DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Memorandum

SUBMISSION: ***Statistical Review and Evaluation of BLA #99-0128***

FROM: ***Vance Berger, Ph.D., HFM-215***

THROUGH: ***Peter A. Lachenbruch, Ph.D., Chief, Biostatistics Branch, HFM-215***

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DATE: ***September 23, 1999***

PRODUCT: *Infliximab*

INDICATION: ***Rheumatoid Arthritis (RA)***

APPLICANT: ***Centocor***

1. BACKGROUND:

Infliximab is licensed as a single dose for the acute treatment of Crohn's disease and for three doses to close enterocutaneous fistulae in patients with fistulizing Crohn's disease. The present supplement to the license application is to extend the indication to patients with rheumatoid arthritis (RA), specifically for the reduction of signs and symptoms in RA patients who have an inadequate response to methotrexate. First described as a clinical entity in 1800, RA is a chronic multisystemic inflammatory disease with prominent autoimmune features, including the floowing:

1. Persistent inflammatory synovitis;
2. Morning stiiffness;
3. Swelling of joints;
4. Swelling of soft tissue of hand joints (proximal interphalangeal, metacarpophalangeal, wrist);
5. Symmetrical soft tissue swelling;
6. Subcutaneous nodules;
7. Serum rheumatoid factor;
8. Radiographic evidence of erosion or periarticular osteopenia in hand or wrist joints.

A diagnosis of RA requires that four of the last seven criteria be fulfilled. The potential for synovial inflammation to cause pain, swelling, and tenderness, with subsequent cartilage destruction, bone erosion, and joint deformities, is a cardinal manifestation of RA. Joint involvement is typically symmetrical, a characteristic not usually found in other forms of arthritis. Systemic, extra-articular symptomatology can include fatigue, fever, weight loss, anemia, rheumatoid nodules, rheumatoid vasculitis, pleuropulmonary manifestations (e.g., pleural disease, interstitial fibrosis), pericardial effusion, Felty's syndrome (RA accompanied by splenomegaly, neutropenia, leg ulcers, thrombocytopenia, and the HLA-DR4 haplotype), keratoconjunctivitis, and osteoporosis. The clinical course of RA can vary considerably. Some patients may experience only mild oligoarticular illness of short duration with minimal joint involvement, while others will experience polyarthritis, accompanied by marked joint deformities. For most patients, however, RA follows an intermediate course. The principal goals in the treatment of RA are to relieve pain, preserve or improve functional capacity, reduce inflammation, and prevent structural damage.

The pharmacologic management of RA usually involves two approaches: symptom control and disease modification. Simple analgesics, such as acetaminophen, NSAIDs (e.g., aspirin, indomethecin, ibuprofen, and naproxen), and, if necessary, low-dose corticosteroids (such as prednisone), have been used as first-line therapy to control the symptoms of RA. They exert minimal effects on disease progression, however. With the long-term and high-dose therapy often required to treat the pain associated with RA, NSAID use can cause a wide spectrum of toxic effects, including gastric irritation, platelet dysfunction, and liver function abnormalities. NSAIDs act by blocking cyclooxygenase, and, consequently, the production of prostaglandins and other mediators of pain and inflammation. Cyclooxygenase, however, exists as two isoforms: COX-1, involved in normal physiologic functioning and gastroprotection, and COX-2, induced by inflammatory mediators. Typically, NSAIDs nonselectively inhibit both COX isoforms, increasing their side-effect liability.

However, selective COX-2 inhibitors, such as meloxicam, appear comparable in efficacy to standard NSAIDs in the treatment of RA, but with an improved gastrointestinal tolerability profile.

Of the available anti-inflammatory drugs, only corticosteroids are known to interfere with the synthesis and actions of cytokines. Although corticosteroids exert both anti-inflammatory and immunosuppressive effects, their serious potential for side effects, such as osteoporosis, muscle weakness, glucose intolerance, and cataracts, limits these agents to short-term use. Current first-line therapy utilizes a variety of agents classified as disease-modifying anti-rheumatic drugs (DMARDs), even though there is little evidence that they actually ameliorate the underlying disease process. These agents include gold, sulfasalazine, hydroxychloroquine, D-penicillamine, and immunosuppressants such as azathioprine and methotrexate. Although the majority of patients seem to improve on DMARD therapy, benefits can be delayed for weeks or months; therefore, these agents are also known as slow acting antirheumatic drugs. In addition, these agents are associated with considerable toxicity, requiring careful patient monitoring. For example, azathioprine may cause blood dyscrasias (thrombocytopenia and leukopenia) or gastrointestinal discomfort.

Recently, the use of methotrexate (MTX), a cytotoxic immunosuppressant and anti-inflammatory agent, has increased significantly in the treatment of RA. In a study that included patients with long-term, progressive RA, MTX was shown to produce clinical improvements, including a decrease in the number of swollen joints and pain, and an increase in grip strength and mobility. In this study, however, 83% of patients experienced at least one adverse event, and 16.5% withdrew because of side effects. Toxicity, which can induce stomatitis, thrombocytopenia, bone marrow suppression, pulmonary lesion, and hepatic fibrosis, is a serious concern with the use of MTX.

2. THE PRESENT SUBMISSION

Six clinical trials, with a total of 660 patients with active RA (of whom 553 were assigned to receive infliximab ar 555 actually did receive infliximab), have investigated infliximab with single and multiple weight djusted intravenous infusions at doses of 1 to 20 mg/kg in the presence and absence of methotrexate. These studies included one Phase I clinical trial (C0168T07); one open-label phase II clinical trial (C01 68T18); three blinded. placebo-controlled phase II clinical studies (C0168T09, C0168T , CO 168T 15/T 17), and a randomized, double-blind, placebo-controlled Phase III trial (C0168T22). he initial trials of infliximab in patients with active, long-standing, erosive RA who had failed DMARD therapy were designed to address issues important for selecting the appropriate dose and sing interval. In the first trial, C0168T07, infliximab therapy at repeated doses of 5 and 10 mg/kg w shown to be effective in reducing the signs and symptoms of RA through the last follow-up evaluation 8 weeks after the last infusion. In C0168T09, a single dose of infliximab at 1 mg/kg was shown to produce a clinical benefit, but that this benefit was less than the clinical benefit observed at s gle doses of 3 or 10 mg/kg. In C0168T15/T17, patients with an inadequate response to 10 mg/wk of MTX responded equally well to single infliximab doses of 5, 10, or 20 mg/kg. Especially notable was that patients receiving repeated infusions of 10 mg/kg had sustained clinical benefits at intervals as long as eight weeks between infusions. The pivotal clinical trial, C0168T22 (T22, ATTRACT), is the focus of this review.

3. PIVOTAL STUDY

T22 is an ongoing placebo-controlled, double-blind, randomized (by the Randomization Center at ——— by using an adaptive stratified design with the investigational sites as the strata) dose-ranging study of chronic treatment of RA with infliximab. The objectives were to evaluate the efficacy and safety of chronic treatment with infliximab in combination with methotrexate (MTX) in patients with active RA despite treatment with MTX. The primary objective was to determine the efficacy and safety of infliximab treatment in reducing clinical signs and symptoms of RA at 30 weeks following the onset of treatment. Additional protocol-specified objectives were to determine the efficacy and safety of infliximab treatment in providing continued reduction in signs and symptoms, reducing disability, retarding joint damage, providing disease remission, and improving quality of life at 1 and 2 years following the onset of treatment.

The following clinical response assessments were performed:

Joint assessment: Each of 68 joints (ACR joint set) were evaluated for tenderness and 66 joints (excluding hips) were evaluated for swelling. An independent assessor performed all joint assessments at each study site;

Duration of morning stiffness: The average duration of morning stiffness during the previous week was assessed in minutes;

VAS of pain: Patients were asked to assess their average pain during the previous week on a VAS whose scale ranged from 0 to 10 cm;

VAS of fatigue: Same type of measurement as for pain;

Patient and evaluator VAS of global disease assessment: The scale for the patient's assessment ranged from "very well" to "very poor". The scale for the evaluator's assessment ranged from "no arthritis activity" to "extremely active arthritis". The evaluator and patient were required to complete the global assessment independently from each other The results of the independent joint assessment were available to the evaluator assessing the patient's global disease;

Disability index of the HAQ: The functional status of the patient was assessed by means of the disability index of the HAQ. The purpose of this 20-question instrument was to assess the degree of difficulty the patient had in accomplishing tasks in eight functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands & chores). *Responses in each area were scored from 0 (no difficulty) to 3 (inability to perform a task);

Quality of life assessment: Patients were assessed by using the SF-36 questionnaire, which is a health survey questionnaire consisting of 11 multi-item scales: Limitations

in physical functioning due to health problems, limitations in usual role activities due to physical health problems, bodily pain, general mental health (psychological distress and well being), limitations in usual role activities due to personal or emotional problems, limitations in social functioning due to physical or mental health problems, vitality (energy and fatigue) and general health perception. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group).

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

20% improvement in swollen joint count (66 joints) and tender joint count (68 joints)

and

20% improvement in at least three of the following five 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 measure by the HAQ;
CRP.

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 (i.e., arthrodesis and joint replacement).

Patients who were not required to continue scheduled efficacy evaluations for lack of efficacy because of 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 the study (e.g., the date of the medication change or surgical procedure), regardless of their actual response data. In the primary analyses at week 30, patients who did not return for evaluation or who had insufficient data to assess their ACR status were considered nonresponders for clinical response. For all other patients, any data recorded were included in all data summaries and analyses.

If a patient had a surgical joint procedure in one of the joints included in the ACR joint set prior to his or her participation in the trial, then those joints were not included in any of the joint assessments for this trial. Patients who had surgery, an intra-articular injection, or a needle aspiration on any of these joints during the study were included as responders if they satisfied the ACR criteria.

If a patients underwent intra-articular injections of corticosteroids or needle aspiration of fluid in a single joint included in the ACR joint set, then that joint was considered to be tender and swollen

thereafter. However, patients who received intra-articular injections of corticosteroids in more than one joint and/or needle aspiration of fluid from more than one 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 for the remainder of the trial.

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.

Patients who discontinued study treatment because of a safety reason (e.g., infusion reaction), but completed to 30-week follow-up evaluation and fulfilled all of the criteria for achieving a clinical response, were considered responders in the primary efficacy analysis.

Patients were considered to have achieved a clinical remission if five of the following six requirements were fulfilled for at least two consecutive months (defined as three 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 for clinical response.

Duration of morning stiffness did not exceed 15 minutes;
No fatigue (<0.5 cm on VAS);
No joint pain (<0.5 cm on VAS);
No joint tenderness or pain on motion;
No soft tissue swelling in joints or tendon sheaths;
CRP (<10 mg/L).

The primary week-30 endpoint was the achievement of a clinical response at the week-30 follow-up visit. The primary analysis was performed on an intention-to-treat basis and compared the proportion of patients who achieved a clinical response in each of the infliximab treatment groups with that of the placebo group, i.e., MTX alone.

Secondary efficacy analyses were performed with patients included in the treatment groups to which they were randomly assigned (intent-to-treat), and included the following:

Rapidity of response: The proportions of patients achieved a clinical response at week-2;

Response rate: The proportion of patients who achieved a clinical response at week 10;

Clinical response over time: The proportion of patients in each treatment group who achieved a clinical response at five or more of the maximum of eight follow-up visits through week 30;

The weighted mean degree of clinical improvement on each of the individual components of the ACR criteria: The area under the clinical improvement versus time curve adjusted for the

length of each follow-up visit and the value of the subsequent visit, divided by the total duration of observation (average degree of clinical improvement over time);

Individual components of the ACR: The patients' assessments of morning stiffness and fatigue, and ESR values;

Improvements in ACR: The proportion of patients who achieved improvements in the ACR criteria of <20%, 20% to <50%, 50% to <70%, 70% to <90%, or >90%;

Consistency of treatment effect among patient groups, defined by demographic factors, baseline disease characteristics, and concomitant medications;

Quality of life: SF-36.

The clinical trial was initially planned to end after all patients had completed 54 weeks and their disease assessed for differences in radiological progression. However, the protocol was amended to extend the trial for two years with an interim analysis of the 54 week data. The 30 week endpoint of T22 represents the pivotal support for the proposed changes in indication. This review is of the 30 week data; the study period is March 3 1, 1997 to August 3 1, 1998. There were 428 patients enrolled. Four infliximab treatment groups were compared with placebo (MTX alone). Patients in each treatment group continued concurrent MTX treatment at the same dose as that received before the study (12.5 mg/wk orally or parentally).

4. RESULTS

4A. ENROLLMENT AND DEMOGRAPHICS

A total of 428 patients were enrolled at 34 study sites. Enrollment for the 30-week endpoint extended between March 3 1, 1997 and January 22, 1998 with the last 30-week evaluation occurring on August 3 1, 1998. The distribution of patients to treatment groups was as follows:

Placebo:	88
3 mg/kg q 8 wks:	86
3 mg/kg q 4 wks:	86
10 mg/kg q 8 wks:	87
10 mg/kg q 4 wks: 8	1
Total:	428

There were 10 patients who received incorrect treatment for one or more infusions:

Placebo (2)
23002: Received 0.5 mg/kg infliximab at infusion 4 (week 10);
33009: Received 0.5 mg/kg infliximab at infusion 3 (week 6);

3 mg/kg q 8 weeks (5)
10005: Received 0.5 mg/kg infliximab instead of placebo at the week- IO interim visit;
10007: Received 0.5 mg/kg infliximab instead of placebo at the week-10 interim visit;
22005: Received 3 mg/kg infliximab instead of placebo at the week-l 8 interim visit;
24002: Received 3 mg/kg infliximab instead of placebo at the week-10 interim visit;
26003: Received placebo instead of 3 mg/kg at the week-22 visit, and also skipped the placebo infusion at the week- 18 interim visit;

10 mg/kg q 8 weeks (1)
31005: Received 0.5 mg/kg infliximab instead of placebo at the week-26 interim visit;

10 mg/kg q 4 weeks (2)
15010: Received placebo instead of 10 mg/kg infliximab at the week-10 visit;
33015: Received 6 incorrect treatments. The patient received 3 mg/kg of infliximab at the first 3 infusions and infusion 5, and placebo at infusions 4 and 6 because the randomization coordinator sent the incorrect treatment preparation forms to the pharmacist. This error was discovered after the week-18 infusion and was corrected for infusions 7 and 8.

The majority of the patients enrolled into T22 were women (77.6%). Of the 428 patients, 389 (90.9%) were Caucasian and the remaining patients were Afro-American (5.1%), Asian (0.7%), or other (3.3%). The median age of the patients was 53.5 (range: 19 to 80 years). The baseline disease

characteristics for the efficacy variables were balanced across all treatment groups. For all patients enrolled, the median duration of RA was 8.4 years (range: 0.5 to 49.9 years), which was relatively short considering the advanced stages of RA in these patients. There were two patients (02009 and 20011) who were lost to follow-up through week 30 due to distance from the study site.

4B. EFFICACY

The primary clinical endpoint was a clinical response defined by an ACR 20% response without a protocol-prohibited change in medication and/or surgical joint procedure at 30 weeks. The primary analysis was conducted on patients randomized to their treatment group even though they may have had discrepancies to that dosing regimen, per the intent-to-treat principle. The sponsor's analysis reveals that at 30 weeks, the numbers of ACR20 responders, by treatment group, were as follows:

Placebo	18/88 (20%)
3 mg/kg q 8 wks	43/86 (50%)
3 mg/kg q 4 wks	43/86 (50%)
10 mg/kg q 8 wks	45/87 (52%)
10 mg/kg q 4 wks	47/81 (58%)

Because the data that was submitted electronically gave somewhat different results, the ACR data are presented and analyzed, at each time point, in this review. The efficacy data were rearranged from the sponsor's presentation, as in the following tables. The presentation is based on counts (not proportions) of non-overlapping categories that exploits the ordered nature of the ACR categories (e.g., ACR50 is better than ACR20 because it implies ACR20). The "I", "N", and "ND" categories were all considered to be "No ACR20". In addition,when data were missing, resulting in fewer than the total number of patients, additional patients were placed into the "No ACR20" category to fill the void. This represents a conservative approach to ensuring that the analysis be based on all randomized patients, per the intent-to-treat approach. The entire data set is presented, but the p-value in the upper-left comer of the table represents a comparison not of all treatment groups, but rather of 3 mg/kg q8 (the intended dose for marketing) to placebo.

Reviewer's Table 4A: ACR Efficacy Data, ATTRACT (T22), Week 2						
p=0.0000	No ACR20	ACR20	ACR50	ACR70	ACR90	Total
Placebo	83	4	1	0	0	88
3 mg/kg q8	61	18	5	2	0	86
3 mg/kg q4	63	16	4	2	1	86
10 mg/kg q8	59	18	8	2	0	87
10 mg/kg q4	58	17	5	1	0	81
Total	324	73	23	7	1	428

The one-sided exact Smimov test performed in StatXact gives a p-value of 0.0000. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with better ACR response at Week 2.

Reviewer's Table 4B: ACR Efficacy Data, ATTRACT (T22), Week 6						
p=0.0010	No ACR20	ACR20	ACR50	ACR70	ACR90	Total
Placebo	71	14	3	0	0	88
3 mg/kg q8	50	24	10	1	1	86
3 mg/kg q4	45	26	12	3	0	86
10 mg/kg q8	47	29	5	6	0	87
10 mg/kg q4	45	21	10	5	0	81
Total	258	114	40	15	1	428

The one-sided exact Smimov test performed in StatXact gives a p-value of 0.0010. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with better ACR response at Week 6.

Reviewer's Table 4C: ACR Efficacy Data, ATTRACT (T22), Week 10						
p=o.oo 10	No ACR20	ACR20	ACR50	ACR70	ACR90	Total
Placebo	71	13	4	0	0	88
3 mg/kg q8	50	16	16	3	1	86
3 mg/kg q4	52	18	11	4	1	86
10 mg/kg q8	43	25	11	8	0	87
10 mg/kg q4	48	19	12	2	0	81
Total	264	91	54	17	2	428

The one-sided exact Smirnov test performed in StatXact gives a p-value of 0.0010. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with better ACR response at Week 10.

Reviewer's Table 4D: ACR Efficacy Data, ATTRACT (T22), Week 14						
p=0.0010	No ACR20	ACR20	ACR50	ACR70	ACR90	Total
Placebo	71	12	4	1	0	88
3 mg/kg q8	50	21	9	5	1	86
3 mg/kg q4	48	22	7	7	2	86
10 mg/kg q8	44	26	10	6	1	87
10 mg/kg q4	36	25	9	11	0	81
Total	249	106	39	30	4	428

The one-sided exact Smirnov test performed in StatXact gives a p-value of 0.0010. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with better ACR response at Week 14.

Reviewer's Table 4E: ACR Efficacy Data, ATTRACT (T22), Week 18						
p=0.0002	No ACR20	ACR20	ACR50	ACR70	ACR90	Total
Placebo	71	12	4	1	0	88
3 mg/kg q8	47	21	10	7	1	86
3 mg/kg q4	45	19	12	8	2	86
10 mg/kg q8	39	20	18	9	1	87
10 mg/kg q4	38	20	14	6	3	81
Total	240	92	58	31	7	428

The one-sided exact Smirnov test performed in StatXact gives a p-value of 0.0002. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with better ACR response at Week 18.

Reviewer's Table 4F: ACR Efficacy Data, ATTRACT (T22), Week 22						
p=0.0000	No ACR20	ACR20	ACR50	ACR70	ACR90	Total
Placebo	67	13	6	2	0	88
3 mg/kg q8	39	26	13	7	1	86
3 mg/kg q4	42	25	12	6	1	86
10 mg/kg q8	39	23	14	9	2	87
10 mg/kg q4	39	21	11	9	1	81
Total	226	108	56	33	5	428

The one-sided exact Smirnov test performed in StatXact gives a p-value of 0.0000. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with better ACR response at Week 22.

Reviewer's Table 4G: ACR Efficacy Data, ATTRACT (T22), Week 26						
p=0.0003	No ACR20	ACR20	ACR50	ACR70	ACR90	Total
Placebo	68	12	5	3	0	88
3 mg/kg q8	44	23	13	4	2	86
3 mg/kg q4	37	23	16	9	1	86
10 mg/kg q8	32	20	18	13	4	87
10 mg/kg q4	32	21	13	15	0	81
Total	212	99	65	44	7	428

The one-sided exact Smirnov test performed in StatXact gives a p-value of 0.0003. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with better ACR response at Week 26.

Reviewer's Table 4H: ACR Efficacy Data, ATTRACT (T22), Week 30						
p=0.0011	No ACR20	ACR20	ACR50	ACR70	ACR90	Total
Placebo	63	17	6	2	0	88
3 mg/kg q8	41	21	16	6	2	86
3 mg/kg q4	41	20	16	8	1	86
10 mg/kg q8	40	21	11	9	6	87
10 mg/kg q4	30	27	14	8	2	81
Total	215	106	63	33	11	428

The one-sided exact Smirnov test performed in StatXact gives a p-value of 0.0011. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with better ACR response at Week 30. Summarizing, the p-value as a function of week of the study was as follows:

Reviewer's Table 4I: P-Value as a Function of Week	
Week	P-Value
2	0.0000
6	0.0010
10	0.0010
14	0.0010
18	0.0002
22	0.0000
26	0.0003
30	0.0011

We see that the time trend, at least of the between-group p-value on ACR response, was highly statistically significant at each time point. However, the p-value was not predictable, in that it did not increase or decrease monotonically, and it also did not increase and then decrease, or decrease and then increase. The time points at which the p-value was lowest (0.0000) were Week 2, and Week 22. The p-value was largest (0.0011) at Week 30.

The sponsor conducted 5 analyses of the clinical response to examine the robustness of the primary analysis at 30 weeks:

1. Patients were considered non-responders if they discontinued study treatment because of an adverse event;

2. Patients were considered non-responders if they discontinued because of a lack of efficacy (but did not have a protocol prohibited change in medication or a surgical joint procedure);

3. Patients were considered non-responders because of lack of efficacy or discontinuation because of adverse event (but did not have a protocol prohibited change in medication or surgical joint procedure);

4. No adjustment in classification for protocol-prohibited change in medication and/or surgical joint procedures;

5. Patients in q 8 week dosing groups who received infliximab on a visit when scheduled to receive placebo considered as non-responders.

None of these analyses changed any of the conclusions based upon the primary analysis, i.e., both the overall treatment effect and pairwise comparisons for each treatment group with placebo were statistically significant. There were 49 patients enrolled who did not meet the entry criteria:

11 patients were not on stable doses of folic acid prophylaxis for at least 4 weeks prior to screening;
1 patient who was not a stable dose of steroids;
1 patient who was not on a stable dose of NSAIDs;
2 patients who received an alkylating agent (cyclophosphamide) prior to study entry;
2 patients who had received another investigational drug within the two months prior to enrollment;
3 patients who were more than 75 years of age;
2 patients who were enrolled with abnormal liver enzymes laboratory values;
1 patients did not sign the informed consent until after screening but did prior to receipt of study drug;
7 patients did not meet the entry criteria regarding MTX: one patient enrolled at a dose of 10 mg/kg, 3 patients were not on a stable dose, 1 patient had an interruption in therapy for more than 2 weeks, and 2 patients were on MTX therapy for less than 3 months prior to enrollment;
22 patients who did not meet the active disease entry criteria: 4 did not meet the criteria for (6 swollen and tender joints, 17 did not qualify for 2 of the CRP, ESR, and morning stiffness criteria and 1 patient did not meet the criteria for both the (6 swollen and tender joints and 2 of three ACR criteria. The distribution among the treatment groups for this violation was 1 patient in placebo, 4 in the 3 mg/kg q 8 week group, 8 patients in the 3 mg/kg q 4 weeks, 3 patients in the 10 mg/kg q 8 weeks group, and 6 patients in the 10 mg/kg q 4 weeks group.

Because of this, additional sensitivity analyses were performed (at Week 30, the pre-specified time point of the primary comparison). The first of these sensitivity analyses was based on excluding patients for whom disease was not active. The analysis of this subset is presented in Table 4J below.

Reviewer's Table 4J: ACR Efficacy Data, ATTRACT (T22), Week 30 Excluding Patients for Whom Disease Was not Active						
p=0.0015	No ACR20	ACR20	ACR50	ACR70	ACR90	Total
Placebo	63	16	6	2	0	87
3 mg/kg q8	39	18	16	5	2	80
3 mg/kg q4	35	20	14	8	1	78
10 mg/kg q8	38	20	11	9	6	84
10 mg/kg q4	29	26	13	6	2	76
Total	204	100	60	30	11	405

The one-sided exact Smirnov test performed in StatXact gives a p-value of 0.0015. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with better ACR response at Week 30 even among those patients for whom disease was active. The second of these sensitivity analyses was based on excluding also those patients who were not on a stable dose of methotrexate. The analysis of this subset is presented in Table 4K below.

Reviewer's Table 4K: ACR Efficacy Data, ATTRACT (T22), Week 30 Excluding Patients for Whom Disease Was not Active Excluding Patients Who Were Not on a Stable Dose of Methotrexate						
p=0.0015	No ACR20	ACR20	ACR50	ACR70	ACR90	Total
Placebo	61	15	6	2	0	84
3 mg/kg q8	39	18	16	5	2	80
3 mg/kg q4	34	20	14	8	1	77
10 mg/kg q8	38	19	11	9	6	83
10 mg/kg q4	28	26	13	6	2	75
Total	200	98	60	30	11	405

The one-sided exact Smirnov test performed in StatXact gives a p-value of 0.0015. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with better ACR response at Week 30 even among those patients for whom disease was active and who were on stable doses of methotrexate. The patients excluded from these two sensitivity analyses are listed below in Table 4L.

Reviewer's Table 4L: ACR Efficacy Data, ATTRACT (T22), Week 30 Patients Excluded from Sensitivity Analyses					
Violation	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q4
Disease Not Active	20003	17018 19005 21008 26003 32001	05010 05014 05017 19013 30004 30007 30011 32005	05008 05021 33013	05006 07001 07019 11011 29003
Not on Stable Methotrexate	08014 10006 11005		11004	17019	030004
Both		26006	07018 11006 12010		04014 21009

Of interest also was the time until durable response. For this analysis, an ACR20 response was considered durable if it lasted up through Week 30. The endpoint was then the time when the durable response began, or the first week of ACR20 response that began the string of consecutive visits with ACR20 response through Week 30. Because this endpoint would not be defined for a patient who did not have a durable response, presented instead is the time of the last visit at which ACR<20. This is equivalent information, but allows for a more compact presentation of the data. For example, if a patient is categorized as Week 30, then a durable response was not achieved. If a patient is categorized as Week 18, then the durable response began on Week 22. Clearly, lower numbers (earlier visits) are better. The data are presented in Table 4M, below.

Reviewer's Table 4M: ACR Efficacy Data, ATTRACT (T22) Week of Last Visit at Which ACR<20										
p=0.0007	0	2	6	10	14	18	22	26	30	Total
Placebo	0	1	1	2	3	7	3	8	63	88
3 mg/kg q8	8	5	3	5	5	5	6	9	40	86
3 mg/kg q4	11	4	2	6	6	4	5	7	41	86
10 mg/kg q8	9	8	4	1	6	7	7	5	40	87
10 mg/kg q4	10	5	3	6	3	4	12	8	30	81
Total	38	23	13	20	23	27	33	37	214	428

The one-sided exact Smirnov test performed in StatXact gives a p-value of 0.0007. This means that the 3 mg/kg q8 dose, compared to placebo, was significantly associated with quicker time until durable response.

There were also 50 records for which ACR_PCT and AACR_PCT do not agree. The patients for which such discrepancies were observed are listed, by week, in Table 4N below.

Reviewer's Table 4N: ACR Efficacy Data, ATTRACT (T22), Week 30 Discrepancies Between ACR_PCT and AACR_PCT, by Week							
Week							
2	6	10	14	18	22	26	30
05017	03001 04018 05015 06027 15007 24007	03005 05017 06028 13005 19013 25010 27005 31008	03004 05018 05021	01008 03008 06019 06020 07025 11010 12002 24006 26003	04020 05013 07016 07020 11003 18008 19002 27003	04018 06024 07025 12002 15016 19012 19014 25004 26007 31006 31009 33006	03001 06004 06013

4C. SAFETY

Through week 54, the number of patients treated with placebo (18/86; 20.9%) who reported a serious adverse event was higher than those patients treated with infliximab (55/342; 16.1%). See the table below.

Treatment Group	Patients with SEAs		Discontinuations due to AEs		Deaths (Week 30)
Placebo	18/86	21%	7/86	8%	0/86
3 mg/kg q 8 wks	10/89	11%	5/89	6%	1/89
3 mg/kg q 4 wks	14/86	16%	8/86	9%	2/86
10 mg/kg q 8 wks	17/87	20%	4/87	5%	1/87
10 mg/kg q 4 wks	14/80	18%	8/80	10%	1/80
All Infliximab	55/342 16%		25/342 7%		5/342

5. SUMMARY

Infliximab appears to be safe and efficacious.

6. CONCLUSIONS

Infliximab should be licensed.