CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BL 103772 / 1007

Trade Name: Remicade

Generic Name: (infliximab)

Sponsor: Centocor, Inc.

Approval Date: December 29, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 1007

APPROVAL LETTER

DEC 2 9 2000

Our STN: BL 103772/1007 (Replaces Ref. No. 99-1234)

Martin Page
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355

Dear Mr. Page:

Your request to supplement your biologics license application for infliximab (Remicade®) to expand the indication to include the inhibition of progression of structural damage in patients with rheumatoid arthritis who have had an inadequate response to methotrexate has been approved.

We acknowledge your agreement to provide additional information on the safety and efficacy of infliximab in combination with methotrexate and to conduct post-marketing studies as described in your commitment letters of December 11, December 18, and December 20, 2000, as outlined below:

1. To further study the safety and efficacy of infliximab in a randomized, placebo-controlled study of 1000 patients with rheumatoid arthritis who are to be treated initially with either 3mg/kg or 10mg/kg of infliximab in combination with methotrexate. This study will include patients who are treated with multiple disease-modifying anti-rheumatic drugs, and will focus upon the effects of infliximab on the development of infections. Patients initially receiving the lower dose of infliximab will be given higher doses if they do not respond to treatment. The protocol will be submitted for CBER review by January 31, 2001 and finalized by April 30, 2001. The study will be initiated by September 30, 2001 and accrual will be completed by September 30, 2002. A final study report will be submitted by September 30, 2004.

2. To collect additional infectious, autoimmune, and neoplastic adverse event data in patients receiving up to 10 mg/kg of infliximab every 4 or 8 weeks in combination with methotrexate. Data regarding tuberculosis and malignancies will be submitted to CBER within 20 days of initial receipt of the information while data on other adverse events will be submitted quarterly. In addition to the safety data collected from patients in the randomized clinical trial described in item 1 above, you will also collect safety data from the following:

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTRR/DARP	M. Marlow	12/29/00	OCTGEN	R. Temple for R.W.	29 Dec 00			
DARP	Lawrence Steinman	12/29/00	DARP	Dixon	1/5/01			

a. Two registries that will each enroll 5000 patients; one for patients with rheumatoid arthritis and the other for patients with Crohn's disease. These registries will complete enrollment within the next 12 to 18 months.

b. Six ongoing or planned Centocor-sponsored trials that involve treatment of patients with infliximab for at least one year in duration.

3. To continue long-term safety follow-up of patients who participated in the earlier conducted studies of infliximab and provide this information to CBER on a periodic basis, at least annually. Patients will be followed for a period of at least five years following the last infusion of infliximab. These earlier conducted studies include C0168T29 (ASPIRE), C0168T21 (ACCENT I) and C0168T26 (ACCENT II).

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. 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 an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

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

Sincerely yours,

Karen D. Weiss, M.D.
Division of Clinical Trial
Design and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 1007

APPROVABLE LETTER

Our STN: BL 103772/1007 (replaces Ref. No. 99-1234)

NOV 29 2000

Mr. Martin Page
Centocor Incorporated
200 Great Valley Parkway
Malvern, PA 19355

Dear Mr. Page:

This letter is in regard to the supplement to your biologics license application for Infliximab (Remicade®) submitted under section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research (CBER) has completed the review of all submissions made relating to this supplement. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

Several issues pertinent to clarifying the safety and effectiveness of Infliximab require additional information that may be obtained from post-marketing studies. We request that you propose studies to address the following issues:

1. The agency has recently received a number of reports suggesting an association between therapy with Remicade and the development of opportunistic infections. Serious and/or atypical infections, some resulting in patient death, have been observed in clinical studies or post-marketing reports with a variety of microorganisms, including *Mycobacterium tuberculosis, Listeria monocytogenes, Pneumocystis carinii, Aspergillus fumigatus,* and *Histoplasmosis capsulatum.*

   In the clinical studies, patients receiving higher doses of Remicade (e.g., 10 mg/kg every 4 weeks) had a higher number of infectious adverse events than patients receiving lower doses (3 mg/kg every 8 weeks). There is also some suggestion from clinical studies and post-marketing reports that therapy with Remicade is associated with exacerbation or prolongation of infections. In addition, the safety database for higher doses of Remicade is relatively small compared to that of lower doses. Therefore, we request that you plan additional clinical studies to further assess the safety of Remicade therapy. Please include in your submission:

   a. plans to collect, analyze and submit to the agency additional data on patients who developed tuberculosis following Remicade therapy.

   b. plans to collect additional infectious, autoimmune, and neoplastic adverse event data in patients receiving 10 mg/kg every 4 or 8 weeks.

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTAR/DARP	M. Marlin	11/29/00	DARP	M. Gorman	11-29-00			
DARP	Theresa	11/29/00	DARP	A. Williams	11-29-00			
OLDA	Wen	11/29/00						

c. plans to conduct a large (e.g., approximately 1000 patient), placebo-controlled, randomized clinical trial that assesses the relationship between therapy with Remicade and the development of opportunistic infections. This study should be powered to adequately exclude at least a two-fold difference in infectious events between the placebo and investigational arms and include a treatment duration on placebo of at least 4 months. To the extent possible, please justify your estimates of the anticipated infectious event rate in the control arm with relevant data from the literature or other sources. Consideration should be given to studying both higher and lower doses of Remicade compared to placebo (see 1b).

d. an updated summary and analysis of the safety data you have collected on patients receiving long-term therapy with Remicade as specified in our letter to you of November 10, 1999.

2. Please develop and submit plans for studying the safety and efficacy of treatment of patients with rheumatoid arthritis with higher doses of Remicade (i.e., 10 mg/kg every 4 or 8 weeks) following therapy with lower doses of Remicade (i.e., 3 mg/kg every 4 or 8 weeks).

Please describe your plans to address the above issues in sufficient detail to permit our evaluation of the adequacy of the proposals. We request that your response include:

- Detailed protocols or, at a minimum, detailed outlines describing all design features of the studies including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.

- Proposed timelines for conducting the studies, including all major milestones for the studies, e.g. finalization of the protocols, completion of enrollment, completion of all patient dosing and follow up, and submission of the final study reports and applicable revised labeling to the FDA.

Please be advised that submission of complete protocols for review and comment should be submitted to your IND and may be cross-referenced in your response to this letter.

3. We acknowledge receipt of your most recent draft of the package insert submitted on November 21, 2000. Please submit revised labeling that incorporates the enclosed editorial changes. Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

You may request a meeting or teleconference with CBER to discuss the steps necessary for approval. Should you wish to have such a meeting, please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products - February, 2000 (http://www.fda.gov/cber/gdlns/mtpdufa.pdf).

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; (3) withdraw the application/supplement; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. In the absence of any of the above responses, CBER may initiate action to deny the application.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Mr. Michael Noska, in the Division of Application Review and Policy at (301) 827-5101.

Sincerely yours,

Karen D. Weiss, M.D.
Director
Division of Clinical Trial Design
and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Our Reference Number: 99-1234

APR 13 2000

Mr. Martin Page
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355-1307

Dear Mr. Page:

This letter is in regard to the supplement to your biologics license application for Infliximab submitted under section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research (CBER) has completed the review of this supplement. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

1. Preliminary comments regarding our review of the clinical efficacy and safety data were sent to you in our January 28, 2000 discipline review letter. Please respond to all issues in that letter. We acknowledge receipt of your amendment dated March 13, 2000. You may cross reference applicable sections of that amendment in your complete response to this letter and those sections will be reviewed as a part of your complete response.

Additional deficiencies may be summarized as follows:

2. You refer to supporting data in the 30-week database submitted in your BLA supplement 99-0128. Our bioresearch monitoring team has identified the following discrepancies between the database in that supplement and in the current supplement:

   a. Subject 21017 had a history of a metatarsal resection prior to randomization and initial infusion. However, this patient is not included in Appendix I-3, "Listings of Patients with Prior Joint Surgeries/Procedures," provided in the BLA supplement 99-0128. Without correct information on baseline surgeries, we cannot accurately assess the van der Heidje scores. Please submit to this BLA supplement a revised and verified list of patients with a prior history of joint surgery and recalculate the van der Heidje scores based on the revised list.

   b. According to the line listings of concomitant medications for subject 21014, the dose of methotrexate was increased from 20 mg/wk to 22.5 mg/kg at an "unknown" time after the initiation of study treatment. During our review of the previous BLA supplement, 99-0128, you explained the documentation regarding the list of prior and concomitant medications used to treat rheumatoid

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTRR/DARP	M. Marlow	4/13/00	OTRR/DCTDA	Kuga	4-13-00			
OTRR/DARP	Villarosa	4/13/00	DTRR	Dufton	4-13-00			
OTRR/DCTDA	Silverstein	4/13/00						

arthritis through week 30 of the study. We understood from your explanation that multiple listings of methotrexate for a given patient were recorded sequentially according to time, that the last listing was the most current dose administered chronically, and that medications begun prior to infusion of study drug were marked as "unknown" in this category. Inspection of the on-site documentation for patient 21014 shows that the investigator increased the dose of methotrexate approximately 15 weeks after initiation of the study because of joint swelling. According to your explanation of the protocol, this patient should be considered a non-responder. However, subject 21014 is listed as a responder in Table 13.10 of the clinical study report. Please explain this discrepancy and verify the clinical status of all patients whose dose of methotrexate was increased at an "unknown" timepoint after initiation of study drug. Please recalculate the proportion of patients whose signs and symptoms responded to treatment with infliximab using the correct definition for non-responders.

c. In our January 28, 2000 discipline review letter of the efficacy data, we noted eight patients who received infusion of study drug through week 54 but for whom there were no radiographic data in Appendix J-16. During the February 25, 2000 telephone conversation between Drs. Greg Harriman, Harlan Weisman, and Kim DeWoody and Ms. Wan Yin Jung of Centocor and Drs. Barbara Matthews and George Mills and Mr. Michael Noska of this office, you informed the Agency that there were no radiographic data for these patients because they did not have films obtained at any timepoint. During the review of the on-site data for patient 21009, the inspector was informed that the week 0 films for this patient were obtained at another hospital and that scores for the three timepoints (weeks 0, 30 and 54) would be submitted with the week 102 data. Please clarify whether or not films were obtained at week 0 and week 54 for the eight patients listed in Table 1 of the January 28, 2000 letter. If films were obtained, please submit interpretations of the films and van der Heijde scores.

3. We reproduced your analysis of the weighted mean change from baseline in HAQ over time through week 54 and found that two p-values estimated using contrast statements in ANOVA differ from those presented in Table 20 of your clinical study report. The p-value for the 3 mg/kg every 8 weeks cohort versus placebo was 0.0358 and the p-value for the 10 mg/kg every 4 weeks cohort verses. placebo was 0.009 rather than the p-value <0.0001 reported for both comparisons. Please verify the analysis and provide SAS program(s) that can efficiently be used to repeat the analysis. In addition, please provide the method used to calculate the HAQ scores so that we can verify your calculation of the HAQ score for each patient using the source data set.

We reserve comment on the proposed labeling until the supplement is otherwise acceptable. You may request a meeting or teleconference with CBER to discuss the steps necessary for approval. Should you wish to have such a meeting, please submit your meeting request as described in the FDA Draft Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products - 3/19/99 (http://www.fda.gov/cber/gdlns/mtpdufadft.pdf).

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the supplement; (2) notify us of your intent to file an amendment; (3) withdraw the supplement; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the supplement. In the absence of any of the above responses, CBER may initiate action to deny the supplement.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

Should you need additional information or have any questions concerning administrative or procedural matters, please contact the Regulatory Project Manager, Mr. Noska, in the Division of Application Review and Policy at (301) 827-5101.

Sincerely yours,

Karen D. Weiss, M.D.
Director
Division of Clinical Trial
Design and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 1007

APPROVED LABELING

REMICADE®
(infliximab)

for IV Injection

DESCRIPTION:

REMICADE® (infliximab) 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.[1-4] 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* by complement or effector cells.[2] Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils,[3] 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 the joints of rheumatoid arthritis patients[5] and the stools of Crohn's disease patients[6] and correlate with elevated disease activity. 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].[4] 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.[4] 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.

Pharmacokinetics

Single intravenous infusions of 3 mg/kg to 20 mg/kg showed a predictable and linear relationship between the dose administered and the maximum serum concentration and area under the concentration-time curve. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Median 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 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 in fistulizing Crohn's disease and rheumatoid arthritis patients 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 in rheumatoid arthritis patients or patients with moderate or severe Crohn's disease retreated with 4 infusions of 10 mg/kg REMICADE at 8-week intervals. The proportion of patients with rheumatoid arthritis who had undetectable infliximab concentrations at 8 weeks following an infusion was approximately 25% for those receiving 3 mg/kg every 8 weeks, 15% for patients administered 3 mg/kg every 4 weeks, and 0% for patients receiving 10 mg/kg every 4 or 8 weeks. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age or weight. It is not known if there are differences in clearance or volume of distribution between gender subgroups or in patients with marked impairment of hepatic or renal function.

CLINICAL STUDIES:

Rheumatoid Arthritis

The safety and efficacy of REMICADE when given in conjunction with methotrexate (MTX) were assessed in a multicenter, randomized, double-blind, placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX (the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy or ATTRACT). 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 intravenous infusion (IV) at weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX. Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or nonsteroidal anti-inflammatory drugs was also permitted.

CLINICAL RESPONSE

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)[7] through 54 weeks (Figure 1).

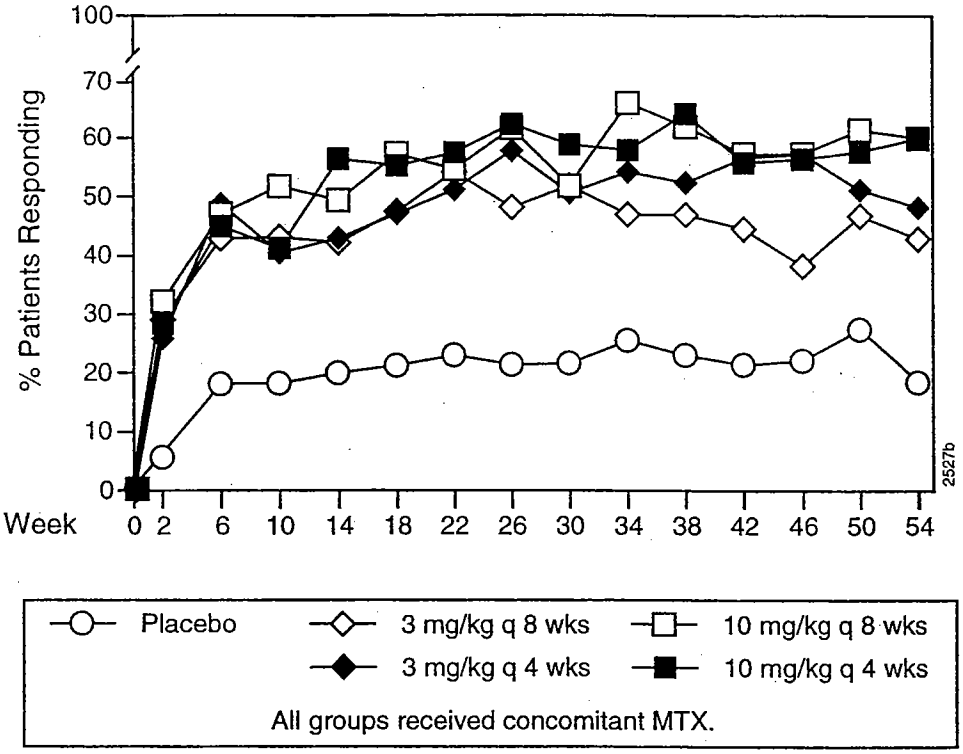


Figure 1 Percentage of Patients who Achieved an ACR 20

Compared to placebo + MTX, all doses/schedules of REMICADE + MTX consistently resulted in greater effects on each component of the ACR 20, except for the HAQ, where only the 3 higher doses/schedules showed improvements in HAQ. Results from patients receiving 3 mg/kg q 8 weeks are shown in Table 1. Responses to the higher doses or more frequent administrations were similarly distributed.

Table 1

COMPONENTS OF ACR 20

Parameter (medians)	Placebo + MTX		3 mg/kg q 8 wks REMICADE + MTX	
	Base-line	Week 54	Base-line	Week 54
No. of Tender Joints	24	16	32	10
No. of Swollen Joints	19	13	19	9
Pain[a]	6.7	6.1	7.0	4.8
Physician's Global Assessment[a]	6.5	5.2	6.1	2.6
Patient's Global Assessment[a]	6.2	6.2	6.6	4.5
Disability Index (HAQ)[b]	1.8	1.5	1.8	1.5
CRP (mg/dL)	3.0	2.3	3.1	0.8

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

All doses/schedules of REMICADE + MTX resulted in a higher number of patients experiencing ACR 50 and ACR 70 compared to placebo + MTX (Table 2).

TABLE 2
PERCENTAGE OF PATIENTS WHO ACHIEVED AN ACR RESPONSE AT WEEKS 30 AND 54

		REMICADE + MTX			
Response	Placebo + MTX	3 mg/kg * q 8 wks	3 mg/kg* q 4 wks	10 mg/kg* q 8 wks	10 mg/kg* q 4 wks
	(n=88)	(n=86)	(n=86)	(n=87)	(n=81)
ACR 50					
Week 30	5%	27%	29%	31%	26%
Week 54	9%	21%	34%	40%	38%
ACR 70					
Week 30	0%	8%	11%	18%	11%
Week 54	2%	11%	18%	26%	19%

* $p < 0.05$ for each outcome compared to placebo

Health outcome measures were assessed by the SF-36 questionnaire. The eight subscales of the SF-36 were combined into two summary scales, the physical component summary (PCS) and the mental component summary (MCS).[9] At week 54, patients treated with 3 mg/kg or 10 mg/kg of REMICADE every 8 or 4 weeks showed significantly more improvement in the PCS compared to the placebo group, and no change in the MCS.

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 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.[10] Approximately 80% of patients had paired x-ray data. Results are shown in Table 3.

TABLE 3
RADIOGRAPHIC CHANGE FROM BASELINE TO WEEK 54

Median (10, 90 percentiles)	Placebo + MTX	REMICADE + MTX				
		3mg/kg q8wks	3mg/kg q4 wks	10mg/kg q8 wks	10mg/kg q4 wks	p-value*
Week 54	(N=64)	(N=71)	(N=71)	(N=77)	(N=66)	
Total Score						
Baseline	55 (14, 188)	57 (15, 187)	45 (8, 162)	56 (6, 143)	43 (7, 178)	
Change from baseline	4.0 (-1.0, 19.0)	0.5 (-3.0, 5.5)	0.1 (-5.2, 9.0)	0.5 (-4.8, 5.0)	-0.5 (-5.7, 4.0)	p<0.001
Erosion Score						
Baseline	25 (8, 110)	29 (9, 100)	22 (3, 91)	22 (3, 80)	26 (4, 104)	
Change from baseline	2.0 (-1.0, 9.7)	0.0 (-3.0, 4.3)	-0.3 (-3.1, 2.5)	0.5 (-3.0, 2.5)	-0.5 (-2.7, 2.5)	p<0.001
JSN Score						
Baseline	26 (3, 88)	29 (4, 80)	20 (3, 83)	24 (1, 79)	25 (3, 77)	
Change from baseline	1.5 (-0.8, 8.0)	0.0 (-2.5, 4.5)	0.0 (-3.4, 5.0)	0.0 (-3.0, 2.5)	0.0 (-3.0, 3.5)	p<0.001

* For comparisons of each dose against placebo

Data on use of REMICADE without concurrent MTX are limited (see *Precautions, Immunogenicity*).[11,12]

Active Crohn's Disease

The safety and efficacy of REMICADE were assessed in a randomized, double-blind, placebo-controlled dose ranging study of 108 patients with moderate to severe active Crohn's disease[13] [Crohn's Disease Activity Index (CDAI) ≥220 and ≤400]. All patients had experienced an inadequate response to prior conventional therapies, including corticosteroids (60% of patients), 5-aminosalicylates (5-ASA) (60%) and/or 6-mercaptopurine/azathioprine (6-MP/AZA) (37%). Concurrent use of stable dose regimens of corticosteroids, 5-ASA, 6-MP and/or AZA was permitted and 92% of patients continued to receive at least one of these medications.

The study was divided into three phases. In the first phase, patients were randomized to receive a single IV dose of placebo, 5, 10 or 20 mg/kg of REMICADE. The primary endpoint was the proportion of patients who experienced a clinical response, defined as a decrease in CDAI by ≥70 points from baseline at the 4-week evaluation and without an increase in Crohn's disease medications or surgery for Crohn's disease. Patients who responded at week 4 were followed to week 12. Secondary endpoints included the proportion of patients who were in clinical remission at week 4 (CDAI <150), and clinical response over time.

At week four, 4 of 25 (16%) of the placebo patients achieved a clinical response vs. 22 of 27 (82%) of the patients receiving 5 mg/kg REMICADE ($p < 0.001$, two-sided, Fisher's Exact test). One of 25 (4%) placebo patients and 13 of 27 (48%) patients receiving 5 mg/kg REMICADE achieved a CDAI <150 at week 4. The maximum response to any dose of REMICADE was observed within 2 to 4 weeks. The proportion of patients responding gradually diminished over the 12 weeks of the evaluation period. There was no evidence of a dose response; doses higher than 5 mg/kg did not result in a greater proportion of responders. Results are shown in Figure 3.

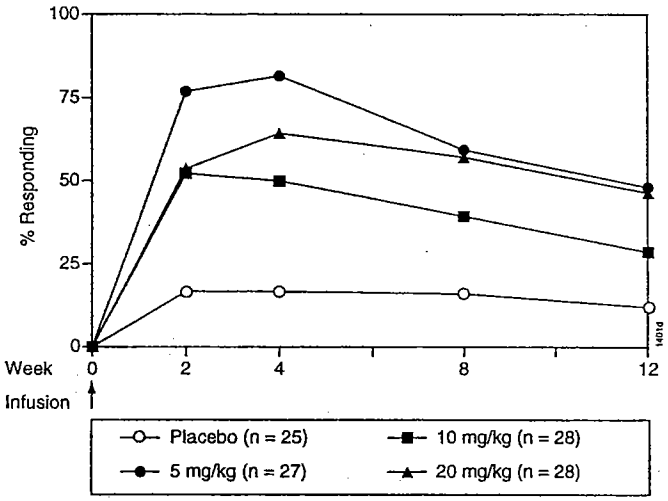


Figure 3 **Response (≥70 point decrease in CDAI) to a Single IV REMICADE or Placebo Dose**

During the 12-week period following infusion, patients treated with REMICADE compared to placebo demonstrated improvement in outcomes measured by the Inflammatory Bowel Disease Questionnaire.

In the second phase, 29 patients who did not respond to the single dose of 5, 10 or 20 mg/kg of REMICADE entered the open label phase and received a single 10 mg/kg dose of REMICADE 4 weeks after the initial dose. Ten of 29(34%) patients experienced a response 4 weeks after receiving the second dose.

Patients who remained in clinical response at week 8 during the first or second phase were eligible for the retreatment phase. Seventy-three patients were re-randomized at week 12 to receive 4 infusions of placebo or 10 mg/kg REMICADE at 8-week intervals (weeks 12, 20, 28, 36) and were followed to week 48. In the limited data set available, no significant differences were observed between the REMICADE and placebo re-treated groups.

Fistulizing Crohn's Disease

The safety and efficacy of REMICADE were assessed in a randomized, double-blind, placebo-controlled study of 94 patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration.[14] Concurrent use of stable doses of corticosteroids, 5-ASA, antibiotics, MTX, 6-MP and/or AZA was permitted, and 83% of patients continued to receive at least one of these medications. Fifty-two (55%) had multiple cutaneously draining fistulas, 90% of patients had fistula(s) in the perianal area and 10% had abdominal fistula(s).

Patients received 3 doses of placebo, 5 or 10 mg/kg REMICADE at weeks 0, 2 and 6 and were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥50% reduction from baseline in the number of fistula(s) draining upon gentle compression, on at least two consecutive visits, without an increase in medication or surgery for Crohn's disease.

Eight of 31 (26%) patients in the placebo arm achieved a clinical response vs. 21 of the 31 (68%) patients in the 5 mg/kg REMICADE arm (p = 0.002, two-sided, Fisher's Exact test). Eighteen of 32 (56%) patients in the 10 mg/kg arm achieved a clinical response.

The median time to onset of response in the REMICADE-treated group was 2 weeks. The median duration of response was 12 weeks; after 22 weeks there was no difference between either dose of REMICADE and placebo in the proportion of patients in response (Figure 4). New fistula(s) developed in approximately 15% of both REMICADE- and placebo-treated patients.

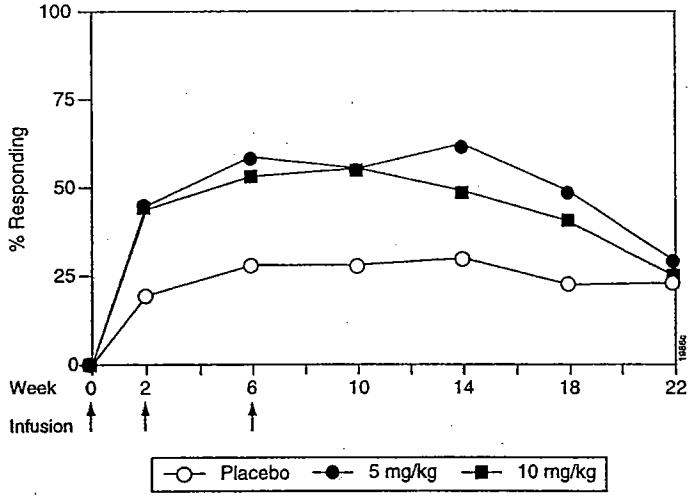


Figure 4 Response [fistula(s) closure] with Three Doses of REMICADE or Placebo

Seven of 60 (12%) evaluable REMICADE-treated patients, compared to 1 of 31 (3.5%) placebo-treated patients, developed an abscess in the area of fistulas between 8 and 16 weeks after the last infusion of REMICADE. Six of the REMICADE patients who developed an abscess had experienced a clinical response (see *ADVERSE REACTIONS, Infections*).

Dose regimens other than dosing at weeks 0, 2 and 6 have not been studied. Studies have not been done to assess the effects of REMICADE on healing of the internal fistular canal, on closure of non-cutaneously draining fistulas (e.g., entero-entero), or on cutaneously draining fistulas in locations other than perianal and periabdominal.

INDICATIONS AND USAGE:

Rheumatoid Arthritis

REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms and inhibiting the progression of structural damage in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate.

Crohn's Disease

REMICADE is indicated for the reduction in signs and symptoms of Crohn's disease in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
The safety and efficacy of therapy continued beyond a single dose have not been established (see ***DOSAGE AND ADMINISTRATION***).

REMICADE is indicated for the reduction in the number of draining enterocutaneous fistulas in patients with fistulizing Crohn's disease.
The safety and efficacy of therapy continued beyond three doses have not been established (see ***DOSAGE AND ADMINSTRATION***).

CONTRAINDICATIONS:

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

WARNINGS:

RISK OF INFECTIONS

SERIOUS INFECTIONS, INCLUDING SEPSIS AND DISSEMINATED TUBERCULOSIS, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS, INCLUDING REMICADE. 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 CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS.

CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT, ACTIVE 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 INCLUDING SEPSIS, REMICADE THERAPY SHOULD BE DISCONTINUED (see ***ADVERSE REACTIONS, Infections***). **PATIENTS SHOULD BE EVALUATED FOR THE RISK OF TUBERCULOSIS, INCLUDING LATENT TUBERCULOSIS.[15] TREATMENT FOR TUBERCULOSIS SHOULD BE INITIATED PRIOR TO TREATMENT WITH REMICADE.**

Hypersensitivity

REMICADE has been associated with hypersensitivity reactions that vary in their time of onset. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of infliximab 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 REMICADE, 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

Infliximab and other agents that inhibit TNF have been associated in rare cases with exacerbation of clinical symptoms and/or radiographic evidence of de-myelinating disease. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system de-myelinating disorders.

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).*

Malignancy

Patients with long duration of Crohn's disease or rheumatoid arthritis and chronic exposure to immunosuppressant therapies are more prone to develop lymphomas (see *ADVERSE REACTIONS, Malignancies/Lymphoproliferative Disease*). The impact of treatment with REMICADE on these phenomena is unknown.

Immunogenicity

Treatment with REMICADE can be associated with the development of antibodies to infliximab. One hundred thirty-four of the 199 Crohn's disease patients treated with REMICADE were evaluated for the development of infliximab-specific antibodies; 18 (13%) were antibody-positive (the majority at low titer, <1:20). Patients who were antibody-positive were more likely to experience an infusion reaction (see *ADVERSE REACTIONS, Infusion-related Reactions).* Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP, AZA or MTX. With repeated dosing of REMICADE, serum concentrations of infliximab were higher in rheumatoid arthritis patients who received concomitant MTX. There are limited data available on the development of antibodies to infliximab in patients receiving long-term treatment with REMICADE. Because immunogenicity analyses are product-specific, comparison of antibody rates to those from other products is not appropriate.

Vaccinations

No data are available on the response to vaccination 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.

Drug Interactions

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. Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants (see *PRECAUTIONS, Immunogenicity* and *ADVERSE REACTIONS, Infusion-related Reactions).*

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential. 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. Tumorigenicity studies in mice deficient in TNFα demonstrated no increase in tumors when challenged with known tumor initiators and/or promoters. 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 conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα.

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 infliximab 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 have not been established.

Geriatric Use

In the ATTRACT study, no overall differences were observed in effectiveness or safety in 72 patients aged 65 or older compared to younger patients. In Crohn's disease 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:

A total of 771 patients were treated with REMICADE in clinical studies. In both rheumatoid arthritis and Crohn's disease studies, approximately 6% of patients discontinued REMICADE because of adverse experiences. The most common reasons for discontinuation of treatment were dyspnea, urticaria and headache. Adverse events have been reported in a higher proportion of patients receiving the 10 mg/kg dose than the 3 mg/kg dose.

Infusion-related Reactions

Acute infusion reactions

An infusion reaction was defined as any adverse event occurring during the infusion or within 1 to 2 hours after the infusion. Nineteen percent of REMICADE-treated patients in all clinical studies experienced an infusion reaction compared to 8% of placebo-treated patients. Among the 4797 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), <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions including anaphylaxis were infrequent. Less than 2% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of infusion. REMICADE infusions beyond the initial infusion in rheumatoid arthritis patients were not associated with a higher incidence of reactions.

Patients with Crohn's disease who became positive for antibodies to infliximab were more likely to develop infusion reactions than were those who were negative (36% vs. 11% respectively). Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion reactions (see *PRECAUTIONS, Immunogenicity and Drug Interactions*).

Reactions following readministration

In a clinical study of forty patients with Crohn's disease 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. Of the 40 patients enrolled, these adverse events occurred in 9 of 23 (39%) who had received liquid formulation which is no longer in use and 1 of 17 (6%) 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 less than 2 years. However, these events have been

observed infrequently in clinical studies and post-marketing surveillance at intervals of less than 1 year.

Infections

In REMICADE clinical studies, treated infections were reported in 32% of REMICADE-treated patients (average of 37 weeks of follow-up) and in 22% of placebo-treated patients (average of 29 weeks of follow-up). The infections most frequently reported were upper respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. No increased risk of serious infections or sepsis were observed with REMICADE compared to placebo in the ATTRACT study. Among REMICADE-treated patients, these serious infections included pneumonia, cellulitis and sepsis. In the ATTRACT study, one patient died with miliary tuberculosis and one died with disseminated coccidioidomycosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Although the relationship to REMICADE is unknown, most of the cases of tuberculosis occurred within the first two months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see *WARNINGS, RISK OF INFECTIONS*). Twelve percent of patients with fistulizing Crohn's disease developed a new abscess 8 to 16 weeks after the last infusion of REMICADE (see *CLINICAL STUDIES, Fistulizing Crohn's Disease*).

Autoantibodies/Lupus-like Syndrome

In the ATTRACT rheumatoid arthritis study through week 54, 49% of REMICADE-treated patients developed antinuclear antibodies (ANA) between screening and last evaluation, compared to 21% of placebo-treated patients. Anti-dsDNA antibodies developed in approximately 10% of REMICADE-treated patients, compared to none of the placebo-treated patients. No association was seen between REMICADE dose/schedule and development of ANA or anti-dsDNA.

Of Crohn's disease patients treated with REMICADE who were evaluated for antinuclear antibodies (ANA), 34% developed ANA between screening and last evaluation. Anti-dsDNA antibodies developed in approximately 9% of Crohn's disease patients treated with REMICADE. The development of anti-dsDNA antibodies was not related to either the dose or duration of REMICADE treatment. However, baseline therapy with an immunosuppressant in Crohn's disease patients was associated with reduced development of anti-dsDNA antibodies (3% compared to 21% in patients not receiving any immunosuppressant). Crohn's disease patients were approximately 2 times more likely to develop anti-dsDNA antibodies if they were ANA-positive at study entry.

In clinical studies, three patients developed clinical symptoms consistent with a lupus-like syndrome, two with rheumatoid arthritis and one with Crohn's disease. All three patients improved following discontinuation of therapy and appropriate medical treatment. No cases of lupus-like reactions have been observed in up to three years of long-term follow-up (see *PRECAUTIONS, Autoimmunity*).

Malignancies/Lymphoproliferative Disease

In completed clinical studies of REMICADE for up to 54 weeks, 7 of 771 patients developed 8 new or recurrent malignancies. These were non-Hodgkin's B-cell lymphoma, breast cancer, melanoma, squamous, rectal adenocarcinoma and basal cell carcinoma. There are insufficient data to determine whether REMICADE contributed to the development of these malignancies. The observed rates and incidences were similar to those expected for the populations studied [16,17] (see *PRECAUTIONS, Malignancy*).

Other Adverse Reactions

Adverse events occurring at a frequency of at least 5% in all patients treated with REMICADE are shown in Table 4. Patients with Crohn's disease who were treated with REMICADE were more

likely than patients with rheumatoid arthritis to experience adverse events associated with gastrointestinal symptoms.

Table 4
ADVERSE EVENTS IN RHEUMATOID ARTHRITIS AND CROHN'S DISEASE STUDIES

	RHEUMATOID ARTHRITIS		CROHN'S DISEASE	
	Placebo (n=133)	REMICADE (n= 555)	Placebo (n=56)	REMICADE (n=199)
Avg. weeks of follow-up	35.9	41.2	14.7	27.0
Respiratory				
Upper respiratory infection	17%	26%	9%	16%
Coughing	7%	13%	0%	5%
Sinusitis	4%	13%	2%	5%
Pharyngitis	6%	11%	5%	9%
Rhinitis	7%	9%	4%	6%
Bronchitis	5%	6%	2%	7%
Gastrointestinal				
Nausea	18%	17%	4%	17%
Diarrhea	14%	13%	2%	3%
Abdominal pain	8%	10%	4%	12%
Vomiting	10%	7%	0%	9%
Dyspepsia	5%	6%	0%	5%
Other				
Headache	14%	22%	21%	23%
Rash	5%	12%	5%	6%
Dizziness	10%	10%	9%	8%
Urinary tract infection	7%	8%	4%	3%
Fatigue	5%	8%	5%	11%
Fever	6%	8%	7%	10%
Pain	8%	8%	5%	9%
Back pain	3%	6%	4%	5%
Pruritus	0%	6%	2%	5%
Arthralgia	2%	6%	2%	5%
Chest pain	5%	5%	5%	6%

Serious adverse events (all occurred at frequencies <2%) by body system in all patients treated with REMICADE are as follows:

Body as a whole: abdominal hernia, asthenia, chest pain, diaphragmatic hernia, edema, fall, pain

Blood: splenic infarction, splenomegaly

Cardiovascular: hypertension, hypotension, syncope

Central & Peripheral Nervous: encephalopathy, dizziness, headache, spinal stenosis, upper motor neuron lesion

Autoimmunity: lupus erythematosus syndrome, worsening rheumatoid arthritis, rheumatoid nodules

Ear and Hearing: ceruminosis

Eye and Vision: endophthalmitis

Gastrointestinal: abdominal pain, appendicitis, Crohn's disease, diarrhea, gastric ulcer, gastrointestinal hemorrhage, intestinal obstruction, intestinal perforation, intestinal stenosis, nausea, pancreatitis, peritonitis, proctalgia, vomiting

Heart Rate and Rhythm: arrhythmia, atrioventricular block, bradycardia, cardiac arrest, palpitation, tachycardia

Liver and Biliary: biliary pain, cholecystitis, cholelithiasis, hepatitis cholestatic

Metabolic and Nutritional: dehydration, pancreatic insufficiency, weight decrease

Musculoskeletal: arthralgia, arthritis, back pain, bone fracture, hemarthrosis, intervertebral disk herniation, joint cyst, joint degeneration, myalgia, osteoarthritis, osteoporosis, spondylolisthesis, symphyseolysis, tendon disorder, tendon injury

Myo-, Endo-, Pericardial and Coronary Valve: angina pectoris, cardiac failure, myocardial ischemia

Neoplasms: basal cell, breast, lymphoma, melanoma, rectal adenocarcinoma, skin

Platelet, Bleeding and Clotting: thrombocytopenia

Psychiatric: anxiety, confusion, delirium, depression, somnolence, suicide attempt

Red Blood Cell: anemia

Reproductive: endometriosis

Resistance Mechanism: abscess, bacterial infection, cellulitis, fever, fungal infection, herpes zoster, infection, inflammation, sepsis

Respiratory: adult respiratory distress syndrome, bronchitis, coughing, dyspnea, pleural effusion, pleurisy, pneumonia, pneumothorax, pulmonary edema, pulmonary infiltration, respiratory insufficiency, upper respiratory tract infection

Skin and Appendages: furunculosis, increased sweating, injection site inflammation, rash, ulceration

Urinary: azotemia, dysuria, hydronephrosis, kidney infarction, pyelonephritis, renal calculus, renal failure, ureteral obstruction

Vascular (Extracardiac): brain infarction, peripheral ischemia, pulmonary embolism, thrombophlebitis deep

White cell and Reticuloendothelial: leukopenia, lymphadenopathy, lymphangitis

A greater proportion of patients enrolled into the ATTRACT study who received REMICADE plus MTX experienced mild, transient elevations (<2 times the upper limit of normal) in AST or ALT (35% and 32% respectively) compared to patients treated with placebo with MTX (24% each). Six (1.8%) patients treated with REMICADE and MTX experienced more prolonged elevations in their ALT.

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 3mg/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.

Crohn's Disease

The recommended dose of REMICADE is 5 mg/kg given as a single intravenous infusion for treatment of moderately to severely active Crohn's disease. In patients with fistulizing disease, an initial 5 mg/kg dose should be followed with additional 5 mg/kg doses at 2 and 6 weeks after the first infusion.

There are insufficient safety and efficacy data for the use of REMICADE in Crohn's disease beyond the recommended duration (see *WARNINGS, Hypersensitivity; ADVERSE REACTIONS, Infusion-related Reactions;* and *INDICATIONS AND USAGE).*

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 (infliximab) 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

REFERENCES:

1. Knight DM, Trinh H, Le J, et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. *Molec Immunol* 1993;30:1443-1453.

2. Scallon BJ, Moore MA, Trinh H, et al. Chimeric anti-TNFα monoclonal antibody cA2 binds recombinant transmembrane TNFα and activates immune effector functions. *Cytokine* 1995;7:251-259.

3. Siegel SA, Shealy DJ, Nakada MT, et al. The mouse/human chimeric monoclonal antibody cA2 neutralizes TNF *in vitro* and protects transgenic mice from cachexia and TNF lethality *in vivo*. *Cytokine* 1995;7:15-25.

4. Data on file.

5. Chu CQ, Field M, Feldmann M, et al. Localization of tumor necrosis factor α in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid arthritis. *Arthritis and Rheum* 1991;34:1125-1132.

6. Braegger CP, Nicholls S, Murch SH, et al. Tumour necrosis factor alpha in stool as a marker of intestinal inflammation. *Lancet* 1992;339:89-91.

7. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* 1995;38(6):727-735.

8. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol* 1982;9(5):789-793.

9. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473-483.

10. Van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. *Arthritis Rheum.* 1992;35(1):26-34.

11. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41(9);1552-1563.

12. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) vs. placebo in rheumatoid arthritis. *Lancet* 1994;344(8930):1105-1110.

13. Targan SR, Hanauer SR, van Deventer SJH, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. *N Engl J Med* 1997;337(15):1029-1035.

14. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398-1405.

15. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221-S247.

16. Greenstein AJ, Mullin GE, Strauchen JA, et al. Lymphoma in inflammatory bowel disease. *Cancer* 1992;69:1119-1121.

17. Jones M, Symmons D, Finn J, et al. Does exposure to immunosuppressive therapy increase the 10 year malignancy and mortality risks in rheumatoid arthritis? A matched cohort study. *Br J Rheum* 1996;35:738-745.

Malvern, PA 19355, USA
1-800-457-6399

License #1242
Revised 1 December 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 1007

MEDICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

MEMORANDUM

DATE: February 25, 2000

FROM: Barbara G. Matthews, MD, MPH
Medical Officer/Team Leader, Infectious Diseases and Immunology Branch, Division of Clinical Trial Design and Analysis (DCTDA)

SUBJECT: Review of BLA supplement 99-1234
Infliximab (REMICADE) for rheumatoid arthritis
Structural Damage)

THROUGH: Karen Weiss, MD
Director of the Division of Clinical Trial Design and Analysis (DCTDA)

William Schwieterman, MD, Branch Chief, Infectious Diseases and Immunology Branch, Division of Clinical Trial Design and Analysis (DCTDA)

TO: File

Review of License Supplement 99-1234 – Infliximab for rheumatoid arthritis (Prevention of Structural Damage)

1.0 Introduction

1.1 Proposed indication and dosing regimens.

Infliximab (REMICADE) is licensed for the acute treatment of Crohn's disease and chronic treatment of the signs and symptoms due to rheumatoid arthritis. The dosage for the acute treatment of Crohn's disease is a single 5 mg/kg dose while the dosing regimen for the closure of enterocutaneous fistulae in patients with fistulizing Crohn's disease is 3 doses of 5 mg/kg at 0, 2 and 6 weeks. Infliximab in conjunction with methotrexate (MTX) is administered as 3 mg/kg at weeks 0, 2, and 6 and then every 8 weeks for the reduction of the signs and symptoms of rheumatoid arthritis in patients who have an inadequate response to methotrexate. This supplemental license application intends tp provide data that will support the indication to

indication is:

For patients with rheumatoid arthritis, REMICADE is indicated for:

- the reduction of signs and symptoms

1.2 Organization of the Review

The clinical data in support of the proposed indication was generated from the continuation of the clinical trial, C0168T22 (ATTRACT), whose week 30 data was the basis for approval of Infliximab for reduction of signs and symptoms of rheumatoid arthritis. Patients continued to be treated and evaluated through week 54 in order to determine the effect of infliximab upon The clinical trial was intended to continue through week 102 in order to evaluate the effect of infliximab upon the patients' physical function. However, based upon the outcome of the week 54 data analysis of the radiographic data by the sponsor, the data safety monitoring board recommended that patients randomized to placebo be informed and permitted to cross-over to treatment with infliximab. This review of the efficacy data evaluates the clinical data generated through week 54 in C0168T22.

The clinical trial design including the eligibility criteria, dosing regimens and study visits for C0168T22 was reviewed in the supplemental license application, BLA99-0128 and will not be reviewed in detail in this review. The reader is also referred to the review of BLA99-0128 for an overview of infliximab and anti-TNF compounds in rheumatoid arthritis and the summary of the patient demographics.

2. Synopsis of C0168T22

Objectives
The primary objective of the week 54 endpoint was to evaluate the safety and efficacy of infliximab in the

Additional objectives of the study at week 54 were to determine the efficacy and safety of infliximab in providing continued reduction in signs and symptoms,

Patient Eligibility
Patients eligible for the study were to have active rheumatoid arthritis as defined by 6 or more swollen and tender joints plus 2 of the following: morning stiffness $\geq$ 45 minutes, ESR $\geq$ 28 mm/h, CRP $\geq$ 20 mg/L while on 4 or more weeks of methotrexate at a dose of $\geq$ 12.5 mg/wk.

Trial Design
C0168T22 is a placebo-controlled, double-blind, randomized study comparing four infliximab treatment regimens with placebo. All patients continued to receive methotrexate throughout the study. The four dosing regimens of infliximab are:

- 3 mg/kg infliximab IV at weeks 0, 2, and 6 with subsequent doses every 4 weeks
- 3 mg/kg infliximab IV at weeks 0, 2, and 6 with subsequent doses every 8 weeks (placebo given at the intervening 4 week period)
- 10 mg/kg infliximab IV at weeks 0, 2, and 6 with subsequent doses every 4 weeks
- 10 mg/kg infliximab IV at weeks 0, 2, and 6 with subsequent doses every 8 weeks (placebo given at the intervening 4 week period)

2.1 Discontinuation of Study Treatment

Table 1 summarizes the number of patients who discontinued treatment through week 54 and the reasons for their discontinuations. The number of patients who discontinued treatment due to lack of efficacy was highest among patients who received placebo. Among the patients who received infliximab, more patients who received the 3 mg/kg every 8 week dosing regimen discontinued study drug due to lack of efficacy compared to the 10 mg/kg dosing regimens. For the remaining three infliximab dosing regimens, patients were just as likely to discontinue due to lack of efficacy as due to the development of an adverse event. Comparison between the 3 mg/kg and 10 mg/kg dosing regimens show that comparable number of patients discontinued due to an adverse event.

Table 1 Number of patients who discontinued treatment through week 54.

	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q 4
Pts randomized	88	86	86	87	81
Pts discontinued	44 (50%)	23 (26.7%)	20 (23.3%)	12 (13.8%)	16 (19.8%)
Reason for discontinuation					
Adverse event	7 (5 serious)	5 (3 serious, 2 infusion Rx)	9 (3 serious, 4 infusion Rx)	4 (2 serious, 1 lupus Rx)	8 (5 serious)
Lack of efficacy	32	17	10	6	7
Other	5	1	1	2	1

(Other includes patients who withdrew consent or discontinued due to noncompliance)

The majority of patients treated with placebo discontinued study treatment due to lack of efficacy with increasing frequency through week 14, with decreased frequency through week 26 where the number of patients who discontinued were steady through week 54.

3. Evaluation of Efficacy

3.1 Radiographic progression

The primary efficacy endpoint at week 54 was the [redacted] as measured by the change from baseline in the van der Heijde modification of the Sharp score, which includes radiographs of both the hand and feet, at baseline and the week 54 follow-up visit. The primary analysis included all patients with complete evaluations at baseline and week 54 in the treatment groups to which they were randomly assigned and compared the median changes in scores from baseline to week 54 in each of the infliximab treatment groups with that of the placebo group, i.e., methotrexate alone. Each patients' posteroanterior radiographs of the hands and feet from baseline and week 54 were read in a randomized, blinded manner by 2 independent reviewers. The reviewer remained blinded to the patient's treatment group, as well as whether the radiograph was a baseline or follow-up film. The van der Heijde modification of the Sharp score was calculated as the sum of the joint space narrowing (JSN) and erosion scores. The variable analyzed for the primary endpoint was the per-patient average of the change from baseline to week 54 in the total van der Heijde score according to the 2 readers. For situations in which radiographs were evaluated by only one of the readers, the score of that reader was used. For patients with missing individual joint evaluations, scores were adjusted for the number of missing joints by dividing by the number of joints assessed and then multiplying by the number of joints in the full joint set. Joints that had had surgery at baseline were not to be included in the calculation of the van der Heijde score.

3.2 Clinical response

A clinical response was defined according to the ACR preliminary definition of improvement, which required:

- 20% improvement in swollen joint count (66 joints) and tender joint count (68 joints), and
- 20% improvement in 3 of the following 5 assessments:
  - patient's assessment of pain (VAS)
  - patient's global assessment of disease activity (VAS)
  - evaluator's global assessment of disease activity (VAS)
  - patient's assessment of physical function as measured by the HAQ
  - CRP (as modified in Protocol Amendment 1).

Patients were considered to have achieved a clinical response if they satisfied the ACR preliminary definition of improvement without requiring initiation of or increases in medications for RA or a surgical joint procedure (e.g., arthrodesis and joint replacement) as described below. A major clinical response was defined for these analyses as a 70% response or greater according to the ACR criteria for 6 continuous months (consecutive scheduled visits spanning at least 26 weeks). A complete clinical response was defined as 6 continuous months (consecutive scheduled visits spanning at least 26 weeks) of remission according to the Pinals remission criteria (see Section 6.1.2.3.6, below) and no radiographic progression (no increase in a patient's modified Sharp score). For endpoints requiring a continuous response for a minimum time (e.g., major clinical response, complete clinical response, remission using the Pinals criteria), if a patient had a visit with a missed observation or a missed visit, the average of the values from the visits before and after the visit with the missing observation were substituted. Where two or more consecutive visits are missed, no substitutions were made.

Patients who had the initiation of treatment with corticosteroids or a DMARD other than MTX, an increase in the dose of MTX or corticosteroids above baseline levels, or a surgical joint procedure that either involved any of the 68 joints in the ACR joint set or affected the assessment of one of those joints, were considered nonresponders from the date of their withdrawal from treatment (e.g., the date of the medication change or surgical procedure), regardless of their actual response data. In the analyses at weeks 30 and 54, patients who did not return for evaluation or who had insufficient data to assess their ACR status were considered nonresponders for clinical response. At other time points, patients who had missing or incomplete evaluations after discontinuing study treatment because of a lack of efficacy that did not involve a protocol-prohibited medication change or joint surgery were considered nonresponders. Patients who had missing or incomplete evaluations after discontinuing because of safety or "other" reasons were not included in analyses at these time points. For all other patients, any data recorded were included in all data summaries and analyses.

If a patient had a surgical joint procedure in 1 of the joints included in the ACR joint set prior to participation in the trial, those joints were not included in any of the joint assessments for this trial. If a patient underwent intra-articular injections of

corticosteroids or needle aspiration of fluid in a single joint included in the ACR joint set, that joint was considered tender and swollen thereafter. However, patients who received intra-articular injections of corticosteroids in more than 1 joint and/or needle aspiration of fluid from more than 1 joint were considered nonresponders as of the date that they received the injection or needle aspiration in their second joint. Patients who received epidural injections of corticosteroids were also considered nonresponders thereafter unless the reason for the injection was clearly documented to be other than rheumatoid arthritis.

For patients who had an incomplete joint set evaluated, the joint count was adjusted to a 68-joint count for pain/tenderness and a 66-joint count for swelling by dividing the number of affected joints by the number of joints evaluated and multiplying by 68 for pain/tenderness or 66 for swelling.

3.3 Clinical remission

Patients were considered to have achieved a clinical remission if 5 of the following 6 requirements were fulfilled for at least 2 consecutive months (defined as 3 consecutive scheduled visits). This definition assumes that clinical remission occurred without an initiation of or increase in medications or an intervening (surgical) joint procedure as described above for clinical response.

- Duration of morning stiffness did not exceed 15 minutes
- No fatigue (less than 0.5 cm on the VAS for fatigue)
- No joint pain (less than 0.5 cm on the VAS for pain)
- No joint tenderness or pain on motion
- No soft tissue swelling in joints or tendon sheaths
- CRP <10 mg/L (as modified by Protocol Amendment 1)

[ ]

4.0 Efficacy Results

The clinical data reviewed for this efficacy review included the clinical data submitted in the supplemental BLA99-1234. Because the history of prior surgeries was not included originally with the supplemental application, the list from the 30week application (99-0128) was used.

4.1 Radiographic results

Review of the clinical data in suppor[redacted]of radiographic progression revealed problems with the clinical datasets submitted and apparent inconsistencies between the available data and the radiographic results such that a complete review of the data in support of the proposed indication could not be conducted. The following problems were identified:

1. Summary of the radiographic data (scores of JSN, erosion scores and total van der Heijde scores for Readers 1 and 2) are provided in the line listing of Appendix J-15 of the license supplement. Appendix A-2 of the license supplement provides the data on study drug administration through week 54. Comparison between these two datasets reveals that radiographic results for 12 patients who received study drug are not provided in Appendix J-15 (Table 2).

Table 2. List of patients who received study drug but for whom there is no radiographic data.

Treatment Group	PID	Last infusion	[redacted] submitted
Placebo	07004	4	No
	07013*	15	Yes
	13008	15	No
	30001	8	No
3 mg/kg q 8	09002*	15	Yes
	13003	15	No
3 mg/kg q 4	07009*	15	Yes
	34003	15	No
10 mg/kg q 4	05018	12	No
	13006	15	No
	21009	15	No
	33015	15	No

*van der Heijde scores for joints recorded in Appendices J-16 through J-22

Radiographic data are missing for some patients in all treatment groups save 10 mg/kg infliximab every 8 weeks. The problem cannot be attributed to loss of follow-up since 9 patients received all 15 infusions of study drug, i.e., through week 54. Surprisingly, individual joint scores for Readers 1 and 2 for three patients (07013, 09002, and 07009) are listed in Appendices J-16 though J-21 of the supplement and their radiographs are included in the [redacted] database submitted with the license application. However, no van der Heijde scores are listed in the summary appendix J-15 for these three patients.

2. We reviewed the radiographic data for patients whose van der Heijde score was recorded as "NE" in the summary listing of radiographic results provided in Appendix J-15 of the license supplement. Fifty-seven of these patients did not have a complete set of radiographs for evaluations, i.e., at both baseline and week 54. However, there are 34 patients with films at baseline and week 54 and have total JSN and/or erosion scores recorded as "NE". (Patient 08008 had baseline radiographs that could not be interpreted so he is considered as having an incomplete set of radiographs for evaluations.) Review of the individual scores of the joints in the hands and feet for both reader 1 and 2 provided in Appendices J-16 through J-21 reveal the scores can be calculated for many of these patients. These patients are listed in Appendix A of this review with comments. There appears to be three factors affecting the calculation of the van der Heijde score:

For some patients, the van der Heijde score was not calculated when the patient had had a surgical procedure to the set of joints in a foot, e.g., arthrodesis of the metatarsal phalange joint (MTP) 1 through 5 of either one or both feet, even though the set of joints in the hands were scored. Although joints that had had surgery at the time of study enrollment were not to be counted in the score, van der Heijde scores can be calculated for these patients with the score limited to the assessable joints, i.e., a set of joints in the hands with or without a set of joints from one or both feet.

There are several patients for whom Reader 1 recorded the radiograph as technically adequate ("2") but scored the set of joints in one or both feet as "ND" with the consequence that the van der Heijde score for that patient by Reader 1 is recorded as "NE" in Appendix J-15. With the exception of patient 22008, Reader 1 scored the same joints in the feet as "ND" at both baseline and at week 54 and thus, the score would be zero at both timepoints. For patients where the joints in only one foot were recorded as "ND", the total score for the set of feet joints could be adjusted on the basis of the score of the joints read in the other foot. Consequently, a van der Heijde score could be calculated for these patients. Omission of the effect of treatment upon the joints in the hands and any joints read in the feet could potentially bias the interpretation of the clinical data in two ways: 1) interpretation of the effect of infliximab on [redacted] s skewed towards the sensitivity and specificity of radiograph interpretation of a single reader (Reader 2 in this instance), and 2) the amount of difference that determines a worsening of the van der Heijde score from baseline is dependent upon inter-reader variability, i.e., what amount of increase in van der Heijde score from baseline for the patient population represents true worsening rather than acceptable variation in interpretation?

We identified three patients (15015, 15007, and 14002) who had the joints in the feet scored by either Reader 1 or Reader 2 and who did not have surgery to these joints at the time of study enrollment. However, in the listing of summary results in Appendix J-15, the final JSN and/or erosion score is recorded as "NE". For example, patient 14002 had had surgery to MTP1-5 of the right and left foot but not the first interphalangeal joint of both feet. These joints were scored for erosions by reader 2 and an adjusted ES could be calculated since the scores for the MTP would be constant, i.e., "0", at both time points.

3. We calculated the van der Heijde scores for a random sample of 23 patients listed in Appendix J-15 using the clinical data provided in Appendices J-16 through J-21 of the license supplement. We found inconsistencies between the calculated score and reported scores for 10 patients whose films were scored by Reader 2 and one patient (15015) whose films were scored by reader 1 (Appendix B). Review of the differences suggest that for Reader 2, a change in the line listing of scores for foot erosions from "0" to "10" results in the erosion score that is recorded in Appendix J-15 by the sponsor. It cannot be determined from the clinical or radiographic data provided how the erosion score for the feet joints should be properly scored. However, a change from "0" to "10" did not account for all of the patients in the our sample, e.g., patient 15015.

Interestingly, review of this discrepancy suggests a retrospective understanding of the number "NDs" ("evaluation not done, or unreadable") recorded for the individual joint scores of erosions and JSN by Reader 1 for radiographs of the feet which he considered radiographically adequate. He may have scored severe erosions and JSN as "ND" to indicate a significant degree of disease in the joint while Reader 2 scored these joints as "10". Apparently, there was no manual with guidance on interpretation provided to the readers such that application of the van der Heijde score would be more consistent.

Summary of the review of radiographic data.

- Given the degree of flaws in the radiographic database, no conclusions regarding the effect of treatment with infliximab on its effect to [redacted] can be made.
- The radiographic portion of the clinical database needs to be corrected and verified prior to its re-analysis.
- The sponsor should consider a re-reading of the radiographic results and submitting a complete database.
- Associations between effect of treatment with infliximab upon structural damage and clinical response, including disability, cannot be investigated until the radiographic database is corrected and verified.

4.2 [redacted]

4.2.1 Sponsor's Analysis

Endpoints required to demonstrate [redacted] of disability include improved in HAQ scores in addition to no worsening in a more general measure of quality of life, such as the SF-36, provided improvement in signs and symptoms have been demonstrated previously or concurrently. According to the amended protocol for C0168T22, disability was assessed by analyzing patients' weighted mean change from baseline HAQ scores through week 54. No concurrent decrease in weighted mean SF-36 mental component summary score compared with the placebo group must be demonstrated for that treatment group over the 54 week period.

Table 3 shows the weighted mean change from baseline in the mental component summary scores of the SF-36. The mental component summary scores of the SF-36 were not significantly different among the treatment groups while the overall [redacted] was [redacted] tients who received infliximab.

Table 3. Weighted mean changes from baseline in SF-36 Mental Component Summary Score through week 54

	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q 4
Pts evaluated	87	84	86	86	79
Mean ± SD	1.3 ± 1.6	1.7 ± 1.7	1.5 ± 1.8	1.4 ± 1.6	1.6 ± 1.7
Median	0.6	1.	0.7	0.9	1.0
p-value vs. placebo		0.05	0.26	0.24	0.08

The HAQ evaluates 8 functional categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Patients score from 0-3 for a series of 2 to 4 questions per category. In this rating system, 0 is normal, 1 is adequate, 2 is limited and 3 is unable to perform a task in that category (Table 4).

Table 4. Weighted mean changes from baseline HAQ through week 54

	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q 4
Pts evaluated	87	86	85	87	81
Mean ± SD	0.2 ± 0.3	0.4 ± 0.3	0.5 ± 0.4	0.5 ± 0.5	0.4 ± 0.4
Median	0.1	0.3	0.3	0.4	0.3
p-value vs. placebo		<0.001	<0.001	<0.001	<0.001

The sponsor evaluated the individual components of the HAQ. Although each component was better in the patients treated with infliximab the improvements were small and not statistically significant even though as an aggregate they were better than placebo. The sponsor also explored the relationship of HAQ with the ACR components using stepwise regression using the AUC for the percent improvement from baseline vs. time for each component. None of the ACR components save for tender joints and evaluator's global assessment of disease severity were significant predictors of HAQ.

4.2.2 FDA analysis of HAQ data.

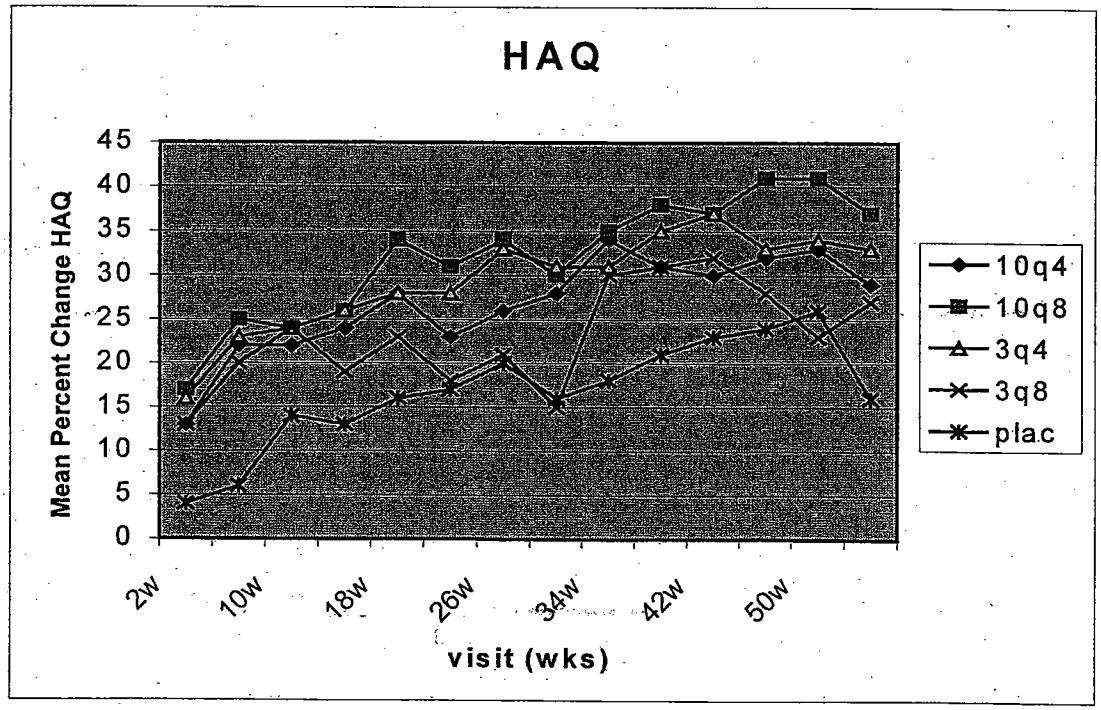
Brief description of HAQ. The HAQ evaluated 8 categories of a patient's ability to function: dressing, rising, eating, walking, hygiene, reach, grip and activities. Patients are requested to score answers to questions within each category as: 0 (normal), 1 (adequate), 2 (limited), and 3 (unable). The HAQ score is calculated by adding the scores and dividing by the total number of components answered.

Area under the Curve (AUC) and Landmark analysis of HAQ.

Because of the problems with the radiographic datasets, we calculated the HAQ for patients using the original data recorded in the SAS datasets. The final scores generated matched those presented by the sponsor. (Note, an error is still possible in the transcription of the clinical data recorded by the patient in the case report form into the SAS datasets.)

The weighted mean change from baseline in analysis of HAQ represents and AUC analysis. This type of analysis provides information on the change in HAQ for all patients with a baseline HAQ throughout the time that the patient remained in the study. Thus, data on patients who discontinue treatment either due to loss of efficacy or adverse event are included in the analysis. An analysis using the AUC provides more information on patients while they are receiving treatment but it provides less information on the durability of response because patients drop out or the curves for the treatment groups begin to converge with continued therapy. In order to depict the nature of the change in HAQ over time, we calculated the percent change from baseline HAQ at each study visit and plotted the graph of the mean percent change for each treatment group (Figure 1). All of the treatment groups improve in their disability scores through the 54 week study period with the greatest improvement in the 10 mg/kg every 8 week dosing regimen and the least in the placebo treated groups. The most consistent effect upon HAQ is seen with the three highest dose regimens of infliximab. A more erratic effect was seen with the licensed dose regimen (3 mg/kg every 8 weeks) with the mean percent change in HAQ score identical or slightly worse at 4 of the 15 visits. The mean AUC of HAQ was significantly different between placebo and each of the infliximab treatment groups, including the 3 mg/kg every 8 weeks dosing regimen..

Figure 1. Mean percent change in HAQ from baseline at each study visit for the 5 treatment groups.



An analysis of the median change in HAQ between baseline and week 54 for the treatment groups (landmark analysis) provides information on the status of the patients at week 54 in comparison with their status at the time of study entry. Overall there is a significant difference in the mean change of baseline HAQ among the five treatment groups using analysis of variance for the five treatment groups. However, a pairwise comparison of the means using the Student-Newman-Keuls test shows that there was a significant difference between the placebo group and patients treated with infliximab at the dosing schedules of 3 mg/kg every 4 weeks and 10 mg/kg every 8 weeks whereas the mean change was not significantly different between the remaining two infliximab treatment groups and placebo although the mean change from baseline HAQ was higher in the infliximab groups (-0.43 vs. –0.28).

Comparison between these two analyses (AUC and landmark) of HAQ indicates that while patients are receiving infliximab they experience a reduction in their physical , out that by week 54 the difference in the effect upon physical disability lessens between patients treated with infliximab and methotrexate compared to those treated with methotrexate alone. Although the difference diminishes, there remains a durable n patients treated with infliximab at 10 mg/kg every 8 weeks or 3 mg/kg every 4 weeks but less so with the licensed dose regimen of 3 mg/kg every 8 weeks. A comparison of these analyses also show that AUC is more sensitive than a landmark analysis of HAQ since the difference in effect of placebo and treatment with 3 mg/kg every 8 weeks of infliximab was significant with the AUC analysis but not with the landmark analysis.

Analysis of HAQ according to the patient's baseline HAQ score.

We wished to evaluate whether there was a difference in treatment effect on the mean change in HAQ at week 54 in patients whose baseline HAQ was >2 and those whose baseline score was ≤ 2 (limited disability). There were 295 patients with a baseline HAQ ≤ 2 and 133 patients with baseline HAQ >2. Using ANOVA, we found a significant difference overall in the mean change in HAQ between baseline and week 54 for patients with baseline HAQ ≤ 2. However, for patients with a baseline HAQ >2 (greater disability), the mean change in HAQ was not significantly different from baseline by week 54. Comparison of the mean change in HAQ among the 5 treatment groups for patients with a baseline HAQ ≤ 2 shows that the mean change in HAQ was significantly different between patients treated with placebo and those treated with 10 mg/kg every 8 weeks but not between placebo and the three remaining infliximab treatment groups although the mean change in the three infliximab groups was higher than that in placebo (0.40 to 0.44 compared to 0.19).

We conducted a similar analysis using a cut-off baseline HAQ of 1.5 and found similar results. There were 174 patients whose baseline HAQ was ≤ 1.5 and 254 patients with baseline HAQ >1.5. Again, the difference between mean change from baseline HAQ was greatest between placebo and the 10 mg/kg q 8 weeks treatment groups for patients with

baseline HAQ $\leq$ 1.5 while there were no differences among the treatment groups in patients whose baseline HAQ was >1.5.

Because HAQ is a component of the ACR criteria used to assess clinical response, we asked whether baseline HAQ as well as treatment group was associated with ACR20 response at week 54. Using a logistic regression analysis, we found that clinical response was associated with the baseline HAQ such that patients with lower baseline HAQ had a better chance of achieving an ACR20 response.

Summary of the review of the clinical data regarding HAQ

- There is a significant difference in the mean change from baseline HAQ between patients treated with placebo and infliximab at a dose of 3 mg/kg every 8 weeks using the AUC analysis but not with a landmark analysis. There was a beneficial effect upon HAQ for patients treated with 10 mg/kg every 8 weeks infliximab and MTX compared to patients treated with placebo and MTX using both types of analysis.

- Patients with less disability at the time that the begin treatment appear to have more improvement in their functional disability as measured by HAQ compared to those with greater disability.

4.3 Clinical response

4.3.1. Sponsor's analysis of clinical response.

A clinical response was defined as an ACR 20% response at week 54 without a protocol-prohibited change in medication and/or a surgical joint procedure. Table 5. shows the percentage of patients in each treatment group who achieved an ACR20 at week 54. After 54 weeks of treatment there appears to be treatment-dependent effect of infliximab on the clinical response.

Table 5. Patients who achieved an ACR20 at week 54

	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q 4
Pts randomized	88	86	86	87	81
ACR20 responders	15 (17%)	36 (41.9%)	41 (47.7%)	51 (58.6%)	48 (59.3%)
p-value vs. placebo		<0.001	<0.001	<0.001	<0.001

Relationship of clinical response to infliximab concentration or dose

The sponsor assessed the median trough concentrations of infliximab for patients as a function of duration of clinical response (ACR20 for different lengths of time) (Figure). The duration of response assessment was divided into 3 categories: 1.) patients who achieved and ACR20 response at 0 or 1 of the 14 visits evaluated through week 54, 2.) patients who achieved and ACR20 response at $\geq$ 2 to <8 of the 14 visits, and 3.) patients who achieved and ACR20 response at $\geq$ 8 out of 14 visits.

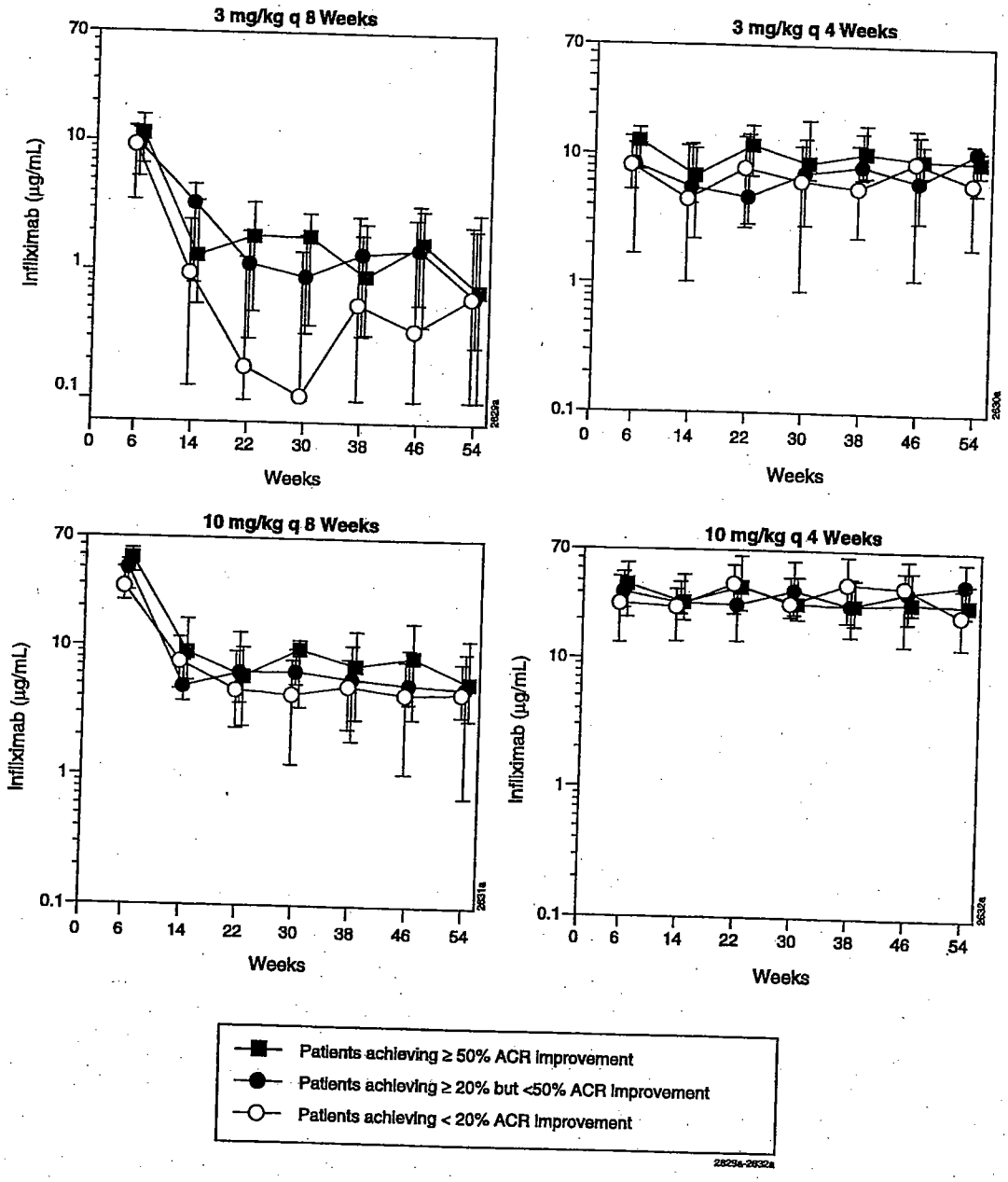


Figure 2. Medium trough serum concentrations for samples collected 4 to 8 weeks following treatment in patients achieving an ACR20 response for various durations. The median and interquartile range serum concentrations are shown for patients who achieved an ACR20 response at ≥ 8 visits, at ≥ 2 to <8 visits, and at 0 or 1 visit. The limit of detection of the infliximab assay is 0.1 µg/mL. Any undetectable median or range infliximab concentrations were graphically represented as equal to 0.1 µg/mL.

The lowest response category (≥ ACR20 for 0 or 1 visit) for the 3 mg/kg every 8 weeks treatment group recorded the lowest median trough serum levels of infliximab. The group responding at a single visit or less had a lower median infliximab trough concentration and the highest response category had the highest median trough concentrations. Following week 14, undetectable infliximab trough concentrations ere observed for ≥ 25% of patients in the 3 mg/kg every 8 weeks treatment group who achieved ACR20 at only 0 or 1 visit, or achieved ACR20 improvement at 2 to 7 visits. Undetectable trough concentrations were also observed at weeks 38, 46 and 54 for ≥ 25% patients in the 3 mg/kg every4 weeks group achieving ACR20 improvement at 0 or 1 visit. These results suggest that there may be some association between short duration of clinical response in the 3 mg/kg treatment groups and undetectable trough infliximab concentrations. However, the association is not apparent between trough serum concentrations and low duration of clinical efficacy for the 10 mg/kg treatment groups.

The proportion of patients with various ranges of ACR response at weeks 30 and 54 are presented in Figure 3, according to the range of trough serum infliximab concentration observed just prior to treatment at these two timepoints. The higher trough infliximab concentrations are associated with a higher percentage of patients achieving higher degrees of ACR response. However, the relationship is not absolute since some patients achieve ≥ ACR70 response with undetectable pre-infusion concentrations of infliximab and some patients do not achieve and ACR20 response while maintaining >10 mcg/ml of infliximab prior to the infusion.

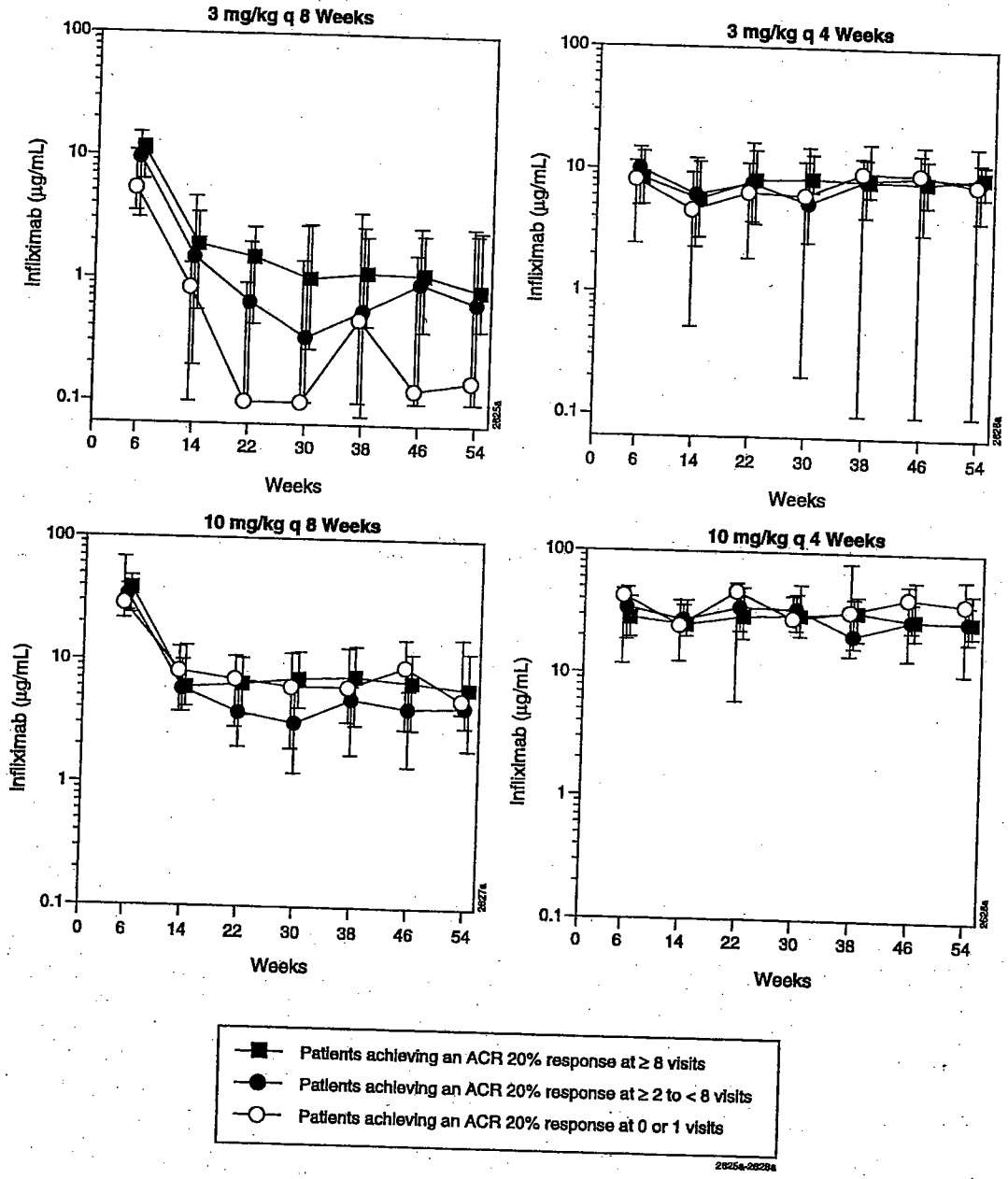


Figure 3. Median trough infliximab concentrations at each time point for patients achieving various ACR response magnitudes. The median and interquartile range serum concentrations for those patients who achieved <20% ACR response, ≥ 20% ACR but <50% ACR improvement, or ≥ 50% ACR response are assessed at each time point. The limit of detection of the infliximab assay i [redacted] able median or range infliximab concentrations were graphically represented as

Clinical Remission.

Patients were considered to have achieved clinical remission if they fulfilled the Pinals criteria for at least 2 consecutive months (3 consecutive visits). Pinals criteria requires fulfillment of 5 of the following 6 requirements: duration of morning stiffness ≤ 15 minutes; no fatigue (<0.5 cm on the VAS for fatigue); no joint pain; no joint tenderness or pain on motion; no soft tissue swelling joints or tendon sheaths; CRP ≤ 10 mg/L. Through week 54, a total of 8 (2.4%) of the 340 infliximab-treated patients achieved clinical remission compared with none of the 88 placebo-treated patients (Table 6); the proportions were not large enough to achieve a significant treatment effect. The greatest number of patients who achieved clinical remission were treated with 10 mg/kg every 8 weeks.

Table 6. Patients who achieved a clinical remission (Pinals criteria).

	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q 4
Pts randomized	88	86	86	87	81
clinical remission	0	1 (1.2%)	1 (1.2%)	4 (4.6%)	2 (2.5%)

Nominal p-value = 0.212

Major Clinical Response.

A major clinical response was defined as an ACR70 for 6 consecutive months (consecutive scheduled visits spanning ≥ 26 weeks). Sixteen (4.7%) of the 340 patients treated with infliximab achieved a major clinical response compared with none of the 88 patients treated with placebo (Table 7); the proportions were not large enough to achieve a significant treatment effect. Again, the largest proportion of patients who achieved a major clinical response were treated with the higher dosing regimen (10 mg/kg) of infliximab.

Table 7. Patients who achieved a major clinical response at week 54.

	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q 4
Pts randomized	88	86	86	87	81
major clinical response	0	3 (3.5%)	3 (3.5%)	7 (8.0%)	3 (3.7%)

Nominal p-value = 0.09

Complete Clinical Response.

A complete clinical response was defined as remission according to the Pinals criteria for 6 consecutive months (consecutive scheduled visits spanning ≥ 26 weeks) and no radiographic progression. According to the sponsor's analysis, no patients achieved a complete clinical response by the week 54 evaluation visit.

4.3.2 FDA Analyses of Clinical Response

Clinical response at week 54 and week 30.

We determined the proportion of patients with ACR20, ACR50 and ACR70 response at week 54 and evaluated the number of patients who had maintained this degree of response from week 30 or attained this degree of response after week 30. Tables 8 through 10 list the number of patients by their ACR20, ACR50 and ACR70 response at weeks 30 and weeks 54. For patients treated with 3 mg/kg infliximab every 8 weeks, there were 36 patients who achieved an ACR20 at week 54. Of these 36, 28 (77.8%) also had an ACR20 response at week 30 and 8 patients achieved ACR20 subsequent to week 30. Similarly for the ACR50 response for the 3 mg/kg every 8 week treatment group, 11/18 patients were ACR50 responders at both weeks 30 and 54 and 7 patients achieved ACR50 subsequent to the week 30 timepoint. The last row of each table provides the number of patients who lost that particular ACR response after week 30 for the different treatment groups.

Table 8. Patient with ACR20 response

	Total	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q 4
Number of pts		88	86	86	87	81
All ACR20 responders at wk54	191	15 (17.1%)	36 (41.9%)	41 (47.8%)	51 (58.6%)	48 (59.3%)
ACR20 at wk54 and at wk 30	149	12 (13.6%)	28 (32.6%)	34 (39.5%)	37 (42.5%)	38 (46.9%)
ACR20 at wk54 but not at wk30	42	3 (3.4%)	8 (9.3%)	7 (8.1%)	14 (16.1%)	10 (12.4%)
ACR20 at wk30 but not at wk54	46	6 (6.8%)	15 (17.4%)	9 (10.5%)	7 (8.1%)	9 (11.1%)

Table 9. Patients with ACR50 response

	Total	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q 4
Number of pts		88	86	86	87	81
All ACR50 responders at wk54	118	7 (8%)	18 (20.9%)	29 (33.7%)	34 (39.1%)	30 (37%)
ACR50 at wk54 and at wk 30	74	3 (3.4%)	11 (12.8%)	22 (25.6%)	23 (26.4%)	15 (18.5%)
ACR50 at wk54 but not at wk30	44	4 (4.6%)	7 (8.1%)	7 (8.1%)	11 (12.6%)	15 (18.5%)
ACR50 at wk30 but not at wk54	23	1 (1.1%)	11 (12.8%)	2 (2.3%)	3 (3.5%)	6 (7.4%)

Table 10. Patients with ACR70 response

	Total	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q 4
Number of pts		88	86	86	87	81
All ACR70 responders at wk54	63	2 (2.3%)	9 (10.5%)	15 (17.4%)	22 (25.3%)	15 (18.5%)
ACR70 at wk54 and at wk 30	32	0 (0%)	2 (2.3%)	8 (9.3%)	14 (16.1%)	8 (9.9%)
ACR70 at wk54 but not at wk30	31	2 (2.3%)	7 (8.1%)	7 (8.1%)	8 (9.2%)	7 (8.6%)
ACR70 at wk30 but not at wk54	8	0 (0%)	5 (5.8%)	1 (1.2%)	1 (1.2%)	1 (1.2%)

Review of the data in the above three tables support the conclusion that a greater proportion of patients treated with infliximab experienced both ACR20 and ACR50 response at week 54. In addition, a greater proportion of patients treated with infliximab maintained a response at both weeks 30 and 54 compared to patients treated with placebo. Interestingly, even though the overall number of placebo-treated patients who achieved an ACR20 response were markedly lower compared to patients treated with infliximab, those patients who did respond in the placebo arm (i.e., methotrexate alone) did show a consistent ACR20 response comparable to infliximab-treated patients. The number of patients who achieved an ACR50 response at week 54 are too small to ascertain a consistent effect from week 30.

These data indicate that patients with rheumatoid arthritis who respond at week 30 to a given treatment appear to maintain that response. A greater proportion of patients treated with infliximab achieve an ACR response compared to patients treated with placebo. Comparison among the four dosing regimens of infliximab suggest that clinical response increases from the 3 mg/kg dosing regimens to those containing 10 mg/kg; the most efficacious dose from the ACR data appears to be 10 mg/kg every 8 weeks.

Consistency of response through week 54 in ACR20 and ACR50 responders

In order to characterize the response over the 54 week period for patients who were responding to treatment at week 54, we calculated the mean change from baseline in ACR at each time point by treatment group for patients categorized by their ACR20 response at weeks 30 and 54. Patients were categorized into three groups: group 1 = ACR20 responders at weeks 54 and 30, group 2 = ACR20 responders at week 54 but not at week 30, and group 3 = ACR20 responders at week 30 but not at week 54. For these analysis, if an ACR could not be calculated for a patient at a given visit then the ACR was assigned a value of 0.

Graphs of the mean change from baseline in ACR response at each visit for the three groups for the two treatment groups, 3 mg/kg every 8 weeks (the licensed dose) and 10 mg/kg every 8 weeks are shown in Figures 4 and 5. We limited the analysis to these two dosing regimens because the 3 mg/kg every 8 weeks regimen is licensed and the 10 mg/kg every 8 weeks appears to be more effective both by the ACR criteria and effect on disability.

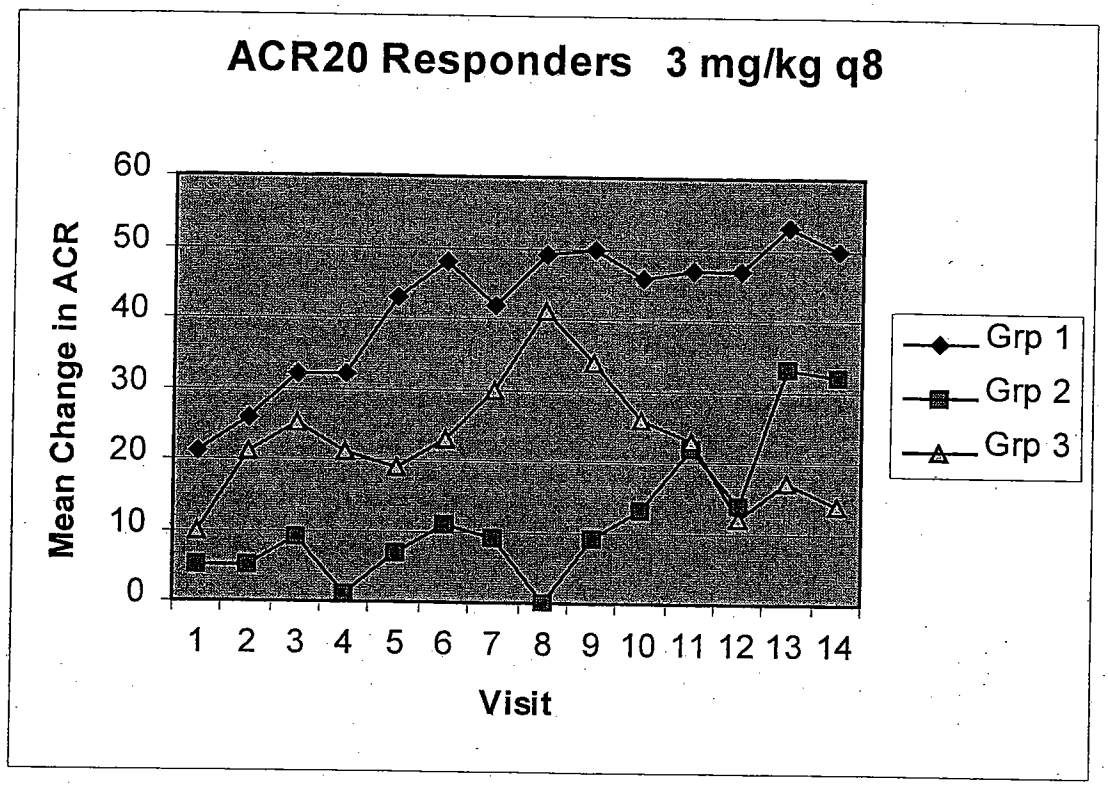


Figure 4. Mean change in ACR from baseline at each visit (visit 9 = week 30 and visit 15 = week 54) for patients who achieved an ACR20 response at week 30 and/or week 54 and who were treated with 3 mg/kg of infliximab every 8 weeks. Group 1 = ACR20 responders at weeks 30 and 54, Group 2 = ACR20 responders at week 54 but not at week 30, and Group 3 = ACR20 responders at week 30 but not at week 54.

Appears This Way
On Original

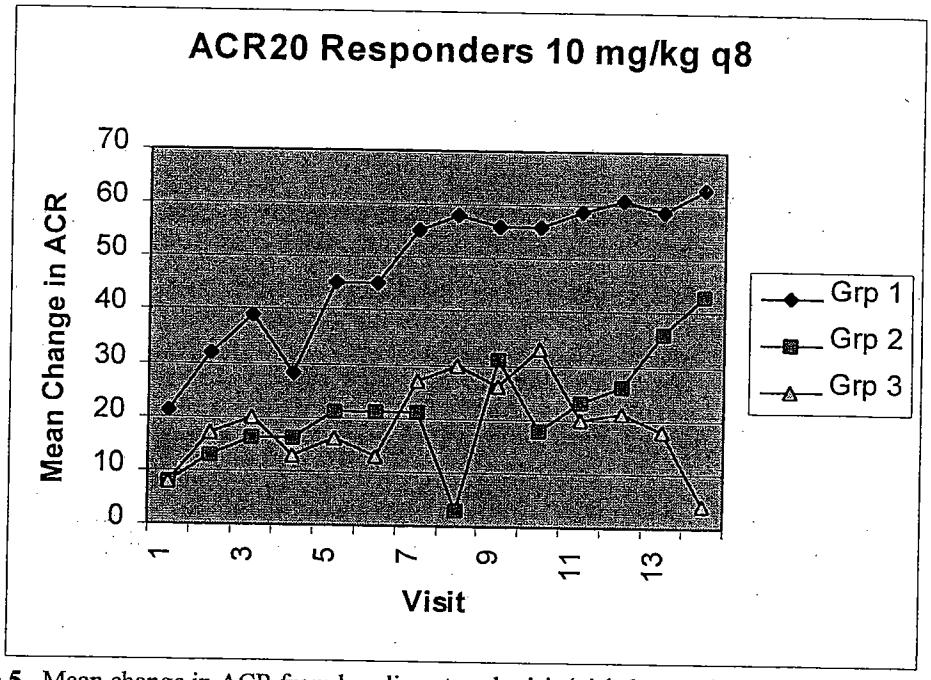


Figure 5. Mean change in ACR from baseline at each visit (visit 9 = week 30 and visit 15 = week 54) for patients who achieved an ACR20 response at week 30 and/or week 54 and who were treated with 10 mg/kg of infliximab every 8 weeks. Group 1 = ACR20 responders at weeks 30 and 54, Group 2 = ACR20 responders at week 54 but not at week 30, and Group 3 = ACR20 responders at week 30 but not at week 54.

Upon review of the two graphs, the following characteristics can be described:

- Except for some uniquely high or low mean ACR at a given visit, the type of response was not erratic in nature for the different response categories for each dosing regimens over the 54 week study period.

- Patients who had an ACR20 response at both weeks 30 and 54 show an increase in the mean ACR through visit 6 or 7 when the mean ACR response appears to level off for both dosing regimens.

- Although the degree of response differs between the two infliximab dosing regimens for patients who have an ACR20 at week 54 but not at week wk 30, the nature of the response is similar, i.e., the mean ACR is consistently lower until about visit 12-13 when the mean ACR increases.

- For patients with an ACR20 response at week 30 but not at week 54, patients in both treatment groups appeared to have a fairly consistent low level response until about visit 10-11 when the response diminished.

A similar analysis of the mean change in ACR from baseline was done for patients with an ACR50 response and are shown in figures 6 and 7. The characteristic of the response was similar to those described above for ACR20 responders.

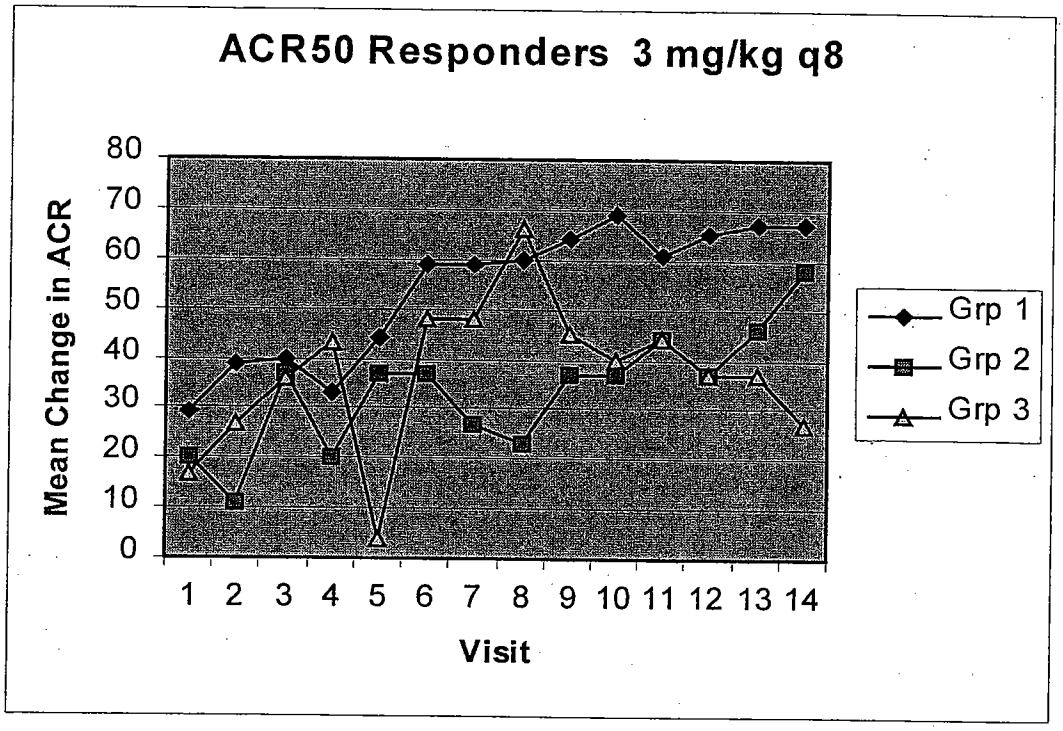


Figure 6. Mean change in ACR from baseline at each visit (visit 9 = week 30 and visit 15 = week 54) for patients who achieved an ACR50 response at week 30 and/or week 54 and who were treated with 3 mg/kg of infliximab every 8 weeks. Group 1 = ACR50 responders at weeks 30 and 54, Group 2 = ACR50 responders at week 54 but not at week 30, and Group 3 = ACR50 responders at week 30 but not at week 54.

Appears This Way
On Original

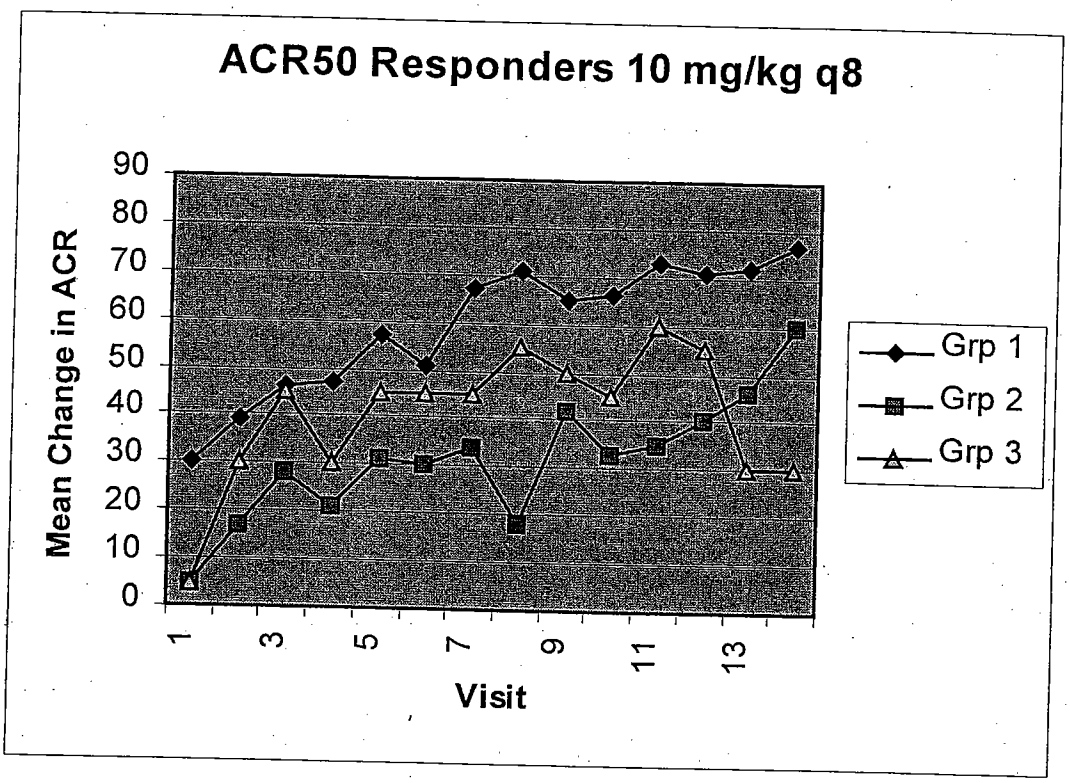


Figure 7. Mean change in ACR from baseline at each visit (visit 9 = week 30 and visit 15 = week 54) for patients who achieved an ACR50 response at week 30 and/or week 54 and who were treated with 10 mg/kg of infliximab every 8 weeks. Group 1 = ACR50 responders at weeks 30 and 54, Group 2 = ACR50 responders at week 54 but not at week 30, and Group 3 = ACR50 responders at week 30 but not at week 54.

AUC Analysis of the ACR in nonresponders (ACR20) at week 54.

Although many investigators recognize its limitations, the ACR20 has been accepted as the measurement of clinical benefit in rheumatoid arthritis trials. Alternative measurements have been suggested, included the AUC of the ACR (i.e., ACRn). Comparison of the proportion of patients who achieve an ACR20 at a given timepoint provides information only at that timepoint while the AUC provides information on the response over time. Both methods have their utility. Although the AUC analysis may be more informative by including the response over the course of the study for all patients, including patients who drop-out of the study, it is a more sensitive analysis. As such, it may not provide an adequate indication of the proportion of patients who respond to a therapy by the end of 6 months.

In order to highlight the sensitivity of the AUC measurement of outcome, we compared the AUC for the ACR by treatment group in patients who failed to achieve an ACR20 response in the ATTRACT trial. Using ANOVA, we found that for ACR20 nonresponders, there was a significant difference in the mean of the AUC of the ACR for patients treated with any dose regimen of infliximab compared to placebo. Therefore, if the AUC were the primary analysis of effect, more patients treated with infliximab would

be considered as having an effect even though they failed to achieve an ACR20 at week 54. As can be seen in the following set of analyses, the AUC is a very useful tool to analyze the response variables in patients who have already been classified as having an effect with therapy.

Area under the curve (AUC) analysis of the ACR and its components in ACR50 responders treated with infliximab.

We conducted an analysis of the AUC for the ACR and its components for patients categorized by their ACR50 response at the weeks 30 and 50 timepoint. Because the ACR50 is a more meaningful clinical response than the ACR20 and there was a consistently large proportion of patients treated with infliximab who experienced an ACR50 at week 54, we limited this analysis to ACR50 responders in patients treated with infliximab, i.e., patients treated with placebo are excluded from the analysis. These limitations of the population analyzed allows greater utility of the AUC analysis as a way to characterize the effects of the ACR components upon outcome (ACR50) in patients treated with infliximab.

In order to achieve an ACR50, patients need to experience a 50% reduction in the number of both their painful and swollen joints and a 50% improvement in 3 of the 5 following criteria: Pain score (VAS), physician's global evaluation (VAS), patient's global evaluation (VAS), HAQ (questionnaire), and CRP. The patients were categorized as: Group 1 = ACR50 responders at weeks 54 and 30 (best response), Group 2 = ACR50 at week 54 but not at week 30 (slow responders), and Group 3 = ACR50 at week 30 but not week 54 (lost response).

Using ANOVA, we found that for all of the patients treated with infliximab and who had an ACR50 response, the type of response (i.e., best, slow, lost) affects the AUC for all of the components of the ACR except CRP. A comparison of the means for all of the components of the ACR, except HAQ and CRP, shows that patients with the best ACR50 type of response (Group 1) had a mean value for that component that was significantly better than patients who had either gained or lost response from week 30 while the AUC for these latter two groups of patients was similar. There was no difference among the patient categorized by type of response on the mean of the AUC for HAQ or CRP. It appears from this analysis that all patients treated with infliximab regardless of their durability of ACR50 response experienced an improvement of the CRP without predicting an affect on the AUC for the ACR.

AUC analysis of the ACR and its components in ACR20 responders at week 54.

In order to explore further the effect of the CRP in the ACR measurement, we compared the means of the AUC for the ACR components in patients who were ACR20 responders at week 54 by their ACR20 response at week 30, i.e., yes/no, using Student's t-test. Patients who were ACR20 responders at both weeks 30 and 54 had a significantly higher mean AUC for each of the ACR components, except CRP, compared to patients who were ACR20 responders at week 54 but not at week 30. This analysis supports the

results of the effect of infliximab treatment on CRP from the analysis of the ACR50 responders and implies that patients treated with infliximab experience a reduction in their CRP regardless of clinical outcome.

In another analysis we asked whether treatment assignment affected the AUC for the ACR and its components in all patients who experienced an ACR20 response at week 54 regardless of their ACR20 response at week 30. Using ANOVA, we found that the AUC for all of the components of the ACR, except CRP, were similar among the five treatment groups. Comparison of the mean AUC for CRP, all patients treated with infliximab had a significantly larger AUC for CRP compared to patients treated with placebo, regardless of the dose regimen of infliximab. These results support the results from the previous analysis, i.e., treatment with infliximab lowers the CRP regardless of clinical outcome as measured by ACR20 or ACR50.

Summary of the Analysis of the Data regarding Clinical Response.

At week 54, patients treated with all dose regimens of infliximab tended to experience clinical benefit as measured by ACR20 compared to patients treated with placebo.

A greater proportion of patients treated with all dose regiments of infliximab achieve an ACR20 and ACR50 at both weeks 30 and 54 compared to patients treated with placebo. The most consistent effect occurs with the 10 mg/kg every 8 week dose regimen of infliximab.

There are a small percentage of patients (8-18%) treated with a dose regimen of infliximab who do not achieve an ACR20 or ACR50 at week 30 but do so by week 54. More patients treated with one of the 10 mg/kg dose regiments compared to the two 3 mg/kg dose regimens experience this "slow" effect.

Approximately 8-17% of patients treated with infliximab lose their week 30 ACR20 response by week 54. The greatest proportion of patients who lose response are those treated with 3 mg/kg of infliximab every 8 weeks. Fewer patients (~2-7%) lose their week 30 ACR50 response by week 54 when treated with infliximab except for the 3 mg/kg every 8 weeks dose regimen where 13% of patients lose their week 30 ACR50 response by week 54.

The AUC analysis of the ACR is a more sensitive analysis than a landmark comparison of mean change from baseline in ACR. Patients treated with infliximab who were aCR20 nonresponders at week 43 had an AUC for ACR that differed significantly from patients treated with placebo.

The effect of treatment with infliximab upon the CRP dose not predict clinical outcome. Patients treated with infliximab experience a reduction in the measurement of CRP regardless of their clinical outcome as measured by their ACR20 or ACR50 response.

Review of the sponsor's pharmacodynamic data suggests that the loss of effect with the 3 mg/kg every 8 week dose may be associated with low serum concentrations of infliximab at the end of treatment interval.

5.0 Recommendations regarding Efficacy

Following the review of the efficacy data, the following recommendations can be made:

- No conclusions can be made regarding the effect of treatment with infliximab upon radiographic progression due to significant and substantial flaws that are prevalent in the radiographic databases.

- Treatment with infliximab [redacted] is measured by HAQ but the effect is minimal compared to placebo in patients treated with the currently licensed dose of 3 mg/kg every 8 weeks. Because of the clinical importance of this claim to patients and the relatively minimal benefit, the data suggest that [redacted] of infliximab be considered in the overall assessment of the proper dose.

- Treatment with infliximab continues to show significant clinical benefit upon the reduction of the sign and symptoms of rheumatoid arthritis in patients treated for one year. Approximately 17% of the patients treated with 3 mg/kg every 8 weeks of infliximab lost their week 30 ACR20 response by week 54 and approximately 9% of patients treated with this dose who were ACR20 nonresponders at week 30 did achieve an ACR20 response at week 54. Information regarding this gain and loss of response with time should be provided in the label.

Appendix A. Patients with radiographs at week 0 and 54 who are categorized according to Reader as "NE" for either erosion score (ES) or joint space narrowing (JSN) in Appendix J-15

Treatment Group	PID	Reader 1		Reader 2		Comment (see footnote for abbreviations)
		ES	JSN	ES	JSN	
Placebo	04029		NE			R foot not scored at baseline & wk54 by R-1
	08001			NE	NE	R&L foot not scored at wk54
	08008	NE	NE	NE	NE	base films inadequate; only 6 hand joints scored by R-1; no joints scored by R-2; Radiographs are incomplete
	13011	NE	NE			R foot not scored at baseline & wk54
	15015		NE		NE	both feet not scored at baseline & wk54 by R-1; all but 4 joints scored by R-2
	31002	NE	NE		NE	R foot not scored at baseline & wk54 by R-1; patient had surgery on all MTP of both feet at study entry
	33009	NE	NE			both hands not scored at base by R-1; L hand not scored at wk54
	33011		NE			R foot not scored at baseline & wk54 by R-1
3 mg/kg q 8 wks	04016		NE			L foot not scored at baseline & wk54 by R-1
	07017		NE		NE	both feet not scored at baseline & wk54 by R-1; feet scored by R-2; patient had JR of MTP1-5 of both feet
	15007		NE			R-1 scored 5/10 feet joints at baseline & wk54
	16006		NE			L foot not scored at baseline & wk54 by R-1
	22006		NE			L foot not scored at baseline & wk54 by R-1
	26003	NE	NE			both feet not scored at baseline & wk54 by R-1
3 mg/kg q 4 wks	08006	NE	NE	NE	NE	both feet not scored at baseline by R-1 or R-2
	09009	NE	NE			R foot not scored at baseline by R-1
	11006			NE		R-2 scored four feet joints at baseline & wk54; pt had surgery of these 4 joints at baseline
	17020	NE	NE		NE	R foot not scored at baseline & wk54 by R-1; feet scored by R-2; pt had surgery to MTP1-5 of both feet at study entry
	20007		NE			L foot not scored at baseline & wk54 by R-1
	21017		NE			both feet not scored at base & wk54 by R-1
	22008		NE			L foot scored ND at base; both feet scored ND at wk54 by R-1
	31003	NE	NE			R foot not scored at baseline & wk54 by R-1
	32005		NE		NE	both feet not scored at baseline & wk54 by R-1; feet scored by R-2; pt. had surgery on MTP1-5 of both feet at study entry
10mg/kg q 8 wks	06008		NE		NE	R foot not scored at baseline & wk54 by R-1; feet scored by R-2; pt. had surgery of MTP1-5 of both feet at study entry
	12005		NE			R foot not scored at baseline & wk54 by R-1
	14002	NE	NE	NE	NE	L foot not scored at baseline & wk54 by R-1; feet scored by R-2; Pt. had surgery of MTP1-5 of both feet at study entry; IP1 joint of both feet had no surgery & read by R-2
	33013		NE			both feet not scored at baseline &wk54 by R-1

Treatment Group	PID	Reader 1		Reader 2		Comment
		ES	JSN	ES	JSN	
10 mg/kg q 4 wks	04005		NE		NE	both feet not scored at baseline & wk54 by R-1; 8 joints of feet scored by R-2; patient had surgery of MTP1-5 of both feet at study entry
	04022		NE			R foot not scored at baseline & wk54 by R-1
	08003				NE	L foot not scored at baseline by R-2
	17012		NE			L foot not scored at baseline & wk54 by R-1
	17016	NE	NE		NE	3/12 joints of feet scored at baseline & wk54 by R-1; all joints of both feet scored by R-2; pt had surgery of MTP1-5 of both feet at study entry
	21001			NE	NE	Both feet not scored at wk54 by R-2
	26004			NE	NE	Both hands not scored at baseline & wk54 by R-2
	28005		NE			R-1 read 6/10 joints of feet at baseline & wk54

Abbreviations in Comments. R-1 = Reader 1, R-2 = Reader 2, R = right, L=left, MTP = metatarsal phalange, JR = joint replacement, ND = Evaluation not done, or unreadable, IP1 = first interphalange.

Appendix B. Comparison van der Heijde scores calculated by FDA and scores recorded in Appendix J-15 for randomly selected patients.

			Reader 1				Reader 2			
PID	dose	time	FDA ES-1	J-15 ES-1	FDA JSN-1	J-15 JSN-1	FDA ES-2	J-15 ES-2	FDA JSN-2	J-15 JSN-2
17008	placebo	base	26.8	26.8	47.2	47.3	80	80	59	59
		wk54	29.6	29.6	56	56	83	83	64	64
04016	3q8	base	53.1	53.1	85	NE	78	158	89	89
		wk54	56.1	56.1	54	NE	75	155	88	88
07010	3q8	base	26	26	57	57	32	32	42	42
		wk54	24.1	24.1	46.4	46.4	29	29	44	44
18003	3q8	base	61	61	69	69	94.1	94.1	53.9	53.9
		wk54	59	59	70	70	90	90	60.2	60.2
26006	3q8	base	36	36	25	25	71.3	71.3	32.1	32.1
		wk54	31	31	36	36	69	69	30	30
04011	3q8	base	48.9	49	58.7	58.7	59	79	64	64
		wk54	55	55	58	58	59	79	66	66
14004	3q4	base	24	24	73.1	73.1	29.5	29.5	37.8	37.8
		wk54	19	19	67.9	67.9	28.3	28.3	36.7	36.8
04012	10q8	base	35.7	35.7	44.9	44.9	51	51	32	32
		wk54	35	35	40	40	48	48	31	31
23003	10q8	base	46.8	46.8	19	19	77	76	25	25
		wk54	44.7	44.7	22	22	72	72	30	30
33005	10q8	base	48	48	97	97	107	155	91	91
		wk54	55	55	101	101	104.8	152.8	92	92
12002	10q4	base	81.7	81.7	87.4	87.4	93.7	153.7	85.8	85.8
		wk54	82.8	82.9	82.9	89.5	91.6	151.7	90	90
18009	10q8	base	43	43	91	91	66	166	91	91
		wk54	44	44	91	91	67	167	91	91
19008	10q4	base	203	203	109	109	198	218	113	113
		wk54	202	202	106	106	196	216	107	107
23001	3q8	base	34	34	49	49	46	96	42	42
		wk54	34	34	54	54	42	92	48	48
07020	placebo	base	95	105	79	79	77	147	45	45
		wk54	97	107	81	81	76	146	46	46
07024	placebo	base	5	5	1	1	12	12	10	10
		wk54	16	16	24	24	23	23	20	20
20001	3q8	base	40.8	40.8	43	43	75	75	32	32
		wk54	46.9	46.9	41	41	80	80	32	32
12010	3q4	base	43.4	43.4	85	85	88	138	78	78
		wk54	46	46	77	77	93	133	72	72
17013	3q4	base	29	29	50	50	46	46	56	56
		wk54	27.5	27.5	53	53	50	50	59	59
09009	3q4	base	77.7	NE	64.6	NE	120.5	120.5	50	50
		wk54	85.7	85.6	64.6	64.6	110	110	50	50
04029	placebo	base	105.6	105.6	83	NE	113	173	102	102
		wk54	106.3	106.3	81	NE	115	175	102	102
07013	placebo	base	33	missing	49	missing	25	missing	41	missing
		wk54	45	missing	59.4	missing	31	missing	46	missing
15015	placebo	base	53.4	42.5	35.5	NE	123.3	56	44.5	NE
		wk54	57	45.6	35.5	NE	124.7	59	43.6	NE

Appendix B. Cont'd.

PID	dose	time	Reader 1				Reader 2			
			FDA ES-1	J-15 ES-1	FDA JSN-1	J-15 JSN-1	FDA ES-2	J-15 ES-2	FDA JSN-2	J-15 JSN-2
04016	3q8	base	53.1	53.1	85	NE	78	158	89	89
		wk54	56.1	56.1	54	NE	75	155	88	88
33005	10q8	base	48	48	97	97	107	155	91	91
		wk54	55	55	101	101	104.8	152.8	92	92
12002	10q4	base	81.7	81.7	87.4	87.4	93.7	153.7	85.8	85.8
		wk54	82.8	82.9	82.9	89.5	91.6	151.7	90	90
18009	10q8	base	43	43	91	91	66	166	91	91
		wk54	44	44	91	91	67	167	91	91
19008	10q4	base	203	203	109	109	198	218	113	113
		wk54	202	202	106	106	196	216	107	107
23001	3q8	base	34	34	49	49	46	96	42	42
		wk54	34	34	54	54	42	92	48	48
07020	placebo	base	95	105	79	79	77	147	45	45
		wk54	97	107	81	81	76	146	46	46
12010	3q4	base	43.4	43.4	85	85	88	138	78	78
		wk54	46	46	77	77	93	133	72	72
04029	placebo	base	105.6	105.6	83	NE	113	173	102	102
		wk54	106.3	106.3	81	NE	115	175	102	102
07013	placebo	base	33	missing	49	missing	25	missing	41	missing
		wk54	45	missing	59.4	missing	31	missing	46	missing
15015	placebo	base	53.4	42.5	35.5	NE	123.3	56	44.5	NE
		wk54	57	45.6	35.5	NE	124.7	59	43.6	NE

Appears This Way
On Original

6.0 Review of Safety Database

During the review of the 30-week data submitted to the license supplement, PLA99-0128, the sponsor submitted a summary analysis of the safety data through the week 52 timepoint. The safety review of that license supplement, 99-0128, included the week-52 data. I reviewed the safety data for the week 54 timepoint in the current supplement, 99-1234, and found no notable changes from the prior review. The reader is referred to the review of the safety data in PLA 99-0128. The following points summarize the review of the safety database at 54 weeks.

6.1 Adverse Events

Through week 54, the body systems for which adverse events were reported in more than one-third of infliximab-treated patients were the respiratory system, GI system, skin, central and peripheral nervous system, body as a whole, musculoskeletal , and resistance mechanisms, in order of decreasing incidence. In each of these body systems, more patients treated with infliximab were reported with events compared with patients treated with placebo. With continued exposure to infliximab from 30 to 54 weeks, there was no apparent increased reports of adverse events for the majority of the systems.

Serious adverse events

Through week 54, the proportion of patients treated with placebo who experience a serious adverse event was comparable to the proportion of patients with serious adverse events who were treated with the 10 mg/kg infliximab dosing regimens and higher than the proportion of patients treated with the 3 mg/kg infliximab dosing regimens (Table 11).

Table 11. Number of patients with a serious adverse event through week 54.

	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q 4
Pts randomized	86	88	86	87	81
Avg wks of follow-up	50	52	54	54	54
Pts with ≥ 1 serious adverse event	19 (22.1%)	10 (11.4%)	14 (16.3%)	17 (19.5%)	16 (19.8%)

Table 12 presents the serious adverse events by patient and separates those that occur before and after week 30.

Table 12. Patients in T22 with serious adverse events at week 30 and week 54 by treatment group.

Treatment group	Patient	Before week 30 (verbatim)	After week 30 (preferred term)
Placebo			
	03003	congestive heart failure; chest pain	
	04020		skeletal pain
	06011	Tendon rupture	
	07008	gastric ulcer; erosive gastritis	fever; chills; diabetes; urinary infection
	11005		bone fracture
	12003		urinary tract infection
	12008	pneumonia; cardiac failure; sepsis; intestinal gangrene; respiratory failure	
	13002		knee pain (synovectomy)
	14001	arrhythmia	
	15008	coughing; vomiting; diarrhea; abdominal pain; fever	
	18001	rheumatoid arthritis flare (twice)	
	19012	peripheral gangrene bilateral foot ulcers	skin ulceration
	24005		bone fracture
	27005	urinary retention; sepsis; thrombosis–deep; congestive heart failure	
	30001	ischemic bowel; ischemic liver; cardiopulmonary failure	
	30009	biliary pain (gallstones)	
	31007	bone fracture	
	32006	hyperglycemia; back pain	
	33011	bone fracture; wound infection	
3 mg/kg q 8 wks			
	01008	bronchitis/pneumonia	
	06016	pulmonary emboli (bilateral): DVT	
	14007		pancreatitis
	15001	C-spine disease	
	15007	Arthralgia	
	16006	bone fracture	
	18003	ischemic heart disease; angina pectoris	skin ulceration; vomiting; nausea; herpes zoster; rheumatoid arthritis flare
	18007	Pancreatitis; pancreatic duct stone; weight loss; back pain	weight decrease; back pain
	19005	Orthopnea; paroxysmal nocturnal dyspnea; tachycardia	dyspnea, AV block complete
	28002		rheumatoid arthritis

Table 12. (cont'd.) Patients in T22 with serious adverse events at week 30 and week 54 by treatment group.

Treatment group	Patient	Before week 30 (verbatim)	After week 30 (preferred term)
3 mg/kg q 4 wks			
	06009	ruptured tendon	biliary pain; diaphragmatic hernia
	06017	rheumatoid arthritis flare	
	10004	anxiety w/suicidal overtones; dehydration w/delirium; tachycardia; creatinine increased; azotemia	
	11006	pneumonia	
	16004	cerumen obstruction of both ears	
	18002	weight loss; cough; abdominal pain; vomiting; night sweats; pneumonia; rheumatoid flare; lymphadenopathy	infection bacterial; infection tubercular; pulmonary edema; resp insufficiency; pneumothorax; abdominal pain; pleural effusion; encephalopathy; hepatitis; cardiac arrest
	20007	DVT; hemarthrosis	bone fracture
	21003	gastrointestinal ulcer; pancreatitis; dehydration	
	21013	microcytic anemia	
	24007	pyelonephritis	
	26009		syncope; nausea
	28001	bacteremia; septic arthritis; spinal cord lesion; respiratory insufficiency	
	30007		brain infarction
	32005		cellulitis
10 mg/kg q 8 wks			
	01006		peripheral ischemia
	02002		cholelithiasis; biliary pain
	02006		appendicitis
	04009		angina; chest pain; bradycardia
	08004	bone fracture; leg pain	
	08010		endometriosis
	12005		arthralgia; joint cyst
	12006	osteoarthritis-cystic	
	14002	pneumonia	
	15009	cellulitis; lymphangitis	
	18009		inflammation
	20009	suicide attempt	
	22001		anemia; thinking abnormal; peritonitis; coccidioidomycosis
	28004	Herpes zoster	
	29001		GI hemorrhage
	30003	dyspnea	
	31005	pneumonia; leukopenia	

Table 12. (cont'd.) Patients in T22 with serious adverse events at week 30 and week 54 by treatment group.

Treatment group	Patient	Before week 30 (verbatim)	After week 30 (preferred term)
10 mg/kg q 4 wks			
	04018	rupture tendons	
	05012	pyelonephritis; confusion; anemia; lung infiltrate; renal failure; hydronephrosis; cellulitis; lymphoma	pyelonephritis; lymphoma; cellulitis; arrythmia
	05018		Infection post knee replacement
	07006	intervertebral disk rupture	
	09008		Pneumonia
	10009	bone pain	
	11011	sepsis	
	12002	coxitis aseptic	
	12007		upper respiratory tract infection
	15016	cellulitis; cracked skin	
	16002		abdominal pain
	17016	tendon rupture	
	25009		Symphysiolysis; spondylotisthesis; osteoarthritis
	27003	breast neoplasm	back pain
	27008	squamous cell carcinoma; melanoma	Melanoma
	33015	CVA	

*Patient 13002 (placebo) is not listed in Attachment 11.2 (patients with serious adverse events) of the license supplement but is listed in a table of patients with serious adverse event within the study report.

Adverse events that resulted in discontinuation from T22

Table 13 lists the serious adverse events associated with discontinuation of study drug. Two patients treated with infliximab discontinued due to sepsis. Cardiac failure resulted in the discontinuation of study drug for 2 patients treated with placebo and for none of the patients treated with infliximab. Three infliximab-treated patients with serious adverse events discontinued treatment due to infusion reactions; two patients experienced dyspnea and one patient experienced hypotension.

Table 13. Number of patients who discontinued treatment due to adverse event by week 54 and type of adverse event reported (WHOART) for each patient discontinued in treatment group*

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	88	86	87	81
Avg weeks follow-up	49.1	51.0	53.8	53.5	53.6
Pts who discontinued	8 (9.3%)	5 (5.7%)	9 (10.4%)	4 (4.6%)	8 (9.9%)
Event per patient					
	33011- bone fracture	18003 – skin ulceration	25004 – urticaria	08004-bone fracture	28005 - dermatitis
	32006-hyperglycemia	25010 – dyspnea	04013-dyspnea	18005-lupus syndrome	15016-cracking of skin
	19012-peripheral gangrene	14007 – pancreatitis	22008 – bursitis	20009-suicide attempt	07006-vertebral disk herniation
	30001-CHF	06016 - PE	28001 – sepsis	02002-abnormal liver function	11011 - sepsis
	03005-CHF	08005 -hot flushes	32005-cellulitis		05012 – pyelonephritis; renal failure
	01016-Anemia		24007-pyelonephritis		27008 - melanoma
	07004-thrombo-cytopenia		01009-hyperglycemia		27003 - breast cancer
	12008 – intestinal gangrene		24004-hypotension		19014-palpitation
			30007-cellulitis		

6.2 Deaths

Through week 54, 8 patients died. Five patients died during the first 30 weeks of the clinical trial period. Five patients received infliximab; one patient from each dosing regimen died with the additional patient from the 3 mg/kg q 4 week regimen. The immediate most probable causes of death identified by the investigators were intestinal gangrene, arrhythmia, and cardiac failure in the placebo-treated patients and pulmonary embolisms, cardiopulmonary failure, disseminated tuberculosis, coccidioidomycosis, and cardiac failure in the infliximab-treated patients.

A descriptive narrative of the deaths in these 8 patients (12008, 14001, 30001, 06016, 28001, 18002, 22001, 05012) in T22 was provided in the review of the consolidated safety database of PLA-990128.

6.3 Malignancies

Six patients enrolled in ATTRACT have been diagnosed with a malignancy. Three were diagnosed prior to week 30 and 2 patients subsequently. Three patients had been treated with 10 mg/kg q 4 weeks and included large cell lymphoma, recurrent breast adenocarcinoma (initial incidence was 9 years prior), and squamous cell and melanoma (both skin cancers occurred in one patient). Two patients had been treated with 10 mg/kg q 8 weeks of infliximab and the malignancies included bassal cell carcinoma and rectal adenoma.

The sixth patient was reported to the IND after the week 54 timepoint. Approximately 2 weeks after the week 70 infusion of study drug, a biopsy of a lymph node in the groin diagnosed squamous cell carcinoma. The patient identifier and study treatment is unknown.

6.4 Infusions Reactions

The prior review summarizes the patients who receive prophylaxis for infusion reactions. It was notable that all 11 patients at site 11 and 12/15 patients at site 01 received prophylactic medicines with each infusions. Most of the patients who continued in the study after week 30 continued to receive prophylactic medications.

Table 14 summarizes the number of patients who had an infusion reaction through weeks 30 and through weeks 54. The incidence of infusion reactions was higher for infliximab-treated patients than for placebo-treated patients at both time points and the overall treatment effect at week 54 remained not statistically significant. (For all of the following tables, patients in the every 8 week groups are counted only by reactions reported with the infliximab (not placebo) infusions.)

Table 15. Incidence of infusion reactions through week 54.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	All Infliximab	Treatment effect p-value
Pts treated	86	88	86	87	81	342	
Avg number of infusions	10	8	13	8	13	11	
Infusions with reactions	17 (1.9%)	22 (3.2%)	55 (4.8%)	36 (4.9%)	26 (2.4%)	139 (3.8%)	
Pts with ≥ 1 infusion reaction	10 (11.6%)	16 (18.2%)	22 (25.6%)	19 (21.8%)	17 (21.0%)	74 (21.6%)	0.21

The types of adverse events through week 54 that were associated with infusion reactions were grouped as nonspecific, dermatological, those related to the cardiopulmonary system, and those related to the injection site. Nonspecific adverse events included headache, nausea, fever, fatigue chills, increased sweating, abdominal pain, paresthesia, etc. Dermatological events included pruritus, urticaria, flushing, rash, erythema, skin discoloration, and folliculitis. Cardiopulmonary included hypertension, dizziness, hypotension, dyspnea, chest pain, hot flushes, tachycardia, vertigo, arrhythmia, and

cyanosis. Injection related events include injection site inflammation, pain, and infiltration. Table 16 summarizes the adverse event related to infusion reactions according to these four categories. The incidence of these categorized events was higher in patients treated with infliximab with the most frequent infusion related events occurring in the 3 mg/kg q 4 weeks cohort.

Table 16. Number of categorized adverse events associated with study drug infusion through week 54

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	88	86	87	81
Avg number of infusions	10	8	13	8	13
Infusions with reactions	16 (1.8%)	21 (3.0%)	53 (4.7%)	37 (5.1%)	26 (2.5%)
Pts with ≥ 1 infusion reaction	10 (11.6%)	16 (18.2%)	22 (25.6%)	19 (21.8%)	17 (21.0%)
Category					
Cardiopulmonary	6 (7.0%)	10 (11.3%)	13 (17.4%)	11 (12.6%)	11 (13.4%)
Dermatological	1 (1.2%)	5 (5.7%)	15 (17.4%)	5 (5.7%)	4 (4.9%)
Nonspecific	8 (9.4%)	9 (10.2%)	28 (32.6%)	17 (19.5%)	11 (13.5%)
Injection related	1 (1.2%)	2 (2.3%)	4 (4.6%)	1 (1.2%)	1 (1.2%)

There were no serious infusion reactions reported through week 54. However, two patients had infusion reactions that were considered by the investigator to be severe.

Data on infusion reactions by treatment group and baseline MTX are summarized in Table 17. There is a suggestion that for the 3 mg/kg every 8 weeks infliximab dosing regimen, patients treated with >20 mg/week of MTX experienced less infusion reactions compared to patients who received the higher infliximab dosing regimens. No HACA data available to determine whether or not this effect may be related to lower incidence of HACA due to greater immunosuppression.

Table 17. Number of patients with any infusion reaction to week 30 by baseline MTX dose.

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	88	86	87	81
Avg number of infusions	10	8	13	8	13
Pts with ≥ 1 infusion reaction	10 (11.6%)	16 (18.2%)	22 (25.6%)	19 (21.8%)	17 (21.0%)
Patients with ≥ 1 reaction by MTX dose					
≤ 12.5 mg/week					
Pts treated	24	27	26	24	19
Pts w/≥ 1 reaction	3 (12.5%)	5 (18.5%)	8 (30.8%)	5 (20.8%)	3 (15.8%)
>12.5 and <20 mg/week					
Pts treated	45	40	40	45	40
Pts w/≥ 1 reaction	5 (11.4%)	9 (22.5%)	9 (22.5%)	12 (26.7%)	8 (20.0%)
≥ 20 mg/week					
Pts treated	17	21	20	18	22
Pts w/ ≥ 1 reaction	2 (11.8%)	2 (9.5%)	3 (25.0%)	2 (11.1%)	6 (18.5%)

6.5 Infections

All Infections

Table 18 summarizes the number of patients in each treatment group who reported an infection and those with an infection that was treated with oral or parenteral antibiotics. The proportion of patients treated with 3 mg/kg infliximab every 8 weeks and who develop an infection were comparable to the proportion of patients with infections who were treated with placebo, i.e., about 35%. Approximately 50% of patients treated with 10 mg/kg infliximab every 8 weeks experienced an infection treated with antimicrobial therapy.

Table 18. Patients with infections treated with antibiotics

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts treated	86	88	86	87	81
Avg weeks follow-up	49.9	51.6	53.7	54.1	54.0
Pts with any infection	52 (60.5%)	60 (68.2%)	58 (67.4%)	66 (75.9%)	64 (79.0%)
Pts with infections treated w/ antibiotics	30 (34.9%)	30 (34.1%)	35 (40.7%)	46 (52.9%)	38 (46.9%)

Serious Infections

Twenty-seven of 342 (7.9%) patients treated with infliximab and 7 of 86 (8.1%) patients treated with placebo experienced a serious infection (Table 19). Through week 30, 14 patients (7.0%) patients treated with infliximab and 5 (5.8%) patients treated with placebo had a serious infection. Serious infections that were reported in more than 1 patients treated with infliximab were pneumonia, cellulitis, pyelonephritis, sepsis, and herpes zoster. At 54 weeks, the 3 mg/kg q 8 week dosing group had the least number of serious infections while the number of patients with serious infections for the remaining three dosing groups were comparable to the placebo-treated patients.

Table 19. Patients with serious infections enrolled in ATTRACT (including after the week 54 timepoint)

	Placebo	3 mg/kg q 8 weeks	3 mg/kg q 4 weeks	10 mg/kg q 8 weeks	10 mg/kg q 4 weeks
Pts treated	86	88	86	87	81
Avg weeks follow-up	49.9	51.6	53.7	54.1	53.3
Pts with ≥ 1 serious infections	7 (8.1%)	3 (3.4%)	9 (10.5%)	8 (9.2%)	7 (8.6%)

A list the patients with serious infections at the various timepoints during the conduct of T22, i.e., by week 30, week 54 and subsequent to week 54 is provided in Table 20. Narratives for these infections are provided in the review of the consolidated safety database in PLA99-0128.

Table 20. List of Patients who Experienced Serious Infections at Timepoints in T22 (ATTRACT)

Dose Group	Through Week 30	Weeks 30-54	After Week 54
Placebo	07008- UTI	15008 – gastroenteritis	12003 – pyelonephritis
	12008 – pneumonia; sepsis	32005 - cellulitis	
	19012 – gangrene; osteomyelitis		
	27005 – pyelonephritis; sepsis		
3 mg/kg q 8 wks			
	01008 – bronchitis; influenza	18003 – skin ulcer; herpes zoster	07011 – cellulitis; septic thrombophlebitis
3 mg/kg q 4 wks			
	11006 – pneumonia	32005 – cellulitis	04014 – cellulitis
	18002 – Strep pneumonia; TB		07009 – skin ulcer
	21003 – pancreatitis		22008 – orthopedic infection
	24007 – pyelonephritis		
	28001 – bacteremia; septic arthritis; osteomyelitis		
10 mg/kg q 8 wks			
	14002 – Strep pneumonia	02006 – ruptured appendix	09001 – viremia
	15009 – cellulitis	22001 – coccidioidomycosis	
	28004 – herpes zoster		
	30003 – influenza		
	31005 – pneumonia		
10 mg/kg q 4 wks			
	05012 – pyelonephritis; cellulitis	09008- pneumonia	04005 – ortho infection
	11011 – sepsis	12007 – Upper respiratory infection	05018 – ortho infection
	15016 – cellulitis (erysipelas)		

6.6 Human Antichimeric Antibodies (HACA)

It is important to understand the potential for patients treated with infliximab to develop HACA for the following reasons:

- We know from an earlier phase 2 trial (T14 reviewed in 99-0128) that infliximab is immunogenic. Lower doses of 1 mg/kg appear to be more immunogenic than the 3 or 10 mg/kg doses. The reasons for the lower immunogenicity of the higher doses is unknown; higher doses of infliximab may cause immunosuppression.

- HACA is a neutralizing antibody: high serum concentrations of HACA is associated with nil serum concentrations of infliximab and the loss of clinical effect. This scenario was seen both in the phase 2 trial, T14, and in patients who developed a delayed-type hypersensitivity reaction.

- In T14, patients treated with methotrexate and infliximab, including those treated with the low dose of 1 mg/kg, did not develop significant HACA.

- Patients with Crohn's disease who were re-exposed to infliximab after a duration >12 months, developed a delayed hypersensitivity-type of reaction with loss of serum concentration of infliximab and loss of efficacy.

- It is unknown if there is an association between the degree of immunogenicity and the formulation of infliximab. Patients in T14 were exposed to liquid formulation while patients in later trials, including ATTRACT (T22), received a [redacted] formulation.

Given the significance of the need to better understand HACA and its relationship to clinical effect and safety, it is unfortunate that the current assay cannot detect HACA when there is circulating concentrations of infliximab. The sponsor evaluated the HACA response in two groups of patients, those who discontinued study treatment through week 30 and those who did not receive study drug for ≥ 8 weeks between year 1 and 2.

Patients who discontinued study treatment. There were 45 of the 342 infliximab-treated patients who discontinued treatment by the week-30 timepoint; HACA samples are available on 33 of these patients. Six of these 33 patients had inconclusive HACA levels (serum infliximab was still detectable). Of the remaining 27 patients, HACA was detected in 3 patients and not detected in 24 patients. All three patients with detectable HACA had been treated with 3 mg/kg every 8 weeks. Two had titers 1:10 and the third had a titer of 1:40. Two of these patients discontinued treatment due to safety reasons and the last discontinued due to loss of efficacy.

Patients with a ≥ 8 week interval between year 1 and 2 of treatment. There were 84 infliximab-treated patients with ≥ 8 week interval between treatment at the end of year 1 and beginning of year 2. HACA was assessed for 76 patients for whom there were samples available. Only 33 of these 76 patients had evaluable samples, i.e., no detectable serum infliximab concentrations. HACA was detected in only 2 of these 33 samples. The titers for these 2 HACA positive patients were 1:320 and 1:40, four weeks after their last infusion. (Samples were obtained at 4 weeks after the last infusion because this was the original sampling schedule in the protocol.) The two patients were randomized to the 3 mg/kg every 4 weeks and 3 mg/kg every 8 weeks dosing regimens. By 20 weeks after their last infusion and prior to retreatment, the HACA levels for these 2 patients decreased from 1:320 to 1:80 and from 1:40 to HACA-negative. There is no information regarding infusion reactions for these 2 patients (or any patient) with retreatment. The patient with the 1:320 titer had urticaria staring 40 minutes after the beginning of the week-30 infusion which resolved with temporary stoppage of the infusion and administration of antihistamines. He did not experience any reactions with subsequent infusions through week 54. The patient with the 1:40 titer did not experience any infusion reactions.

6.7 Autoimmune Disorders

As discussed in the prior BLA (99-0128), there has been one patient enrolled in ATTRACT who developed a lupus-like syndrome. In addition, there were 2 patients in previous trials who were treated with infliximab and who developed an autoimmune disorder (see Review of the consolidated safety ~~data~~base for PLA99-0128). One patient had rheumatoid arthritis while the other patient had received infliximab in a clinical trial evaluating the efficacy of infliximab for treatment of Crohn's disease.

Appears This Way
On Original

6.8 Conclusion regarding safety data from T22

The conclusions regarding the safety data from T22 (ATTRACT) are the same as those stated in the review of PLA-99-0128:

- The comparison of adverse events in patients treated with infliximab and placebo is limited by the relatively small number of patients in each of the dosing regimens. Comparison of all infliximab treated patients compared to placebo does not provide a fair assessment of risk because of the great discordance in the number of patient-years in those exposed to infliximab compared to placebo.

- Overall, patients treated with infliximab experienced more adverse event compared to patients treated with placebo. A greater proportion of patients treated with infliximab discontinued study drug due to adverse event compared to placebo.

- Patients treated with infliximab may have a slightly higher risk of infections, particularly, upper respiratory tract infections. Patients may also have difficulty responding to milder infections such that more serious infections occur, e.g., urinary tract infections progressing to pyelonephritis, the need to be hospitalized for cellulitis.

- A greater proportion of patients treated with infliximab experienced infusion reactions and there were more cardiopulmonary and dermatological types of reactions in patients treated with infliximab.

- The development of HACA and any associated risk cannot be determined from the data collected to date from T22.

- A greater proportion of patients treated with infliximab developed autoimmune antibodies and there was one case of a lupus type of reaction in a patient treated with infliximab in T22 (ATTRACT). The number of patients and incidence of autoimmune reactions are too small to extrapolate to the patient population with rheumatoid arthritis.

- Treatment with infliximab may potentiate some of the adverse effects of MTX. A slightly higher proportion of patients treated with infliximab and MTX experienced ulcerative stomatitis and had mild elevations in their liver function tests. Although there were no serious adverse events that could be attributed to the combined therapies, the patients who discontinued therapy due to abnormal liver enzymes were treated with infliximab and MTX. As stated earlier, the numbers are too small to make any conclusions.

7.0 Recommendations for Licensure

- Treatment with infliximab continues to show clinical benefit as measured by ACR after one year of treatment.
  - The 3 mg/kg every 8 week dose regimen shows clinical benefit as measured by the ACR20 and ACR50 compared to placebo.
  - Increased clinical benefit is seen with the 10 mg/kg every 8 week dosing regimen as measured by ACR20, ACR50 and durability of ACR response between weeks 30 and 54. Increased benefit is also seen with respect to the [redacted] assessment, HAQ. The safety profile of the 10 mg/kg every [redacted] sing regimen is acceptability although there appears to be a potential for increased risk of infections.
  - The difference between the 3 mg/kg and 10 mg/kg infliximab doses is related to some extent with drug concentration since more patients in the 3 mg/kg groups, particularly every 8 weeks, experienced efficacy and there were more patients with trough levels of zero.
  - The correlation between serum concentration of infliximab and clinical benefit as measured by ACR is not all-inclusive since patients with adequate serum concentrations of infliximab failed to show clinical benefit.
- The effect of the 3 mg/kg every 8 week dosing regimen upon improvement of [redacted] s not as robust as the higher dosing regimens. The measurement tool for this outcome, the HAQ questionnaire, is subjective so a more robust difference between this licensed and placebo would be more persuasive that there really is a meaningful effect of this dose upon the patient's [redacted]

To: Barbara Matthews

From: George Mills

Date: March 1, 2000

RE: Complete Review: Centocor BLA, 99-1234

Complete Review of BLA supplement 99-1234 and Regulatory Recommendation:

I have completed my clinical imaging review of the BLA supplement with attention to the [redacted] database of the radiographic images at multiple timepoints. My review is unable to accomplish the regulatory evaluation and determination of validity of the primary and secondary endpoints due to multiple discovered inconsistencies in the BLA supplement's submitted datasets.

Therefore, due to the extent and nature of the discovered BLA supplement's inconsistencies, comparative analysis of the BLA supplement's clinical findings datasets to the [redacted] dataset of radiographs can not be completed with any assurance of reliable and meaningful results for CBER's regulatory decision.

My final report and recommendations are the requests for information documented in the Disciple Review letter of Jan. 28, 2000 (attachment I) as follows:

- new information request, an independent dataset from [redacted] document the receipt, handling and processing of the radiographs (item 4., attached Discipline Review letter, Jan. 28, 2000)

- new information request with clarification of submitted information (Appendices A-2, J-15, J-16, J-17, J-18, J-19, J-20, and J-21). as submitted in the Discipline Review letter(item 1 and 2, attached Discipline Review letter, Jan. 28, 2000).

- New information request for the sponsor to provide clarification of inconsistencies in the independent scoring findings by the two radiograph reviewers. (item 2 and 3, attached Discipline Review letter, Jan. 28, 2000).

- Complete (new) information for the revised SAS submitted to the supplement on December 7, 1999 (item 6, attached Discipline Review letter, Jan. 28, 2000).

To complete the review record, I have attached my review documentation (attachment II).

Summary Documentation of the BLA Supplement Submission

The BLA supplement submission is based on the Clinical Study Report at 54-Weeks for the pivotal phase III clinical trial, Protocol C0168T22. The trial is a placebo-controlled, double-blinded
randomized multicenter **(34 sites: 19 US; 3 Canadian; 12 European)** clinical trial utilizing Anti-TNF Chimeric Monoclonal Antibody (cA2; infliximab) in patients with "active Rheumatoid Arthritis despite Methotrexate treatment" (ATTRACT). Four infliximab treatment regimens were evaluated and compared with placebo. All patients continued to receive MTX during the study.

The study dates: Enrollment 31 March 1997/ongoing (54-Week Cut-off 11 February 1999) with additional endpoints at week 102 to be analyzed and reported in future reports.

The objectives of this trial are to evaluate the efficacy and safety of chronic treatment with infliximab in combination with Methotrexate (MTX) in patients with active rheumatoid arthritis (RA) despite treatment with MTX.

- The primary objective at 30 weeks following the onset of treatment iss to evaluate the efficacy and safety of infliximab treatment in reducing clinical signs and symptoms of RA;

- the primary objective of the week-54 analyses presented in this report is to evaluate the safety and efficacy of infliximab in

Patient Selection (Main Criteria for Inclusion)

Patients who were eligible for this study were to have been diagnosed with RA according to the American Rheumatism Association (ARA) criteria, and despite treatment with MTX (a stable dose of 12.5 mg/wk of MTX given orally or parenterally) with the following:

- evidence of active disease (6 or more swollen and tender joints plus 2 of the following:
- morning stiffness > 45 min,
- erythrocyte sedimentation rate [ESR] > 28 mm/h,
- C-reactive protein [CRP] > 20 mg/L)

Study Agent Administration

Patients in each of the 4 infliximab treatment groups are to receive an infusion at weeks 0, 2, and 6;

- 2 groups were to receive 3 mg/kg infusions and
- the other 2 groups were to receive 10 mg/kg infusions.

After 6 weeks, treatments were to be continued through 1 year with

- one of the 3 mg/kg and one of the 10 mg/kg groups receiving infliximab infusions every 4 weeks (q 4 weeks), and
- the other 3 mg/kg and 10 mg/kg groups receiving infliximab infusions every 8 weeks (q 8 weeks), with placebo infusions at the intervening 4-week visits.
- Patients in the placebo treatment group received placebo infusions at weeks 0, 2, and 6, then every 4 weeks thereafter.

  Patients were to be offered retreatment during the second year according to the treatment regimen to which they were originally randomly assigned.

Evaluation of Efficacy

The primary week-54 endpoint is the [redacted], as measured by the change from baseline in the van der Heijde modification of the Sharp score, which utilizes radiographs of both the hands and feet, at the week-54 follow-up visit.

The primary analysis includes all patients with complete evaluations at baseline and week 54 in the treatment groups to which they were randomly assigned and compared the change in the van der Heijde modification of the Sharp score from baseline to week 54 among patients in each of the infliximab treatment groups with that of the placebo group (ie, MTX alone).

Additional analyses were performed to examine the robustness of the primary analysis for [redacted] structural damage at week 54.

Secondary efficacy assessments included

- number of new erosions,
- radiologic progression, and
- structural damage of the hands only;

Statistical Methodology

The primary efficacy analysis included all patients with complete evaluations at baseline and week 54 in the treatment groups to which they were randomly assigned.

The change from baseline to week 54 was compared among the treatment groups by using analyses of variance of van der Waerden normal scores.

The chi-square test was used to compare the proportion of patients achieving categorical endpoints. If there was a significant overall treatment effect, then comparisons of each of the infliximab treatment groups with the placebo group were performed by using the same test, except for safety endpoints, where pairwise comparisons versus control were performed by using Fisher's exact test.

Secondary continuous response parameters were compared by using an analysis of variance on the van der Waerden normal scores. The consistency of treatment benefit was examined by using plots of differences in mean changes from baseline between treatment groups with 95% confidence intervals.

Study Population/Patient Disposition

A total of 428 patients from 34 study sites were enrolled in this trial.

Of the 340 patients who were randomly assigned infliximab treatment,

1. 86 were assigned 3 mg/kg q 8 wks,
2. 86 were assigned 3 mg/kg q 4 wks,
3. 87 were assigned 10 mg/kg q 8 wks,
4. 81 were assigned 10 mg/kg q 4 wks.
5. 88 patients were assigned placebo.

Study Population Characteristics

majority of the patients (77.6%) were women, which reflects the overall distribution of RA in men and women in the general population.

Most (90.9%) of the 428 patients were white;

their ages ranged between 19 and 80 years (median of 53.5 years).

median duration of disease in the enrolled patients was 8.4 years,

at baseline: median number of swollen joints:20 and tender joints: 31.

Nearly one-fourth of the study population had undergone joint replacement surgery

approximately one-half of the patients had extensive anatomical destruction (Stage III and IV) and limited functional capacity (Class III and IV) prior to enrollment in the study, thereby demonstrating the severity of the RA in much of the study population.

Approximately one-half of the patients in the study population had been on MTX therapy for 3 or more years and approximately one-third of the total study population had received an estimated cumulative dose of 3 g or more of MTX.

A subpopulation of 82 patients had early RA (ie, RA for > 3 years' duration).

ATTACHMENT I

SERVICES

Our Reference Number: 99-1234

JAN 28 2000

Mr. Martin Page
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355

Dear Mr. Page:

This letter is in regard to your supplemental biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has reviewed the clinical efficacy section of your supplemental biologics license application for Infliximab. Preliminary comments, deficiencies, and information requests identified during this review are summarized as follows:

1. Data regarding the administration of study drug for each patient are listed in Appendix A-2 and the summary data for each patient's total van der Heijde score of their radiographs are listed in Appendix J-15. The two data sets are inconsistent, as evidenced by the following:

   a. Radiographic results for 12 patients who received study drug as recorded in Appendix A-2, including 9 of 12 patients who received all 15 infusions through Week 54, are not included in Appendix J-15 (Table 1). Please comment, and provide these data to the BLA supplement.

   b. Individual joint scores calculated by Readers 1 and 2 for patients numbered 07013, 09002, and 07009 are provided in Appendices J-16 through J-21 and their radiographs are included in the database assembled by ______. However, data summarizing the van der Heijde scores for these patients are not included in Appendix J-15. Please comment, and provide these data to the BLA supplement.

2. We have reviewed the radiographic data for patients whose van der Heijde scores were recorded as "NE" (summarized radiographic scores not available) in the summary listing of radiographic results for Readers 1 and 2 in Appendix J-15. Complete sets of radiographs were not available for evaluation of fifty-seven of these patients, i.e., at both baseline and Week 54. However, there are 34 patients with films at both baseline and Week 54 who have total scores for joint space narrowing (JSN) and/or erosion (ES) recorded as "NE" for Reader 1 and/or Reader 2 in Appendix J-15 (Table 2). It is unclear why a total van der Heijde score is not provided in this table for these patients

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTRR/DARP	M. [illegible]	1/28/00	DARP	Dixon	1/28/00			
OTRR/DBLOI	[illegible]	1/28/00						
OTRR/DCMT	[illegible]	1/28/00						

since it appears that a score for the reader can be calculated from data provided in Appendices J-16 through J-21. We have the following comments on these findings:

a. A total van der Heijde score was not calculated for patients who had undergone a surgical procedure to the foot prior to study entry, even though radiographic data from the hands were available and could be used for this purpose. The study protocol specifies that joints altered by surgery before the time of study enrollment are not to be included in the score. There was no pre-specified plan to exclude patients for whom an erosion score and/or JSN score for a set of joints would be zero. Please calculate the van der Heijde score for these patients using data from assessable joints, and include these data in the primary analysis.

b. A total van der Heijde score was not calculated when Reader-1 scored erosions or joint space narrowing in one or both feet as "ND" (evaluation not done, or unreadable) even though the reader considered the films adequate. With the exception of patient 22008 in this patient subgroup, Reader 1 scored the joints in the feet as "ND" at both baseline and at Week 54. According to the protocol, when a reader was unable to score a joint, the van der Heijde score was to be adjusted by dividing the score component (i.e., the JSN or ES) by the number of joints evaluated and then multiply by the number of joints in that set. Therefore, by this method, when the set of joints in only one foot was scored, an overall van der Heijde score could be calculated for the set of joints in the feet by using relevant data from the other foot. Similarly, when the same set of joints in both feet are scored "ND" at both baseline and Week 54, such that the ES or score for JSN would be zero for the feet, an overall van der Heijde score could be calculated using data derived from the hand joints. Please comment and submit van der Heijde scores for these patients in an amendment to the supplement that also includes a revised analysis using these data.

c. Appendix I-3 provided in your previous BLA supplement (99-0128) provides the history of joint surgery at the time of study enrollment. According to this appendix, patients numbered 15015, 15007, and 14002 did not have a history of surgery at the time of study enrollment in joints of the feet that were scored by Readers 1 and 2. The final ES and/or JSN scores for these patients are recorded as "NE" in Appendix J-15. For example, patient 14002 had surgery performed on MTP joints 1-5 of both feet, but not on the first interphalangeal joint (IP1) of either foot. Although Reader 2 scored both IP1 joints for erosions, and Reader 1 scored the right IP1 joint for erosions, the ES is recorded as "NE" in Appendix J-15 for both readers. Please comment and provide the ES and/or JSN scores for these patients in a revised primary analysis.

3. As part of our review, we calculated a total van der Heijde score for Readers 1 and 2 in a random sample of 23 patients listed in Appendix J-15 using the readers' scores for erosions and JSN listed in Appendices J-16 through J-21. We found inconsistencies between the calculated scores and those reported in Appendix J-15 for 10 of these patients whose films were scored by Reader 2 (primarily in the calculation of the erosion score) and for one patient (15015) whose films were scored by Reader 1 (Table 3). (For patient 15015, we calculated a score for JSN based upon Reader 1's score of the joints in the hands.) We have the following comments on these findings:

   a. It appears that changing scores in the line listings for foot erosions from "0" to "10" results in the erosion score which is recorded in the summary listing for all but one patient. It cannot be determined from the clinical data provided in the line listings how the ES for the feet joints should be properly scored. A change from "0" to "10" in the ES scores does not appear to resolve all of the discrepancies found in our review. For patient 15015, the ES for Reader 2 is recorded as 56 in Appendix J-15 but the ES for the set of joints in the feet alone is 65 and the total ES is 123.3 when the clinical data provided in Appendices J-16 through J-21 are used to calculate scores. Please comment, and submit a revised database to the supplement where appropriate.

   b. We suggest a possible explanation for some of the observed inconsistencies between the two readers in their interpretation of severely diseased joints of the feet. Reader 1 may have scored severe erosions and JSN as "ND" to indicate a significant degree of disease in the joint. However, it appears that Reader 2 recorded fewer joints as "ND" and may have scored destroyed joints as "10". Please comment, and provide the definition used by Reader 1 for "ND".

4. Because of the inconsistencies and problems associated with the clinical database noted in items 2 and 3 above, and because of significant variations in the interpretation of the scans between the two readers as reflected in the widely divergent van der Heijde scores, please submit the SAS transport file database and line listings assembled by he following patient listings should be included in your submission:

   a. All patients with any radiographs submitted or received.

   b. All patients entered into the digital imaging review system for independent review.

   c. All patients reviewed by the independent reviewers.

d. All patients with any radiographs received by _____ who were not entered into the digital imaging system or who were not reviewed by the independent reviewers, including explanatory notes for their exclusion.

5. Please note that for each patient, the _____ radiographic database should include the following:

a. Site number and patient number for all patients with any radiograph.

b. Radiographic data tracking history for all radiographs for each patient to include the following:

i. The protocol timepoints and the actual imaging dates for each radiograph and the number of radiographs for each patient at all timepoints.

ii. The extremity imaged for each radiograph.

iii. Quality assurance and quality control comments regarding film quality, and documentation of any request for additional information made by _____ rom the clinical site to support analysis of the submitted radiograph.

iv. Confirmation that each radiograph was or was not entered for the independent review.

v. Confirmation that the radiograph was or was not interpreted by the independent reviewers.

vi. All scoring values completed in the independent review for each radiograph by reviewer 1 and reviewer 2.

6. The revised SAS transport files submitted to the supplement on December 7, 1999 with data on the joint space narrowing and erosion scores are incomplete. The last patient included in the data set entitled ad_eros.xpt is patient number 17017, while the last patient listed in the data set ad_jsn.xpt is patient number 19011. Please submit complete SAS datasets to the BLA supplement.

Due to the extent and nature of these deficiencies in the efficacy data in the clinical section of your supplement, we are unable to complete a thorough review of the submitted efficacy data. Given the large number of inconsistencies in the radiographic database, and the significant differences between the two readers' interpretation of the radiographs, we strongly suggest that you consider a plan to re-read all of the films as soon as possible to generate a new database in

which more meaningful inferences can be derived. Before you initiate these studies, please submit a written proposal to the Agency that includes detailed instructions to the readers so that the radiographs may be consistently and accurately scored.

Review of the remaining sections of your BLA supplement, including the safety database, is continuing; however, based on a preliminary review of the safety data in the clinical sections of the supplemental license application, we have the following comments and requests for additional information:

7. Our preliminary review of the safety data on serious infections includes the Safety Update Reports submitted on April 30, 1999 and June 18, 1999 as well as the safety data submitted in the current supplemental license application. We have identified four additional patients with serious infections who are not included in Table 54 of Section 8, "Serious infections reported after week 30".

   a. Patient 15008 (placebo) was hospitalized following the development of coughing, diarrhea, vomiting, left abdominal pain, and fever. She is described in the June 18, 1999 Safety Update and included in the line listing of serious adverse events in the current supplemental license application but not in Table 54.

   b. Patient 07011 (3 mg/kg Infliximab q 8 wks) was hospitalized because of stasis ulcers of the left lower extremity, cellulitis and septic thrombophlebitis. She is included in the April 30, 1999 Safety update.

   c. Patient 04014 (3 mg/kg Infliximab q 4 wks) was hospitalized for treatment of cellulitis and is described in the April 30, 1999 Safety Update.

   d. Patient 22008 (3 mg/kg Infliximab q 4 wks) was admitted for a surgical procedure following an infected bunion and is described in the April 30, 1999 Safety Update.

   Please comment, and submit a revised safety database to the supplement which includes these patients as having experienced a serious infection.

8. You conducted an analysis of the human anti-chimeric antibody (HACA) on 84 infliximab-treated patients who had an interval of 8 or more weeks between completion of 54 weeks of treatment (infusion 15) and possible re-treatment in the second year of

the study (infusion 16). Serum samples were available for seventy-six patients in this group, however, HACA could not be assayed in 43 patients because of detectable serum concentrations of infliximab. Please submit the following:

a. A listing of the 84 patients treated with infliximab and the interval between infusions 15 and 16 for each of them.

b. The HACA results for the 76 patients with available serum samples.

c. A summary of the clinical response and/or adverse events relevant to re-exposure to infliximab in patients who received infusion 16 after an interval of 8 or more weeks.

These comments are being provided to you prior to the completion of our review of your entire supplement to give you preliminary, advance notice of clinical issues that have been identified. Please note that these comments are subject to change as the complete review of your application is finalized. Final comments, if any, will be communicated to you at a later date after the review of the application is complete. You may, but are not required to, respond to these preliminary comments. If you respond, we may or may not consider your response prior to taking a complete action on your application. If your response is determined to constitute a major amendment, you will be notified of this decision in writing. Review of the remaining sections of your supplement is continuing.

Should you need additional information or have any questions concerning administrative or procedural matters, please contact the Regulatory Project Manager, Mr. Michael Noska, at (301) 827-5101.

Sincerely yours,

Barbara Matthews, M.D., M.P.H.
Committee Chair
Division of Clinical Trial
Design and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Attachments

cc: [redacted] (comments received 01/27/00)
HFM-573/G. Mills
HFM-579/L. Black
HFM-579/L. Paserchia
HFM-215/B. Zhen
HFM-650/D. Bower
HFM-220/F. Varricchio
HFM-579/Martin D. Green
HFM-588/M. Noska
HFM-582/W. Schwieterman
HFM-585/G. Jones
HFM-585/L. Burbank

CBER:DARP:B.Matthews:M.Noska:1/27/00:Dixon:1/28/00
(S:\Noska\Letters\License\99-1234DR.doc)

CORR: DISCIPLINE REVIEW LETTER: CLINICAL SECTION

Table 1. Patients who received study drug but are not included in Appendix J-15 (Radiographic Results).

Treatment Group	PID	Last infusion	submitted
Placebo	07004	4	No
	07013*	15	Yes
	13008	15	No
	30001	8	No
3 mg/kg q 8	09002*	15	Yes
	13003	15	No
3 mg/kg q 4	07009*	15	Yes
	34003	15	No
10 mg/kg q 4	05018	12	No
	13006	15	No
	21009	15	No
	33015	15	No

* van der Heijde scores for joints recorded in Appendices J-16 through J-22

Table 2. Patients with radiographs at week 0 and 54 who are categorized according to Reader as "NE" for either erosion score (ES) or joint space narrowing (JSN) in Appendix J-15

Treatment Group	PID	Reader 1		Reader 2	
		ES	JSN	ES	JSN
Placebo	04029		NE		
	08001			NE	NE
	08008	NE	NE	NE	NE
	13011	NE	NE		
	15015		NE		NE
	31002	NE	NE		NE
	33009	NE	NE		
	33011		NE		
3 mg/kg q 8 wks	04016		NE		
	07017		NE		NE
	15007		NE		
	16006		NE		
	22006		NE		
	26003	NE	NE		
3 mg/kg q 4 wks	08006	NE	NE	NE	NE
	09009	NE	NE		
	11006			NE	
	17020	NE	NE		NE
	20007		NE		
	21017		NE		
	22008		NE		
	31003	NE	NE		
	32005		NE		NE
10mg/kg q 8 wks	06008		NE		NE
	12005		NE		
	14002	NE	NE	NE	NE
	33013		NE		
10 mg/kg q 4 wks	04005		NE		NE
	04022		NE		
	08003				NE
	17012		NE		
	17016	NE	NE		NE
	21001			NE	NE
	26004			NE	NE
	28005		NE		

Table 3. Discrepancies between calculated van der Heijde scores and scores recorded in Appendix J-15 for randomly selected patients.

PID	Dose	Time	Reader 1				Reader 2			
			Calculated ES-1	J-15 ES-1	Calculated JSN-1	J-15 JSN-1	Calculated ES-2	J-15 ES-2	Calculated JSN-2	J-15 JSN-2
04016	3q8	base	53.1	53.1	85	NE	78	158	89	89
		wk54	56.1	56.1	54	NE	75	155	88	88
33005	10q8	base	48	48	97	97	107	155	91	91
		wk54	55	55	101	101	104.8	152.8	92	92
12002	10q4	base	81.7	81.7	87.4	87.4	93.7	153.7	85.8	85.8
		wk54	82.8	82.9	82.9	89.5	91.6	151.7	90	90
18009	10q8	base	43	43	91	91	66	166	91	91
		wk54	44	44	91	91	67	167	91	91
19008	10q4	base	203	203	109	109	198	218	113	113
		wk54	202	202	106	106	196	216	107	107
23001	3q8	base	34	34	49	49	46	96	42	42
		wk54	34	34	54	54	42	92	48	48
07020	placebo	base	95	105	79	79	77	147	45	45
		wk54	97	107	81	81	76	146	46	46
12010	3q4	base	43.4	43.4	85	85	88	138	78	78
		wk54	46	46	77	77	93	133	72	72
04029	placebo	base	105.6	105.6	83	NE	113	173	102	102
		wk54	106.3	106.3	81	NE	115	175	102	102
15015	placebo	base	53.4	42.5	36.5	NE	123.5	56	44.5	NE
		wk54	57	45.6	38.5	NE	124.7	59	43.6	NE

ATTACHMENT II

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 1007

PHARMACOLOGY REVIEW

Memorandum:

To File:	BLA 99-1234
From:	Lauren E. Black, Ph.D., Reviewing Pharmacologist 2/15/00
Through:	M. David Green, Ph.D., Branch Chief, Clinical Pharmacology and Toxicology Branch
and	
Through:	Karen Weiss, M.D., Director, Division of Clinical Trials Design and Analysis
Subject:	Pharmacology/Toxicology Review of the infliximab BLA
Product:	**Remicade®**,
	Infliximab (cA2), chimeric (human/murine) IgG1 for use in Crohn's Patients
Sponsor:	Centocor, Inc.
Date:	2/15/00
Indication:	

OVERVIEW:

Infliximab has been the subject of a prior approved BLA and a BLA supplement. No pharmacology and toxicology objections have been offered to either approval. Currently the sponsor is conducting a chronic evaluation of an analogous antibody, cV1q, in mice. Final study results are not ready yet; however, finalization was agreed by FDA and Centocor staff to not be required for approval of this BLA supplement. In summary, no new toxicology studies have been done.

PHARMACOLOGY:

A new efficacy study of murine A2 (the murine parent monoclonal for infliximab) has been conducted in transgenic mice line Tg197 which consituitively express human TNFalpha and develop polyarthritis starting at 4 weeks of age- these mice are so affected if unmedicated, they must be sacrificed at 6-14 weeks of age to ensure humane treatment. This study was conducted to provide evidence in an animal model, that blockade of TNF after (the model) disease is established at 6 weeks, can afford the opportunity for joint healing. Disease status was tracked by clinical arthritis score (based on decreee of paw swelling and additionally by complete histologic exam conducted on ankle, knee and metatarsal joints in rear limbs, and elbow, wrist, and metacarpal joints in forelimbs. Evaluations were made of synovitis, pannus formation, marginal erosions, periosteitis, fasciitis, architectural changes, and overall score in animals that were sacrificed at 6 weeks of treatment with mA2 or saline, and after 16 weeks of treatment with mA2; durability of shortterm improvement in responses to mA2 was not investigated. Saline controls were sacrificed at week 6 as well, having displayed severe disease. In this model of human TNF induced joint damage,

TOXICOLOGY SUMMARY (as previously reported):

Chimeric A2 showed no unexpected reactivity (or cross-reactivity) in *in vitro* human tissue cross-reactivity assessment, nor mutagenicity, local intolerance, or other systemic toxicities that would preclude its use in patients. Since the chimpanzee is the only species other than humans whose TNFa bind to cA2, safety studies in this species are considered the only studies that can provide relevant safety information on cA2 administration to humans; due to animal use restrictions on this endangered species, these animals may not be necropsied to provide histopathology data, and therefore study outcomes are limited to clinically

observable signs, as well well as results from noninvasive testing such as clinical chemistry and hematology assessments. Following some problems attibutable to high doses of ketamine anesthetic required for animal handling, the studies with cA2 in chimpanzees showed that cA2 was well tolerated at doses up to 30 mg/kg/day for at least 3 consecutive days and at doses up to 15 mg/kg/day for at least 5 days. No cA2-related signs of toxicity, including abnormal hepatic or hematologic effects, were observed during these chimpanzee studies. The nonclinical studies provided primary support for activity and safety for cA2-treated Crohn's disease patients; no further studies in chimpanzees were requested by the FDA. The sponsor was encouraged instead to pursue further safety characterizations using an analogous monoclonal antibody.

Doses of an analogous anti-mouse TNFa monoclonal antibody, cV1q, which were shown to be active in a mouse model of disease, when given to pregnant mice during organogenesis, caused no embryofetal toxicities, and when given to mice to evaluate male fertility, caused no deleterious effects on male fertility parameters. These studies were necessitated due to the absence of crossreactivity of cA2 in species other than chimpanzees. A chronic toxicity study of the rat anti-mouse TNFa antibody, in being conducted in mice further support the safety of extended dosing with infliximab in patients.

PRODUCT LABELING:
No significant changes in preclinical toxicology sections of the label are expected at this time.

CONCLUSIONS:
Based on review of the pharmacology and toxicology data, the safety of infliximab is adequately supported, and no objection is offered to approving this licensing application supplement.

REVIEWER: _____
Lauren E. Black, Ph.D., Reviewing Pharmacologist, DCTDA, CBER

CONCURRENCE: _____
Martin David Green, Ph.D., Branch Chief, Clinical Pharmacology and Toxicology Branch, DCTDA, CBER

cc:
M.D. Green, Ph.D., HFM-579
L.E. Black, Ph.D., HFM-579
K. Brorson, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 1007

STATISTICAL REVIEW(S)

PROTOCOL C0168T22 (ATTRACT)

1.0 Introduction

This trial was a placebo-controlled, double-blind, randomized study of chronic treatment with infliximab in approximately 400 patients. A total of 428 patients were actually enrolled. Four infliximab treatment groups were evaluated and compared with a placebo group. Patients in each of the 4 infliximab treatment groups were to receive an infusion at weeks 0, 2, and 6; 2 groups were to receive 3 mg/kg infusions and the other 2 groups were to receive 10 mg/kg infusions. After 6 weeks, treatments were to be continued through 1 year with one of the 3 mg/kg and one of the 10 mg/kg groups receiving treatment every 4 weeks, and the other 3 mg/kg and 10 mg/kg groups receiving treatment every 8 weeks. Patients in each of the five groups continued concurrent MTX treatment at the same dose as that received before the study. This report presents data obtained through week 54 only. Data collected after the week-54 cut-off will be presented in (a) future report(s).

The primary endpoint was the [redacted] as measured by the change from baseline in the van der Heijde modification of the Sharp score, which includes radiographs of both the hands and feet, at baseline and the week-54 follow-up visit. Certain endpoints which were originally considered to be primary were subsequently designated as secondary to reduce the complexity of the primary analyses and to better account for the use of Type I error, as well as to comply with recommendations of the FDA (see OAP Amendments 1 and 2 in Attachment 3). The achievement of a clinical response (ACR ≥20%) at the 54-week follow-up visit was evaluated as a secondary endpoint to support the findings at week 30. Improvement in disability was assessed at week 54 by analyzing the weighted mean change from baseline in the patients' HAQs. The total radiologic score for hands only was analyzed and reported as a secondary analysis. [redacted] was assessed by determining the number of newly involved joints and evaluating the van der Heijde erosion score. In addition, the proportion of patients who showed radiologic progression, defined as an increase from baseline in the van der Heijde modification of the Sharp score that is larger than the smallest detectable difference (SDD), were also evaluated.

2.0 Radiographic Results

The primary endpoint was the [redacted] as measured by the change from baseline to week-54 follow-up visit in the total sharp score. The primary analysis included all patients with complete evaluations at baseline and week 54 in the treatment groups to which they were randomly assigned. The change from baseline to week 54 was compared among the treatment groups by using analyses of variance of van der Waerden normal scores. If there was a significant overall treatment effect (p=0.025), comparisons of the infliximab treatment groups with the placebo group were to be made by using contrast statements. A shown in Table 2 (p.17, Vol. 5, Item 8), the results of the primary endpoint analysis indicate that infliximab-treated patients had significantly less progression of structural damage from baseline to week 54, as

measured by the van der Heijde modification of the Sharp scores, than patients who received placebo. In accordance with the Operational and Analytical Plan (OAP), the first statistical test performed was an analysis of the overall treatment effect. This analysis showed statistically significant ($p < 0.001$) differences among the treatment groups. Moreover, pairwise comparisons showed that the change from baseline in total radiologic scores of the hands and feet at week 54 in each of the 4 infliximab treatment groups was statistically significantly ($p < 0.001$) lower than that in the placebo group.

Table 2 Change from baseline in total radiologic scores of the hands and feet at week 54[a]

		Infliximab					Treatment Effect p-Value
	Placebo	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks	All Infliximab Regimens	
Pts randomized	88	86	86	87	81	340	
Change from baseline at week 54							
Pts evaluated	63	71	71	77	66	285	
Mean ± SD	6.97 ± 10.35	1.17 ± 5.96	1.09 ± 7.85	0.37 ± 4.46	-0.48 ± 3.52	0.55 ± 5.70	
Median	4.00	0.50	0.00	0.50	-0.50	0.00	< 0.001
IQ range	(0.50, 9.81)	(-1.50, 3.00)	(-3.00, 3.00)	(-1.50, 2.00)	(-2.50, 1.75)	(-2.00, 2.50)	
Range	(-4.50, 61.03)	(-9.78, 37.00)	(-23.50, 26.65)	(-11.50, 19.78)	(-10.07, 7.90)	(-23.50, 37.00)	
p-value vs placebo		< 0.001	< 0.001	< 0.001	< 0.001		

[a] Total radiologic scores of the hands and feet are based on the van der Heijde modification of the Sharp score.

2.1 Comments

a. The intent-to-treat (ITT) population has not been used in the analysis for this endpoint. An analysis should have been conducted using all randomized patients.

b. Because some mistakes in the radiographic data were found during the review of the on-site data, further review on this endpoint is pending upon response and possibly re-submission of the data sets from the sponsor.

3.0

According to regulatory guidance, endpoints required to demonstrate include improvement in HAQ scores in addition to no worsening in a more general

been demonstrated previously or concurrently. Improvement in physical disability was assessed by analyzing the patients' weighted mean changes from baseline HAQ scores in conjunction with weighted mean SF-36 mental component summary scores through week 54. The individual subscales of the HAQ were compared among the treatment groups by using an ANOVA on van der Waerden normal scores for the weighted mean scores over time. If any of these analysis were significant at the 0.05 level, the results for each of the infliximab-treated groups were to be compared with the placebo (MTX-alone) group by using contrast statements.

The results in the following table (p.37, Vol. 5, Item 8) indicate that overall [redacted] patients who received any of the infliximab treatment regimens compared with patients who received placebo ($p < 0.001$ in pairwise comparisons). Moreover, the weighted mean change from baseline in the mental component summary scores of the SF-36 were not significantly different among the treatment groups, including placebo (treatment effect p-value = 0.332). In fact, the weighted mean changes from baseline mental component summary scores in each of the infliximab treatment groups are numerically higher than that in the placebo group and, thus, there was not only no worsening in these scores through 54 weeks of treatment, there was also a trend toward improvement. The overall physical component summary scores of the SF-36 also were significantly improved from baseline through week 54 in patients who received infliximab treatment (treatment effect $p < 0.001$). Moreover, a significant treatment effect ($p < 0.001$) was observed for each of the physical component scores (i.e., physical functioning, role-physical, bodily pain, and general health scores). Significant improvements were also observed in the vitality and social functioning.

Table 11 : Weighted mean change from baseline in HAQ over time through week 54*

	Placebo	Infliximab 3 mg/kg q 8 Wks	Infliximab 3 mg/kg q 4 Wks	Infliximab 10 mg/kg q 8 Wks	Infliximab 10 mg/kg q 4 Wks	All Infliximab Regimens
Pts randomize	88	86	86	87	81	340
Pts evaluated	87	86	86	87	81	339
Mean ± SD	0.2 ± 0.3	0.4 ± 0.3	0.5 ± 0.4	0.5 ± 0.5	0.4 ± 0.4	0.4 ± 0.4
Median	0.1	0.3	0.3	0.4	0.3	0.3
P-value vs. placebo		< 0.001	< 0.001	< 0.001	< 0.001	

*: Note that the weighted mean change from baseline HAQ scores was calculated so that positive values indicate less disability than at baseline.

3.1 Comments

a. This reviewer has tried to reproduce results in Table 11 and found that two p-values estimated using contrast statements in ANOVA are different from what the sponsor has presented. The p-value for '3 mg/kg q8 wks' vs. placebo was 0.0358 and the p-value for '10 mg/kg q4 wks' vs. placebo was 0.009 rather than the p-value<0.001 reported for both

comparisons. For verification, the sponsor needs to provide the SAS program(s) that can be efficiently used to repeat the analysis.

b. This reviewer is unable to repeat the sponsor's calculation on HAQ score for each patient using the original source data set (HAQ.XPT) since no detailed method for HAQ calculation in this submission is available. The sponsor should provide the standard procedure for calculating HAQ scores.

c. Landmark analysis of HAQ

In order to look at the change in HAQ over time, This reviewer calculated the change from baseline HAQ at each study visit and plotted the graph of mean change for each treatment group as shown in Figure 1.

We consider the change in HAQ between baseline and week 54 as the important variable for landmark analysis. There is an overall significant difference in the mean change from baseline to week 54 ($p=0.0129$) among the five groups. When comparing results for each of the infiximab treated groups with placebo using contrast statement in ANOVA, mean in the placebo group was not significantly lower than those in patients treated with infliximab 10q4 and treated with infliximab 3q8 ($p=0.1125$ and $p=0.0817$, respectively). However, both comparisons using Wilcoxon rank sum test resulted in statistically significant differences ($p=0.0481$ and $p=0.0173$, respectively).

Patients with missing measures of HAQ at week 50 had a mean HAQ score of 1.7 at week 54 compared to 1.2 for those who had HAQ assessment at week 50 ($p<0.0001$). This suggests that patients with missing HAQ may have outcomes worse than the ones without missing data. Therefore, a worst outcome analysis was conducted by assigning a HAQ score of 3 for patients without HAQ evaluation at any of the visits and repeating the above analysis. The results are shown in Figure 2. The pairwise comparisons of each of the infiximab treated groups against the placebo showed significant differences using both methods (ANOVA and Wilcoxon rank sum test).

Summary: There is evidence that each of the infliximab treated groups is different from the placebo group in the change from baseline HAQ to week 54. A minimal improvement of 0.15 in HAQ score for the infliximab treated group over the placebo group was observed in this study and its clinical benefit may require further evaluation. The non-significant results from comparing the placebo group with ' 3 mg/kg every 8 weeks' group or with '10 mg/kg every 4 weeks' group using ANOVA could be due to: 1) statistical test based on normality assumption may not be sensitive enough to detect the difference; 2) the sample size may not be sufficiently powered for the comparisons since the study was not originally designed for the landmark analysis.

d. Landmark analysis of HAQ according to the baseline HAQ score

In a subset of patients with baseline HAQ score ≤ 2, there were statistically significant differences between the placebo group and each of the infliximab groups in the change

from baseline HAQ to week 54. Further analyses using subsets of patients with baseline HAQ score > 2 or HAQ $\leq$1.5 or HAQ>1.5 did not show any statistically significant differences.

4.0 Clinical Response

A clinical response was defined as an ACR 20% response at week 54 without a protocol-prohibited change in medication and/or a surgical joint procedure. The results of this analysis, which was performed on an intention-to-treat basis, indicated that infliximab-treated patients had greater response rates than those who received placebo. Pairwise comparisons showed that in each case, the response rates for each infliximab treatment group were significantly greater than that in the placebo group ($p < 0.001$). The response rate for placebo treatment group was 17.0%, whereas the response rates for the infliximab treatment groups 3 mg/kg q 8 wks, 3 mg/kg q 4 wks, 10 mg/kg q 8 wks, and 10 mg/kg q 4 wks were 41.9%, 47.7%, 58.6%, and 59.3%, respectively.

4.1 Comments

a. This reviewer has checked the sponsor's analysis on the clinical response at week 54 and found that results agree with what the sponsor has presented.

Figure 1: Change from baseline in HAQ
Per Evaluable Subset Analysis

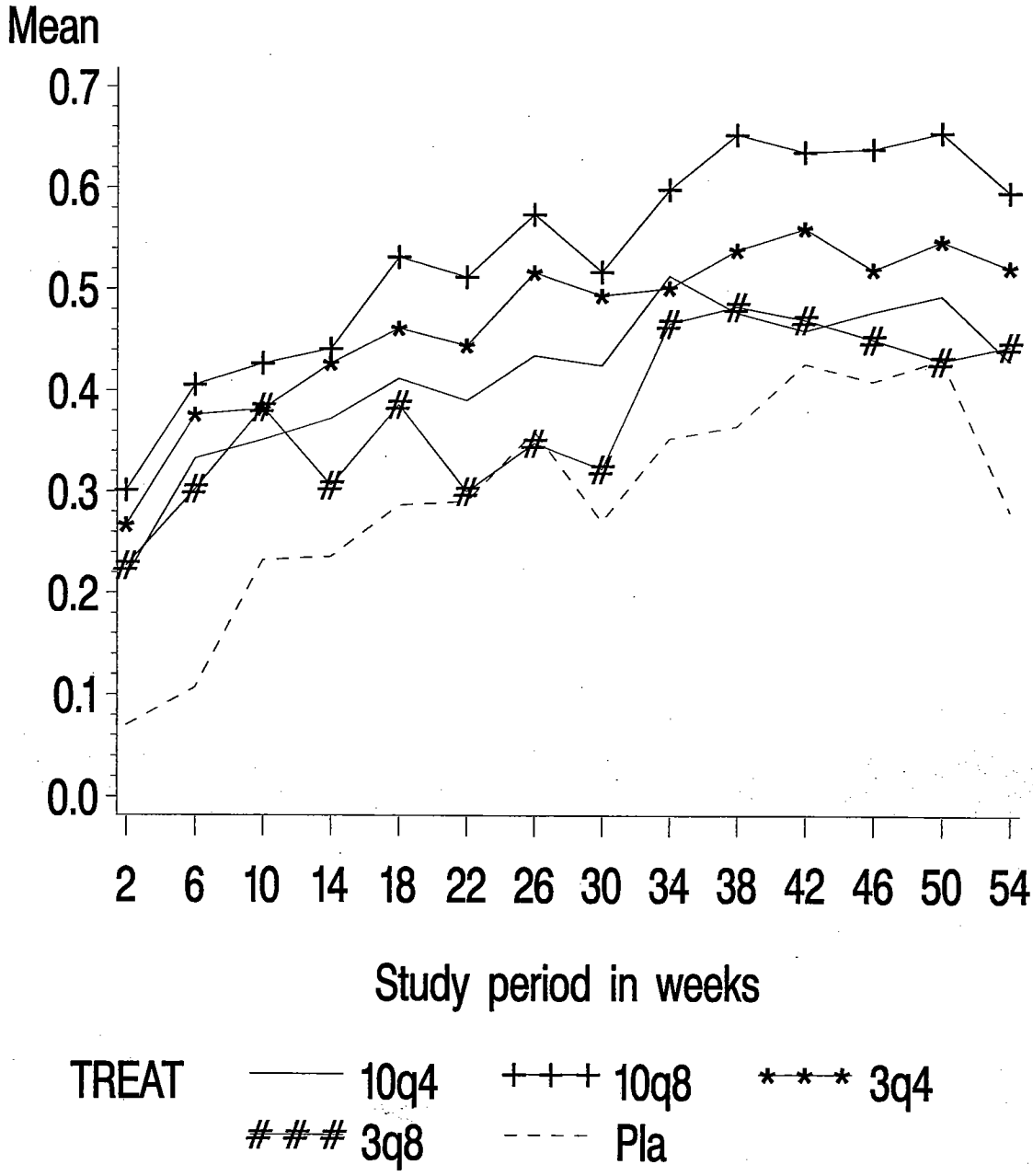
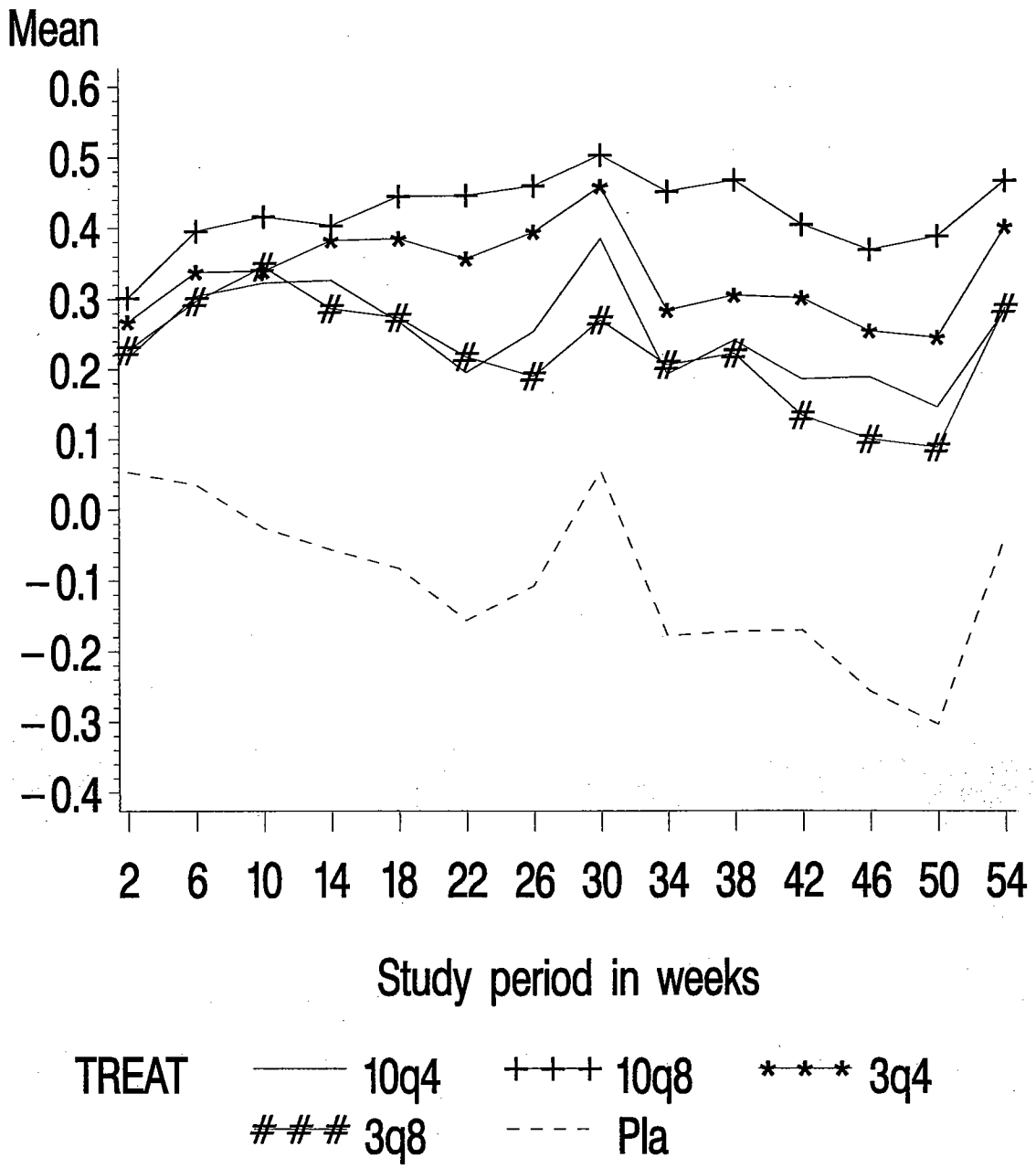


Figure 2: Change from baseline in HAQ
Worst Outcome Analysis



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 1007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

Date: 3-10-00 (final)

From: Lori A. Paserchia, MD 3/10/00
Clinical Pharmacology Reviewer, Clinical Pharmacology/Toxicology Branch, Division of Clinical Trial Design and Analysis

Through: Martin D. Green, PhD MDG
Branch Chief, Clinical Pharmacology/Toxicology Branch, Division of Clinical Trial Design and Analysis

Karen Weiss, MD KW
Director, Division of Clinical Trial Design and Analysis

Subject: Clinical Pharmacology Review of BLA 99-1234, Remicade (Supplement)

To: Center/Division/Office- DARP, OTRR
Primary Clinical Reviewer- Barbara Matthews, MD

Please see attached review.

EXECUTIVE SUMMARY

Infliximab (Remicade, cA2) is a chimeric IgG1κ monoclonal antibody produced by a recombinant cell line from a genetically-engineered form of the mouse monoclonal antibody prototype, A2. Infliximab binds with high affinity to soluble and transmembrane human TNFα. The resultant inhibition of TNFα binding with its receptors prevents the biological activities of TNF α including: induction of pro-inflammatory cytokines such as IL-1 and IL-6, and enhancement of leukocyte migration and activation. Infliximab is normally-glycosylated and has an approximate molecular weight of 149,100 daltons.

Infliximab is currently licensed for the reduction of signs and symptoms in patients with rheumatoid arthritis (RA) who either have had an inadequate response to methotrexate (MTX), or
It is also licensed for the reduction of signs and symptoms in Crohn's disease. This supplement to the BLA (sBLA) contains safety, efficacy and pharmacokinetic (PK) data in support of the following indication for RA: for the The proposed intravenous dosing regimen for this new indication is 3 mg/kg once during weeks 0, 2, and 6 and every 8 weeks thereafter, in combination with MTX. For subjects with a suboptimal response, the dose may be increased to a maximum of 10 mg/kg every

The PK information in this sBLA is contained in 1 thin volume (27 pages) and is intended to be supplemental to the information submitted in BLA99-0128. The PK assessment in BLA99-0128 included data from only the first 30 weeks of study C0168T22. The current sBLA contains the plasma infliximab concentration versus time data from all 54 weeks of study C0168T22. An evaluation of the relationship of clinical response to infliximab concentration or dose was also performed.

The PK results submitted in this sBLA do not add any new information compared to the results submitted in BLA99-0128. Infliximab doses 3 or 10 mg/kg administered intravenously either every 4 or 8 weeks produced a dose-linear increase in steady state trough concentrations. Evidence of accumulation was not present. Steady state was achieved by 22 weeks after initiation of dose administration. The derivation of PK parameters was not performed.

An evaluation of the dose-response relationship, where response consisted of the change in the ACR20, revealed a greater proportion of nonresponders in the 3 mg/kg dose level, regardless of dosing interval. The concentration-response relationship demonstrated similar findings; the nonresponders had statistically significantly lower plasma infliximab concentrations than did responders. The PK dataset was too small to confidently perform a demographic subset analysis for each dosing regimen.

The PK information submitted in this sBLA does not indicate any obvious licensure issues or a need to revise the Clinical Pharmacology section of the labeling.

Clinical Pharmacology Review of BLA 99-1234 (infliximab, Remicade)

Protocol C0168T22: A placebo-controlled, double-blinded, randomized clinical trial of anti-TNF chimeric monoclonal antibody (cA2; infliximab) in patients with active rheumatoid arthritis despite methotrexate treatment (ATTRACT).

Methods

This was a randomized, 5-arm, multicenter, placebo-controlled, Phase 3 study in subjects with rheumatoid arthritis (RA) who were on a stable dose of at least 12.5 mg/week of methotrexate (MTX). The infliximab dose levels were 3 or 10 mg/kg iv, or placebo. All doses were given over a duration of at least 2 hr during week 0, 2 and 6 followed either by every 4 week dosing thereafter (placebo, 3 and 10 mg/kg) or every 8 weeks thereafter (3 or 10 mg/kg). The [redacted] ormulation was administered (lots 96E06, 97A07, 97A10, 97C07, and 97E08). DMARD therapy other than MTX was not permitted. The dose of MTX was to be ≥12.5 mg/wk. Concurrent and stable use of oral steroids or NSAIDs was permitted.

Blood sampling for the measurement of serum infliximab concentration was performed at peak/trough for each infusion through week 6 and then at trough every 8 weeks through week 54. Serum infliximab concentrations were determined with a [redacted] µg/mL). Serum infliximab concentrations of subjects who 1) discontinued study treatment, 2) skipped an infliximab infusion, 3) received an incorrect infusion, or 4) received an incomplete infliximab infusion (< 80% of the total scheduled infusion volume) were included in the data listings, but values from samples obtained after any of these deviations from the planned dosing regimen were not included in any summary calculations. There were no plans to derive PK parameters; only summary statistics for the concentration v. time data were submitted.

Results

Plasma Concentration v. Time

This sBLA contains the PK dataset and results for 428 subjects; 340/428 subjects received infliximab and 88/428 received placebo. Any subject who did not receive all infusions or received the wrong dose was not included in the PK analyses from that point onward.

A table of the concentration v. time summary statistics is located in Appendix 1 and the corresponding graphs are located in Appendix 2. Dose-linearity is seen for the 3 and 10 mg/kg dose levels based on the Cmax and Cmin (trough) for both the every-4-week and the every-8-week regimens. Steady state appears to be achieved by week 22 for all the dosing regimens

For the proposed dosing regimen of 3 mg/kg every-8-weeks (graph with open diamonds; second graph in Appendix 2), the steady state median trough is 1.0 ug/mL. The reason for the dip below 1 ug/mL in the median trough during Week 30 is unknown. The demographic profile of these subjects did not reveal any differences based on gender, race or age-- when compared to the demographic profile for the entire study population. Assay limitations at this low plasma concentration could be a factor but there is no hint of this problem for the other timepoints. The clinical significance of the dip in trough at Week 30 is unknown.

The limitations of the HACA assay, namely assay interference by the presence of infliximab in the plasma, precluded a meaningful analysis of the effects of HACA on the PK of infliximab.

Dose/Concentration v. Response

As shown in Appendix 3, there is a suggestion of a concentration-response relationship for the 3 mg/kg every-8 week dosing regimen. For this analysis, efficacy was measured by the number of visits with an ACR of 20% and then grouped into 3 distinct response categories. The lowest efficacy response category was associated with the lowest median infliximab concentration at each visit during the 54-week study. In fact, during steady state all but 1 of the measurement timepoints had a infliximab concentration of 0.1 ug/mL (i.e., essentially zero for the infliximab assay). The reason for the lower infliximab concentrations in this group is unknown. One possibility is an increased clearance due to HACA formation, although it is impossible to prove this due to the limitations of the HACA assay.

To examine this concentration-response finding further, an independent analysis was performed for all subjects who had an infliximab concentration of ≤ 0.1 ug/mL. To briefly explain, I sorted the PK dataset for all subjects in the 3 mg/kg every-8-week dose group who had ≥3 timepoints (number of timepoints chosen arbitrarily by me) with an infliximab concentration of ≤ 0.1 ug/mL. Fifteen of 86 randomized subjects met this criterion. Separately, Dr. Barbara Matthews categorized all subjects in the 3 mg/kg every-8-week dose group into 1 of 4 ACR20 efficacy response categories:

1= steady (an efficacy response was seen for the duration of the study)
2= gain (no efficacy response was seen until the latter stages of the study)
3= lose (an efficacy response was seen initially but then waned)
4= none (an efficacy response was never seen)

Then, the efficacy response category for each of the 15 subjects with ≥3 timepoints with an infliximab concentration of ≤ 0.1 ug/mL was examined. The results:

Efficacy Response Category	# (%) of Subjects
Steady	3 (20)
Gain	2 (13)
Lose	2 (13)
None	6 (40)
Withdrawn from study	2 (13)
	15 (100)

Clearly, more subjects had no, or lost an, efficacy response than had a steady, or gained an, efficacy response (8/13= 62% v. 5/13= 38%, respectively) however the sample size is too small to drawn conclusions with confidence.

The remaining 3 dosing regimens (shown in Appendix 4) did not demonstrate any median concentration-response relationship. The median infliximab concentration was very similar for all 3 categories. The reason(s) for similar infliximab plasma levels producing very different efficacy responses is unknown.

Conclusions:

- The PK information submitted in this sBLA supports the information submitted in BLA99-0128.
- No labeling revisions to the Clinical Pharmacology section are necessary.
- There are no outstanding issues.

(printed from BLA 99-1234)

Appendix 1 (1073)

Table 2 Serum concentration of infliximab through week 6 for all patients[a]

	Infliximab Treatment Regimen					
	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	3 mg/kg combined	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks	10 mg/kg combined
Pts randomized	86	86	172	87	81	168
Week 0 (1 hr postinfusion 1)						
Pts evaluated	86	86	172	85	80	165
Mean ± SD	70.2 ± 20.8	73.0 ± 26.2	71.6 ± 23.6	221.7 ± 71.0	235.9 ± 92.3	228.6 ± 82.1
Median	68.6	68.1	68.5	219.1	215.2	217.4
Interquartile range	(53.1, 81.3)	(57.4, 82.2)	(56.3, 82.1)	(183.3, 246.5)	(182.7, 260.1)	(182.8, 250.8)
Range	(39.9, 128.3)	(0.0, 191.2)	(0.0, 191.2)	(99.3, 646.9)	(25.1, 685.0)	(25.1, 685.0)
Week 2 (preinfusion 2)						
Pts evaluated	86	86	172	87	76	163
Mean ± SD	15.6 ± 6.0	16.9 ± 12.8	16.3 ± 10.0	57.6 ± 23.1	54.8 ± 26.3	56.3 ± 24.6
Median	15.0	14.8	14.9	52.8	48.9	50.7
Interquartile range	(11.8, 19.2)	(11.9, 17.9)	(11.8, 18.1)	(42.5, 70.7)	(38.5, 66.3)	(40.4, 69.4)
Range	(0.8, 32.1)	(3.4, 109.1)	(0.8, 109.1)	(23.3, 181.1)	(16.1, 160.8)	(16.1, 181.1)
Week 2 (1 hr postinfusion 2)						
Pts evaluated	86	85	171	85	79	164
Mean ± SD	91.8 ± 35.3	92.9 ± 29.7	92.4 ± 32.6	299.1 ± 124.2	300.3 ± 137.7	299.7 ± 130.5
Median	84.5	89.7	87.4	271.0	265.0	269.9
Interquartile range	(66.2, 103.4)	(75.8, 96.8)	(71.9, 101.3)	(230.7, 353.9)	(208.6, 353.5)	(217.8, 353.7)
Range	(45.8, 287.7)	(47.3, 213.7)	(45.8, 287.7)	(70.7, 784.6)	(108.0, 924.1)	(70.7, 924.1)
Week 6 (preinfusion 3)						
Pts evaluated	84	84	168	86	80	166
Mean ± SD	10.0 ± 7.1	9.0 ± 6.2	9.5 ± 6.6	37.9 ± 19.8	33.2 ± 19.0	35.7 ± 19.5
Median	9.4	8.9	9.1	36.6	29.0	33.9
Interquartile range	(4.0, 13.0)	(4.8, 13.6)	(4.2, 13.3)	(24.3, 46.4)	(17.1, 45.4)	(22.4, 46.4)
Range	(0.0, 30.2)	(0.0, 27.9)	(0.0, 30.2)	(7.9, 113.9)	(1.7, 79.1)	(1.7, 113.9)
Week 6 (1 hr postinfusion 3)						
Pts evaluated	83	84	167	86	78	164
Mean ± SD	83.8 ± 30.1	84.5 ± 26.7	84.2 ± 28.4	278.1 ± 119.4	276.2 ± 103.7	277.2 ± 111.9
Median	78.3	79.1	78.8	254.4	248.2	250.9
Interquartile range	(62.0, 101.7)	(68.1, 97.5)	(65.6, 97.7)	(218.9, 309.6)	(215.0, 330.9)	(216.6, 318.2)
Range	(25.5, 211.2)	(40.4, 181.6)	(25.5, 211.2)	(0.0, 836.8)	(106.3, 808.8)	(0.0, 836.8)

[a] Infliximab is measured in µg/mL.

PKT101

(printed from BLA 99-1234)

Appendix 1 (2 of 3)

Table 3 Serum concentration of infliximab from week 14 through week 54 for all patients[a]

	Infliximab Treatment Regimen			
	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks
Pts randomized	86	86	87	81
Week 14 (preinfusion 5[b])				
Pts evaluated	78	81	84	76
Mean ± SD	2.8 ± 5.6	7.4 ± 6.9	8.8 ± 7.3	30.2 ± 18.6
Median	1.3	5.5	6.1	25.7
Interquartile range	(0.3, 3.5)	(2.0, 11.6)	(4.0, 11.6)	(19.2, 38.0)
Range	(0.0, 45.2)	(0.0, 29.6)	(0.0, 34.5)	(2.4, 85.2)
Week 14 (1 hr postinfusion 5[b])				
Pts evaluated	75	79	80	72
Mean ± SD	71.9 ± 25.4	81.4 ± 26.5	250.0 ± 99.2	271.1 ± 94.7
Median	69.7	77.2	232.5	242.7
Interquartile range	(55.1, 84.6)	(62.6, 93.4)	(206.9, 270.9)	(216.8, 317.4)
Range	(0.4, 147.7)	(37.5, 194.0)	(12.8, 764.1)	(121.5, 758.5)
Week 22 (preinfusion 7[b])				
Pts evaluated	71	76	80	68
Mean ± SD	1.5 ± 1.8	9.4 ± 8.0	8.0 ± 9.0	35.8 ± 22.3
Median	1.0	8.0	5.6	31.9
Interquartile range	(0.0, 2.4)	(3.2, 14.2)	(2.4, 9.9)	(19.3, 51.7)
Range	(0.0, 9.6)	(0.0, 40.2)	(0.0, 60.3)	(1.5, 97.1)
Week 30 (preinfusion 9[b])				
Pts evaluated	67	75	77	65
Mean ± SD	1.5 ± 2.0	9.6 ± 8.3	7.7 ± 7.1	35.3 ± 22.9
Median	0.5	7.6	6.2	30.3
Interquartile range	(0.0, 2.7)	(4.0, 13.4)	(2.5, 10.5)	(21.2, 45.3)
Range	(0.0, 11.5)	(0.0, 41.2)	(0.0, 36.7)	(0.0, 105.3)

(printed from BLA 99-1234)

Appendix 1 (3 of 3)

Table 3 Serum concentration of infliximab from week 14 through week 54 for all patients[a] (continued)

	Infliximab Treatment Regimen			
	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks
Week 38 (preinfusion 11[b])				
Pts evaluated	63	69	71	61
Mean ± SD	1.6 ± 1.8	9.6 ± 7.2	7.9 ± 7.5	35.0 ± 23.9
Median	0.9	8.2	5.8	30.0
Interquartile range	(0.2, 2.6)	(4.8, 12.8)	(2.7, 12.0)	(18.2, 43.5)
Range	(0.0, 9.3)	(0.0, 40.8)	(0.0, 39.6)	(0.0, 121.8)
Week 46 (preinfusion 13[b])				
Pts evaluated	59	64	68	60
Mean ± SD	2.2 ± 4.9	9.9 ± 7.5	7.8 ± 7.3	36.3 ± 22.4
Median	1.0	8.6	5.8	28.8
Interquartile range	(0.0, 2.7)	(4.6, 13.7)	(2.8, 11.1)	(19.7, 52.9)
Range	(0.0, 35.6)	(0.0, 33.7)	(0.0, 40.1)	(0.0, 95.0)
Week 54 (preinfusion 15[b])				
Pts evaluated	57	63	68	58
Mean ± SD	1.5 ± 1.7	9.3 ± 7.1	7.5 ± 7.7	34.1 ± 21.4
Median	0.7	8.8	4.8	27.9
Interquartile range	(0.0, 2.4)	(3.9, 12.1)	(2.8, 9.9)	(20.5, 45.5)
Range	(0.0, 7.3)	(0.0, 33.9)	(0.0, 40.1)	(0.0, 89.9)

[a] Infliximab is measured in µg/mL.
[b] Infusion number was counted sequentially, regardless of whether the treatment was with placebo or infliximab.

PKT101a

(printed from BLA 99-1234)

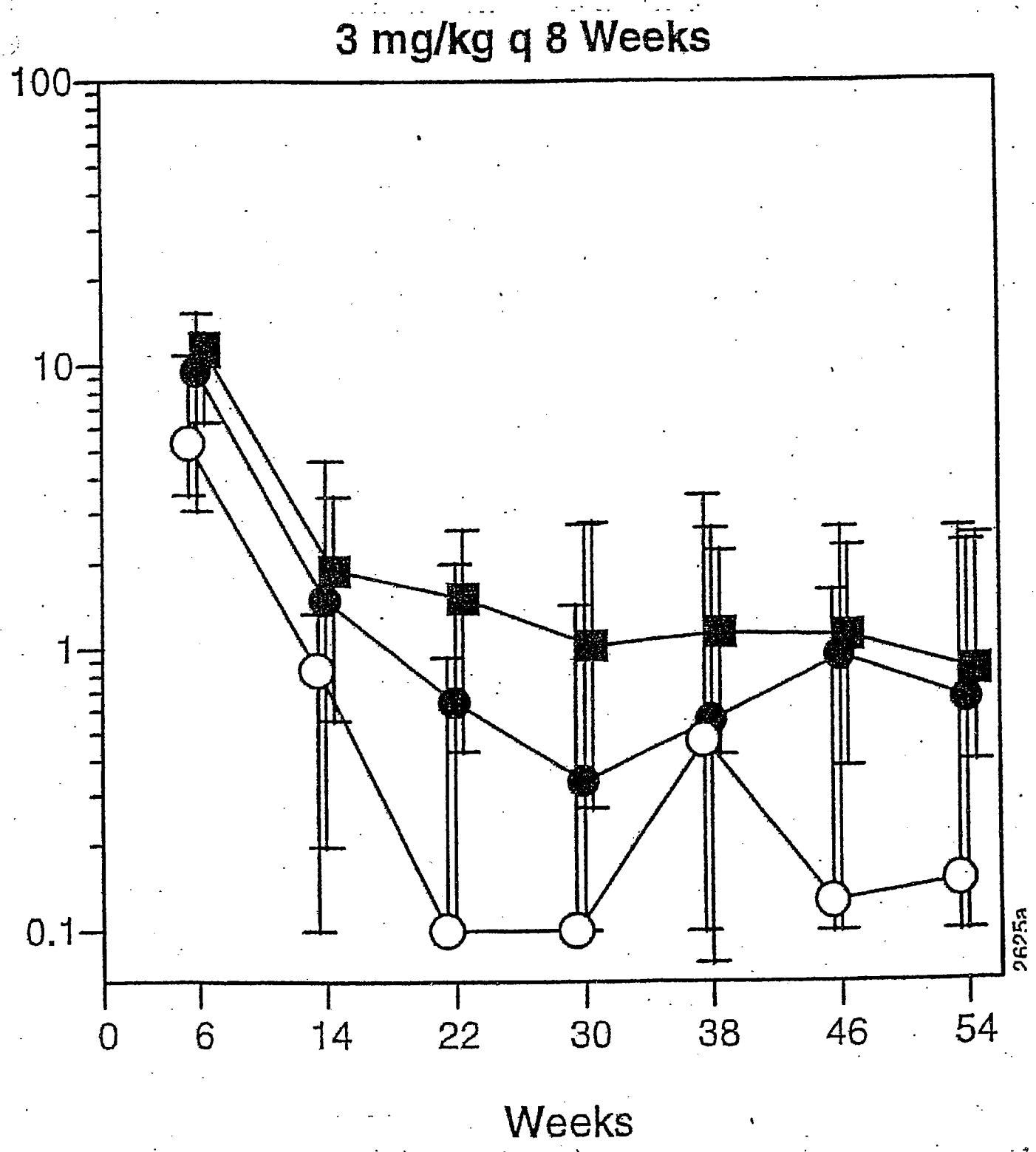
Appendix 2
(1 of 2)

(printed from BLA 761234)

Appendix 2
(2 of 2)

(printed from BLA 99-1234)

Appendix 3



(printed from BLA 99-1234)

Appendix 4

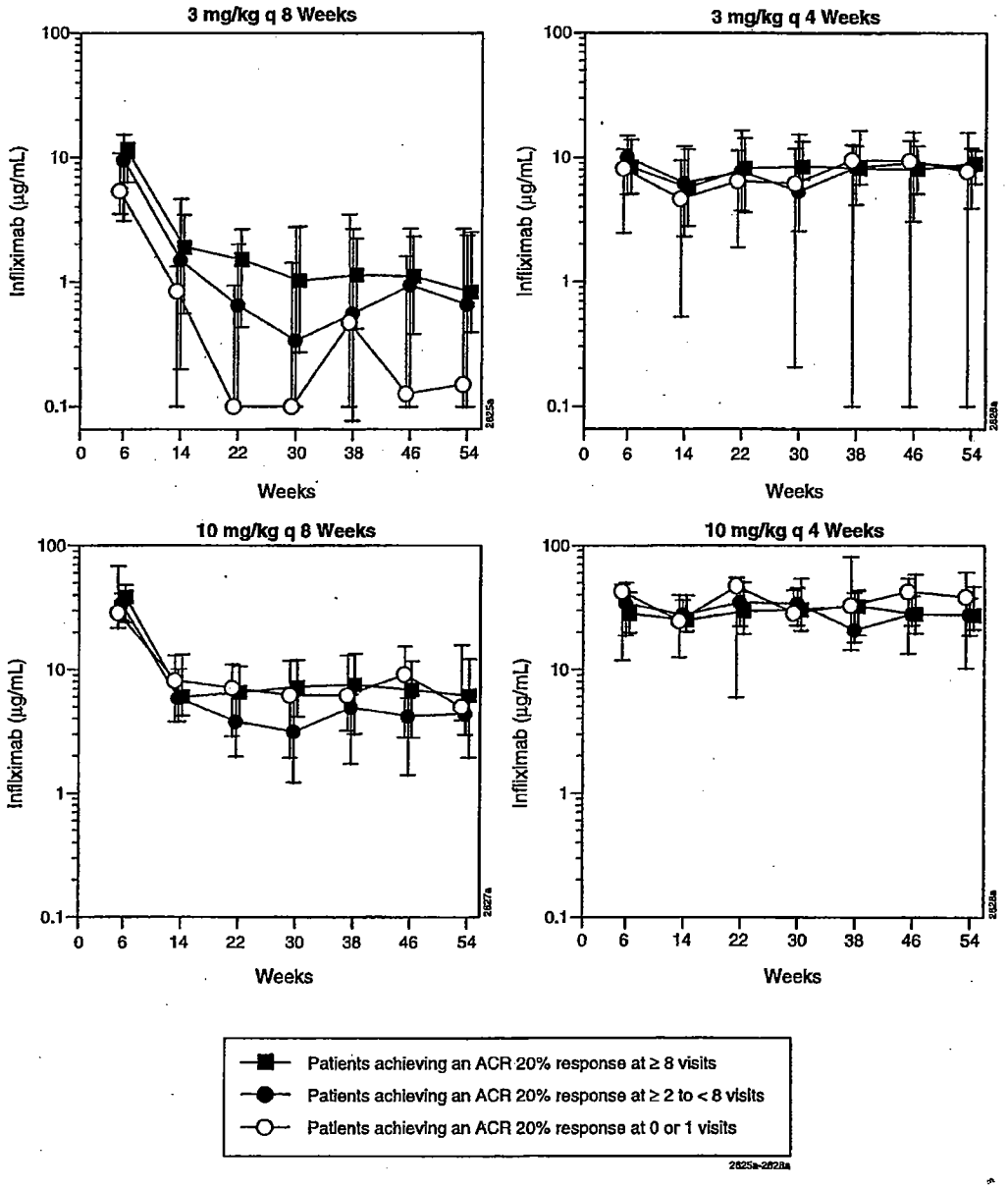


Figure 3 **Median trough serum concentrations for samples collected 4 to 8 weeks following treatment in patients achieving an ACR 20% response for various durations.** The median and interquartile range serum concentrations are shown for patients who achieved an ACR 20% response at ≥ 8 visits, at ≥ 2 to < 8 visits, and at 0 or 1 visit. The limit of detection of the infliximab assay is 0.1 µg/mL. Any undetectable median or range infliximab concentrations were graphically represented as equal to 0.1 µg/mL.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 1007

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Our Reference Number: 99-1234 JAN 2 8 2000

Mr. Martin Page
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355

Dear Mr. Page:

This letter is in regard to your supplemental biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has reviewed the clinical efficacy section of your supplemental biologics license application for Infliximab. Preliminary comments, deficiencies, and information requests identified during this review are summarized as follows:

1. Data regarding the administration of study drug for each patient are listed in Appendix A-2 and the summary data for each patient's total van der Heijde score of their radiographs are listed in Appendix J-15. The two data sets are inconsistent, as evidenced by the following:

   a. Radiographic results for 12 patients who received study drug as recorded in Appendix A-2, including 9 of 12 patients who received all 15 infusions through Week 54, are not included in Appendix J-15 (Table 1). Please comment, and provide these data to the BLA supplement.

   b. Individual joint scores calculated by Readers 1 and 2 for patients numbered 07013, 09002, and 07009 are provided in Appendices J-16 through J-21 and their radiographs are included in the database assembled by [redacted]. However, data summarizing the van der Heijde scores for these patients are not included in Appendix J-15. Please comment, and provide these data to the BLA supplement.

2. We have reviewed the radiographic data for patients whose van der Heijde scores were recorded as "NE" (summarized radiographic scores not available) in the summary listing of radiographic results for Readers 1 and 2 in Appendix J-15. Complete sets of radiographs were not available for evaluation of fifty-seven of these patients, i.e., at both baseline and Week 54. However, there are 34 patients with films at both baseline and Week 54 who have total scores for joint space narrowing (JSN) and/or erosion (ES) recorded as "NE" for Reader 1 and/or Reader 2 in Appendix J-15 (Table 2). It is unclear why a total van der Heijde score is not provided in this table for these patients

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
DTRA/DARP	M. Marlin	1/28/00	DARP	DIXON	1/28/00			
DTRA/DCBQ	[illegible]	1/28/00						
DTRA/DCBQ	[illegible]	1/28/00						

since it appears that a score for the reader can be calculated from data provided in Appendices J-16 through J-21. We have the following comments on these findings:

a. A total van der Heijde score was not calculated for patients who had undergone a surgical procedure to the foot prior to study entry, even though radiographic data from the hands were available and could be used for this purpose. The study protocol specifies that joints altered by surgery before the time of study enrollment are not to be included in the score. There was no pre-specified plan to exclude patients for whom an erosion score and/or JSN score for a set of joints would be zero. Please calculate the van der Heijde score for these patients using data from assessable joints, and include these data in the primary analysis.

b. A total van der Heijde score was not calculated when Reader-1 scored erosions or joint space narrowing in one or both feet as "ND" (evaluation not done, or unreadable) even though the reader considered the films adequate. With the exception of patient 22008 in this patient subgroup, Reader 1 scored the joints in the feet as "ND" at both baseline and at Week 54. According to the protocol, when a reader was unable to score a joint, the van der Heijde score was to be adjusted by dividing the score component (i.e., the JSN or ES) by the number of joints evaluated and then multiply by the number of joints in that set. Therefore, by this method, when the set of joints in only one foot was scored, an overall van der Heijde score could be calculated for the set of joints in the feet by using relevant data from the other foot. Similarly, when the same set of joints in both feet are scored "ND" at both baseline and Week 54, such that the ES or score for JSN would be zero for the feet, an overall van der Heijde score could be calculated using data derived from the hand joints. Please comment and submit van der Heijde scores for these patients in an amendment to the supplement that also includes a revised analysis using these data.

c. Appendix I-3 provided in your previous BLA supplement (99-0128) provides the history of joint surgery at the time of study enrollment. According to this appendix, patients numbered 15015, 15007, and 14002 did not have a history of surgery at the time of study enrollment in joints of the feet that were scored by Readers 1 and 2. The final ES and/or JSN scores for these patients are recorded as "NE" in Appendix J-15. For example, patient 14002 had surgery performed on MTP joints 1-5 of both feet, but not on the first interphalangeal joint (IP1) of either foot. Although Reader 2 scored both IP1 joints for erosions, and Reader 1 scored the right IP1 joint for erosions, the ES is recorded as "NE" in Appendix J-15 for both readers. Please comment and provide the ES and/or JSN scores for these patients in a revised primary analysis.

3. As part of our review, we calculated a total van der Heijde score for Readers 1 and 2 in a random sample of 23 patients listed in Appendix J-15 using the readers' scores for erosions and JSN listed in Appendices J-16 through J-21. We found inconsistencies between the calculated scores and those reported in Appendix J-15 for 10 of these patients whose films were scored by Reader 2 (primarily in the calculation of the erosion score) and for one patient (15015) whose films were scored by Reader 1 (Table 3). (For patient 15015, we calculated a score for JSN based upon Reader 1's score of the joints in the hands.) We have the following comments on these findings:

   a. It appears that changing scores in the line listings for foot erosions from "0" to "10" results in the erosion score which is recorded in the summary listing for all but one patient. It cannot be determined from the clinical data provided in the line listings how the ES for the feet joints should be properly scored. A change from "0" to "10" in the ES scores does not appear to resolve all of the discrepancies found in our review. For patient 15015, the ES for Reader 2 is recorded as 56 in Appendix J-15 but the ES for the set of joints in the feet alone is 65 and the total ES is 123.3 when the clinical data provided in Appendices J-16 through J-21 are used to calculate scores. Please comment, and submit a revised database to the supplement where appropriate.

   b. We suggest a possible explanation for some of the observed inconsistencies between the two readers in their interpretation of severely diseased joints of the feet. Reader 1 may have scored severe erosions and JSN as "ND" to indicate a significant degree of disease in the joint. However, it appears that Reader 2 recorded fewer joints as "ND" and may have scored destroyed joints as "10". Please comment, and provide the definition used by Reader 1 for "ND".

4. Because of the inconsistencies and problems associated with the clinical database noted in items 2 and 3 above, and because of significant variations in the interpretation of the scans between the two readers as reflected in the widely divergent van der Heijde scores, please submit the SAS transport file database and line listings assembled by [redacted] he following patient listings should be included in your submission:

   a. All patients with any radiographs submitted or received.

   b. All patients entered into the digital imaging review system for independent review.

   c. All patients reviewed by the independent reviewers.

d. All patients with any radiographs received by ——— who were not entered into the digital imaging system or who were not reviewed by the independent reviewers, including explanatory notes for their exclusion.

5. Please note that for each patient, the ——— radiographic database should include the following:

a. Site number and patient number for all patients with any radiograph.

b. Radiographic data tracking history for all radiographs for each patient to include the following:

i. The protocol timepoints and the actual imaging dates for each radiograph and the number of radiographs for each patient at all timepoints.

ii. The extremity imaged for each radiograph.

iii. Quality assurance and quality control comments regarding film quality, and documentation of any request for additional information made by ——— om the clinical site to support analysis of the submitted radiograph.

iv. Confirmation that each radiograph was or was not entered for the independent review.

v. Confirmation that the radiograph was or was not interpreted by the independent reviewers.

vi. All scoring values completed in the independent review for each radiograph by reviewer 1 and reviewer 2.

6. The revised SAS transport files submitted to the supplement on December 7, 1999 with data on the joint space narrowing and erosion scores are incomplete. The last patient included in the data set entitled ad_eros.xpt is patient number 17017, while the last patient listed in the data set ad_jsn.xpt is patient number 19011. Please submit complete SAS datasets to the BLA supplement.

Due to the extent and nature of these deficiencies in the efficacy data in the clinical section of your supplement, we are unable to complete a thorough review of the submitted efficacy data. Given the large number of inconsistencies in the radiographic database, and the significant differences between the two readers' interpretation of the radiographs, we strongly suggest that you consider a plan to re-read all of the films as soon as possible to generate a new database in

which more meaningful inferences can be derived. Before you initiate these studies, please submit a written proposal to the Agency that includes detailed instructions to the readers so that the radiographs may be consistently and accurately scored.

Review of the remaining sections of your BLA supplement, including the safety database, is continuing; however, based on a preliminary review of the safety data in the clinical sections of the supplemental license application, we have the following comments and requests for additional information:

7. Our preliminary review of the safety data on serious infections includes the Safety Update Reports submitted on April 30, 1999 and June 18, 1999 as well as the safety data submitted in the current supplemental license application. We have identified four additional patients with serious infections who are not included in Table 54 of Section 8, "Serious infections reported after week 30".

   a. Patient 15008 (placebo) was hospitalized following the development of coughing, diarrhea, vomiting, left abdominal pain, and fever. She is described in the June 18, 1999 Safety Update and included in the line listing of serious adverse events in the current supplemental license application but not in Table 54.

   b. Patient 07011 (3 mg/kg Infliximab q 8 wks) was hospitalized because of stasis ulcers of the left lower extremity, cellulitis and septic thrombophlebitis. She is included in the April 30, 1999 Safety update.

   c. Patient 04014 (3 mg/kg Infliximab q 4 wks) was hospitalized for treatment of cellulitis and is described in the April 30, 1999 Safety Update.

   d. Patient 22008 (3 mg/kg Infliximab q 4 wks) was admitted for a surgical procedure following an infected bunion and is described in the April 30, 1999 Safety Update.

   Please comment, and submit a revised safety database to the supplement which includes these patients as having experienced a serious infection.

8. You conducted an analysis of the human anti-chimeric antibody (HACA) on 84 infliximab-treated patients who had an interval of 8 or more weeks between completion of 54 weeks of treatment (infusion 15) and possible re-treatment in the second year of

the study (infusion 16). Serum samples were available for seventy-six patients in this group, however, HACA could not be assayed in 43 patients because of detectable serum concentrations of infliximab. Please submit the following:

a. A listing of the 84 patients treated with infliximab and the interval between infusions 15 and 16 for each of them.

b. The HACA results for the 76 patients with available serum samples.

c. A summary of the clinical response and/or adverse events relevant to re-exposure to infliximab in patients who received infusion 16 after an interval of 8 or more weeks.

These comments are being provided to you prior to the completion of our review of your entire supplement to give you preliminary, advance notice of clinical issues that have been identified. Please note that these comments are subject to change as the complete review of your application is finalized. Final comments, if any, will be communicated to you at a later date after the review of the application is complete. You may, but are not required to, respond to these preliminary comments. If you respond, we may or may not consider your response prior to taking a complete action on your application. If your response is determined to constitute a major amendment, you will be notified of this decision in writing. Review of the remaining sections of your supplement is continuing.

Should you need additional information or have any questions concerning administrative or procedural matters, please contact the Regulatory Project Manager, Mr. Michael Noska, at (301) 827-5101.

Sincerely yours,

Barbara Matthews, M.D., M.P.H.
Committee Chair
Division of Clinical Trial
Design and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Attachments

cc: HFM-570/B. Matthews (comments received 01/27/00)
HFM-573/G. Mills
HFM-579/L. Black
HFM-579/L. Paserchia
HFM-215/B. Zhen
HFM-650/D. Bower
HFM-220/F. Varricchio
HFM-579/Martin D. Green
HFM-588/M. Noska
HFM-582/W. Schwieterman
HFM-585/G. Jones
HFM-585/L. Burbank

CBER:DARP:B.Matthews:M.Noska:1/27/00:Dixon:1/28/00
(S:\Noska\Letters\License\99-1234DR.doc)

CORR: DISCIPLINE REVIEW LETTER: CLINICAL SECTION

Table 1. Patients who received study drug but are not included in Appendix J-15 (Radiographic Results).

Treatment Group	PID	Last infusion	submitted
Placebo	07004	4	No
	07013*	15	Yes
	13008	15	No
	30001	8	No
3 mg/kg q 8	09002*	15	Yes
	13003	15	No
3 mg/kg q 4	07009*	15	Yes
	34003	15	No
10 mg/kg q 4	05018	12	No
	13006	15	No
	21009	15	No
	33015	15	No

* van der Heijde scores for joints recorded in Appendices J-16 through J-22

Table 2. Patients with radiographs at week 0 and 54 who are categorized according to Reader as "NE" for either erosion score (ES) or joint space narrowing (JSN) in Appendix J-15

Treatment Group	PID	Reader 1		Reader 2	
		ES	JSN	ES	JSN
Placebo	04029		NE		
	08001			NE	NE
	08008	NE	NE	NE	NE
	13011	NE	NE		
	15015		NE		NE
	31002	NE	NE		NE
	33009	NE	NE		
	33011		NE		
3 mg/kg q 8 wks	04016		NE		
	07017		NE		NE
	15007		NE		
	16006		NE		
	22006		NE		
	26003	NE	NE		
3 mg/kg q 4 wks	08006	NE	NE	NE	NE
	09009	NE	NE		
	11006			NE	
	17020	NE	NE		NE
	20007		NE		
	21017		NE		
	22008		NE		
	31003	NE	NE		
	32005		NE		NE
10mg/kg q 8 wks	06008		NE		NE
	12005		NE		
	14002	NE	NE	NE	NE
	33013		NE		
10 mg/kg q 4 wks	04005		NE		NE
	04022		NE		
	08003				NE
	17012		NE		
	17016	NE	NE		NE
	21001			NE	NE
	26004			NE	NE
	28005		NE		

Table 3. Discrepancies between calculated van der Heijde scores and scores recorded in Appendix J-15 for randomly selected patients.

PID	Dose	Time	Reader 1				Reader 2			
			Calculated ES-1	J-15 ES-1	Calculated JSN-1	J-15 JSN-1	Calculated ES-2	J-15 ES-2	Calculated JSN-2	J-15 JSN-2
04016	3q8	base	53.1	53.1	85	NE	78	158	89	89
		wk54	56.1	56.1	54	NE	75	155	88	88
33005	10q8	base	48	48	97	97	107	155	91	91
		wk54	55	55	101	101	104.8	152.8	92	92
12002	10q4	base	81.7	81.7	87.4	87.4	93.7	153.7	85.8	85.8
		wk54	82.8	82.9	82.9	89.5	91.6	151.7	90	90
18009	10q8	base	43	43	91	91	66	166	91	91
		wk54	44	44	91	91	167	167	91	91
19008	10q4	base	203	203	109	109	198	218	113	113
		wk54	202	202	106	106	196	216	107	107
23001	3q8	base	34	34	49	49	46	96	42	42
		wk54	34	34	54	54	42	92	48	48
07020	placebo	base	95	105	79	79	77	147	45	45
		wk54	97	107	81	81	76	146	46	46
12010	3q4	base	43.4	43.4	85	85	188	138	78	78
		wk54	46	46	77	77	193	133	72	72
04029	placebo	base	105.6	105.6	83	NE	113	173	102	102
		wk54	106.3	106.3	81	NE	115	175	102	102
15015	placebo	base	53.4	42.5	93.5	NE	123.3	56.1	44.5	NE
		wk54	57	42.56.1	93.5	NE	124.7	59	43.6	NE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Our Reference Number: 99-1234

DEC 14 1999

Mr. Martin Page
Centocor, Incorporated
200 Great Valley Parkway
Malvern, PA 19355-1307

Dear Mr. Page:

This letter is in regard to the supplement to your biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has completed an initial review of your supplement dated October 15, 1999 for Infliximab (Remicade™) for [redacted] patients with rheumatoid arthritis to determine its acceptability for filing. In accordance with 21 CFR 601.2(a) the application is considered to be filed effective today's date.

This acknowledgment of filing does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the application/supplement, we shall advise you in writing as to what action has been taken and request additional information if needed.

As of April 1, 1999, 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 (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 601.27, please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 601.27.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 601.27 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTR/DARP	M. Mahn	12/14/99						
DARP	12-18-99							
DARP	12-14-99							

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Mr. Michael Noska, at (301) 827-5101.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

cc:	B. Matthews	HFM-582
	G. Mills	HFM-573
	K. Brorson	HFM-561
	L. Black	HFM-579
	L. Paserchia	HFM-579
	B. Zhen	HFM-215
	D. Bower	HFM-650
	F. Varricchio	HFM-220
	M. Noska	HFM-588
	G. Jones	HFM-585
	RIMS	HFM-110

CBER:DARP:M.Noska:12/10/99:amw:12/10/99:mn:12/14/99:amw:12/14/99

(S:\Noska\Letters\License\Filing_99-1234.doc)

MILESTONE: FILING LETTER - (FA)

Fill-ins:

(1) Reference Number assigned.
(2) Name of the Authorized Official.
(3) Manufacturer's Date of application/supplement.
(4) Location/Product name: Quote name of product using proper name and trademark, if any. Include the dosage form designation if practicable and indication.
(5) Name of the DARP Regulatory Coordinator.

MEMORANDUM

Date: December 10, 1999

To: BLA File (Reference Number 99-1234)

From: Michael A. Noska, M.S. MAN
Regulatory Coordinator
OTRR/DARP/AAB

Subject: Minutes of Filing Meeting for BLA Clinical Supplement from Centocor ——— in patients with rheumatoid arthritis using Infliximab (Chimeric Monoclonal Antibody, cA2), held November 30, 1999 from 2:00-4:00, WOC I/200 South

Attendees: Barbara Matthews, Kurt Brorson, Bo Zhen, Debra Bower, Lori Paserchia, Lauren Black, William Schwieterman, Karen Weiss, George Mills, Fred Varricchio, Michael Noska

Dr. Lori Paserchia noted that the PK section of the package insert has been revised. The applicant made reference to a previous BLA supplement (99-0128) but did not provide the supporting data. This was discussed as a potential filing issue but it was concluded that the data in the current supplement are adequate.

Dr. Lauren Black did not have any filing issues.

Dr. Kurt Brorson noted that the strikeout version of the package insert was outdated and incorrect. Dr. Barbara Matthews stated that she would be able to provide the review team with a correct version.

Dr. Fred Varricchio commented on the fact that post-marketing safety information apparently has not been submitted. Dr. Matthews noted that she had received and reviewed safety updates from the company.

Dr. George Mills presented his filing review using overhead slides which are attached to this memorandum. The data which have been submitted are not consistent with the applicant's prospective plan. It appears that Centocor has performed a subset analysis instead of the original intent-to-treat analysis. Dr. Matthews noted that there appears to be a difference in the procedures used by the two radiographic readers. There is no manual describing the instruction given to the readers. Also, the radiographic manual, which was described in the application and in the Phase 3 protocol, was not submitted. This manual would have been used to prescribe the radiographic techniques and could explain some of the discrepancies noted.

Dr. Bo Zhen stated that he was able to open the SAS files and locate data. However, it was concluded that the datasets were not appropriately configured to allow merging of the data. Also, data appears to be missing from the SURGPR file.

It was decided that the applicant would be contacted by telephone and asked to correct the deficiencies in the SAS datasets and submit the [redacted] manual by close-of-business on December 7, 1999. If they could not meet this requirement, the supplement would not be filed.

The meeting was concluded.

Martin Page
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355

October 18, 1999

Dear Mr. Page:

REFERENCE NUMBER 99-1234 has been assigned to your recent supplement to your biologics license application for Infliximab to expand the indication to include [redacted] n patients with rheumatoid arthritis, received on October 15, 1999.

All future correspondence or supportive data relating to this supplemental application should bear the above REFERENCE NUMBER and be addressed to the Director, Division of Application Review and Policy, Office of Therapeutics Research and Review, HFM-585, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD, 20852-1448.

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.

Should you need to discuss the technical aspects of this supplement, you may obtain the name of the chairperson of the review committee by contacting this division at 301-827-5101. Any questions concerning administrative or procedural matters should also be directed to this division.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

bcc: Ref. No. File
Director, Product Release Staff, HFM-235
Red Folder
Mike Noska

OTRR/DARP: J. Dixon:10-18-99:10-20-99
S:\Dixon\Refno.99\99-1234.pas.doc
REF NO. ASSIGNMENT – PRE-APPROVAL SUPPLEMENT (ZPAS)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: October 18, 1999

To: BLA File

From: Karen Weiss, M.D., HFM-570 KWeiss

Subject: Designation of Priority for BLA Review
Sponsor: Centocor, Inc.
Product: Infliximab [Chimeric Monoclonal Antibody (cA2) to Tumor Necrosis Factor]
Indication: [redacted] tients with rheumatoid arthritis

The review status of this file, when submitted as a BLA supplement, is designated to be:

- ☐ Standard (10 mo.)
- ☑ Priority (~~4~~ 6 mo.) man