infusion day must be completed prior to infusion.

[a] Chest x-ray must be performed at screening if none performed within 3 months prior to the first administration of study agent. A repeat chest x -ray must be performed within 6 to 10 weeks after the first administration of study agent, except for patients in North America.

[b] Only the concomitant medication review will occur at screening and baseline.

[c] Vital signs obtained prior to infusion, approximately every 30 minutes during infusion, and 1 hour after the completion of the

infusion.
[d] Partial Mayo score will be determined (ie, Mayo score without sigmoidoscopy or colonoscopy).
[e] Endoscopy subscore taken during the screening sigmoidoscopy (or colonoscopy) will be used for baseline Mayo.
[f] Screening (prior to infusion) sigmoidoscopy must be performed within 2 weeks prior to week-O visit. At least 72 hours must elapse between a colonoscopy with polypectomy or multiple biopsies and the baseline (week-O) visit. A colonoscopy will replace a sigmoidoscopy, if screening for dysplasia or polypectomy is required.
[g] Quality-of-life assessments: IBDQ and SF-36.
[h] If 2 weeks or greater have elapsed between the screening visit and the baseline (week-O) visit, a repeat serum pregnancy test is required at baseline for all women of childbearing potential.
[i] Taken prior to study infusion for all women of childbearing potential.
[j] Blood for serum infliximab concentration to be obtained prior to infusion and 1 hour after the end of the infusion.
[k] Patients who develop a delayed hypersensitivity reaction, an infusion reaction resulting in discontinuation of study infusions, an infusion reaction considered by the investigator to be of severe intensity, or an infusion reaction classified as a serious adverse event, will have a 7 mL tube of blood drawn for the determination of antibodies to infliximab at the time of the reaction.
[l] Documentation of previous biopsy confirming the diagnosis of ulcerative colitis will be acceptable, if results from the screening biopsy are not yet available.
[m] Blood for serum infliximab concentration to be obtained prior to the infusion.
[n] A tuberculin skin test must be performed within 1 month prior to the first administration of study agent. In countries outside the United States and Canada, all subjects (except those who received previous BCG vaccination) who have a negative initial tuberculin skin test must undergo a second test, prior to the first administration of study agent, 1 to 3 weeks after the initial test.
[o] Will not be performed for patients who enter the study extension prior to the week-42 visit.
[P] Study site personnel will contact patients following this visit to collect adverse events occurring within 3 days of the week-42 blood draw.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103772 / S-5113

STATISTICAL REVIEW(S)

8/25/05

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number: 103772 / 5113

Drug Name: Remicade® (Infliximab)

Indication(s): Reducing signs and symptoms, [redacted] clinical remission, [redacted] mucosal healing, and [redacted] eliminating corticosteroid use in patients with moderately to severely active Ulcerative Colitis who have had an inadequate response to conventional therapy. b(4)

Applicant: Centocor, Inc.

Date: March 24, 2005

Review Priority: Priority

Biometrics Division: Biologics Therapeutics Statistical Staff, HFD-711

Statistical Reviewer: Janice Derr, Ph.D.

Concurring Reviewers: Boguang Zhen, Ph.D., BTSS Team Leader

Medical Division: Division of Therapeutics Biologics Internal Medicine Products, HFD-108

Clinical Team: Li Liang, M.D., Medical Reviewer

Jeffrey Siegel, M.D., Team Leader

Marc Walton, M.D., Division Director

Project Manager: Christi Stark

Keywords: adaptive allocation, clinical studies, Cochran-Mantel-Haenszel, labeling, missing data, multi-center, data imputation, double-blind, sensitivity analysis, integrated safety

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1. EXECUTIVE SUMMARY

Remicade® (infliximab) is a genetically engineered, monoclonal antibody. Infliximab interferes with the biological activity of human tumor necrosis factor alpha, a protein that promotes inflammation in the body. Remicade for intravenous infusion was approved in 1998 and is currently indicated for rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis.

Amendment 5113 is a Supplemental Biological License Application (sBLA) to extend the indication of Remicade in the treatment of patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response to conventional therapy. Support for this label extension is based on the results of two Phase III clinical trials. FDA reviewed the protocols and the Statistical Analysis Plan for these two studies.

The Phase 3 development program for the UC indication has a fast track designation, and the sBLA in Amendment 5113 has a priority review status, because the proposed indication represents an unmet medical need in a serious or life-threatening disease.

1.1 Conclusions and Recommendations

Efficacy Conclusions: Based on an evaluation of the two Phase III studies, this reviewer concludes that the results for the primary efficacy endpoint were reasonably robust in each study (TABLE 21, TABLE 22). The major secondary efficacy endpoints and other efficacy endpoints were consistent and supportive to the results for the primary efficacy endpoint in each study. The statistical evaluation supports the conclusion that infliximab was superior to the placebo with respect to clinical response, clinical remission and mucosal healing at week 8 and week 30 of each study.

Safety Conclusions: Malignant event rates were obtained from an integrated summary of 19 studies of infliximab in different disease populations. The malignant event rates, expressed per 100 patient-years of follow-up, were generally greater in infliximab-treated patients than in placebo-treated patients. However, this reviewer recommends that the adjusted event rates be interpreted carefully, because the placebo-treated patients in general had shorter follow-up times than the infliximab-treated patients. In addition, this reviewer suggests that the event rates from the combined infliximab studies and incidence rates from the Surveillance, Epidemiology and End Results (SEER) Database may not be directly comparable. Comparisons between malignant event rates from the infliximab studies and the general population (from the SEER Database), while useful, should be interpreted carefully.

Recommendations: There are no additional recommendations.

1.2 Brief Overview of Clinical Studies

The evaluation of the effectiveness and safety of infliximab for patients with active ulcerative colitis is based on Study C0168T37 ("ACT 1") and Study C0168T46 ("ACT 2"). Both studies were conducted in adult patients who had active ulcerative colitis. Each study was conducted independently and analyzed separately. ACT 1 enrolled 364 patients, of whom 152, or 42%, were in the United States. ACT 2 also enrolled 364 patients, of whom 172, or 47%, were in the United States. Patients were randomized to one of three groups: placebo, infliximab at 5 mg/kg, or infliximab at 10 mg/kg. Study drug was administered by infusion at weeks 0, 2, and 6, and every 8 weeks thereafter through week 46 for ACT 1 and week 22 for ACT 2.

The primary endpoint was the "yes/no" occurrence of a clinical response at week 8. Clinical response was defined as a decrease from baseline in the Mayo score by $\geq$ 30% and $\geq$ 3 points, accompanied by a decrease in the rectal bleeding subscore of $\geq$ 1 or a rectal bleeding subscore of 0 or 1. Clinical response at week 30, clinical remission at week 8, clinical remission at week 30, and mucosal healing at week 8 were major secondary endpoints in this study. The quality of life for patients in this study was evaluated using the inflammatory bowel disease questionnaire (IBDQ), the 36-item short form health survey (SF-36) and the EQ-5D.

1.3 Statistical Issues and Findings

Study implementation: This reviewer evaluated the statistical aspects of design, implementation and analysis from the ACT 1 and ACT 2 studies. On the basis of this evaluation, this reviewer concluded that the implementation of the studies did not raise concerns from a statistical perspective.

Efficacy: This reviewer confirmed the results presented by Centocor for the primary efficacy endpoint and for selected secondary efficacy endpoints in ACT 1 and ACT 2. The results from each study support the superiority of infliximab compared with placebo in clinical endpoints of response and remission at 8 weeks and at 30 weeks. The robustness of conclusions about the primary efficacy outcome, the percentage of patients in clinical response at week 8, was demonstrated from the pre-specified sensitivity analysis and by additional analyses. These analyses involved different versions of the analysis data set and modifications to the decision rules for missing data.

Because more patients dropped out before week 8 in the placebo group than the infliximab groups, this reviewer conducted additional analyses to evaluate how the study conclusions were affected by the rules for classifying early dropouts. Results from the major secondary efficacy outcomes in each study supported the conclusion that infliximab was superior to placebo with respect to clinical remission at week 8, clinical remission at week 30, clinical response at week 30, and mucosal healing at week 8.

There was a consistent infliximab treatment benefit versus placebo for subgroups based on gender and age at enrollment. The number of non-Caucasian patients was not large enough to make interpretations about race. The percentage of patients in clinical response at week 8 was similar at each level of corticosteroid refractory status.

The results from the primary endpoint, the major secondary endpoints and selected other efficacy endpoints from each study is summarized in TABLE 1.

TABLE 1. Response, remission and mucosal healing in ACT 1 and ACT 2 studies

	ACT 1 Study			ACT 2 Study		
	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg
Patients randomized	121	121	122	123	121	120
Clinical response						
Week 8	37%	69%*	62%*	29%	65%*	69%*
Week 30	30%	52%*	51%*	26%	47%*	60%*
Sustained response (both Week 8 and Week 30)	23%	49%*	46%*	15%	41%*	53%*
Clinical remission						
Week 8	15%	39%*	32%*	6%	34%*	28%*
Week 30	16%	34%*	37%*	11%	26%*	36%*
Sustained remission (both Week 8 and Week 30)	8%	23%*	26%*	2%	15%*	23%*
Mucosal healing						
Week 8	34%	62%*	59%*	31%	60%*	62%*
Week 30	25%	50%*	49%*	30%	46%*	57%*

* $p<0.05$, pairwise comparison, infliximab dose group compared with placebo (the analysis of the combined infliximab groups vs. placebo was also significant at $p<0.05$).

Safety: Centocor presented an integrated summary of malignancy events from 19 studies, in which a total of 4292 patients were treated with infliximab (as a randomized treatment assignment and/or as an open-label treatment) and 1265 patients were treated with placebo only. The disease populations in these studies included moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis. More infliximab-treated patients developed malignancies than placebo-treated patients in the combined results from 19 studies. When the observed results were adjusted for follow-up time, which tended to be shorter in placebo-treated patients, the malignant event rates per 100 patient-years of follow-up were generally greater in the infliximab-treated patients than in the placebo-treated patients. In order to compare the malignancy event rates from the infliximab studies with those in the general population, Centocor obtained the incidence rates for malignancies from the Surveillance, Epidemiology and End Results (SEER) Database. Centocor calculated an expected incidence rate for the combined infliximab study population, based on age-, sex-, and race-specific incidence rates from the SEER Database. They concluded that the observed number of "all malignancy" events was similar to the expected number in the infliximab-treated patients, but was lower than expected in the placebo-treated patients. They also noted that the observed

number of lymphoma events was greater than the expected number in the infliximab-treated patients from all studies and from the rheumatoid arthritis studies.

2. INTRODUCTION

2.1 Overview

Remicade® (infliximab) is a genetically engineered, monoclonal antibody that binds specifically to human tumor necrosis factor alpha (TNFα). TNFα is a protein that promotes inflammation in the body. Infliximab neutralizes the biological activity of TNFα by inhibiting it from binding with its receptors. Remicade is supplied as a sterile, white, lyophilized powder for reconstitution and intravenous infusion.

Remicade was approved in 1998. The current approved indications are the following:

- Rheumatoid arthritis: To be used in conjunction with methotrexate, for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis;

- Crohn's disease: For reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have an inadequate response to conventional therapy; and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fiscula closure in patients with fistulizing Crohn's disease;

- Ankylosing spondylitis: For reducing signs and symptoms in patients with active ankylosing spondylitis;

- Psoriatic arthritis: For reducing signs and symptoms of active arthritis in patients with psoriatic arthritis.

Amendment 5113 is a Supplemental Biological License Application (sBLA) to extend the indication of Remicade to include the treatment of patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy. Centocor proposes to support this label extension from the results of two Phase III clinical trials conducted in patients with moderately to severely active UC. FDA reviewed the protocols and the Statistical Analysis Plan for these studies.

The Remicade Phase 3 development program was designated Fast Track in June 2004, for the reduction of signs and symptoms of ulcerative colitis (as determined by the return to normal or near normal stool frequency and rectal bleeding), the induction and maintenance of remission, mucosal healing, and the reduction in the need for a colectomy in patients with active ulcerative

colitis who are intolerant of, or unresponsive to corticosteroids, aminosalicylates, and/or immunosuppressive agents (azthioprine and 6-MP).

FDA gave Amendment 5113 a priority review status because, if approved, Remicade would be a significant improvement in the effectiveness of a serious or life-threatening disease, i.e., patients with moderately to severely active colitis. Remicade, if approved for this indication, would fulfill unmet medical needs provided by conventional therapies for UC.

Scope of Statistical Review: Pivotal Efficacy and Safety Studies

The evaluation of the effectiveness and safety of infliximab for patients with active ulcerative colitis is based on Study C0168T37 ("ACT 1") and Study C0168T46 ("ACT 2"). Both studies were conducted in adult patients who had active ulcerative colitis. Characteristics of the patient population for each study are summarized in TABLE 2.

Both ACT 1 and ACT 2 were phase III, double-blind, placebo-controlled, parallel-group, multi-center studies. Each study had three groups: placebo, 5 mg/kg infliximab and 10 mg/kg infliximab. The treatment was administered by infusion at weeks 0, 2, 6, and every 8 weeks thereafter through week 46 for ACT 1 and through week 22 for ACT 2 (TABLE 2). ACT 1 enrolled 364 patients, of whom 152, or 42%, were in the United States (TABLE 3). ACT 2 also enrolled 364 patients, of whom 172, or 47%, were in the United States (TABLE 4).

Each study was conducted independently and analyzed separately. The pre-specified primary efficacy variable was the "yes/no" occurrence of a clinical response at week 8. Major secondary efficacy endpoints were clinical response at week 30, clinical remission at week 8, clinical remission at week 30 and mucosal healing at week 8.

TABLE 2. Design of ACT 1 and ACT 2 studies

	ACT 1 (Study C0168T37)	**ACT 2 (Study C0168T46)**
Study period	3/19/02 – 9/23/04	6/4/02 – 9/8/04
Number of sites	62 (25 in the U.S.)	55 (26 in the U.S.)
Total number of patients enrolled	364 (152 in the U.S.)	364 (172 in the U.S.)
Number of patients randomized:		
placebo	121	123
infliximab 5 mg/kg	121	121
infliximab 10 mg/kg	122	120
Eligibility requirements common to both studies	• Active ulcerative colitis, Mayo score between 6 and 12 points, inclusive, at baseline. • Endoscopic evidence of active colitis (endoscopy subscore of ≥ 2.)	
Eligibility requirements that are study-specific:	At least 1 of the following criteria: o Current treatment with at least 1 of the following: oral corticosteroids, 6 mercaptopurine (6-MP), or azathioprine (AZA). o Failed to successfully taper, tolerate or respond to oral corticosteroids within the past 18 months. o Failed to tolerate or respond to 6-MP or AZA within the previous 5 years.	At least 1 of the following criteria: o Current treatment with at least 1 of the following: oral corticosteroids, 6 mercaptopurine (6-MP), or azathioprine (AZA), or 5-ASA compounds. o Failed to successfully taper, tolerate or respond to oral corticosteroids within the past 18 months. o Failed to tolerate or respond to 6-MP or AZA within the previous 5 years. o Failed to tolerate ot respond to 5-ASA compounds within the previous 18 months.
Duration of Treatment	46 weeks	22 weeks

TABLE 3. Regional location of investigative centers of ACT 1

Region	Country	Number of sites	Number of patients
North America	United States	25	152
	Canada	6	31
Europe	Belgium	3	66
	Denmark	3	26
	Germany	4	16
	Spain	3	7
	United Kingdom	4	15
Southern Hemisphere	Argentina	1	2
	Australia	9	36
	New Zealand	4	13
	Totals	62	364

Note: The regions shown in this table were the levels of the stratification variable "Region" in the primary efficacy analysis for ACT 1.

TABLE 4. Regional location of investigative centers of ACT 2.

Region	Country	Number of sites	Number of patients
North America	United States	26	172
	Canada	4	24
Europe	Austria	2	38
	Czech Republic	2	13
	France	5	28
	Italy	2	7
	Netherlands	4	13
	Switzerland	3	7
	United Kingdom	3	5
Israel	Israel	4	57
	Totals	55	364

Note: The regions shown in this table were the levels of the stratification variable "Region" in the primary efficacy analysis for ACT 2.

2.2 Data Sources

The sponsor submitted this BLA including the data to the FDA CBER Electronic Document Room (CBER EDR). The submission is recorded in the CBER EDR as indicated in TABLE 5. The data sets were submitted in SAS v.5 transport format.

TABLE 5. Data sources for ACT 1 and ACT 2.

ACT 1 (Study C0168T37)	STN 103772\5113\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5351-stud-rep-contr\c0168t37
ACT 2 (Study C0168T46)	STN 103772\5113\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5351-stud-rep-contr\c0168t46

3. STATISTICAL EVALUATION

The ACT 1 and ACT 2 studies had a similar design and statistical analysis plan. For each review topic of the statistical evaluation, the two studies will be reviewed together.

3.1 Evaluation of Efficacy

3.1.1. Study implementation

This reviewer concluded that the implementation of the ACT 1 and ACT 2 studies did not raise concerns from a statistical perspective. Both studies had a reasonably balanced 1:1:1 allocation to the three treatment groups. Each treatment group had a similar distribution across the stratification variable, corticosteroid refractory status. Approximately 70% in each treatment group were not refractory to corticosteroids. Although both studies had protocol amendments that modified the eligible patient population, these amendments took place after more than 90% of the patients had been enrolled. An interim analysis of two efficacy endpoints was pre-specified in an interim analysis plan, for an assessment of futility only. Both studies were continued after an interim assessment of the ACT 1 data.

The random allocation process: This reviewer verified that the ACT 1 and ACT 2 studies each had a reasonably balanced 1:1:1 allocation to the three treatment groups (TABLE 6). Approximately 70% of each treatment group consisted of patients who were not refractory to corticosteroids (TABLE 6). Centocor used an adaptive stratified randomization design in order to ensure relatively even treatment balance within site and corticosteroid refractory status (CRS) subgroups. The minimization algorithm used a biased-coin assignment that was based on Pocock and Simon (1975)[1]. Two balancing factors were used in the minimization algorithm: site (62 levels for ACT 1, 55 levels for ACT 2) and CRS (2 levels). The minimization algorithm was used to achieve balance in the allocation of treatment group at the levels of each factor. Balance of treatment group assignment within the CRS levels of a site was not specifically controlled. The algorithm was designed to maintain balance only at the individual factor margins, not at the cross-classification cell levels.

[1] Pocock, S.J. and R. Simon, 1975. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31: 103-115.

Because many sites had a small number of patients and may have posed a challenge to the allocation algorithm, this reviewer evaluated the allocation at different size classes of sites: 1-2 patients/site, 3-8 patients/site, 9-15 patients/site and single sites having 35 (ACT 2), 36 (ACT 2) and 45 (ACT 1) patients. In general, the allocation process resulted in reasonable balance in assignment to treatment group within each of the size classes of sites (see TABLE 7 and TABLE 8). The greatest imbalance in treatment allocation involved 11 sites with one to two patients per site in ACT 2. In this size class, 43.8% (7 out of 16) were allocated to infliximab 10 mg/kg and 25.0% (4 out of 16) were allocated to infliximab 5 mg/kg (TABLE 8). However, this imbalance did not affect a large number of patients.

TABLE 6. Allocation to treatment groups and stratification by steroid refractory status, ACT 1 and ACT 2.

	ACT 1			ACT 2		
	Not Steroid Refractory	Steroid Refractory	Total	Not Steroid Refractory	Steroid Refractory	Total
Infliximab 10 mg/kg	84	38	122	86	34	120
Infliximab 5 mg/kg	85	36	121	86	35	121
Placebo	83	38	121	87	36	123
Total	252	112	364	259	105	364

TABLE 7. Size of site and allocation to treatment groups, ACT 1.

Size class: Number of patients / site	ACT 1	Number of patients assigned to each treatment group (%)			
	Number of sites	Infliximab 10 mg/kg	Infliximab 5 mg/kg	Placebo	Total number of patients
1-2	19	10 (34.5%)	8 (27.6%)	11 (37.9%)	29
3-8	29	44 (30.8%)	48 (33.6%)	51 (35.7%)	143
9-14	13	53 (36.1%)	50 (34.0%)	44 (29.93%)	147
45	1	15 (33.3%)	15 (33.3%)	15 (33.3%)	45
Totals	62 sites	122 (33.5%)	121 (33.2%)	121 (33.2%)	364

TABLE 8. Size of site and allocation to treatment groups, ACT 2.

Size class: Number of patients / site	ACT 2	Number of patients assigned to each treatment group (%)			
	Number of sites	Infliximab 10 mg/kg	Infliximab 5 mg/kg	Placebo	Total number of patients
1-2	11	7 (43.8%)	4 (25.0%)	5 (31.3%)	16
3-8	32	55 (34.0%)	55 (34.0%)	52 (32.1%)	162
9-15	10	35 (30.4%)	39 (33.9%)	41 (35.7%)	115
35	1	12 (34.3%)	11 (31.4%)	12 (34.3%)	35
36	1	11 (30.6%)	12 (33.3%)	13 (36.1%)	36
Totals	55 sites	120 (33.0%)	121 (33.2%)	123 (33.8%)	364

Amendments to the study protocol: Although the ACT 1 and ACT 2 studies each had a protocol amendment that modified the eligible patient population, these amendments took place before most of the patients had been enrolled. The amendments changed one of the eligibility criteria by increasing the time frame for classifying a patient as having failed other therapy. The large majority of patients in each study (at least 94% for ACT 1 and at least 95% for ACT 2) were enrolled after the date of the respective amendments, based on each patient's date of first study infusion. For this reason this reviewer concluded that it was not necessary to adjust or otherwise account for this change as part of the statistical analysis.

Interim analysis: The interim analysis was pre-specified in the interim analysis plan (IAP), for an assessment of futility only. Based on the results from the interim assessment of the ACT 1 study, both studies were continued without further interim assessments.

The IAP specified that an interim analysis of the ACT 1 data would take place after the first 180 randomized patients completed 8 weeks on study. An additional interim analysis of the ACT 2 data would be conducted provisionally, depending on the results of the ACT 1 interim analysis. The IAP specified the use of conditional power, using the method described by Lan and Wittes (1988)[2]. Conditional power would be calculated for the primary endpoint (clinical response at week 8) and one of the major secondary endpoints (clinical remission at week 8). FDA reviewed the interim assessment plan submitted under IND 5389/529. Because the interim assessment plan did not include plans to stop the studies for an early determination of efficacy, FDA did not request a formal stopping rule and alpha spending function.

3.1.2. Patient disposition

A key finding that affects the primary and other efficacy endpoints is the difference between the placebo and the infliximab groups in the retention of patients. In both ACT 1 and ACT 2, more patients in the placebo group departed from the study, and more patients departed earlier, in comparison with the two infliximab dose groups. The difference in retention between the placebo and the infliximab groups is apparent at week 8, the landmark date for the primary efficacy variable. This difference affects the extent to which the rules for imputation are used in the placebo group and the infliximab groups. For this reason, the rules of imputation are a focus of the sensitivity analysis for the primary endpoint (see part 3.1.5).

In ACT 1, 67.8% of the placebo patients remained in the study, while 87.6% of infliximab 5 mg/kg group and 86.9% of infliximab 10 mg/group remained in the study (see

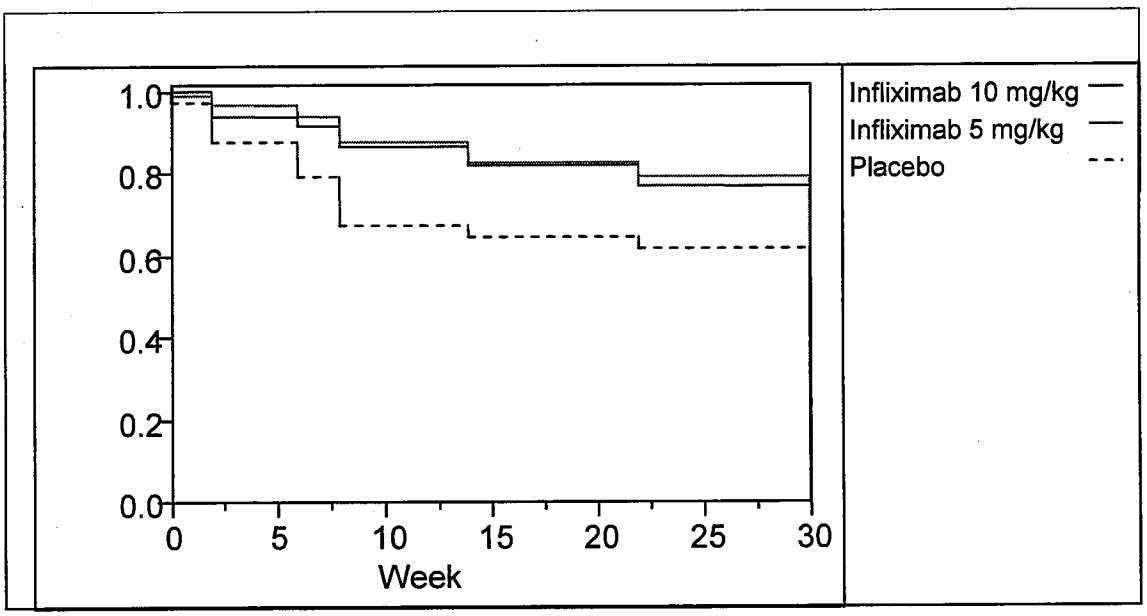
[2] Lan, K.K.G., and J. Wittes, 1988. The *B*-value: A tool for monitoring data. Biometrics 44: 579-585.

FIGURE 1 and TABLE 9). In ACT 2, 65.0% of patients in the placebo group, and 88.4% of patients in the infliximab 5 mg/kg group and 87.5% of patients in the infliximab 10 mg/kg group remained in the study at week 8 (see FIGURE 2 and TABLE 10). The two infliximab dose groups had very similar dynamics of retention in each study.

A total of 37.9% (ACT 1) and 29.1% (ACT 2) of patients permanently discontinued study infusions, with approximately twice as many patients in the placebo treatment group permanently discontinuing study infusions as those in either the 5 mg/kg or 10 mg/kg infliximab treatment groups (TABLE 11 for ACT 1, TABLE 12 for ACT 2). The most common reason for permanently discontinuing study infusions was lack of efficacy, which occurred approximately two times more frequently in the placebo treatment group than in either of the two infliximab treatment groups. Within the infliximab treatment groups, the percentage of patients who discontinued study infusions due to a lack of efficacy was similar (TABLE 11 for ACT 1, TABLE 12 for ACT 2). Flow charts of patient disposition are depicted in FIGURE 3 for ACT 1 and FIGURE 4 for ACT 2.

Overall, 26.1% (ACT 1) and 26.9% (ACT 2) of the patients terminated the study, with approximately twice as many patients in the placebo treatment group terminating the study than in either the 5 mg/kg or 10 mg/kg infliximab treatment groups (TABLE 13 for ACT 1, TABLE 14 for ACT 2). For each study, the two most common reasons for terminating the study were "withdrawal of consent" and "other."

FIGURE 1. ACT 1, Kaplan-Meier plot, showing the proportion of patients remaining in the study at each clinic visit, up to week 30.



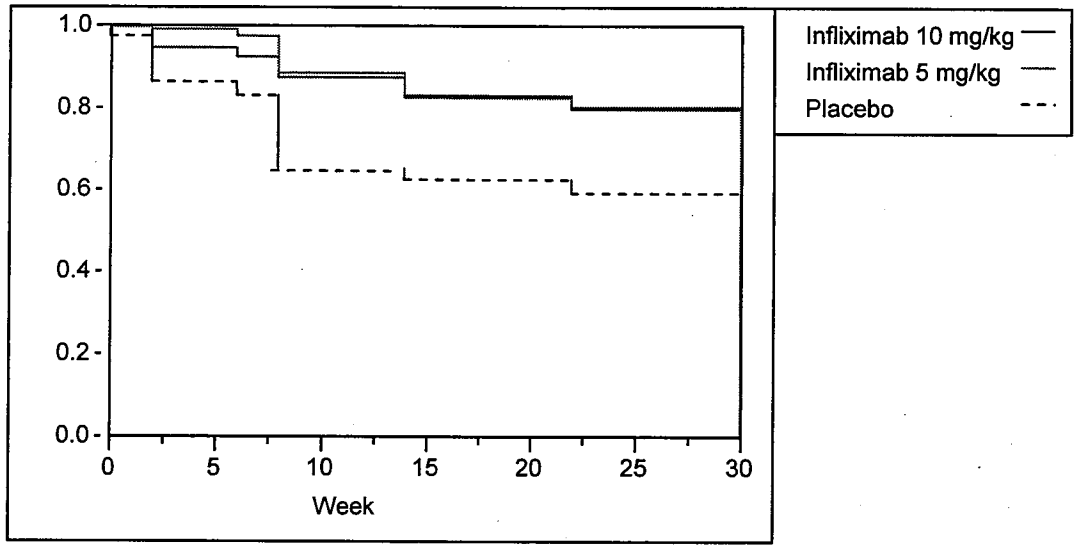
Source: ACT 1 Disposition database, "DSLSVIS" variable (Visit associated with latest visit date)

TABLE 9. ACT 1: The percentage of patients remaining in the study at each clinic visit, up to week 30.

		Week						
		0	**2**	**6**	**8**	**14**	**22**	**30**
Placebo	No. of patients with last visit on this week	3	12	10	14	4	3	75
	Cumulative no. of patients with last visit on this week or earlier	3	15	25	39	43	46	121
	Percentage remaining in the study	97.5%	87.6%	79.3%	67.8%	64.5%	62.0%	62.0%
Infliximab 5 mg/kg	No. of patients with last visit on this week	1	3	3	8	6	4	96
	Cumulative no. of patients with last visit on this week or earlier	1	4	7	15	21	25	121
	Percentage remaining in the study	99.2%	96.7%	94.2%	87.6%	82.6%	79.3%	79.3%
Infliximab 10 mg/kg	No. of patients with last visit on this week	0	7	3	6	6	6	94
	Cumulative no. of patients with last visit on this week or earlier	0	7	10	16	22	28	122
	Percentage remaining in the study	100.0%	94.3%	91.8%	86.9%	82.0%	77.1%	77.1%

Source: ACT 1 Disposition database, "DSLSVIS" variable (Visit associated with latest visit date)

FIGURE 2. ACT 2, Kaplan-Meier plot, showing the proportion of patients remaining in the study at each clinic visit, up to week 30.



Source: ACT 2 Disposition database, "DSLSVIS" variable (Visit associated with latest visit date)

TABLE 10. ACT 2: The percentage of patients remaining in the study at each clinic visit, up to week 30

		Week						
		0	**2**	**6**	**8**	**14**	**22**	**30**
Placebo	No. of patients with last visit on this week	3	14	4	22	3	4	73
	Cumulative no. of patients with last visit on this week or earlier	3	17	21	43	46	50	123
	Percentage remaining in the study	97.6%	86.2%	82.9%	65.0%	62.6%	59.3%	59.3%
Infliximab 5 mg/kg	No. of patients with last visit on this week	0	1	2	11	7	3	97
	Cumulative no. of patients with last visit on this week or earlier	0	1	3	14	21	24	121
	Percentage remaining in the study	100.0%	99.2%	97.5%	88.4%	82.6%	80.2%	80.2%
Infliximab 10 mg/kg	No. of patients with last visit on this week	0	6	3	6	5	4	96
	Cumulative no. of patients with last visit on this week or earlier	0	6	9	15	20	24	120
	Percentage remaining in the study	100.0%	95.0%	92.5%	87.5%	83.3%	80.0%	80.0%

Source: ACT 2 Disposition database, "DSLSVIS" variable (Visit associated with latest visit date)

TABLE 11. ACT 1: Number of patients who permanently discontinued study infusions through week 30 by reason for discontinuation; randomized patients.

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Total
Subjects randomized	121	121	122	364
Subjects who discontinued study infusions	66 (54.5%)	34 (28.1%)	38 (31.1%)	138 (37.9%)
Reason for discontinuation				
Required by protocol due to total colectomy	1 (0.8%)	1 (0.8%)	1 (0.8%)	3 (0.8%)
Adverse event	9 (7.4%)	7 (5.8%)	9 (7.4%)	25 (6.9%)
Lack of efficacy	50 (41.3%)	25 (20.7%)	24 (19.7%)	99 (27.2%)
Other	6 (5.0%)	1 (0.8%)	4 (3.3%)	11 (3.0%)

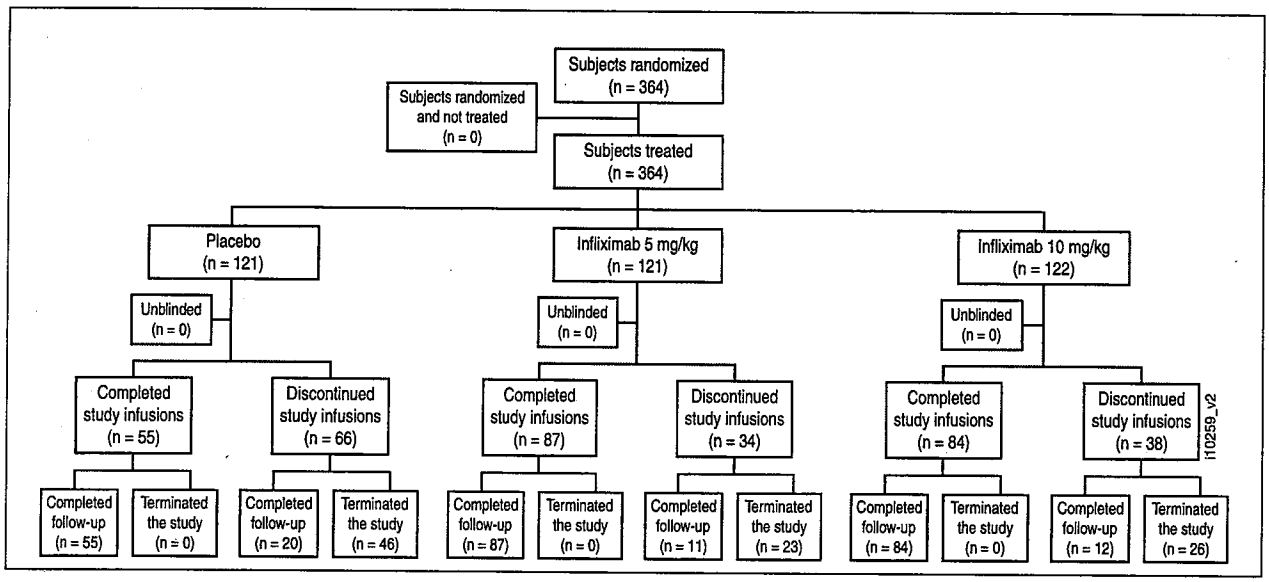
Source: ACT 1 Clinical Study Report, Table 4, p. 62/478

TABLE 12. ACT 2: Number of patients who permanently discontinued study infusions through week 30 by reason for discontinuation; randomized patients.

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Total
Subjects randomized	123	121	120	364
Subjects who discontinued study infusions	56 (45.5%)	24 (19.8%)	26 (21.7%)	106 (29.1%)
Reason for discontinuation				
Required by protocol due to total colectomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adverse event	12 (9.8%)	2 (1.7%)	5 (4.2%)	19 (5.2%)
Lack of efficacy	40 (32.5%)	20 (16.5%)	20 (16.7%)	80 (22.0%)
Other	4 (3.3%)	2 (1.7%)	1 (0.8%)	7 (1.9%)

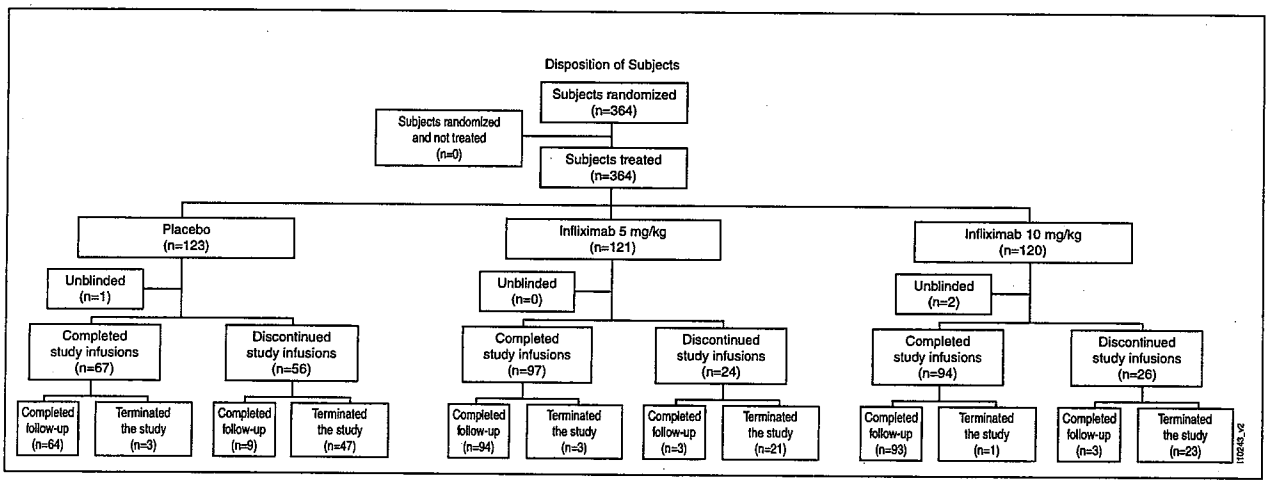
Source: ACT 2 Clinical Study Report, Table 4, p. 59/410.

FIGURE 3. ACT 1: Disposition of patients.



Source: ACT 1 Clinical Study Report, Figure 1, p. 61/478

FIGURE 4. ACT 2: Disposition of patients.



Source: *ACT 2 Clinical Study Report, Figure 1, p. 58/410.*

TABLE 13. ACT 1: Number of patients who terminated the study through week 30 by reason for termination; randomized patients.

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Total
Subjects randomized	121	121	122	364
Subjects who terminated study	46 (38.0%)	23 (19.0%)	26 (21.3%)	95 (26.1%)
Reason for termination				
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	1 (0.8%)	2 (1.7%)	1 (0.8%)	4 (1.1%)
Withdrawal of consent	24 (19.8%)	8 (6.6%)	11 (9.0%)	43 (11.8%)
Other	21 (17.4%)	13 (10.7%)	14 (11.5%)	48 (13.2%)

Source: *ACT 1 Clinical Study Report, Attachment 1.5, p. 161/478.*

TABLE 14. ACT 2: Number of patients who terminated the study through week 30 by reason for termination; randomized patients.

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Total
Subjects randomized	123	121	120	364
Subjects who terminated study	50 (40.7%)	24 (19.8%)	24 (20.0%)	98 (26.9%)
Reason for termination				
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	5 (4.1%)	5 (4.1%)	1 (0.8%)	11 (3.0%)
Withdrawal of consent	20 (16.3%)	7 (5.8%)	13 (10.8%)	40 (11.0%)
Other	25 (20.3%)	12 (9.9%)	10 (8.3%)	47 (12.9%)

Source: ACT 2 Clinical Study Report, Attachment 1.5, p. 147/410.

3.1.3. Patient demographic and baseline characteristics

The baseline demographic characteristics were similar across the treatment groups (TABLE 15 for ACT 1; TABLE 16 for ACT 2). Among all patients in ACT 1, 61% were men, 93% were Caucasian, and the median age was 40 years. Among all patients in ACT 2, 59% were men, 95% were Caucasian, and the median age was 38 years.

The clinical disease characteristics at baseline were generally similar across the treatment groups in both studies (TABLE 17 for ACT 1; TABLE 18 for ACT 2). However, in ACT 1, the 10 mg/kg infliximab treatment group had a longer median duration of disease than either the 5 mg/kg infliximab or placebo treatment groups (TABLE 17). Among all randomized patients in ACT 1, the median duration of ulcerative colitis was 4.7 years, and 30.8% were refractory to corticosteroids (TABLE 17). Among all randomized patients in ACT 2, the median duration of ulcerative colitis was 4.9 years and 28.8% were refractory to corticosteroids (TABLE 18). The distribution of Mayo scores was similar across all treatment groups in each study, as was the distribution of the four Mayo subscores at baseline (TABLE 19 for ACT 1; TABLE 20 for ACT 2).

TABLE 15. ACT 1: Summary of demographics at baseline; randomized patients.

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Total
Subjects randomized	121	121	122	364
Sex				
n	121	121	122	364
Male	72 (59.5%)	78 (64.5%)	72 (59.0%)	222 (61.0%)
Female	49 (40.5%)	43 (35.5%)	50 (41.0%)	142 (39.0%)
Race				
n	121	121	122	364
Caucasian	111 (91.7%)	116 (95.9%)	113 (92.6%)	340 (93.4%)
Black	2 (1.7%)	1 (0.8%)	3 (2.5%)	6 (1.6%)
Asian	1 (0.8%)	2 (1.7%)	1 (0.8%)	4 (1.1%)
Other	7 (5.8%)	2 (1.7%)	5 (4.1%)	14 (3.8%)
Age (yrs)				
n	121	121	122	364
Mean ± SD	41.4 ± 13.7	42.4 ± 14.3	41.8 ± 14.9	41.9 ± 14.2
Median	40.0	42.0	39.0	40.0
IQ range	(33.0, 52.0)	(30.0, 52.0)	(29.0, 53.0)	(30.0, 53.0)
Range	(18.0, 77.0)	(18.0, 81.0)	(18.0, 75.0)	(18.0, 81.0)
Weight (kg)				
n	121	121	122	364
Mean ± SD	76.8 ± 16.2	80.0 ± 17.8	76.9 ± 17.1	77.9 ± 17.1
Median	75.0	79.0	76.1	76.5
IQ range	(65.0, 86.0)	(67.0, 90.4)	(64.3, 87.3)	(65.8, 88.0)
Range	(46.0, 128.0)	(40.0, 146.4)	(46.0, 159.0)	(40.0, 159.0)

Source: ACT 1 Clinical Study Report, Table 5, pp. 65-66/478

TABLE 16. ACT 2: Summary of demographics at baseline; randomized patients.

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Total
Subjects randomized	123	121	120	364
Sex				
n	123	121	120	364
Male	71 (57.7%)	76 (62.8%)	68 (56.7%)	215 (59.1%)
Female	52 (42.3%)	45 (37.2%)	52 (43.3%)	149 (40.9%)
Race				
n	123	121	120	364
Caucasian	117 (95.1%)	116 (95.9%)	111 (92.5%)	344 (94.5%)
Black	5 (4.1%)	2 (1.7%)	1 (0.8%)	8 (2.2%)
Asian	0 (0.0%)	0 (0.0%)	5 (4.2%)	5 (1.4%)
Other	1 (0.8%)	3 (2.5%)	3 (2.5%)	7 (1.9%)
Age (yrs)				
n	123	121	120	364
Mean ± SD	39.3 ± 13.5	40.5 ± 13.1	40.3 ± 13.3	40.0 ± 13.3
Median	37.0	40.0	39.0	38.0
IQ range	(28.0, 49.0)	(30.0, 50.0)	(31.0, 50.0)	(29.0, 50.0)
Range	(18.0, 82.0)	(18.0, 71.0)	(20.0, 76.0)	(18.0, 82.0)
Weight (kg)				
n	123	121	120	364
Mean ± SD	76.1 ± 17.4	78.4 ± 17.8	79.6 ± 20.6	78.0 ± 18.6
Median	74.7	77.0	75.0	75.0
IQ range	(61.0, 87.1)	(64.3, 88.0)	(67.1, 91.9)	(64.0, 89.1)
Range	(42.1, 126.0)	(48.0, 125.4)	(49.4, 177.3)	(42.1, 177.3)

Source: ACT 2 Clinical Study Report, Table 5, p. 63/410.

TABLE 17. ACT 1: Summary of clinical disease characteristics at baseline; randomized patients

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Total
Refractory to corticosteroids				
n	121	121	122	364
Yes	38 (31.4%)	36 (29.8%)	38 (31.1%)	112 (30.8%)
No	83 (68.6%)	85 (70.2%)	84 (68.9%)	252 (69.2%)
UC disease duration (yrs)				
n	121	121	122	364
Mean ± SD	6.2 ± 5.9	5.9 ± 5.4	8.4 ± 8.1	6.9 ± 6.7
Median	4.4	4.1	5.9	4.7
IQ range	(2.1, 9.2)	(2.3, 7.3)	(2.8, 11.0)	(2.3, 9.4)
Range	(0.2, 32.2)	(0.2, 25.5)	(0.3, 42.1)	(0.2, 42.1)
UC symptoms duration (yrs)				
n	121	121	122	364
Mean ± SD	7.4 ± 6.6	6.9 ± 5.5	9.4 ± 8.5	7.9 ± 7.0
Median	5.0	5.0	6.5	6.0
IQ range	(3.0, 10.0)	(3.0, 9.0)	(3.0, 12.0)	(3.0, 10.0)
Range	(0.5, 40.0)	(0.3, 25.0)	(0.5, 43.0)	(0.3, 43.0)

Source: ACT 1 Clinical Study Report, Attachment 1.11, p. 184/478

TABLE 18. ACT 2: Summary of clinical disease characteristics at baseline; randomized patients.

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Total
Subjects randomized	123	121	120	364
UC disease duration (yrs)				
n	123	121	120	364
Mean ± SD	6.5 ± 6.7	6.7 ± 5.3	6.5 ± 5.8	6.6 ± 5.9
Median	3.7	5.2	4.7	4.9
IQ range	(1.6, 9.1)	(2.6, 9.2)	(2.3, 8.6)	(2.2, 8.8)
Range	(0.2, 28.3)	(0.5, 28.2)	(0.4, 27.7)	(0.2, 28.3)
UC symptoms duration (yrs)				
n	123	120	120	363
Mean ± SD	7.2 ± 7.0	8.2 ± 7.0	7.7 ± 6.3	7.7 ± 6.8
Median	4.5	6.4	5.3	5.5
IQ range	(2.0, 10.6)	(3.1, 12.0)	(3.0, 10.0)	(2.8, 10.6)
Range	(0.3, 29.0)	(1.0, 40.0)	(0.4, 28.0)	(0.3, 40.0)
Refractory to corticosteroids				
n	123	121	120	364
Yes	36 (29.3%)	35 (28.9%)	34 (28.3%)	105 (28.8%)
No	87 (70.7%)	86 (71.1%)	86 (71.7%)	259 (71.2%)

Source: ACT 2 Clinical Study Report, Attachment 1.12, pp. 167-168/410.

TABLE 19. ACT 1: Summary of the Mayo score at baseline; randomized patients

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Total
Subjects randomized	121	121	122	364
Mayo score (0-12)				
n	121	121	122	364
Mean ± SD	8.4 ± 1.8	8.5 ± 1.7	8.4 ± 1.4	8.5 ± 1.6
Median	8.0	9.0	8.5	8.0
IQ range	(7.0, 10.0)	(7.0, 10.0)	(7.0, 9.0)	(7.0, 10.0)
Range	(6.0, 12.0)	(4.0, 12.0)	(6.0, 12.0)	(4.0, 12.0)
Stool frequency subscore				
n	121	121	122	364
Normal number of stools	0 (0.0%)	2 (1.7%)	0 (0.0%)	2 (0.5%)
1-2 stools more than normal	20 (16.5%)	18 (14.9%)	12 (9.8%)	50 (13.7%)
3-4 stools more than normal	28 (23.1%)	29 (24.0%)	32 (26.2%)	89 (24.5%)
5 or more stools more than normal	73 (60.3%)	72 (59.5%)	78 (63.9%)	223 (61.3%)
Rectal bleeding subscore				
n	121	121	122	364
No blood seen	28 (23.1%)	15 (12.4%)	21 (17.2%)	64 (17.6%)
Streaks of blood with stool less than half the time	37 (30.6%)	33 (27.3%)	37 (30.3%)	107 (29.4%)
Obvious blood with stool most of the time	37 (30.6%)	57 (47.1%)	52 (42.6%)	146 (40.1%)
Blood alone passed	19 (15.7%)	16 (13.2%)	12 (9.8%)	47 (12.9%)
Endoscopy subscore				
n	121	121	122	364
Normal or inactive disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mild disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate disease	74 (61.2%)	73 (60.3%)	88 (72.1%)	235 (64.6%)
Severe disease	47 (38.8%)	48 (39.7%)	34 (27.9%)	129 (35.4%)
Physician's global assessment subscore				
n	121	121	122	364
Normal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mild disease	5 (4.1%)	7 (5.8%)	3 (2.5%)	15 (4.1%)
Moderate disease	87 (71.9%)	93 (76.9%)	100 (82.0%)	280 (76.9%)
Severe disease	29 (24.0%)	21 (17.4%)	19 (15.6%)	69 (19.0%)

Source: ACT 1 Clinical Study Report, Attachment 1.13, p. 186/478.

TABLE 20. ACT 2: Summary of the Mayo score at baseline; randomized patients.

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Total
Subjects randomized	123	121	120	364
Mayo score (0-12)				
n	123	121	120	364
Mean ± SD	8.5 ± 1.5	8.3 ± 1.5	8.3 ± 1.6	8.4 ± 1.5
Median	9.0	8.0	8.0	8.0
IQ range	(7.0, 10.0)	(7.0, 9.0)	(7.0, 9.0)	(7.0, 9.5)
Range	(6.0, 12.0)	(6.0, 12.0)	(5.0, 12.0)	(5.0, 12.0)
Stool frequency subscore				
n	123	121	120	364
Normal number of stools	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.3%)
1-2 stools more than normal	16 (13.0%)	19 (15.7%)	19 (15.8%)	54 (14.8%)
3-4 stools more than normal	34 (27.6%)	31 (25.6%)	37 (30.8%)	102 (28.0%)
5 or more stools more than normal	73 (59.3%)	71 (58.7%)	63 (52.5%)	207 (56.9%)
Rectal bleeding subscore				
n	123	121	120	364
No blood seen	19 (15.4%)	18 (14.9%)	18 (15.0%)	55 (15.1%)
Streaks of blood with stool less than half the time	34 (27.6%)	51 (42.1%)	37 (30.8%)	122 (33.5%)
Obvious blood with stool most of the time	56 (45.5%)	41 (33.9%)	49 (40.8%)	146 (40.1%)
Blood alone passed	14 (11.4%)	11 (9.1%)	16 (13.3%)	41 (11.3%)
Endoscopy subscore				
n	123	121	120	364
Normal or inactive disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mild disease	1 (0.8%)	0 (0.0%)	2 (1.7%)	3 (0.8%)
Moderate disease	72 (58.5%)	72 (59.5%)	76 (63.3%)	220 (60.4%)
Severe disease	50 (40.7%)	49 (40.5%)	42 (35.0%)	141 (38.7%)
Physician's global assessment subscore				
n	123	121	120	364
Normal	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Mild disease	3 (2.4%)	6 (5.0%)	4 (3.3%)	13 (3.6%)
Moderate disease	97 (78.9%)	95 (78.5%)	96 (80.0%)	288 (79.1%)
Severe disease	22 (17.9%)	20 (16.5%)	20 (16.7%)	62 (17.0%)

Source: ACT 2 Clinical Study Report, Attachment 1.14, p. 170/410.

3.1.4. Intention-to-treat database

This reviewer concluded that the intention-to-treat (ITT) database was constructed according to the rules that were specified in the protocol. This conclusion is based on a review of selected cases. Cases were selected to represent different decision paths through the rules that governed how they would be classified in the ITT database. For example, the selected cases represented different patterns of missing and non-missing Mayo subscores; some were designated as treatment failures, and some had insufficient data. This reviewer tracked the development and classification of these cases from the preliminary datasets through to the ITT efficacy database, and also evaluated the statistical programming statements that were used to express the rules. From this assessment, this reviewer confirmed that the selected cases did follow the rules for determining the efficacy endpoints.

The statistical analysis of the primary efficacy outcome used the database constructed from the intent-to-treat (ITT) principle. The protocol identified rules for constructing the primary efficacy outcome in the following circumstances:

- Missing Mayo subscores: If one, two, or, at most, three out of the four Mayo subscores were missing at a specific visit, then the last available value for each missing subscore was carried forward to compute a full Mayo score and a partial Mayo score at that visit. If all four subscores were missing at a specific visit, the Mayo score was considered missing at that visit.

- Treatment failure: A patient who experienced any of the following circumstances was classified as a treatment failure, and this overrode the classification that would be obtained from the actual Mayo score: (a) a colectomy [partial or full] or ostomy; (b) study infusions discontinued due to lack of efficacy; (c) a protocol-prohibited medication change between week 0 and week 8. A patient with one or more of these circumstances was considered not to have achieved clinical response at week 8, regardless of the actual computation of clinical response based on the Mayo score.

- Insufficient data: Patients with insufficient data at the week 8 visit, defined as patients who discontinued the study prior to the week 8 visit or patients who were missing all four subscores of the Mayo score at the week 8 visit, were considered not to have achieved clinical response at week 8.

3.1.5. Primary efficacy endpoint and analyses

Primary efficacy endpoint: The primary endpoint was the "Yes/No" occurrence of a clinical response at week 8, which was defined as a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1, at week 8.

Primary statistical analysis method for primary efficacy endpoint: Centocor used a Cochran-Mantel-Haenszel chi-square test, stratified by six strata, defined by the combination of two levels of corticosteroid refractory status and three regions. FDA and Centocor discussed two statistical issues with respect to the statistical analysis plan for the primary efficacy evaluation:

1. *Using a two stage procedure and controlling Type I error.* FDA concurred with Centocor that their proposed two stage procedure would provide strong control of Type I error. The two stage procedure was as follows: In the first stage, the two infliximab treatment groups were combined and compared with the placebo treatment group. If this test was statistically significant at $\alpha = 0.05$, then the second stage of the analysis was implemented. The second stage was a pairwise comparison of each infliximab treatment group with the placebo treatment group, with each test evaluated at a two-sided α of 0.05. A positive study result consisted of a statistically significant stage one test and at least one statistically significant stage two test.

2. *Combining data from sites within a region and using a stratified Cochran-Mantel-Haenszel (CMH) test.* FDA concurred that Centocor could combine data from sites by region. The rationale for combining sites was the expectation that many sites would enroll only a small number of patients. In the ACT 1 study, the three regions were North America, Europe, and the Southern Hemisphere (TABLE 3). In the ACT 2 study, the three regions were North America, Europe, and Israel (TABLE 4). The CMH test was stratified by the combination of corticosteroid refractory status and region (a total of six levels). FDA also requested a sensitivity analysis, using a CMH test stratified by corticosteroid refractory status and center, with an algorithm for combining data from centers with "sparse" tables (i.e., 0 patients in one or more levels defined by the combination of treatment group and corticosteroid refractory status). Centocor agreed and submitted their algorithm for combining centers with sparse tables.

Results of the primary analysis: This reviewer confirmed the results presented by Centocor for the primary analysis in ACT 1 and ACT 2. In both studies, the comparisons between the infliximab 5 mg/kg group vs. placebo and between the inflimiximab 10 mg/kg group vs. placebo were statistically significant (TABLE 21, TABLE 22). This reviewer also confirmed the percentage of patients in clinical response at week 8 in each group, using the pre-specified rules for the Intention-to-Treat data set to allow for partially missing Mayo scores, treatment failures, and insufficient data at week 8 (TABLE 21, TABLE 22) .

Sensitivity analysis for primary efficacy endpoint:
The sensitivity analysis that was pre-specified in the statistical analysis plan produced results that were consistent with the primary analysis (see analyses #1 through #4 in TABLE 21 and TABLE 22). Each of the four analyses that were part of the sensitivity analysis follows the decision rules for constructing the analysis population and the statistical analysis model for the primary analysis, except for departures as described below:

Analysis #1. For patients who discontinued the study prior to the week 8 visit and for patients missing all four of the Mayo subscores at week 8, carry forward the last available value to impute missing data (instead of classifying them as non-responders).

Analysis #2. Suspend the treatment failure rules and, instead, carry forward the last available value to impute missing data.

Analysis #3. Exclude patients who have at least one major protocol deviation.

Analysis #4. Use the corrected strata for patients for which the corticosteroid refractory status was misspecified at the time of randomization.

In addition to the pre-specified sensitivity analysis, this reviewer conducted additional analyses in order to assess how the results were affected by the larger numbers of early dropouts in the placebo group than in the infliximab groups. For example, patients were analyzed only if they stayed in the study through week 8 (Analysis #5). Biased imputation rules were used that favored imputing the placebo group dropouts as responders and infliximab group dropouts as non-responders (Analysis #6 and #7). Even with these modifications, the infliximab groups had a larger percentage of responders than the placebo group, although the difference between the placebo and the infliximab groups was not as great as it was in the primary analysis (see TABLE 21 and Table 22, analyses #5, #6 and #7).

Analyses #5, #6, and #7 followed the rules and analysis model for the primary efficacy analysis, except for the departures that are described below:

Analysis #5. Create a subset of the ITT database, consisting only of patients who stayed in the study for the first 8 weeks.

Analysis #6. If a patient was in the placebo group and dropped out of the study prior to week 8, then classify the patient as "in clinical response."

Analysis #7. If a patient was in the placebo group, dropped out of the study prior to week 8, but was not classified as a treatment failure according to the treatment failure rules, then classify the case as "in clinical response."

In addition to the analyses already described, Centocor conducted one more analysis, and this reviewer conducted two more analyses. These analyses evaluated the robustness of the study conclusions to changes in the analysis model and to changes in the inclusion of study sites in the analysis. They are described below with respect to how each analysis departed from the decision rules and analysis model for the primary efficacy evaluation:

Analysis #8. Centocor: Stratify the Cochran-Mantel-Haenszel test by corticosteroid refractory status and center, using an algorithm to combine centers that have sparse data.

Analysis #9. FDA: Exclude the two sites with the largest number of patients from the ITT database (Site 30 in Leuven, Belgium and site 43 in Bopnheiden, Belgium).

Analysis #10. FDA: Conduct an exact statistical test, stratified by the corticosteroid refractory status and region (six strata as in the primary analysis).

The results from these additional modifications also supported the conclusion that infliximab was superior to placebo with respect to the percentage of patients in clinical response at week 8 (see TABLE 21 and TABLE 22, analyses #8, #9 and #10).

TABLE 21. ACT 1: Number of patients in clinical response at week 8, results of primary efficacy analysis, the pre-specified sensitivity analysis, and additional analyses

	Description of sensitivity analysis Number of patients randomized	Placebo 121	Infliximab 5 mg/kg 121	Infliximab 10 mg/kg 122
	Primary efficacy analysis	45/121 37.2%	84/121 69.4%*	75/122 61.5%*
	Pre-specified sensitivity analysis			
1.	For patients who discontinued the study prior to the week 8 visit and for patients missing all four of the Mayo subscores at week 8, carry forward the last available value to impute missing data (instead of classifying them as non-responders).	46/121 38.0%	84/121 69.4%*	75/122 61.5%*
2.	Suspend the treatment failure rules and, instead, carry forward the last available value to impute missing data.	52/121 43.0%	87/121 71.9%*	76/122 62.3%*
3.	Exclude patients who have at least one major protocol deviation.	44/120 36.7%	84/119 70.6%*	74/121 61.2%*
4.	Use the corrected strata for patients for which the corticosteroid refractory status was misspecified at the time of randomization.	45/121 37.2%	84/121 69.4%*	75/122 61.5%*
	Other analyses (not pre-specified)			
5.	FDA: Create a subset of the ITT database, consisting only of patients who stayed in the study for the first 8 weeks.	45/96 46.9%	84/114 73.7%*	75/112 67.0%*
6.	FDA: If a patient was in the placebo group and dropped out of the study prior to week 8, then classify the patient as "in clinical response."	70/121 57.9%	84/121 69.4%	75/122 61.5%

	Description of sensitivity analysis Number of patients randomized	Placebo 121	Infliximab 5 mg/kg 121	Infliximab 10 mg/kg 122
7.	FDA: If a patient was in the placebo group, dropped out of the study prior to week 8, but was not classified as a treatment failure according to the treatment failure rules, then classify the case as "in clinical response."	54/121 44.6%	84/121 69.4%*	75/122 61.5%*
8.	Centocor: Stratify the Cochran-Mantel-Haenszel test by corticosteroid refractory status and center, using an algorithm to combine centers that have sparse data.	45/121 37.2%	84/121 69.4%*	75/122 61.5%*
9.	FDA: Exclude the two sites with the largest number of patients from the ITT database (Site 30 in Leuven, Belgium and site 43 in Bopnheiden, Belgium).	39/104 37.5%	71/106 67.0%*	68/107 63.6%*
10.	FDA: Conduct an exact statistical test, stratified by the corticosteroid refractory status and region (six strata as in the primary analysis).	45/121 37.2%	84/121 69.4%*	75/122 61.5%*

* $p < 0.05$, pairwise comparison, infliximab dose group compared with placebo (the analysis of the combined infliximab groups vs. placebo was also significant at $p<0.05$).

Sources from the ACT 1 Clinical Study Report:
Primary efficacy analysis: Attachment 3.1, p. 197/478
Sensitivity analysis 1. Attachment 3.2, p. 198/478
Sensitivity analysis 2. Attachment 3.3, p. 199/479
Sensitivity analysis 3. Attachment 3.4, p. 200/479
Sensitivity analysis 4. Attachment 3.5, p. 201/479
Other analysis 8. Attachment 3.6, p. 202/479

TABLE 22. ACT 2: Number of patients in clinical response at week 8, results of primary efficacy analysis, the pre-specified sensitivity analysis, and additional analyses

	Description of sensitivity analysis Number of patients randomized:	Placebo 123	Infliximab 5 mg/kg 121	Infliximab 10 mg/kg 120
	Primary efficacy analysis	36/123 29.3%	78/121 64.5%*	83/120 69.2%*
	Pre-specified sensitivity analysis			
1.	For patients who discontinued the study prior to the week 8 visit and for patients missing all four of the Mayo subscores at week 8, carry forward the last available value to impute missing data (instead of classifying them as non-responders).	37/123 30.1%	78/121 64.5%*	83/120 69.2%*
2.	Suspend the treatment failure rules and, instead, carry forward the last available value to impute missing data.	40/123 32.5%	79/121 65.3%*	83/120 69.2%*

	Description of sensitivity analysis Number of patients randomized:	Placebo 123	Infliximab 5 mg/kg 121	Infliximab 10 mg/kg 120
3.	Exclude patients who have at least one major protocol deviation.	35/122 28.7%	78/121 64.5%*	81/117 69.2%*
4.	Use the corrected strata for patients for which the corticosteroid refractory status was misspecified at the time of randomization.	36/123 29.3%	78/121 64.5%*	83/120 69.2%*
	Other analyses (not pre-specified)			
5.	FDA: Create a subset of the ITT database, consisting only of patients who stayed in the study for the first 8 weeks.	36/102 35.3%	78/118 66.1%*	83/111 74.8%*
6.	FDA: If a patient was in the placebo group and dropped out of the study prior to week 8, then classify the patient as "in clinical response."	57/123 46.3%	78/121 64.5%*	83/120 69.1%*
7.	FDA: If a patient was in the placebo group, dropped out of the study prior to week 8, but was not classified as a treatment failure according to the treatment failure rules, then classify the case as "in clinical response."	42/123 34.2%	78/121 64.5%*	83/120 69.2%*
8.	Centocor: Stratify the Cochran-Mantel-Haenszel test, using the six stratification levels created by the combination of three regions (combining across sites within region) and the two corticosteroid refractory status levels.	36/123 29.3%	78/121 64.5%*	83/120 69.2%*
9.	FDA: Exclude the two sites with the largest number of patients from the ITT database (Site 30 in Leuven, Belgium and site 43 in Bopnheiden, Belgium).	29/94 30.9%	64/93 68.9%*	66/96 68.8%*
10.	FDA: Exact statistical test, stratified by pooled site and corticosteroid refractory status. The treatment failure rules and missing data rules used for the primary analysis were applied for this analysis.	36/123 29.3%	78/121 64.5%*	83/120 69.2%*

* $p < 0.05$, pairwise comparison, infliximab dose group compared with placebo (the analysis of the combined infliximab groups vs. placebo was also significant at $p<0.05$).

Sources from the ACT 2 Clinical Study Report:
Primary efficacy analysis: Attachment 3.1, p. 181/410
Sensitivity analysis 1. Attachment 3.2, p. 182/410
Sensitivity analysis 2. Attachment 3.3, p. 183/420
Sensitivity analysis 3. Attachment 3.4, p. 184/410
Sensitivity analysis 4. Attachment 3.5, p. 185/410
Other analysis 8. Attachment 3.6, p. 186/410

3.1.6. Secondary efficacy endpoints and analysis

Results from the statistical analysis of major secondary efficacy endpoints added supportive evidence to the findings from the primary efficacy endpoint (see endpoints #1-#4 in TABLE 23 and TABLE 24). The following four clinical endpoints were pre-specified in the protocol as major secondary efficacy endpoints:

1. Clinical remission at week 8. Clinical remission was defined as a Mayo score ≤ 2 points with no individual subscore > 1. If a patient was considered to be a treatment failure for clinical response at week 8, this patient was also a treatment failure for clinical remission at week 8.

2. Clinical remission at week 30. Patients who had a colectomy or ostomy, who discontinued study infusions due to lack of efficacy, or who had protocol-prohibited medication changes, prior to the week 30 visit, were considered to not have achieved clinical remission at week 30, regardless of the computation of the Mayo score. Once a patient was categorized as a treatment failure, they were considered a treatment failure from that time on through week 30.

3. Clinical response at week 30. The definition of clinical response used for the week 30 endpoint was the same as that used for the primary endpoint.

4. Mucosal healing at week 8. Patients were considered to not have achieved mucosal healing if they had any of the treatment failure rules, regardless of their mucosal healing status based on the endoscopy subscore. If a patient discontinued from the study prior to a visit or had a missing endoscopy subscore at a visit, they were considered not to have achieved mucosal healing at that visit.

Centocor also evaluated the clinical endpoints of sustained clinical response (i.e., clinical response at both week 8 and week 30), sustained clinical remission (i.e., clinical remission at both week 8 and week 30), and mucosal healing at week 30 (see endpoints #5-#7 in TABLE 23). This reviewer evaluated the same clinical response and remission variables, using two subsets of the ITT population. For the endpoints up to week 8, the subset included patients who had complete data through week 8. For the endpoints up to week 30, the subset included patients with complete data through week 30 (see endpoints #8 through #12 in TABLE 23). The results from these additional evaluations supported the conclusion that infliximab is superior to placebo in clinical response and remission outcomes at week 8 and week 30.

TABLE 23. ACT 1. Secondary efficacy endpoints, summary of results.

	Number of patients randomized	Placebo 121	Infliximab 5 mg/kg 121	Infliximab 10 mg/kg 122
	Major secondary efficacy endpoints			
1.	Clinical remission at week 8.	18/121 14.9%	47/121 38.8%*	39/122 32.0%*
2.	Clinical remission at week 30.	19/121 15.7%	41/121 33.9%*	45/122 36.9%*
3.	Clinical response at week 30.	36/121 29.8%	63/121 52.1%*	62/122 50.8%*
4.	Mucosal healing at week 8	41/121 33.9%	75/121 62.0%*	72/122 59.0%
	Other efficacy endpoints			
5.	Centocor: Sustained clinical response (i.e., in clinical response at both week 8 and week 30)	28/121 23.1%	59/121 48.8%*	56/122 45.9%*
6.	Centocor: Sustained clinical remission (i.e., in clinical remission at both week 8 and week 30)	10/121 8.3%	28/121 23.1%*	32/122 26.2%*
7.	Centocor: Mucosal healing at week 30.	30/121 24.8%	61/121 50.4%*	60/122 49.2%*
8.	FDA: Clinical remission at week 8, in the subset of patients who completed the first 8 weeks.	18/96 18.8%	47/114 41.2%*	39/112 34.8%*
9.	FDA: The percentage of patients in clinical response at week 30, in the subset of patients who completed the 30-week study.	36/75 48.0%	63/96 65.6%*	62/94 66.0%*
10.	FDA: Clinical remission at week 30, in the subset of patients who completed the 30-week study.	19/75 25.3%	41/96 42.7%*	45/94 47.9%*
11.	FDA: Sustained clinical response, in the subset of patients who completed the 30-week study.	28/75 37.3%	59/96 61.5%*	56/94 59.6%*
12.	FDA: Sustained clinical remission, in the subset of patients who completed the 30-week study.	10/75 13.3%	28/96 29.2%*	32/94 34.0%*

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg
Number of patients randomized	**121**	**121**	**122**

* $p < 0.05$, pairwise comparison, infliximab dose group compared with placebo (the analysis of the combined infliximab groups vs. placebo was also significant at $p<0.05$).

Sources from the ACT 1 Clinical Study Report:
1. and 2. Table 8, p. 75/478
3. Table 7, p. 74/478
4. Figure 4, p. 77/478
5. Table 9, p. 80/478
6. Table 10, p. 81/478
7. Attachment 3.12, p. 210/478

[a] The totals for the 30-week completers are obtained from the sponsor's database *DISPOSIT*, using the variable *DSLSVIS* (the last recorded clinic visit). For the ACT1 study, the totals do not correspond with the totals reported by Centocor for 30-day completers in the two infliximab groups. The totals reported in the ACT 1 Clinical Study Report, Figure 1 (p. 61/478) in the category "completed follow-up" are 98 (87 + 11) for the infliximab 5 mg/kg group and 96 (84 + 12) for the infliximab 10 mg/kg group (see FIGURE 3 in this review). This discrepancy appeared to be due to four cases that were coded as "completed" by the variable *DSSTAT* ("completer" or "discontinued" with respect to the 30-week landmark) but in fact these four cases did not appear to have week 30 clinic visits. This discrepancy did not affect the decisions based on the statistical analysis of the week 30 efficacy variables.

TABLE 24. ACT 2. Secondary efficacy endpoints, summary of results.

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg
Number of patients randomized:	**123**	**121**	**122**
Major secondary efficacy endpoints			
1. Clinical remission at week 8.	7/123 5.7%	41/121 33.9%*	33/120 27.5%*
2. Clinical remission at week 30.	13/123 10.6%	31/121 25.6%*	43/120 35.8%*
3. Clinical response at week 30.	32/123 26.0%	57/121 47.1%*	72/120 60.0%*
4. Mucosal healing at week 8	38/123 30.9%	73/121 60.3%*	74/120 61.7%*
Other efficacy endpoints			

	Number of patients randomized:	Placebo 123	Infliximab 5 mg/kg 121	Infliximab 10 mg/kg 122
5.	Centocor: Sustained clinical response (i.e., in clinical response at both week 8 and week 30)	19/123 15.4%	50/121 41.3%*	64/120 53.3%*
6.	Centocor: Sustained clinical remission (i.e., in clinical remission at both week 8 and week 30)	3/123 2.4%	18/121 14.9%*	27/120 22.5%*
7.	Centocor: Mucosal healing at week 30.	37/123 30.1%	56/121 46.3%*	68/120 56.7%*
8.	FDA: Clinical remission at week 8, in the subset of patients who completed the first 8 weeks.	7/102 6.9%	41/118 34.8%*	33/111 29.7%*
9.	FDA: Clinical response at week 30, in the subset of patients who completed the 30-week study.	32/73 43.8%	57/97 58.8%*	72/96 75.0%*
10.	FDA: Clinical remission at week 30, in the subset of patients who completed the 30-week study.	13/73 17.8%	31/97 32.0%*	43/96 44.8%*
11.	FDA: Sustained clinical response, in the subset of patients who completed the 30-week study.	19/73 26.0%	50/97 51.5%*	64/96 66.7%*
12.	FDA: Sustained clinical remission, in the subset of patients who completed the 30-week study.	3/73 4.1%	18/97 18.6%*	27/96 28.1%*

* $p < 0.05$, pairwise comparison, infliximab dose group compared with placebo (the analysis of the combined infliximab groups vs. placebo was also significant at $p<0.05$).

Sources from the ACT 2 Clinical Study Report:
1. and 2. Table 8, p. 72/410
3. Table 7, p. 71/410
4. Figure 4, p. 73/410
5. Table 9, p. 76/410
6. Table 10, p.77/410
7. Attachment 3.12, p. 194/410

3.1.7. Efficacy Conclusions based on ACT 1 and ACT 2 studies

This reviewer confirmed the results presented by Centocor for the primary efficacy endpoint and for selected secondary efficacy endpoints in ACT 1 and ACT 2. The results from each study support the superiority of infliximab compared with placebo in clinical endpoints of response and remission at 8 weeks and at 30 weeks. The robustness of conclusions about the primary

efficacy outcome, the percentage of patients in clinical response at week 8, was demonstrated from the pre-specified sensitivity analysis and by additional analyses. These analyses involved different versions of the analysis data set and modifications to the decision rules for missing data. Because more patients dropped out before week 8 in the placebo group than the infliximab groups, this reviewer conducted additional analyses to evaluate how the study conclusions were affected by the rules for classifying early dropouts. The results from the primary efficacy endpoint, the major efficacy endpoints and selected other efficacy endpoints support the conclusion that infliximab was superior to placebo with respect to clinical response at week 8, week 30 and sustained response for both week 8 and week 30; for clinical remission at week 8, week 30 and sustained remission for both week 8 and 30, and for mucosal healing at week 8 and week 30.

3.2 Evaluation of Safety

Centocor presented an integrated safety analysis from pooled safety data on 728 patients through the Week 30 visit from the ACT 1 and ACT 2 studies. With respect to the occurrence of malignancy events, Centocor presented a more broadly integrated analysis, including information from nineteen studies, covering the indications that are already on the Remicade label: moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis as well as ulcerative colitis.

3.2.1. Integrated safety analysis from the ACT 1 and ACT 2 studies.

Safety evaluations in the ACT 1 and ACT 2 studies were based on patients who received at least 1 infusion of study agent, including partial infusions. Patients were analyzed according to the actual treatment they received. All 728 patients were treated; 484 patients received infliximab, either 5 mg/kg (242 patients) or 10 mg/kg (242 patients), and 244 patients received placebo. Through week 30, patients in the combined infliximab treatment group had an average of 21.5 weeks of treatment and an average of 26.9 weeks of follow-up compared with those in the placebo treatment group who had an average of 16.1 weeks of treatment and an average of 22.2 weeks of follow-up. The lower treatment and follow-up times in the placebo group were due to the higher rates of discontinuation of study infusions and study termination among patients who were in the placebo treatment group.

Adverse events (AEs)

Treatment-emergent adverse events (AEs) were summarized by treatment group and World Health Organization Adverse Reaction Terminology (WHOART) system organ class and preferred term. Treatment-emergent AEs were summarized in tables with counts and percentages with 1 or more of the specified AEs by treatment group.

The most frequently occurring AEs ($\geq$ 10% of patients) among infliximab-treated patients occurred in a similar proportion of patients in the combined infliximab treatment group and in

the placebo treatment group. These events were headache (17.4% versus 18.0%); upper respiratory infection (13.0% versus 15.2%); colitis ulcerative (12.6% versus 18.9%); arthralgia (12.0% versus 9.0%); and abdominal pain (10.5% versus 11.9%).

The gastrointestinal (GI) system was the most common system-organ class of AE reported among all patients: 39.5% of patients in the combined infliximab treatment group and 44.7% of patients in the placebo treatment group. The most common events in the GI system-organ class coded to the preferred terms of colitis ulcerative (12.6% of patients in the combined infliximab treatment group and 18.9% in the placebo treatment group) and abdominal pain (10.5% of patients in the combined infliximab treatment group and 11.9% in the placebo treatment group). One stricture was reported in a patient in the 5 mg/kg infliximab treatment group. One bowel perforation was reported in a patient in the placebo treatment group. Among patients in the combined infliximab treatment group, there were no reported cases of intestinal obstructions, peritonitis, or bowel perforations.

Deaths

No deaths occurred through week 30 in either the ACT 1 or ACT 2 study. Centocor reported the event of one patient who died after discontinuing the ACT 1 study and two patients who died after completing the main part of the ACT 2 study.

Other serious adverse events (SAE)

An SAE was defined as any AE occurring at any dose that resulted in: 1) death; 2) a life-threatening event; 3) inpatient hospitalization or prolongation of existing hospitalization; 4) persistent or significant disability/incapacity; 5) congenital anomaly or birth defect; or 6) other important medical event that, based on medical judgment, may have jeopardized the patient and/or required medical or surgical intervention to prevent one of the outcomes listed under 1) through 5).

Centocor noted that the most frequently reported SAE was worsening of ulcerative colitis, which occurred in 10.7% of patients in the placebo treatment group compared with 6.2% in the combined infliximab treatment group. The proportions of patients with other reported SAEs were similar among the combined infliximab and placebo treatment groups.

Other significant adverse events

This section presents AEs that resulted in permanent discontinuation of study infusions. In both studies, the most common AE resulting in discontinuation was due to events that represented a worsening of ulcerative colitis. Centocor noted that 6.0% of all randomized patients in ACT 1 and ACT 2 permanently discontinued study infusions due to an AE. This proportion was higher among patients in the placebo treatment group (8.6%) than those in the 5 mg/kg or 10 mg/kg infliximab treatment groups (3.7% and 5.8%, respectively).

Serious infections

In ACT 1 and ACT 2, 11 patients (2.3%) in the combined infliximab treatment group had a serious infection compared with 3 patients (1.2%) in the placebo treatment group. Of these 14 serious infections, there were two reports each of pneumonia, abscess, fever, and gastroenteritis. There was one case of pulmonary tuberculosis.

Centocor noted that during the ACT 2 study extension, 1 patient (Patient 104-004) randomized to the 5 mg/kg infliximab treatment group developed histoplasmosis that progressed to death. The patient who died with pulmonary histoplasmosis in ACT 2 came from the Ohio River Valley, where histopasmosis is endemic. The sponsor commented that histoplasmosis may be an opportunistic infection that is seen in patients whose immune system has been suppressed.

Clinical laboratory evaluations

Safety was also assessed by measuring numerous hematology and chemical laboratory parameters. For each of these laboratory parameters, summary statistics (n, median, range) were provided by treatment group for the laboratory value at selected times during the study. In addition, shift tables were provided for each of the laboratory parameters. These shift tables provide the number and percentage of patients with a low, normal, or high laboratory value at a specific postbaseline time point for each of the classifications of low, normal, and high at baseline. The baseline value for a patient was defined as the value closest, but prior, to the first administration of study agent. In addition, change from baseline was defined as the assessment at the postbaseline visit minus the assessment at baseline.

Markedly elevated ALT or AST values were defined as values that were both > 150 IU/L and an increase from baseline of $\geq$ 100%. Centocor reported that eight patients had a markedly elevated ALT value: 1 patient in the placebo treatment group, 3 patients in the 5 mg/kg infliximab treatment group, and 4 in the 10 mg/kg infliximab treatment group. Three patients had a markedly elevated AST value: none in the placebo, 2 patients in the 5 mg/kg infliximab treatment group, and 1 in the 10 mg/kg infliximab treatment group. One patient had a markedly abnormal ALT on 2 occasions. All other events of elevated transaminase were single markedly elevated events. No patients discontinued study infusions due to an elevated transaminase.

Malignancies

There were 3 malignancies reported through Week 30 among ACT 1 and ACT 2 patients, one in the placebo treatment group and 2 in the 5 mg/kg infliximab treatment group. There were no lymphomas reported.

3.2.2. Integrated analysis of malignant events from multiple studies

More infliximab-treated patients developed malignancies than placebo-treated patients in the combined results from 19 studies in different disease populations (TABLE 25). When the observed results were adjusted for follow-up time, which tended to be shorter in placebo-treated patients than in infliximab-treated patients, the malignant event rates per 100 patient-years of follow-up were generally greater in the infliximab-treated patients than in placebo-treated patients (TABLE 25). In order to compare the malignancy event rates from the infliximab studies with those in the general population, Centocor obtained the incidence rates for malignancies from the Surveillance, Epidemiology and End Results (SEER) Database, using the 1973-2000 version which was released in 2002. The database provides incidence rates for each combination of 5-year age categories, gender, and race categories (Caucasian, Black, Asian and "other"). Centocor calculated an expected incidence in the combined infliximab study population, based on a weighted sum of the SEER incidence rates. The weights were proportionate to the number of subjects in each demographic category from the combined infliximab studies. For "all malignancies," the observed number of malignancy events was similar to the expected number in the infliximab-treated patients, and was somewhat less than expected in the placebo-treated patients. However, the observed number of lymphoma events was greater than the expected number in the infliximab-treated patients from all studies and from the rheumatoid arthritis studies (TABLE 25).

TABLE 25. Malignancy events in an integrated analysis of 19 studies of infliximab, considering the controlled and open-label portions of the studies.

	3 Ulcerative Colitis Studies		8 Rheumatoid Arthritis Studies		All 19 Studies [1]	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Subjects treated	248	492	788	2363	1265	4292
Lymphoma						
Total subject-years of follow-up	105	252	584	2428	776	3787
Median subject-years of follow-up	0.6	0.6	0.4	1.0	0.5	1.0
Observed number of lymphoma events	0	0	0	2	0	4
Expected number of lymphoma events [2]	0.02	0.05	0.14	0.62	0.18	0.84
Lymphoma event rate per 100 patient-years [3]	0.00	0.00	0.00	0.08	0.00	0.11
All malignancies [4]						
Total subject-years of follow-up	105	251	583	2425	775	3782
Median subject-years of follow-up	0.6	0.6	0.4	1.0	0.5	1.0
Observed number of malignancy events	0	2	1	18	1	26
Expected number of malignancy events	0.44	1.12	4.34	18.64	5.10	23.38
Malignancy event rate per 100 patient-years	0.00	0.80	0.17	0.74	0.13	0.69

	3 Ulcerative Colitis Studies		8 Rheumatoid Arthritis Studies		All 19 Studies [1]	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab

[1] Disease populations were: Moderately to severely active rheumatoid arthritis (8 studies), Crohn's disease (6 studies), psoriatic arthritis (1 study), ankylosing spondylitis (1 study) and ulcerative colitis (3 studies).

[2] The expected number of subjects was obtained from the incidence rate in the Surveillance, Epidemiology and End Results (SEER) Database, using the 1973-2000 version which was released in 2002. The SEER incidence rates were adjusted by the composition of age group, gender and race demographics of the combined studies of infliximab.

[3] The malignancy rate per 100 patient-years was obtained from: [(Observed number of subjects)/(Total subject-years of follow-up)]X100

[4] "All malignancies" excludes nonmelanoma skin cancers.

Source: Amendment 0011, Table 1, Attachment 3, Tables Supporting Updated Labeling Information, p. 2/12

This reviewer verified a selection of summary statistics from the assessment of malignancy events, including a selection of malignancy event rates per 100 patient-years, and the age-, gender-, and race- adjusted incidence rates from the SEER Database. This reviewer recommends that the adjusted event rates per 100 patient-years be interpreted carefully, because the placebo-treated patients in general had shorter follow-up times than the infliximab-treated patients. In addition, this reviewer suggests that the event rates from the combined infliximab studies and incidence rates from the SEER Database may not be directly comparable. A comparison of the two rates can be useful, but should be interpreted carefully.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

To examine the consistency of infliximab efficacy based on demographic features, Centocor calculated odds ratios for the combined infliximab groups compared with placebo for the primary efficacy endpoint, clinical response at week 8, for subgroups defined by gender, race and age. These odds ratios, along with the 95% confidence intervals, are depicted in FIGURE 5 and FIGURE 6.

Centocor concluded that there was a consistent infliximab treatment benefit versus placebo for subgroups based on gender and age at enrollment. The number of non-Caucasian patients was not large enough to make interpretations about race.

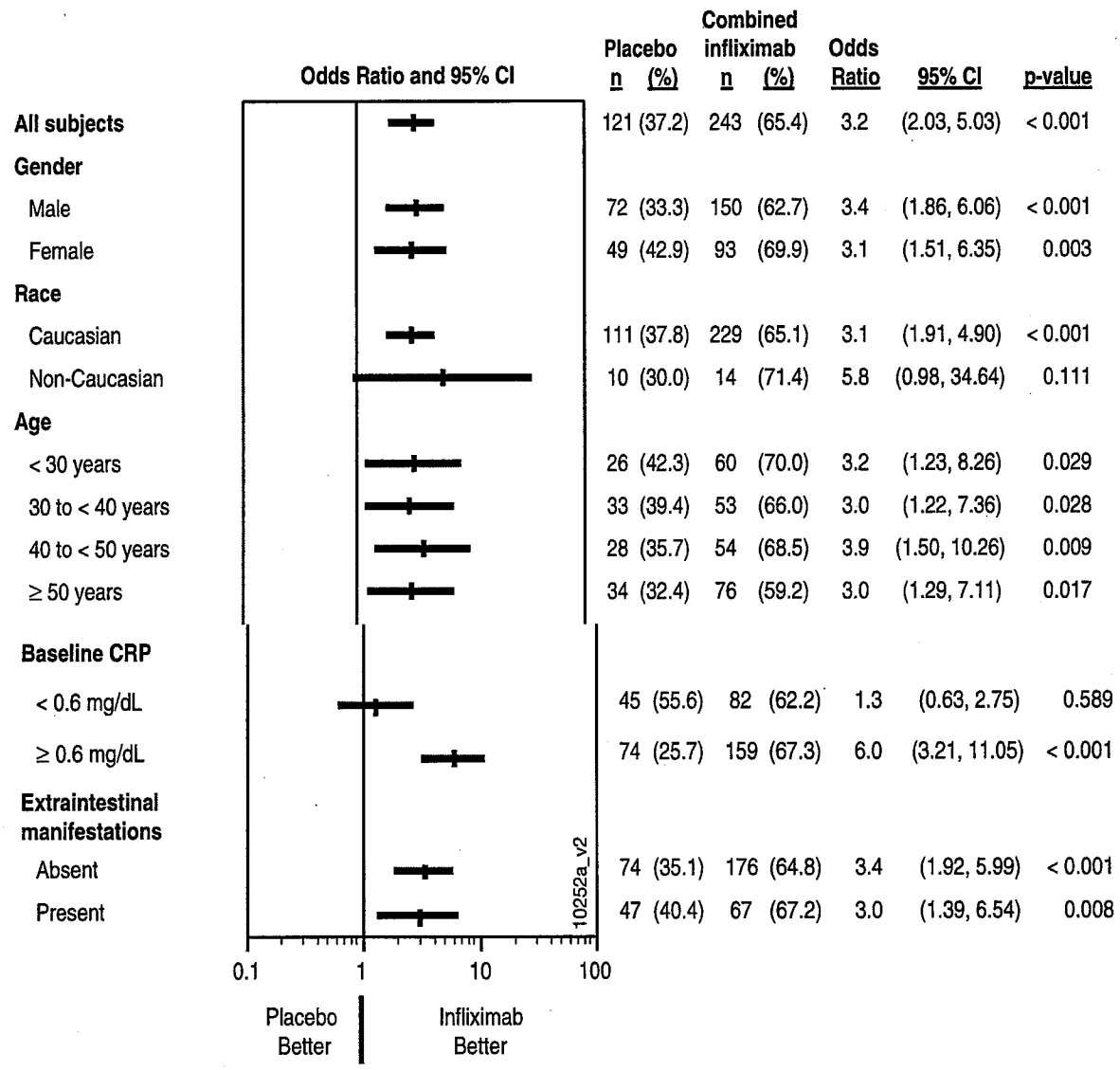
4.2 Other Special/Subgroup Populations

Corticosteroid refractory status (CRS) was the stratification variable used in randomization. Regardless of CRS, greater number of patients in the infliximab treatment groups were in clinical response at week 8 compared with patients in the placebo treatment group (TABLE 26). The percentage of patients in clinical response at week 8 was similar, in the range of 63% to 77%, regardless of whether or not the patients were refractory to corticosteroids.

Centocor noted that a differential response to infliximab was observed in ACT 1 in patients who had C-reactive protein (CRP) levels <0.6 mg/dL at baseline compared with those who had CRP ≥ 0.6 mg/dL at baseline (FIGURE 5). They commented that placebo patients in the <0.6 mg/dL CRP subgroup had a relatively high clinical response rate at week 8, which was similar to that of the response rate in the combined infliximab treatment group. This differential response to infliximab with respect to CRP status was not a feature in the ACT 2 study (FIGURE 6).

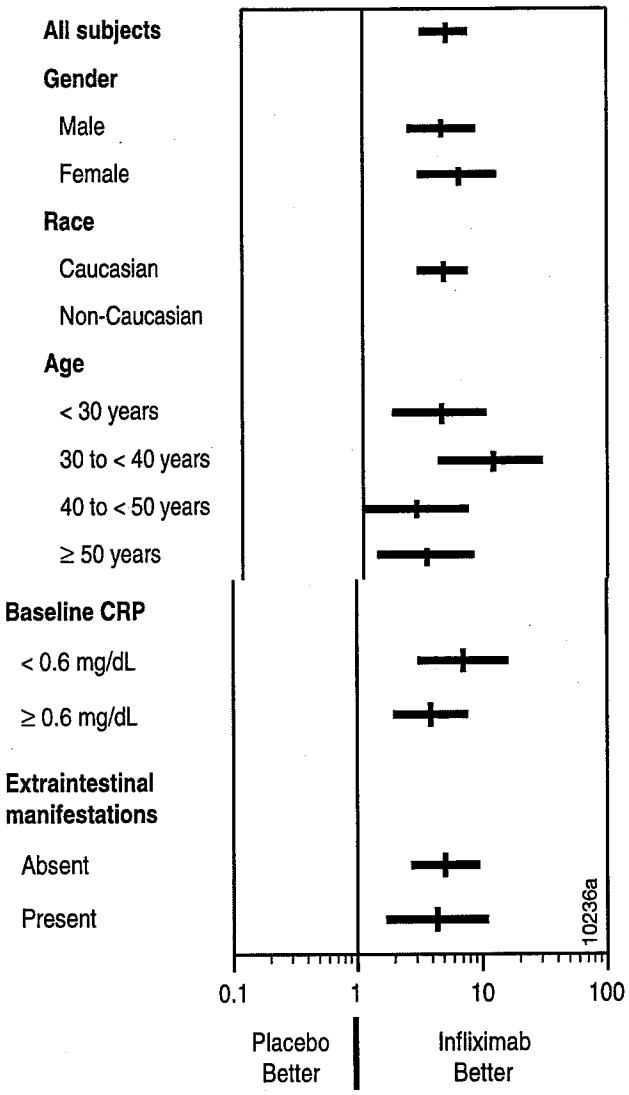
Centocor also provided odds ratios and confidence intervals for other subgroups in the ACT 1 and ACT 2 clinical study reports. They concluded in general that the percentage of patients in clinical response at week 8 in the infliximab groups compared with placebo was similar among the other subgroups that they evaluated.

FIGURE 5. ACT 1. Odds ratios and 95% confidence intervals for comparing the proportion of patients in clinical response at week 8 in the infliximab group (combined) vs. placebo group by selected baseline characteristics.



Source: ACT 1 Clinical Study Report, Figures 9 and 10, pp. 91-92/478

FIGURE 6. ACT 2. Odds ratios and 95% confidence intervals for comparing the proportion of patients in clinical response at week 8 in the infliximab group (combined) vs. placebo group by selected baseline characteristics.



	Placebo n	Placebo (%)	Combined Infliximab n	Combined Infliximab (%)	Odds Ratio	95% CI	p-value
All subjects	123	(29.3)	241	(66.8)	4.9	(3.03, 7.80)	< 0.001
Gender							
Male	71	(23.9)	144	(59.0)	4.6	(2.42, 8.66)	< 0.001
Female	52	(36.5)	97	(78.4)	6.3	(2.99, 13.21)	< 0.001
Race							
Caucasian	117	(30.8)	227	(67.4)	4.7	(2.88, 7.52)	< 0.001
Non-Caucasian	6	(0.0)	14	(57.1)	NC		0.058
Age							
< 30 years	36	(30.6)	56	(66.1)	4.4	(1.80, 10.88)	0.002
30 to < 40 years	37	(18.9)	63	(73.0)	11.6	(4.30, 31.31)	< 0.001
40 to < 50 years	21	(42.9)	59	(67.8)	2.8	(1.01, 7.80)	0.079
≥ 50 years	29	(31.0)	63	(60.3)	3.4	(1.33, 8.60)	0.017
Baseline CRP							
< 0.6 mg/dL	49	(30.6)	99	(75.8)	7.1	(3.31, 15.17)	< 0.001
≥ 0.6 mg/dL	72	(27.8)	140	(60.0)	3.9	(2.10, 7.23)	< 0.001
Extraintestinal manifestations							
Absent	88	(28.4)	169	(66.9)	5.1	(2.90, 8.93)	< 0.001
Present	35	(31.4)	72	(66.7)	4.4	(1.84, 10.37)	0.001

Source: ACT 2 Clinical Study Report, Figures 9 and 10, pp. 86-87/410

TABLE 26. ACT 1 and ACT 2. Number of patients in clinical response at week 8 by corticosteroid refractory status

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg
ACT 1: Corticosteroid refractory patients	12/34 35.3%	24/31 77.4%*	21/31 67.7%*
ACT 1: Noncorticosteroid refractory patients	33/87 37.9%	60/90 66.7%*	54/91 59.3%*
ACT 2: Corticosteroid refractory patients	12/32 37.5%	19/30 63.3%	19/29 65.5%*
ACT 2: Noncorticosteroid refractory patients	24/91 26.4%	59/91 64.8%*	64/91 70.3%*

* $p<0.05$, infliximab dose group vs. placebo

Sources:
ACT 1 Clinical Study Report: Table 12, p. 89/478
ACT 2 Clinical Study Report: Table 12, p. 84/410

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The collective evidence in support of the efficacy of infliximab for the proposed indication comes from the consistency of results from the two Phase III clinical studies. This consistency is demonstrated in several ways: (1) Each study demonstrated the superiority of infliximab to placebo in the primary efficacy endpoint; (2) The results from each study were robust to modifications in the statistical analysis; and (3) The results from the major secondary and other efficacy endpoints were consistent and supportive of the primary endpoint in each study; (4) There was a consistent infliximab treatment benefit versus placebo for subgroups based on gender and age at enrollment; and (5) The percentage of patients in clinical response at week 8 was similar for each level of corticosteroid refractory status.

A statistical issue that had the potential to affect the primary and other efficacy endpoints was the difference between the placebo and the infliximab groups in the retention of patients. In both studies, more patients in the placebo group departed from the study, and more patients departed earlier, in comparison with the two infliximab groups. This difference affected the extent to which the rules for imputation were used in each group. For this reason, this reviewer conducted additional sensitivity analyses to evaluate how the study conclusions were affected by the rules for classifying early dropouts. From these additional analyses, this reviewer concluded that the

infliximab groups had a greater percentage of patients in clinical response at week 8 than the placebo group under a range of different imputation rules.

5.2 Conclusions and Recommendations

Efficacy Conclusions: Based on an evaluation of the two Phase III studies, this reviewer concludes that the results for the primary efficacy endpoint were reasonably robust in each study. The major secondary efficacy endpoints and other efficacy endpoints were consistent and supportive to the results for the primary efficacy endpoint in each study. The statistical evaluation supports the conclusion that infliximab was superior to the placebo with respect to clinical response, clinical remission and mucosal healing at week 8 and week 30 of each study.

Safety Conclusions: Because Remicade is already approved for use in several indications, a safety database has been established, and information about the safety of Remicade is already on the label. This amendment included an integrated summary of 19 studies of infliximab in different disease populations. Estimates of malignant event rates from the integrated summary, expressed per 100 patient-years of follow-up, were generally greater in infliximab-treated patients than in placebo-treated patients. However, this reviewer recommends that the adjusted event rates be interpreted carefully, because the placebo-treated patients in general had shorter follow-up times than the infliximab-treated patients. In addition, this reviewer suggests that the event rates from the combined infliximab studies and incidence rates from the Surveillance, Epidemiology and End Results (SEER) Database may not be directly comparable. Comparisons between malignant event rates from the infliximab studies and the general population (from the SEER Database), while useful, should be interpreted carefully.

Recommendations: There are no additional recommendations.

SIGNATURES/DISTRIBUTION LIST

Janice Derr, Ph.D.:
Date: 8/25/05

Janice Derr 8/25/05

Concurring Reviewer(s):

Boguang Zhen, Ph.D.:

Boguang Zhen 8/25/05

Aloka Chakravarty, Ph.D.:

Aloka Chakravarty 8/26/05

cc:
HFD-109/Christi Stark
HFD-108/Li-Ching Liang, M.D.
HFD-108/Jeffrey Siegelman, M.D.
HFD-711/Janice Derr, Ph.D.
HFD-711/Aloka Chakravarty, Ph.D.
HFD-700/Charles Anello, Ph.D.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103772 / S-5113

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

STN 103772/5113
6/6/05

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 103772.5113 Supplement Type (e.g. SE5): SE1 Supplement Number: N/A

FDA Received Date: March 2[illegible], 2005 Action Date: Sept. 23, 2005

HFD 109 Product and Proprietary names/dosage form: Infliximab 5mg/kg, 10mg/kg IV

Applicant: Centocor, Inc. Therapeutic Class: N/A

Indication(s) previously approved:
rheumatoid arthritis, Psoriatic arthritis
Crohn's disease, Fistulizing Crohn's Disease
Ankylosing Spondylitis,

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response to conventional therapy

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☒ **No: Please check all that apply:** ☒ **Partial Waiver** ☒ **Deferred** ☐ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**

If studies are fully waived, then pediatric information is complete for this indication. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.** 0	**Tanner Stage**	
Max	**kg**	**mo.**	**yr.** <11	**Tanner Stage**	

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**

☑ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.** 11	**Tanner Stage** pre-adolescent
Max____	**kg**____	**mo.**____	**yr.** 18	**Tanner Stage** adolescent

Reason(s) for deferral:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other: Awaiting data from Crohn's disease in children study

Date studies are due (mm/dd/yy): May 2009

If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

This page was completed by:
CRISTI STARIC
Regulatory Project Manager

cc: NDA/BLA #
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03;revised 8-10-04 for RMS/BLA use)

****
*** TX REPORT ***
****

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PAGES SENT	3
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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

~~**OFFICE OF NEW DRUGS**~~

OFFICE OF DRUG EVALUATION VI

DIVISION OF REVIEW MANAGEMENT AND POLICY

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1451 Rockville Pike
Rockville, Maryland 20852-1448
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FACSIMILE TRANSMISSION RECORD

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FAX TO: Grace Carmouze / HFD-960

Facsimile Telephone No. (301) 827-7727 **Voice Telephone No.** (301) 827-7274

FROM: Cristi Stark / HFD-109

Facsimile Telephone No. (301) 827-5397 **Voice Telephone No.** (301) 827-4358

DATE: 6/6/05 **TIME:**

MESSAGE: Attached is the pediatric page for STN 103772/5113. This is a new indication (ulcerative colitis) for Centocor's Infliximab. Thanks! Please call to confirm receipt.

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

~~**OFFICE OF NEW DRUGS**~~

OFFICE OF DRUG EVALUATION VI

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MESSAGE: Attached is the pediatric page for STN 103772/5113. This is a new indication (ulcerative colitis) for Centocor's Infliximab. Thanks! Please call to confirm receipt.

SIN 103772/5113

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2005.002.A.0099
APPLICATION TYPE	BLA
SUBMISSION NUMBER	103772
SUBMISSION CODE	Serial Submission 5113
LETTER DATE	12 June 2005
DATE OF CONSULT REQUEST	10 July 2005
REVIEW DIVISION	HFD-109
MEDICAL TEAM LEADER	Jeffrey Seigel
REVIEW DIVISION PM	Cristi Stark
SEALD REVIEWER(S)	Jane Scott
REVIEW COMPLETION DATE	18 August 2005
ESTABLISHED NAME	Infliximab
TRADE NAME	Remicade®
THERAPEUTIC CLASS	Immune response modulator
APPLICANT	Centocor
PRIORITY DESIGNATION	S
ENDPOINT(S) CONCEPT(S)	Disease impact, health-related quality of life
INSTRUMENT(S)	Inflammatory Bowel Disease Questionnaire (IBDQ); [redacted] b(4)
FORMULATION	IV infusion
DOSING REGIMEN	5 mg/kg REMICADE or 10 mg/kg REMICADE reconstituted in 10mL sterile water for injection at baseline and weeks 2, 6, 14 and 22
INDICATION	Treatment of ulcerative colitis
INTENDED POPULATION(S)	patients with moderate to severe active ulcerative colitis (Mayo score 6-12) who fail to respond or are intolerant to oral corticosteroids, 6-mercaptopurine (6-MP), or azathioprine

Table of Contents

1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Therapeutic Biological Internal Medicine Products regarding the adequacy of the Inflammatory Bowel Disease Questionnaire (IBDQ) and the — b(4)
to support proposed claims regarding the efficacy of infliximab (Remicade®) for the treatment of ulcerative colitis (UC). The review compared proposed changes to the Remicade® product label [1] with the published studies describing the development and validation of the IBDQ as a measure of the impact of inflammatory bowel disease on subjective health status in patients with UC.[2, 3] The Division questioned whether information on these endpoints is appropriate for inclusion in the clinical studies section of a product label, and whether SEALD considered these — instruments adequate to support statements in labeling.

Key Findings from the SEALD Review:

1. In general, it is possible to include information based on well developed and valid endpoint assessments in the clinical trials section of the package insert if there is substantial evidence to support the statements made and the statements are not false or misleading.

[ ] b(4)

3. The IBDQ can be considered a disease-specific health-related quality of life (HRQL) assessment. The IBDQ assesses the impact of IBD and its treatment on physical, social, and emotional well-being, the three basic domains of HRQL.
4. The clinical trial results and protocols were not submitted for SEALD review. The Division is encouraged to review the study reports and protocols to confirm that the IBDQ was included among the study endpoints in the protocol, that the statistical analysis plan properly addressed multiple comparisons introduced by these endpoints, and that the results on which the proposed label statements are based accurately reflect the findings from adequately controlled clinical trials sufficient to met standards of substantial evidence.

Throughout this document, hypertext references to documents reviewed are noted in brackets [ ].

2 RECOMMENDATIONS ON REGULATORY ACTION

Section 2 provides recommendations regarding the adequacy of the endpoints the Sponsor proposes as support for desired labeling claims.

1. [ ] b(4)

[ ] b(4)

2. Appropriateness of the IBDQ to support labeling statements.
   a. The IBDQ was developed using methods recommended for patient reported outcome (PRO) assessments for clinical trials, including input from patients with UC, Crohn's disease and other inflammatory bowel diseases. It captures the three basic domains (physical, social, and emotional) that impact health-related quality of life in patients with UC in its bowel, systemic, social and emotional domain scores.
   b. The total IBDQ score would be appropriate to support labeling claims regarding improvement in IBD-related HRQL if all of the following requirements were met:
      i. the IBDQ total score was prespecified as an endpoint in the trials
      ii. statistical analyses adequately accounted for multiple comparisons
      iii. results for the total score were consistent with those for all four IBDQ domains (i.e., none of the domains indicated a worsening associated with Remicade® therapy) and
      iv. the observed difference in scores between placebo and Remicade®-containing treatment groups are statistically and clinically meaningful.

3 ENDPOINT REVIEW

This Study Endpoints and Label Development (SEALD) team review is provided as a response to a request for consultation by HFD-109 regarding the adequacy of IBDQ to support statements in labeling for the product label for Remicade® for the treatment of ulcerative colitis (UC).

3.1 Endpoint Review Methodology

The methodology used to review and respond to the Division's questions regarding the adequacy of the IBDQ [redacted] scores for evaluating change in health-related quality of life involved the following steps: b(4)

1) review question or request submitted by Review Division
2) review product label language proposed by the Sponsor
3) review key articles to evaluate the adequacy of the endpoint's
   a. development
   b. measurement properties (reliability, validity, ability to detect change, how to interpret scores)
   c. translations and adaptations
   d. how the instrument has performed in other studies
4) review protocols and study results to evaluate implementation of endpoint assessments, respond to Division question, and identify concerns and recommendations

3.2 Division's Consult Request

"Centocor has submitted a supplement to Remicade for use in the treatment of ulcerative colitis. The proposed labeling includes some quality of life claims in the Clinical Studies and indication

sections. The claims are based on the inflammatory bowel disease questionnaire (IBDQ), and the physical and mental component summary scores of the generic health-related —— Centocor has submitted a reference to validate the IBDQ. Please evaluate the proposed claims and the cited reference for substantial evidence. Should you have any questions about the supplement, please contact Cristi Stark, RPM." b(4)

3.3 Documents reviewed

The following documents were reviewed for this consultation:

[1] Proposed revision to the Remicade® product label submitted by Centocore as "STN: BL 103772/5113 – Centocor Proposed Revisions (redlined)" dated August 11, 2005.

[2] Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989 Mar; 96(3): 804-10.

[3] Irvine JE, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, Saibil F, McDonald JWD for the Canadian Crohn's Relapse Prevention Trial. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. *Gastroenterology* 1994; 106:287-296.

[4] Probert CSJ, Hearing SD, Schreiber S, Kuhbacher T, Ghosh S, Arnott IDR, Forbes A. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomized controlled trial. *Gut* 2003; 52: 998-1002.

[5] Feagan BG, Yan S, Bala M, Bao W, Lichtenstein GR. The Effects of Infliximab Maintenance Therapy on Health-Related Quality of Life. *Am J Gastroenerol* 2003;98(1):2232-2238.

In addition, a PubMed search identified a number of articles reporting on studies that included the IBDQ in patients with ulcerative colitis.

3.4 Endpoint Review Notes: HRQL in UC as measured by the IBDQ

A description of the IBDQ and the SEALD review notes follow.

3.4.1 Description of the IBDQ as a measure of HRQL in UC

The IBDQ consists of 32 questions each with 7-level Likert responses. The questions reflect four dimensions:

- Bowel symptoms (10 items)
- Systemic symptoms (5 items)
- Emotional function (12 items)
- Social function (5 items)

Time for completion: - Interviewer-administered IBDQ: 20 min
- Self-administered IBDQ: 15 min

Scoring: An unweighted sum of the items in each content domain is produced, with a total of the all item scores reported as the IBDQ score (min/max: 32/224 where higher reflects better HRQL). The total IBDQ score is more likely to describe physical symptoms and effects of IBDQ due to the larger number of items retained that relate to the physical impact of IBD (10 bowel and 5 systemic items). Higher scores for domains and total scores are assumed to reflect better HRQL.

3.4.2 Development of the IBDQ

The IBDQ was developed based on an initial literature review, followed by a series of 77 in-depth interviews with patients with Crohn's disease, UC, and other inflammatory bowel diseases. Patients (n=97; 54 with Crohn's, 43 with UC) were interviewed to confirm the content of the IBDQ and to reduce the 150 item pool to a briefer assessment for clinical trials.[2] Items chosen most frequently and those rated as most important were retained. Figure 1 (below) provides a graphical summary of the process used to develop and evaluate the reliability and validity of the IBDQ.

The IBDQ that emerged from this process contained 30 items that were serially pretested to identify poorly worded questions and to improve item presentation. Clinicians who had practices heavily weighted with IBD patients were presented with the reduced questionnaire and asked for feedback; on the basis of their responses, two additional items were added. The final IBDQ includes 10 questions relating to bowel symptoms, five questions relating to systemic symptoms (i.e., sleep disturbance, fatigue/lack of energy, and weight loss) 12 questions relating to emotional function, and five questions relating to social function. The response options for each question are framed as a seven-point scale in which "7" represents best function and "1" represents worst function. Thus, the maximum (best) score is 70 for the bowel symptoms dimension; 35 for the systemic symptoms dimension; 84 for the emotional function dimension; and 35 for the social function dimension.

Initial administration of the IBDQ takes a maximum of 30 min, and usually between 15 and 25 min. Follow-up administration takes a maximum of 25 min, and usually between 10 and 20 min. The structure and content of the questionnaire are described in Appendix 4.1.

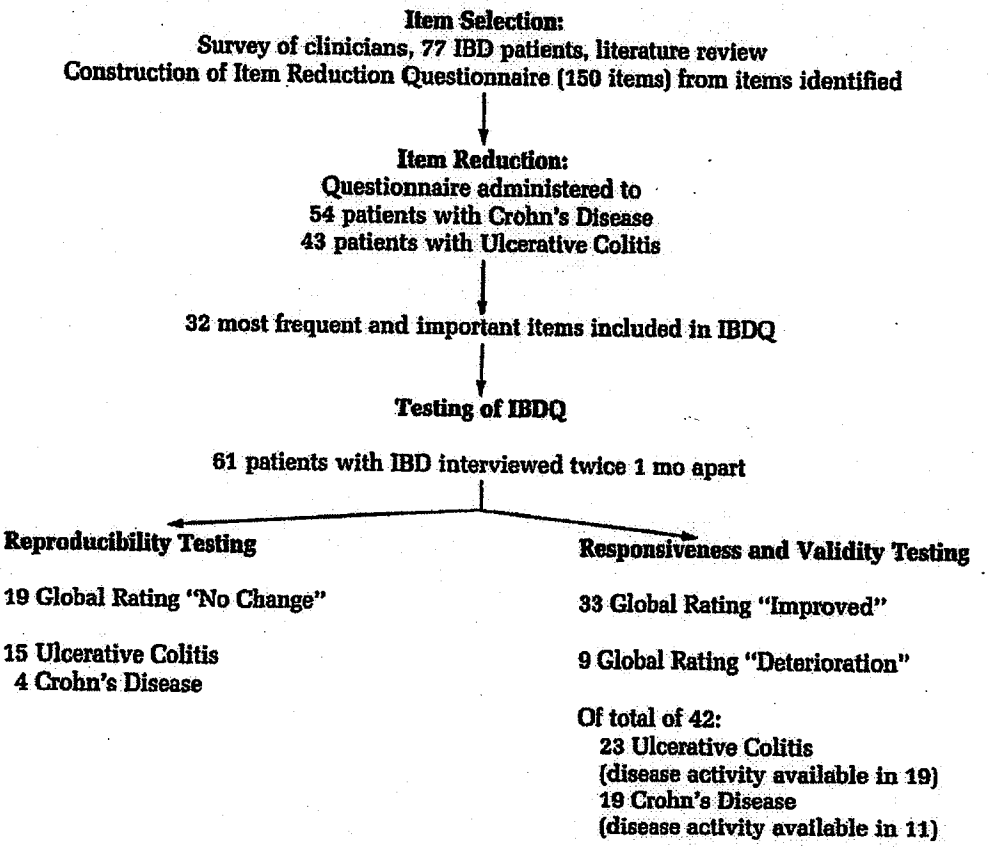

Figure 1. **Development and testing of IBDQ.**

3.4.3 Validation of the IBDQ for UC

When development and pretesting of the IBDQ had been complete, 61 patients with ulcerative colitis or Crohn's disease were interviewed twice by a single interviewer, with 1 month elapsing between interviews. All patients had histologically confirmed IBD. At each interview the IBDQ and a general measure of physical and emotional function developed by the Rand Corporation were administered. For patients whose disease was considered active by their gastroenterologist at the time of the initial assessment, the Van Hees index of disease activity (Crohn's disease) or the St. Mark's index (ulcerative colitis) was calculated. However, disease activity measures were available only for those subjects seen by a physician at both assessments. Of the 61 patients tested, this was true for 19 patients with ulcerative colitis and 11 with Crohn's disease.

Assessment of disease activity included only the patients with ulcerative colitis because there were too few Crohn's patients with stable disease. At the follow-up interview patients were asked whether their disease activity had deteriorated, remained the same, or improved. If they had improved or deteriorated, the degree of change was quantified using a seven-point Likert scale from "almost the same, hardly any better (or worse)" through "moderately better (or worse)" to "a very great deal better (or worse)." Similar global ratings were elicited for fatigue and emotional function. A relative or spouse who lived in the same household was also asked to

make global assessments of the patient's change in disease activity, fatigue, and emotional function. At the second interview, patients were classified into two groups by disease activity as changed or unchanged. The former group was considered clinically "unstable," the latter clinically "stable." Measures of reproducibility, responsiveness, and validity were extracted from these data.

Reliability (reproducibility) of the IBDQ scores was assessed as the standard deviation of the differences between baseline and follow-up in the 15 patients with UC who reported that their IBD had not changed in the past month. The standard deviation of the differences can be compared to the mean score across both administrations to yield a within-person coefficient of variation. The coefficient of variation for the four dimension scores ranged from 0.06 to 0.15 (all evidenced low variability).

Responsiveness of the IBDQ was estimated based on the change in scores associated with the 42 (32 with UC; 19 with Crohn's) patients whose global rating showed improvement or deterioration at the 4 week follow-up interview.

Validity of the IBDQ reported in the original development article [2] involved review of data from 42 subjects who reported change in their global rating of disease activity. Before examining the data, the developers made a number of predictions concerning the IBDQ findings they expected if it is really measuring health status. These predictions are listed below and for each, the observed result follows.

1. The patient's global rating of change in disease activity should relate closely (correlation, >0.5) with change in the bowel symptoms dimension of the IBDQ. Correlation observed, 0.42; $p = 0.003$. [We have never required confirmation of these things....]

2. The patient's global rating of change in tiredness should relate closely (correlation, >0.5) to change in the systemic symptoms dimension of the IBDQ. Correlation observed, 0.36; $p = 0.009$.

3. The patient's global rating of change in emotional function should relate closely (correlation, >0.5) to change in the emotional function dimension of the IBDQ. Correlation observed: 0.52, $p < 0.001$.
4. The physician's global rating of change in IBD activity should relate moderately well (correlation, >0.4) to change in the bowel symptoms dimension of the IBD. Correlation observed, 0.30; $p = 0.053$.

5. The relative's global rating of change in IBD should relate moderately well (correlation, >0.4) to change in the bowel symptoms dimension of the IBDQ. Correlation observed, 0.38; $p = 0.006$.

6. The relative's global rating of change in tiredness should relate moderately well (correlation, >0.4) to change in the systemic symptoms dimension of the IBDQ. Correlation observed, 0.17; $p = 0.14$.

7. The relative's global rating of change in emotional function should relate moderately well (correlation, >0.4) to change in the emotional function dimension of the IBDQ. Correlation observed, 0.35; p = 0.11.

8. There should be some relation (correlation, >0.3) between change in the disease activity index and change in the bowel symptoms dimension of the IBDQ. Correlation observed, 0.33; p = 0.082.

9. There should be some relation (correlation, > 0.3) between change in the disease activity index and change in the systemic symptoms dimension of the IBD. Correlation observed, 0.036; p = 0.442.

10. Change in the emotional function dimension of the IBDQ should relate closely (correlation, >0.5) with change in the emotional function dimension of the Rand questionnaire. Correlation observed, 0.76; p < 0.001.

The developer notes that ,in general, the correlations were slightly lower than those predicted. In two cases (relation between IBDQ systemic symptoms and both relative's global rating of fatigue and change in ulcerative colitis disease activity) the result was substantially different from that predicted.

3.4.4 Interpretation of IBDQ scores

Two published studies report on the IBDQ as an endpoint in clinical trials examining the effect of infliximab (Remicade®) suggest the amount of change in IBDQ scores that would be meaningful. [4, 5] A third study, by McColl et al. [6], found that the IBDQ could distinguish between people with IBD at different symptom levels but failed to find any association between IBDQ scores and extent of IBD (based on Colitis Activity Index scores).

Probert et al. [4] studied the effect of two 5-mg/kg infusions of infliximab (or placebo) given 2 weeks apart to 28 patients with glucocorticoid resistant ulcerative colitis. The infliximab treated patients had 13 point higher baseline IBDQ scores on average than did placebo, and had 11 points more increase (on average) than placebo in IBDQ total scores at week 6 post treatment. Overall, the study found no statistically significant benefit of adding infliximab to standard therapy.

Feagan et al. [5] studied the long-term effects of infliximab on patients with Crohn's disease and found that all patients treated with infliximab had a mean increase in IBDQ scores of that corresponded to the number of doses of infliximab received. Feagan et al. state that an IBDQ score of $\geq$ 170 is evidence of remission of Crohn's disease and that an increase of $\geq$ 16 points on the total IBDQ score is considered a clinically meaningful improvement based on the report by Irvine et al. [3] Based on these values, IBDQ scores showed no evidence of clinically meaningful improvement associated with infliximab.

Table 3: Mean Change from Baseline in the IBDQ at Wk 10, 30, and 54; All Patients Randomized as week 2 Responders (Total n=335)

	Week 10		Week 30			Week 54		
	Single	Triple Dose	Single	5-mg/kg Maint.	10-mg/kg Maint.	Single	5-mg/kg Maint.	10-mg/kg Maint.
IBDQ total	28.9	37.8	14.0	27.1	31.7	8.9	22.1	30.2
Bowel	8.0	12.4	3.5	8.1	10.8	1.9	6.9	9.7
Emotional	9.6	11.9	5.0	8.6	9.8	2.8	6.8	9.9
Social	5.8	6.6	2.8	5.2	5.6	2.2	4.1	4.8
Systemic	5.4	6.9	2.7	5.3	5.5	1.9	4.4	5.8

from Feagan et al. [5]

Comments:

1. The Irvine et al. validation study of the IBDQ did not make a clear statement about the amount of change in IBDQ scores that would be clinically meaningful in Crohn's disease trials. Irvine et al. provide several tables of mean change in IBDQ scores that could provide insight into the clinical meaning of changes in scores. Table 6 (Stable versus Relapse Crohn's Patients) found the following differences between stable and relapsing patients for the IBDQ scores:
   - total score -32.64
   - bowel -11.26
   - emotional -11.54
   - systemic -6.51
   - social -6.22

   It is important to remember that these scores are simple sums of scales consisting of different numbers of items. These numbers suggest an average drop of 1.02 per item was associated with relapsing Crohn's disease. This does not confirm the value of 16 as a clinically meaningful change in IBDQ scores reported by Feagan et al.
2. There was no clear estimate of how much change in IBDQ scores is clinically meaningful to patients.

3.4.5 Translation and Adaptation of the IBDQ

The IBDQ has been translated or culturally adapted from the original Canadian English version to the following languages/cultures:

Danish
Dutch (The Netherlands, Belgium)
English (Australia, Ireland, the UK)
French (France, Belgium)
German, Greek, Hebrew, Italian, Japanese, Korean
Norwegian, Portuguese, Spanish, Swedish

It is not clear that all of these translations have been conducted in a manner recommended for questionnaires used in clinical trials. Nor is it clear that all would produce equally valid data.

3.4.6 Conclusions regarding the IBDQ

1. The IBDQ was developed using the methods recommended for development of PRO instruments for clinical trials.

2. It has demonstrated sensitivity to changes in short term and longer-term studies. IBDQ scores are reproducible (reliable) and have demonstrated validity in known-group comparisons as well as construct validation against other HRQL instruments where it has been more sensitive than generic measures of HRQL.
3. It has been used in clinical trials and community studies where it has demonstrated some evidence of known groups validity [5, 6] as well as responsiveness to treatments [3, 5] and to relapse in Crohn's disease [5] and UC [3].
4. The interpretation of group differences in IBDQ scores that would be meaningful to patients has not been clearly established.

b(4)

4 APPENDICES

4.1 The Inflammatory Bowel Disease Questionnaire (IBDQ)

Appendix 4.1 provides the text of the IBDQ as described in Guyatt et al., [2]

"The IBDQ includes 32 questions. The wording is deliberately repetitious, as experience has taught us that the repetition ensures subjects' understanding. The questions are grouped into four categories: bowel symptoms (B), systemic symptoms (S), emotional function (E), and social function (SF). Response options are consistently presented as seven-point scales. An example of the way the questions are structured follows:

(B) 1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from the WHITE card in front of you.

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUEMCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

The working structure of the other questions is identical, and appropriate seven-point scales are offered for each question. The content of the remaining 31 questions is as follows:

Domain	IBDQ Item
(S)	2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last two weeks?
(E)	3. How often during the last two weeks have you felt frustrated, impatient, or restless?
(SF)	4. How often during the last two weeks have you been unable to attend school or work because of your bowel problem?
(B)	5. How much of the time during the last two weeks have your bowel movements been loose?
(S)	6. How much energy have you had during the last two weeks?
(E)	7. How often during the last two weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem?
(SF)	8. How often during the last two weeks have you had to delay or cancel a social engagement because of your bowel problem?
(B)	9. How often during the last two weeks have you been troubled by cramps in your abdomen?
(S)	10. How often during the last two weeks have you felt generally unwell?
(E)	11. How often during the last two weeks have: you been troubled because of fear of not finding a wash- room?
(SF)	12. How much difficulty have you had, as a result of your bowel problems. doing leisure or sports activities you would have liked to have done during the last two weeks?
(B)	13. How often during the last two weeks have you been troubled by pain in the abdomen?
(S)	14. How often during the last two weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night?
(E)	15. How often during the last two weeks have you felt depressed or discouraged?
(SF)	16. How often during the last two weeks have you had to avoid attending events where there was no washroom close at hand?
(B)	17. Overall, in the last two weeks, how much of a problem have you had with passing

large amounts of gas?

(S) 18. Overall, in the last two weeks, how much of a problem have you had maintaining, or getting to, the weight you would like to be at?

(E) 19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last two weeks have you had felt worried or anxious?

(B) 20. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?

(E) 21. How often during the last two weeks have you felt relaxed and free of tension?

(B) 22. How much of the time during the last two weeks have you had a problem with rectal bleeding with your bowel movements?

(E) 23. How much of the time during the last two weeks have you felt embarrassed as a result of your bowel problem?

(B) 24. How much of the time during the last two weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels are empty?

(E) 25. How much of the time during the last two weeks have you felt tearful or upset?

(B) 26. How much of the time during the last two weeks have you been troubled by accidental soiling of your underpants?

(E) 27. How much of the time during the last two weeks have you felt angry as a result of your bowel problem?

(SF) 28. To what extent has your bowel problem limited sexual activity during the last two weeks?

(B) 29. How much of the time during the last two weeks have you been troubled by feeling sick to your stomach?

(E) 30. How much of the time during the last two weeks have you felt irritable?

(E) 31. How often during the last two weeks have you felt lack of understanding from others?

(E) 32. How satisfied, happy, or pleased have you been with your personal life during the past two weeks?

5 REFERENCES

[1] Proposed revision to the Remicade® product label submitted by Centocore as "STN: BL 103772/5113 – Centocor Proposed Revisions (redlined)" dated August 11, 2005.

[2] Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989 Mar; 96(3): 804-10.

[3] Irvine JE, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, Saibil F, McDonald JWD for the Canadian Crohn's Relapse Prevention Trial. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. *Gastroenterology* 1994; 106:287-296.

[4] Probert CSJ, Hearing SD, Schreiber S, Kuhbacher T, Ghosh S, Arnott IDR, Forbes A. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomized controlled trial. *Gut* 2003; 52: 998-1002.

[5] Feagan BG, Yan S, Bala M, Bao W, Lichtenstein GR. The Effects of Infliximab Maintenance Therapy on Health-Related Quality of Life. *Am J Gastroenerol* 2003;98(1):2232-2238.

[6] McColl E, Han SW, Barton JR, Welfare MR. A comparison of the discriminatory power of the Inflammatory Bowel Disease Questionnaire and the SF-36 in people with ulcerative colitis. Qual of Life Res 2004; 13(4): 805-811.

draft	8/18/05 js
comment	8/18/05 lbb
revised	8/18/05 js
concur	8/1/805 lbb

43 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

APR 08 2005

Centocor, Incorporated
Attention: Stella S. Jones, Ph.D.
Vice President, Worldwide Regulatory Affairs
200 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Jones:

SUBMISSION TRACKING NUMBER (STN) BL 103772/5113 has been assigned to your recent supplement to your biologics license application for Infliximab received on March 24, 2005, to provide for a new indication for patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response to conventional therapy.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 827-4358.

Sincerely,

Earl Dye

Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

CONCURRENCE PAGE

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