FDA Briefing Document

March 4, 2003 meeting of Arthritis Advisory Committee

UPDATE ON THE TNF-" BLOCKING AGENTS

I. INTRODUCTION

The intent of this document is to summarize the efficacy data that resulted in the licensure of the three tumor necrosis factor (TNF) blocking agents and to provide a more comprehensive update on their safety. The three products, Etanercept (Enbrel), Infliximab (Remicade) and Adalimumab (Humira) are indicated for treatment of patients with RA. Clinical studies have shown the products to improve signs and symptoms, inhibit the progression of structural damage, and impact functional outcomes in patients with RA. The efficacy section will begin with a summary of Adalimumab, the newest of the TNF blocking therapies.

While all these agents have demonstrated efficacy in patients with active RA despite treatment with other DMARDs (disease modifying anti-rheumatic drugs), they have also been associated with certain uncommon but serious adverse events. Most of these events have come to light through the post-marketing passive surveillance program. At the time of approval of the first two TNF blocking agents, the total numbers of patients treated and extent of exposure from controlled clinical trials and the open label extension studies were relatively limited. As will be summarized in the safety section of this document, the post market safety updates and data from controlled clinical trials in other settings have triggered several different FDA actions, including updates to the prescribing information in the package inserts, communications to health care providers (Dear Health Care Provider Letters) a safety update on August 17, 2001 to the AAC, as well as presentations at ACR and other national and international meetings and publications in journals. This safety update will summarize safety data from the randomized controlled trials contained in the Biologics License Application (BLA) of Adalimumab for RA, and provide an update on safety information for Remicade and Enbrel. One major focus of this safety update will be a more in-depth review of the cases of lymphomas that have developed in patients treated with TNF blocking therapy. We specifically seek the committee's advice on issues regarding the association between these products and lymphoma and input regarding how to best transmit this information in prescribing information.

II. EFFICACY OF TNF BLOCKING AGENTS

A. Humira

Humira is a human-derived recombinant IgG1 monoclonal antibody engineered by gene technology. Humira binds to TNF-α but not TNF-β and has a half-life of approximately 2 weeks. It was approved for use in patients with RA December 31, 2002. The paragraphs below summarize the major efficacy findings; the Humira safety summary is presented in Section III. Appendix A provides the full medical review of the BLA.

The sponsor conducted four randomized, double-blind efficacy studies in patients ≥ age 18 with active rheumatoid arthritis diagnosed according to American College of

Rheumatology (ACR) criteria. Patients had at least 6 swollen and 9 tender joints. Adalimumab was administered subcutaneously in combination with MTX (12.5 to 25 mg, Studies I and III) or as monotherapy (Study II) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV).

Study I (DE009) evaluated 271 patients who had failed therapy with at least one but no more than four DMARDs and had inadequate response to MTX. Doses of 20, 40 or 80 mg of HUMIRA or placebo were given every other week for 24 weeks.

Study II (DE011) evaluated 544 patients who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of HUMIRA were given as monotherapy every other week or weekly for 26 weeks.

Study III (DE 019) evaluated 619 patients who had an inadequate response to MTX. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to 52 weeks. Study III had an additional primary endpoint at 52 weeks of inhibition of disease progression (as detected by X-ray results).

Study IV (DE031) assessed safety in 636 patients who were either DMARD-naive or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of HUMIRA or placebo every other week for 24 weeks.

Table 1 summarizes the ACR 20, 50, and 70 findings.

Table 1 : Summary of Percentage of ACR20, ACR50, and ACR70 Responses for All Adalimumab Studies At 6 and 12 Months at the recommended dose

Study		**Adalimumab 40 mg Q2w**	**Placebo/ Comparator**
	24 or 26 Weeks		
I Dose ranging + MTX	**ACR20**	**67**	**13**
	ACR50	**54**	**7**
	ACR70	**24**	**3**
II Monotherapy	**ACR20**	**46**	**20**
	ACR50	**22**	**8**
	ACR70	**12**	**2**
III (+ MTX)	**ACR20**	**63**	**30**
	ACR50	**39**	**10**
	ACR70	**21**	**3**
IV (Added to Usual Clinical Practice)	**ACR20**	**53**	**35**
	ACR50	**29**	**11**
	ACR70	**15**	**3**
III (+ MTX)	**52 Weeks**		
	ACR20	**55**	**25**
	ACR50	**42**	**10**
	ACR70	**23**	**5**

ACR Responses in Placebo-Controlled Trials (Percent of Patients)

The results of the components of the ACR response criteria for Studies II and III are shown in the table below. Improvement was seen in all components and was maintained to week 52.

Components of ACR Response

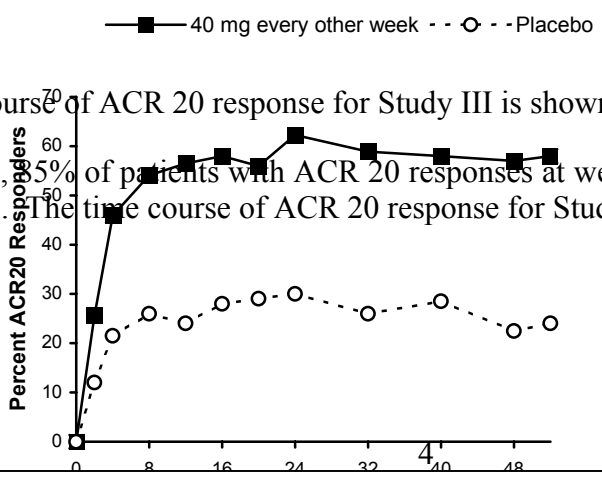
Parameter (median)	Study II				Study III			
	Placebo N=110		HUMIRA[a] N=113		Placebo/MTX N=200		HUMIRA[a]/MTX N=207	
	Baseline	Wk 26	Baseline	Wk 26	Baseline	Wk 24	Baseline	Wk 24
Number of tender joints (0-68)	35	26	31	16*	26	15	24	8*
Number of swollen joints (0-66)	19	16	18	10*	17	11	18	5*
Physician global assessment[b]	7.0	6.1	6.6	3.7*	6.3	3.5	6.5	2.0*
Patient global assessment[b]	7.5	6.3	7.5	4.5*	5.4	3.9	5.2	2.0*
Pain[b]	7.3	6.1	7.3	4.1*	6.0	3.8	5.8	2.1*
Disability index (HAQ)[c]	2.0	1.9	1.9	1.5*	1.5	1.3	1.5	0.8*
CRP (mg/dL)	3.9	4.3	4.6	1.8*	1.0	0.9	1.0	0.4*

[a] 40 mg HUMIRA administered every other week

[b] Visual analogue scale; 0 = best, 10 = worst

[c] Disability Index of the Health Assessment Questionnaire[2]; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

* $p<0.001$, HUMIRA vs. placebo, based on mean change from baseline



The time course of ACR 20 response for Study III is shown in figure 1.

In Study III, 85% of patients with ACR 20 responses at week 24 maintained the response at 52 weeks. The time course of ACR 20 response for Study I and Study II were similar.

Figure 1: Study III ACR 20 Responses over 52 Weeks

In Study III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The results are shown in Table 3. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone.

Table 3 Radiographic data - change in score compared to baseline

	Placebo/MTX	HUMIRA/MTX 40 mg every other week	Placebo/MTX-HUMIRA/MTX (95% Confidence Interval*)	P-value**
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	<0.001
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	<0.001
JSN score	1.0	0.1	0.9 (0.3, 1.4)	0.002

*95% confidence intervals for the differences in change scores between MTX and HUMIRA.
**Based on rank analysis

The optimal dose of adalimumab is 40 mg sc every other week when given in combination with MTX. Higher doses were not more effective. In study II, which did not include MTX, although adalimumab 40 mg every other week was effective (46% ACR20 responses at 6 months), 40 mg weekly was associated with higher response rates (53% ACR20 responses at 6 months). Comparisons across trials must be carried out with caution; however, the higher point estimates of the response rates in 6-month trials of adalimumab 40 mg every other week with MTX suggest that the addition of MTX to adalimumab is more effective.

In all four studies, Humira showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ) from baseline to the end of study, and significantly greater improvement than placebo in the health-outcomes as assessed by The Short Form Health Survey (SF 36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS). However, the duration of the longest study (12 months) was not sufficient to permit a claim of Improvement in Physical Function as delineated in the RA Guidance.

Most patients enrolled in the controlled trials of adalimumab were offered the opportunity to roll over into a long-term open-label extension study. To assess tolerability of adalimumab treatment over time, the data from clinical trials were analyzed to determine

what fractions of patients who were allowed to continue treatment for 1, 2, 3 or 4 years chose to do so. As shown in Table 4, 70% of patients who began treatment with adalimumab chose to continue for 2 years and approximately 60% chose to continue for 3 years.

Table 4: Percent of Adalimumab-Treated Subjects Choosing to Remain on Treatment

Years of exposure	# exposed	Total possible	**% choosing to remain on treatment**
<1 yr	2468	2468	100%
≥ 1 yr	1990	2444	81%
≥ 2 yrs	1258	1795	70%
≥ 3 yrs	331	534	62%
≥ 4 yrs	142	254	56%
≥ 5 yrs	41	89	46%

B. Enbrel efficacy summary

The efficacy of Enbrel for improvement in signs and symptoms of rheumatoid arthritis was established in 3 randomized controlled trials. One efficacy trial was a study of Enbrel or placebo added onto background therapy in patients who had failed one or more DMARDs (study I, Table 5). Approximately 60% of patients had an ACR20 response at 6 months compared to approximately 10% of add-on placebo-treated patients. Similar results were seen in a randomized controlled trial of Enbrel added to background methotrexate in patients with active disease despite methotrexate (study II). A median improvement of approximately 50-60% was seen in each of the components of the ACR20. Continued durable responses have been seen for up to 36 months in open-label extension treatment trials when patients received Enbrel without interruption. The third randomized trial was an active controlled trial that compared a rapid dose escalation of methotrexate to Enbrel in patients with early RA (see section VI for more details)

Most patients enrolled in the controlled trials of etanercept were offered the opportunity to roll over into a long-term open-label extension study. To assess tolerability of etanercept treatment over time, the data from clinical trials were analyzed to determine what fractions of patients who were allowed to continue treatment for 1, 2, 3 or 4 years chose to do so. As shown in Table 6, 73% of patients who began treatment with etanercept chose to continue for 2 years and approximately 50% chose to continue on study receiving etanercept for 3 years. It should be noted that these figures provide a conservative estimate of the proportion of patients who elected to continue etanercept as some patients dropped out of the study and received etanercept by prescription once it once approved.

Radiographic findings at 1 and 2 year time-points are shown in Table 7. Effects were seen on erosion and the joint space narrowing components of the Sharp score. Etanercept is also approved for treatment of polyarticular-course juvenile rheumatoid arthritis and for patients with psoriatic arthritis.

Table 5: **ACR Responses in Placebo- and Active-Controlled Trials (Percent of Patients)**

	Placebo Controlled				Active Controlled	
	Study I		Study II		Study III	
	Placebo	ENBREL[a]	MTX/Placebo	MTX/ENBREL[a]	MTX	ENBREL[a]
Response	N = 80	N = 78	N = 30	N = 59	N = 217	N = 207
ACR 20						
Month 3	23%	62%[b]	33%	66%[b]	56%	62%
Month 6	11%	59%[b]	27%	71%[b]	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
ACR 50						
Month 3	8%	41%[b]	0%	42%[b]	24%	29%
Month 6	5%	40%[b]	3%	39%[b]	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
ACR 70						
Month 3	4%	15%[b]	0	15%[b]	7%	13%[c]
Month 6	1%	15%[b]	0	15%[b]	14%	21%[c]
Month 12	NA	NA	NA	NA	22%	25%

a. 25 mg ENBREL SC twice weekly.
b. $p < 0.01$, ENBREL vs. placebo.
c. $p < 0.05$, ENBREL vs. MTX.

Table 6: Percent of Etanercept-Treated Subjects Choosing to Remain on Treatment

Years of exposure	Early RA (N)	Later RA (N)	Total (N)	**Percent (%)**
≥ 1 yr	482	606	1088	81%
≥ 2 yrs	433	547	980	73%
≥ 3 yrs	295	501	796	52%
≥ 4 yrs	245	450	695	52%

Table 7: Mean Radiographic Change Over 6 and 12 Months in Study III

		MTX	25 mg ENBREL	MTX-ENBREL (95% Confidence Interval*)	P-value
12 Months	Total Sharp score	1.59	1.00	0.59 (-0.12, 1.30)	0.110
	Erosion score	1.03	0.47	0.56 (0.11, 1.00)	0.002
	JSN score	0.56	0.52	0.04 (-0.39, 0.46)	0.529
6 Months	Total Sharp score	1.06	0.57	0.49 (0.06, 0.91)	0.001
	Erosion score	0.68	0.30	0.38 (0.09, 0.66)	0.001
	JSN score	0.38	0.27	0.11 (-0.14, 0.35)	0.585

* 95% confidence intervals for the differences in change scores between MTX and ENBREL

C. Remicade Efficacy Summary

The efficacy of Remicade in combination with MTX, for improving the signs and symptoms of rheumatoid arthritis and for inhibition of progression of structural damage, was established in the ATTRACT trial of patients with active rheumatoid arthritis despite treatment with methotrexate. As shown in Table 8, treatment with Remicade increased the proportion of patients with ACR20 at 6 and 12 months. Efficacy was seen with each of the 4 dosing regimens, ranging from 3 mg IV q8w to 10 mg IV q4w. Similar response rates were seen at 6 months with each of the dose regimens. However, for patients in the lowest dose group, there was a trend towards decreasing rates of ACR20 response between 6 months and 1 year. Higher rates of ACR 50 and 70 responses were also seen with Remicade.

Remicade has also demonstrated efficacy for improvement in physical function in RA, based on 2-year data from the ATTRACT trial. The sponsor's primary analysis was the 2-year weighted mean change in HAQ (Table 9). The means for the weighted mean change in HAQ increased from 0.3 u for patients receiving placebo to 0.4-0.5 for infliximab-treated patients. The median values for the weighted mean change in HAQ was 0.1 u in the placebo arm and 0.3-0.4 for the 4 infliximab-treated arms. Both the global differences between treatment arms and each of the pairwise comparisons between infliximab and placebo were highly statistically significant. Multiple other analyses of HAQ showed robust and consistent effects -- including a sustained improvement in HAQ of ≥0.3 u, a benefit that exceeds the level of 0.22 u that has been demonstrated to be clinically meaningful. (see Appendix B, Tables 26-28)

Table 8: PERCENTAGE OF PATIENTS WHO ACHIEVED AN ACR RESPONSE AT WEEKS 30 AND 54

		REMICADE + MTX			
		3 mg/kg [a]		10 mg/kg [a]	
Response	Placebo + MTX (n=88)	q 8 wks (n=86)	q 4 wks (n=86)	q 8 wks (n=87)	q 4 wks (n=81)
ACR 20					
Week 30	20%	50%	50%	52%	58%
Week 54	17%	42%	48%	59%	59%
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%

[a] $p < 0.05$ for each outcome compared to placebo

Table 9: Weighted Mean Change from Baseline in HAQ

	Infliximab				
	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 randomized	88	86	86	87	81
Change from baseline through week 102					
Pts evaluated	88	86	85	87	81
Mean ± SD	0.3 ± 0.4	0.4 ± 0.3	0.5 ± 0.5	0.5 ± 0.5	0.4 ± 0.4
Median	0.1	0.4	0.4	0.4	0.3
IQ range	(0.0, 0.4)	(0.1, 0.6)	(0.1, 0.7)	(0.2, 0.9)	(0.1, 0.5)
Range	(0.0, 1.6)	(0.0, 1.5)	(0.0, 1.7)	(0.0, 1.7)	(0.0, 2.2)
p-value vs placebo		0.006	< 0.001	< 0.001	0.002

In the ATTRACT trial, all patients were initially offered one year of treatment. Of the subjects randomized to receive infliximab, 79% (268 of 340) remained on treatment for the full year. Subjects who completed one year of treatment were then offered a second year of therapy. Of the 268 who completed the first year, 76% (203 patients) remained

on therapy through the end of the second year. Thus of the 340 patients initially begun on infliximab, 60% remained on therapy for the full two years.

The ATTRACT trial also assessed inhibition of progression of structural damage based on the 12-month change in the total Sharp score. As shown in Table 10, patients in the placebo arm (i.e. receiving background MTX) experienced a rate of progression of 4 u/yr, while patients in the 4 infliximab arms (receiving MTX plus infliximab) had rates of progression of between –0.5 and 0.5. The differences between infliximab and placebo were highly statistically significant. The rates of progression of both erosion scores and joint space narrowing scores (JSN) were also reduced in the infliximab arms.

Table 10: **RADIOGRAPHIC CHANGE FROM BASELINE TO WEEK 54**

Median (10, 90 percentiles)	Placebo + MTX (n=64)	REMICADE + MTX 3 mg/kg q 8wks (n=71)	REMICADE + MTX 3 mg/kg q 4 wks (n=71)	REMICADE + MTX 10 mg/kg q 8 wks (n=77)	REMICADE + MTX 10 mg/kg q 4 wks (n=66)	p-value[a]
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

[a] For comparisons of each dose against placebo

Infliximab is also approved for the treatment of Crohn's Disease.

III. SAFETY REVIEW OF TNF BLOCKING AGENTS

A. General

An extensive update of the safety experience with Enbrel and Remicade was provided to the AAC at the August 17, 2001 meeting. The update focused on the following serious events that were observed during postmarketing experience with either or both products: demyelinating disease, seizures, aplastic anemia, intestinal perforation, cutaneous lupus rash, tuberculosis and other opportunistic infections, and lymphomas. The August 2001 briefing document is provided in appendix C. The more recent post-marketing experience with Remicade and Enbrel in the RA population has not resulted in new types of adverse events, and controlled clinical trial experience for new indications (e.g., psoriatic arthritis) in general have not resulted in new findings, though two exceptions deserve more discussion: safety findings in patients with congestive heart failure (CHF) and cases of hepatic toxicity in patients with Crohn's disease receiving Remicade for long term maintenance. A more comprehensive review of all cases of lymphomas associated with the TNF blocking therapies will be presented in section V, following the safety review of Humira.

B. CHF

Promising data from animal models of CHF and elevated levels of TNF-α observed in patients with CHF led to the conduct of clinical trials of TNF-blockers in CHF. Two large pivotal trials of etanercept, termed RECOVER and RENAISSANCE, were begun but were halted early because of lack of improvement with treatment (see appendix D for full study report).

Subsequently, the FDA reviewed the AERS database for post-marketing reports of CHF with etanercept and infliximab. The search revealed 51 reports of CHF among patients receiving TNF blockers, of whom 30 were receiving etanercept and 21 were receiving infliximab. Half the cases had a documented history of risk factors for CHF, including myocardial infarction, coronary heart disease, hypertension, diabetes, or pulmonary disease. The median interval from the first dose of TNF antagonists to CHF diagnosis or worsening was 3.5 months. Three patients died from CHF. The cases included 10 patients aged < 50 years old. Three of these 10 had risk factors for CHF. Echocardiography demonstrated a median ejection fraction of 20% for 9 of these patients. All patients discontinued TNF-blocking agents when CHF was diagnosed. Three had complete resolution of CHF; 6 partially improved with therapy and one died. CHF – Remicade

Centocor investigated the use of infliximab in a phase 2 trial in NYHA class III or IV CHF. Patients were randomized to receive placebo or infliximab 5 or 10 mg/kg at 0, 2

and 6 weeks. No improvement was seen in the clinical status of patients at 14 weeks with

infliximab. The study was stopped early for safety reasons when an increased incidence of mortality and hospitalization for worsening heart failure was observed in infliximab-treated patients, particularly those treated at the higher dose. A Dear Doctor letter was issued warning clinicians not to start infliximab in patients with CHF (see appendix E for full study report).

As described above, a search of the AERS database revealed post-marketing reports of CHF with infliximab. Some cases occurred in patients under 50 years of age.

C. Hepatoxicity - Remicade

In the ATTRACT trial of infliximab used in combination with methotrexate, elevations in transaminases (AST or ALT) were observed more frequently than in patients receiving methotrexate alone. The elevations observed were mild (<2 times the upper limit of normal) or moderate (≥ 2 times the upper limit of normal but < 3 times the upper limit of normal). These findings are reported in the package insert.

Elevations in transaminases were also observed in the ACCENT I trial of Crohn's Disease, a study to evaluate the safety and efficacy of maintenance Remicade. In this trial, 190 patients/arm received infliximab 5 mg/kg initially and were then randomized to receive maintenance with placebo or infliximab 5 or 10 mg/kg every 8 weeks. Patients were receiving concomitant treatment with a variety of immunomodulatory agents, including 6-MP, methotrexate or mycophenolate mofetil. Most were not receiving methotrexate. Review of the ACCENT I trial showed that patients randomized to receive 5 or 10 mg/kg infliximab maintenance treatment were more likely to have moderate elevations in AST than placebo-treated patients (8 in placebo arm, 14 in 5 mg/kg infliximab arm, 10 in 10 mg infliximab arm). None of the patients with elevations in AST or ALT developed clinical liver impairment. These data suggest that use of infliximab is associated with mild to moderate elevations of transaminases even when used without concomitant methotrexate.

D. Humira Safety Review

The International Conference on Harmonisation Guidance document entitled E1:"The Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long Term Treatment of Non-life-threatening Conditions" sets forth a minimum set of

standards for safety evaluation[1]. It recommends a minimum duration of exposure of at least 300-600 patients treated for at least 6 months and at least 100 treated for 1 year, and a total exposure (at any dose) of approximately 1500 patients. At the end of Phase 2 meeting for adalimumab, CBER recommended that the sponsor acquire a safety database larger than stated above to be able to provide better estimates of adverse events related to the potentially immunosuppressive properties of the product. The Agency recommended that the sponsor study concomitant exposure with DMARDs and other treatments typically used in clinical practice, and that the safety data-base consist at least 1000 patients treated with the recommended dose for at least one year. As a result of this shift in thinking about extent of safety data at the time of a BLA, the Humira safety database was larger than the safety databases available at the time of approval for the other two TNF blocking agents and considerably larger than the minimum ICH recommendations. The pre-marketing experience included a total of 2334 patients; 2073 exposed for 6 months and 1497 exposed for greater than one year. Humira was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. Most patients received the recommended dose of 40 mg HUMIRA every other week.

The analysis of this safety database poses some specific challenges given that 1) most of the patient exposure is from open-label extension studies that lacked a concurrent control and 2) some serious events are expected in the patient population under study, including some deaths, serious infections, lymphomas, and other malignancies. The possible role of adalimumab in increasing the risk of these events was assessed in a number of ways including: a) comparison of event rates vs. placebo; b) comparison to epidemiologic databases; c) examination of event rates as a function of duration of exposure to adalimumab.

Table 11 summarizes events reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. Adverse event rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week.

[1] International Conference on Harmonisation. "E1: Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs. Available at http://www.fda.gov/cber/guidelines

Table 11: Adverse Events Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

Adverse Event (Preferred Term)	HUMIRA 40 mg subcutaneous Every Other Week (N=705) Percentage	Placebo (N=690) Percentage
Respiratory		
Upper respiratory infection	17	13
Sinusitis	11	9
Flu syndrome	7	6
Gastrointestinal		
Nausea	9	8
Abdominal pain	7	4
Laboratory Tests*		
Laboratory test abnormal	8	7
Hypercholesterolemia	6	4
Hyperlipidemia	7	5
Hematuria	5	4
Alkaline phosphatase increased	5	3
Other		
Injection site pain	12	12
Headache	12	8
Rash	12	6
Accidental injury	10	8
Injection site reaction**	8	1
Back pain	6	4
Urinary tract infection	8	5
Hypertension	5	3

* Laboratory test abnormalities were reported as adverse events in European trials

** Does not include erythema and/or itching, hemorrhage, pain or swelling

The most common adverse events associate with Humira included mild-moderate injection site reactions and non-serious infections. In the placebo-controlled trials, the rate of infection was 5 per patient year in the HUMIRA treated patients and 4 per patient

year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on Humira after the infection resolved.

Serious adverse events include infections, malignancies, demyelinating events, and lupus-like events. These types of events have been previously described in the safety update in August 2001 for the other TNF-blocking therapies.

1. *Serious Infections*

The incidence of serious infections was 0.04 per patient year in HUMIRA treated patients and 0.02 per patient year in placebo-treated patients. The most common organs affected by serious infections among adalimumab-treated patients were pulmonary, musculoskeletal, skin, gastrointestinal, and genitourinary. Skin, musculoskeletal and urinary infections were among those infections most frequently associated with sepsis. The rate of serious infections did not increase with the longer durations of exposure in the open label extension trials. Two patients died and 13 patients withdrew from studies as a result of serious infections. The serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis. The label includes a bolded warning about not initiating Humira in patients with active infections and caution with a history of recurrent infection or predisposition to infection.

For both adalimumab and placebo-treated patients, the rate of serious infections and deaths due to serious infections were lower among patients <65 years of age. Increasing age among adalimumab-treated patients was associated with an increased occurrence of malignancies, SAEs, AEs leading to withdrawals, and AEs resulting in dose interruption compared to age-matched placebo-treated patients. The percentage of patients with fatal AEs, which only occurred in the adalimumab–treated group, was also higher with advancing age.

Thirteen cases of tuberculosis (TB), including miliary, lymphatic, peritoneal, and pulmonary were reported in clinical trials. Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. Implementation of pre-treatment screening at the end of phase I with intradermal PPD in the US, chest x-rays in Europe, and appropriate prophylactic anti-tuberculosis treatment in accordance with CDC Guidelines, was associated with a marked reduction in the rate of active TB. However, other variables may have also contributed to the lower rate of TB later in the clinical development program, including less exposure to higher doses of adalimumab and possibly recruitment of fewer patients at high risk of latent TB infection. While cases were observed at all doses, the incidence of tuberculosis reactivations was particularly increased at doses of Humira that were higher than the recommended dose. All patients recovered after standard antimicrobial therapy.

No deaths due to tuberculosis occurred during the clinical trials. The label includes a box warning for patients to be evaluated for active or latent tuberculosis infection with a tuberculin skin test prior to initiating treatment and, if latent infection is diagnosed, appropriate prophylaxis in accordance with the Centers for Disease Control and Prevention guidelines. The label also recommends that patients be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur. In addition to TB, six cases of invasive opportunistic infections caused by histoplasma, aspergillus, and nocardia were also reported in clinical trials.

2. Malignancies

Among 2468 rheumatoid arthritis patients treated in clinical trials with Humira for a median of 24 months, 48 malignancies of various types were observed, including 10 patients with lymphoma. The Standardized Incidence Ratio (SIR) (ratio of observed rate to age-, gender- and race-adjusted expected frequency in the general population) for malignancies was 1.0 (95% CI, 0.7, 1.3) and for lymphomas was 5.4 (95% CI, 2.6, 10.0). An increase of up to several fold in the rate of lymphomas has been reported in the rheumatoid arthritis patient population, and may be further increased in patients with more severe disease activity. [2,3] The other malignancies observed during use of Humira were breast, colon-rectum, uterine-cervical, prostate, melanoma, gallbladder-bile ducts, and other carcinomas. A more comprehensive review of malignancies with particular emphasis on the incidence of lymphoma, is discussed in section V.

3. Demyelinating Events

Three cases of possible demyelinating disease were observed during the clinical development program of adalimumab. One patient presented with optic neuritis; one with paresthesias and one with lower extremity numbness. Demyelinating disease has been observed in studies of many TNF blockers, including etanercept, infliximab, and lenercept (see article by Mohan *et al* in attachments). Two of the 3 subjects had complete recovery, the other has residual leg numbness.

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[2] Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis : nested case-control study. *BMJ* 1998; **517**: 180-1

[3] Abstract. Wolfe F. Inflammatory activity, but not methotrexate or prednisone use predicts Non-Hodgkin's lymphoma in rheumatoid arthritis: a 25-year study of 1,767 RA patients. *ACR Plenary II* 1998: **931**

4. Autoantibodies and Lupus Like Syndrome

In the controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. One patient out of 2334 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patient improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown. A few cases of isolated skin rash and serositis with positive serologies were seen. A worldwide search of the safety database (reported November 26, 2002) revealed sketchy descriptions of 4 cases of pleural effusion, 3 cases of pericarditis, and 1 case of pericarditis and pleuritis among adalimumab-treated patients. Several of these cases were evaluated for drug-induced lupus erythematosus, but no evidence was found.

IV. Long-Term Safety

A. Mortality

1. *Adalimumab*

Eight patients (7 treated with adalimumab and 1 treated with placebo) died as a result of AEs during the controlled portions of the randomized trials. However, considerably more patients were treated with adalimumab than with placebo in the controlled trials. Correcting for the different exposures, deaths were calculated to have occurred at a rate of 0.3/100 patient-years (CI, 0.23, 0.82) among placebo-treated patients, 0.9/100 patient-years (CI, 0.23, 1.55) among all adalimumab-treated patients, and 1.3/100 patient-years (CI, 0.16, 2.35) among patients receiving the proposed recommended dose. Twenty-four deaths were observed overall among the adalimumab-treated patients in the clinical development program. Since the trials included a significant number of older patients, 22% age 65 to 75 and 5% over age 75, some deaths were expected. Even though the majority of patients enrolled in these studies were females, the majority of the deaths occurred in male subjects. No predominant cause of death was observed. The categories of deaths were cardiovascular (7), malignancy (6), infections (5), gastrointestinal (3), and respiratory, trauma, and hepatic necrosis (1 each).

Since most of the patient exposure was from open-label extension studies, there are no concurrent controls for comparison. To provide an estimate as to whether the mortality rate is higher than expected, the mortality rate was compared to that predicted based on sex and age-matched rates in the general US population. Determination of the Standardized Mortality Rate (SMR) for comparison of the observed death rate to the age-

adjusted expected frequency of deaths for the whole group of Humira-treated patients was 0.72 [CI, 0.46, 1.05]. These data, based on relatively short-term exposure, do not indicate a higher death rate with Humira treatment.

2. Etanercept

Safety and efficacy data were recently reviewed by the agency for patients treated with etanercept in long-term open-label clinical trials for three years. As shown in Table 12, 546 patients have received etanercept for at least 3 years and 427 for 4 years. A total of 14 deaths were observed in the clinical trials safety database. Of these, 5 (36%) were cardiovascular in nature, 4 (29%) were related to malignancies, 2 (14%) were infectious, 1 (7%) was pulmonary and 2 (14%) were unclassified (Table 13). Since there is no concurrent control group, historical data were obtained from the Olmsted County database of RA patients for comparison. As shown in Table 14, the percent of patients dying of cardiovascular, infectious and pulmonary causes were similar. A lower proportion of deaths were related to malignancies in the Olmsted County database (10%) than in the etanercept database (29%).

To determine how the number of deaths observed in the etanercept database compared with the number expected for a group of adults in the general population, the expected number of deaths was calculated using the National Vital Statistics Report (Kochanek, 2001) adjusting for age and sex (Table 15). For all adults in the database, as well as for adults participating in the MTX combination trial and for the children with JRA, the observed number of deaths was lower than the expected rate. No trends were seen to indicate an increase in the death rate with longer exposure to etanercept.

Table 12: Duration of treatment of patients being following in etanercept long-term safety studies

	Adults			Pediatric Patients (n = 69)	All Etanercept (n = 782)
	Total Adults (n = 713)	Adults w/o 16.14 (n = 628)	16.14 (n = 85)		
Mean duration of dosing period (days)	932	926	975	824	922
Number (%) of patients who received etanercept during:					
Year 1 (0 – 365 days)	713 (100)	628 (100)	85 (100)	69 (100)	782 (100)
Year 2 (366 – 730 days)	553 (78)	479 (76)	74 (87)	52 (75)	605 (77)
Year 3 (731 – 1095 days)	498 (70)	430 (68)	68 (80)	48 (70)	546 (70)
Year 4 (1096 – 1460 days)	403 (57)	358 (57)	45 (53)	24 (35)	427 (55)
Year 5 (1461 – 1825 days)	71 (10)	71 (11)	0 (0)	0 (0)	71 (9)

Table 13: Deaths occurring among all adults in the long-term database

Study of Occurrence/ Pt. No.	Age/ Sex	Day of Death	Days on Etanercept	Event
016.0008/0003	69/M	200	199	Myocardial infarction
016.0018/0314	60/F	853	853	Cardiac arrest
016.0018/0336	73/F	770	717	Myocardial infarction
016.0018/0407	60/F	977	977	Respiratory failure
016.0018/0450	62/F	1015	996	Fever of unknown origin
016.0018/0620	76/F	1365	1334	Acute cardiac arrest/ myocardial infarction
016.0018/1137	67/F	513	509	Cardiac arrest
016.0018/1228	57/M	482	481	Cardiac arrest secondary to biliary cancer
016.0018/1492	78/F	451	447	Lung cancer
016.0018/1562	52/F	353	342	Septicemia
016.0018/1571	43/F	1059	1048	Lung cancer
016.0018/1631	62/F	404	383	Injury accident
016.0018/1702	57/M	697	685	Post-operative retroperitoneal hematoma
016.0019/0110	57/F	126	106	Ovarian cancer

Table 14: Mortality in the etanercept long-term database compared to population-based database

Cause of death	Etanercept long-term database 14 deaths / 1819 patient-years	Olmsted County MN database 279 deaths / 6350 patient-years
Cardiovascular	36%	39%
Malignancy	29%	10%
Infectious	14%	15%
Pulmonary	7%	11%
Cerebrovascular	0%	9%
Other	14%	16%

Table 15: Expected number of deaths in the general population compared to observed number of deaths in etanercept long-term database

	Expected *	Observed
Total Adults	19.031	14
Adults without 016.0014	17.722	14
016.0014	1.309	0
Pediatric Patients	0.053	0
All Etanercept	19.084	14

2. *Infliximab*

Eleven deaths occurred during the 2 years of the ATTRACT trial: 4 deaths in the placebo arm and 3, 2, 1 and 1 in the 3 mg/kg q8wk and q4wk and 10 mg/kg q8wk and q4wk arms, respectively. Three deaths occurred in the second year of the study: 1 on placebo and 2 on infliximab. One death on infliximab was due to a ruptured abdominal aortic aneurysm. The other was a patient who developed a pneumothorax after their week-86 dose of infliximab. The patient had a chest tube inserted, but developed a bronchopleural fistula requiring surgical repair. He subsequently developed ARDS and sepsis.

B. Other Long-Term Safety Data

1. *Etanercept*

As stated above, the FDA recently reviewed 3-year data from open-label follow-up studies on patients receiving continued treatment with etanercept. The 3-year data included 85 RA patients from a study of methotrexate co-administration, 628 adult RA patients from other studies involving etanercept monotherapy and 69 pediatric patients receiving etanercept monotherapy from the JRA trial. The data on patients taking etanercept for 3 years do not indicate any new safety concerns beyond those identified at the time of initial approval and through spontaneous post-marketing reports. In particular, there was no evidence of increased mortality, or increases in the rate of malignancies compared to the general population. Serious infections were observed, but the rate is within the range reported in RA populations not receiving etanercept. No increase was seen in the rate of SAEs, malignancies or serious infections with increased duration of exposure.

2. *Infliximab*

The agency recently reviewed safety data from the second year of the ATTRACT trial. The rate of SAEs was similar in the infliximab and placebo arms (29% vs. 33%, respectively). When SAEs that could be ascribed to rheumatoid arthritis were excluded, there were 10 other SAEs in the placebo arm, compared to 17, 7, 13, and 8 in the 4

infliximab arms. The major non-RA-related category of SAE in the placebo arm was infections, which accounted for 5 of 14 SAEs, compared to 3/17, 3/7, 4/13 and 2/8 in the 4 infliximab arms. Malignancies represented 2 of the patients with SAEs in the placebo arm and 1, 0, 3 and 1 in each of the 4 infliximab arms. No other patterns of increase in individual SAEs were observed in the infliximab-treated patients and no patterns of increase in any category of SAEs were noted. No dose-related pattern of increase in SAEs was observed with infliximab.

The number of patients experiencing an infection that required treatment with antibiotics was analyzed. The duration of follow-up was 29% longer for infliximab-treated patients than for those receiving placebo. Overall the incidence of infections requiring antibiotics was 43% for patients receiving placebo and 60% for those receiving infliximab, a 39% higher rate. Infections occurring more frequently among infliximab-treated patients than controls included sinusitis (12% vs. 6%), urinary tract infection (12% vs. 8%), pharyngitis (85 vs. 4%), infection not-otherwise specified (6% vs. 2%), pneumonia (4% vs. 2%), and cellulitis (4% vs. 1%). An analysis of the occurrence of treated infections over time did not indicate that the incidence of infections increased with longer durations of treatment.

Serious infections were defined as those which constituted a definite hazard to the patient and included vital organ-system dysfunction or physicochemical impairment that was irreversible or required treatment. Any fatal, life-threatening, severely or permanently disabling infection was categorized as serious as were any that led to initial or prolonged hospitalization. Similar proportions of subjects developed serious infections in placebo- and infliximab-treated groups during the 2 years of the ATTRACT trial. No specific serious infection appeared at a clearly higher frequency in infliximab-treated patients. Because of the limited number of patients followed in the ATTRACT trial, one cannot make definite conclusions about whether infliximab treatment is associated with an increase in serious infections.

V. MALIGNANCIES INCLUDING LYMPHOMAS

A. General comments/Considerations for labeling

Lymphomas have been observed in clinical trials of patients receiving each of the approved TNF blocking agents. As more long-term data have accumulated, it has become possible to calculate observed and expected rates based on large databases in the general population to determine the relative frequency of lymphomas in the treated population. Standardized incidence ratios (SIRs) for lymphoma for each of the approved TNF blocking agents are higher than that in the general population. Interpretation of the comparative rates of lymphoma with the TNF blocking agents is complicated by the observation in several reports of approximately 2-fold higher lymphoma rates in the general RA population. In addition, several reports have indicated that patients with higher levels of disease activity/inflammation have several-fold higher rates of

lymphoma.[4,5] A 4-5 fold increased rate of lymphoma has been observed in patients with moderately active RA and higher rates in patients with highly active disease. Most of the patients enrolled in trials of the TNF blocking agents had highly active disease.

Since the standardized incidence ratio for lymphoma seen in the trials of TNF blocking agents is in the range of that seen for patients with the level of disease activity who enrolled in trials of TNF blockers, it could be argued that the rates of lymphoma are not higher than expected. However, the patient population for the two epidemiologic studies of lymphoma incidence in RA patients with active disease is not identical to the population in the trials of TNF blockers. Also the data collected in those epidemiologic studies was from an earlier time when background lymhoma rates were different and standard treatment of RA was different.

Because of the uncertainties surrounding the calculation of the expected rate of lymphoma in the RA population studied in the trials of adalimumab, the agency asked Abbott to include in the Humira label 1) the number of lymphomas and malignancies seen; 2) the standardized incidence ratio of malignancies and lymphomas compared to the general population; 3) information on the estimates of lymphoma rates in RA patients and in RA patients with highly active disease. The agency is considering including similar language with analogous information in the labels of the other approved TNF blocking agents as well as for other potentially immunosuppressive biologic agents for RA where lymphomas have been observed.

B. Etanercept

To address the issue of the risk of lymphoma in patients receiving etanercept, the agency recently reviewed all the data on cases of lymphoma in patients in clinical trials and in post-marketing reports. Lymphomas have been observed in rheumatoid arthritis patients receiving etanercept. Among 3389 patients representing 7364 pt-yrs a total of 9 cases of lymphomas including 3 Hodgkin's diseases and 6 non Hodgkin's lymphomas (NHL) have been reported from patients received one or more doses of etanercept with median exposure of 2.2 years in either the clinical trials or extension studies as of August, 2002. Of these 9 cases, 6 were observed in patients in clinical trials receiving treatment with etanercept or during the prespecified follow-up period following completion of their participation in the trial. An additional 3 cases were reported after the follow-up period. Two developed lymphoma 2 and 9 months after discontinuation of etanercept. The

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[4] Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study *BMJ* 1998; 517:180-181.

[5]Abstract. Wolfe F. Inflammatory activity, but not methotrexate or prednisone use predicts non-Hodgkin's lymphoma in rheumatoid arthritis: a 25-year stud7 of 1767 RA patients. *ACR Plenary II* 1998: 931

second of these patients had received azathioprine for 9 months before lymphoma onset. The third cases was a patient initially diagnosed with large granular lymphocytic leukemia after 2 doses of etanercept.

If the number of 6 lymphomas is used in the calculations, then the standardized incidence ratio (SIR) for lymphoma in etanercept RA trials is 2.31 (expected =2.6, 95% CI 0.85, 5.03). If the larger number of 9 lymphomas is used, then an SIR of 3.47 is obtained (expected =2.6, 95% CI 1.59, 6.59). The SIR is calculated from incident cases in the trials divided by the expected incidence in the general population for an age, gender and race- matched cohort, not a non-etanercept RA population. The majority of population-based epidemiological analyses indicates that patients with RA have a higher incidence of lymphoma compared to the general population. The estimated risk of developing lymphoma in patients with RA is reported in the range of 1.5 to 8.7 fold compared to the general population. The observed SIR of 2.3-3.5 seen in etanercept RA clinical trials falls within this range.

The characteristics of the 8 cases of lymphoma are as follows:

- 3 Hodgkin's disease and 5 NHL
- Mean age 66.
- 4 are male and 4 are female.
- Mean time to onset is 630 days (range, 4 days to 1403 days)
- The majority of etanercept RA patients who developed lymphoma had significant disease activity prior to etanercept therapy.

The point estimate of the proportion of patients with Hodgkin's disease from clinical trials is greater than expected, but the small number (1-3) is associated with very broad confidence intervals.

The number of lymphomas from post-marketing adverse event reports through November 2, 2002 (4 years after initial product approval) is 70 (representing an estimated 205,923 pt-yrs in the US and 20,055 pt-yrs in non U.S.). This yields a reporting rate of 0.03/100 pt-yrs. The expected rate in the general population is 0.03 cases/100 pt-yrs (based on the NCI/SEER database, 2001, adjusted for the age and gender distribution of etanercept patients. It must be taken into account that the observed reporting rate of 0.03/100 pt-yrs represents an underestimate of the true incidence because of underreporting. The degree of underreporting is unknown.

- The mean age of patients receiving etanercept is 52 years with 50% receiving concurrent corticosteroids and 65% receiving concurrent methotrexate.
- The median age of patients diagnosed with lymphoma while receiving etanercept is 61+/- 11 years (S.D.).
- Majority of the patients with lymphomas are female (69%).
- The average duration of treatment with etanercept at time of diagnosis of lymphoma is 14+/- 12 months (S.D.) (range 0.5 to 42 months).

- The time to onset ranges from 1.4 to 39.5 months without a distinct pattern emerging with analysis of different histological subtypes.
- The most common indication for use of etanercept is RA (83%). Others include psoriatic arthritis, Still's disease and lupus.
- Of patients with lymphoma, 60% have a history of concurrent or past exposure to methotrexate, 13% had received past or concomitant therapy with azathioprine, infliximab, or cyclosporine.
- Most lymphomas are non-Hodgkin's lymphomas (NHL, 90%); 10% are Hodgkin's disease.

Among NHL cases, histology indicated: diffuse large B cell 44%; mantle 6%; peripheral T cell 8%; T cell chronic lymphocytic leukemia/polylymphocytic leukemia 8%; follicular 11%; small lymphocytic lymphoma/B cell chronic lymphocytic leukemia 17%; Waldenstrom's macroglobulinemia 6%.

C. Infliximab

The FDA recently reviewed all the reports of malignancies, including lymphomas in the clinical trial experience with infliximab. In the clinical development program up to and including the ATTRACT trial, 555 patients were observed in the studies in RA. Four cases of lymphoma were observed in the RA patients and two in trials of Crohn's Disease patients. Recently Centocor has completed a one year treatment phase of the ASPIRE trial in early RA patients. The trial is still blinded. A total of 1050 patients are enrolled in the ASPIRE trial, randomized to receive placebo or infliximab in addition to background methotrexate. No lymphomas have been observed in the ASPIRE trial.

A standardized incidence ratio for lymphomas and malignancies was calculated as shown in Table 16. Because the ASPIRE trial has not been unblinded, a worst-case-scenario was used to calculate the malignancy rate, where all were attributed to infliximab. As shown in the table, the SIR for malignancies did not exceed "1" for all RA patients. However, the SIR for lymphomas was 6.35, with a lower limit of the 95% confidence interval that excluded 1. The SIR for lymphoma was 8.7 for Crohn's Disease patients.

Limited data are available for placebo-treated patients (Table 17). No lymphomas were observed among the 430 placebo-treated subjects, although the expected number based on the general US population was only 0.14. In comparing the rate of lymphomas in infliximab-treated and placebo-treated patients it should be kept in mind that the number of patients observed on placebo were considerably smaller and the median duration of exposure was relatively short.

Table 16: Malignancies in infliximab-treated patients in clinical trials, adjusted for age, gender and race

Population	N	Total Subject-Yrs Follow-up	Median Subject-Yrs Follow-up	Malignancy	Observed No. cases	Expected No. Cases	SIR	SIR 95% Conf. Interval[a]
All Studies	2421	4148	1.00	Lymphoma	6	.86	6.98	[2.56, 15.19]
				All Malignancies[b]	27	23.55	1.15	[0.76, 1.67]
All CD Studies	1106	1646.2	1.37	Lymphoma	2	.23	8.70	(1.05, 31.41]
				All Malignancies[b]	10	4.84	2.07	[0.99, 3.80]
All RA Studies	1298	2458	0.8	Lymphoma	4	0.63	6.35	[1.73, 16.26]
				All Malignancies[b]	17	18.62	0.91	[0.53, 1.46]

[a]Confidence intervals based on exact method

[b]All malignancies includes lymphomas and excludes nonmelanoma skin cancers, which are not included in the SEER database.

Table 17: Malignancies in placebo-treated patients in clinical trials, adjusted for age, gender and race

Population	n	Total Subject-Yrs Follow-up	Median Subject-Yrs Follow-up	Malignancy	Observed No. cases	Expected No. Cases	SIR	SIR 95% Conf. Interval[a]
All Studies	489	691	0.32	Lymphoma	0	0.15	0	[NC]
				All Malignancies[b]	4	4.31	0.93	[0.25, 2.38]
All CD Studies	56	95	2.45	Lymphoma	0	0.01	0	NC
				All Malignancies[b]	2	0.19	10.52	[1.27, 38.02]
All RA Studies	430	590	0.32	Lymphoma	0	0.14	0	NC
				All Malignancies[b]	2	4.10	0.49	[0.06, 1.76]

[a]Confidence intervals based on exact method

[b]All malignancies includes lymphomas and excludes nonmelanoma skin cancers, which are not included in the SEER database.

D. Adalimumab

In this clinical development program, malignancies (Table 18) were observed at frequency rates approximating the expected rate in the general population. The Standardized Incidence Ratio (SIR) was 1.00 [95% CI, 0.7, 1.3] (standard ratio of observed rate to age-adjusted expected frequency) except for neoplasms of the immune system which were observed at a greater rate than expected (Table 19). A total of ten lymphomas, primarily Non Hodgkin's lymphoma, was observed in patients treated with adalimumab. The observed SIR for all lymphomas was 5.4 (95% CI, 2.6, 10.0) compared to the general population. The increased incidence of lymphomas observed among these adalimumab-treated patients raised concerns about whether adalimumab increases the risk of development of lymphomas. Published literature suggests that RA patients have

an approximately 2-fold higher risk of lymphoma than the general population.[6] Furthermore, RA patients with highly active disease have an even greater risk of lymphomas, in the same range as the SIR reported for adalimumab-treated patients.[7] Analysis of the time-to-onset of the cases of lymphoma seen with adalimumab did not provide evidence of a relationship to duration of adalimumab therapy (Table 20).

[6] Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis : nested case-control study. *BMJ* 1998; **517**: 180-1

[7] Abstract. Wolfe F. Inflammatory activity, but not methotrexate or prednisone use predicts Non-Hodgkin's lymphoma in rheumatoid arthritis: a 25-year study of 1,767 RA patients. *ACR Plenary II* 1998: **931**

Table 18: Cancer Incidence Analysis in Clinical Development Program

Cancer Site	Observed in BLA [1]	Observed in Interim Safety Update [2]	Observed in Final Safety Update [3]
Exposure	**2334 patients median 12 months**	**2467 patients median 19.3 months**	**2468 patients median 24 months**
All Sites	**30**	**38**	**48**
All lymphomas	**4**	**8**	**10**
NHL		**7**	
Hodgkin's D		**1**	
Breast	**4**	**5**	7
Colon – rectum	**3**	**4**	**6**
Cervix – Uteri	**3**	**3**	**5**
Prostate	**4**	**4**	**5**
Melanoma	**2**	**2**	**3**
Gallbladder – bile ducts	**1**		**2**
Adenocarcinoma (unknown origin)	**2**		**2**
Other	**7**	**11**	**8**
Non-melanoma skin cancers	**24**	**32**	**36**
Basal cell		**23**	
Squamous cell		**9**	

1 Data available through August 31, 2001
2 Data available through March 29, 2002
[3] Data available through August 31, 2002

Table 19: Comparative Expected Cancer Incidence Rates In the Adalimumab Clinical Development Program Through August 31, 2002

Cancer Type *	Observed	Expected	SIR	95% CI
All Sites	46	45.82	1.00	(0.7 – 1.3)
All Lymphomas	10	1.85	5.42	(2.6 – 10.0)
NHL	9	1.70	5.28	(2.4 – 10.0)
Hodgkin's Disease	1	0.14	7.09	(0.1 – 39.5)
Breast	7	11.15	0.63	(0.3 – 1.3)
Colon	5	4.75	1.05	(0.3 – 2.5)
Lung	1	6.67	0.15	(0.0 – 0.8)
Melanoma	3	1.53	1.97	(0.4 – 5.7)
Prostate	5	4.45	1.12	(0.4 – 2.6)
Uterine	4	2.30	1.74	(0.5 – 4.4)
Other sites	11	13.12	0.84	(0.4 – 1.5)
a) Non-Melanoma Skin Cancers **				
b) Basal Cell	23	20.12	1.14	(0.7 – 1.7)
Squamous Cell	9	3.79	2.37	(1.1 – 4.5)

* Cancer rates used were 1992-1999 SEER rates

** Skin cancer rates used were 1977-1978 NCI study rates

Table 20 : Lymphoma Incidence Rates by Duration of Treatment with Adalimumab

Exposure Interval Until Time of Event - Months	Number/Total (%)	N(N/100 patient-years)
0 - < 6	2/2468 (0.08)	2 (0.2)
6 -< 12	1/2216 (0.05)	1 (0.1)
12 - <18	1/1867 (0.05)	1 (0.1)
18 - < 24	2/1395 (0.14)	2 (0.4)
24 - < 30	1/619 (0.16)	1 (0.4)
30 - < 36	0/375 (0.00)	0 (0.0)
36 - < 42	0/321 (0.31)	1 (0.8)

Table 21 summarizes the cases of lymphoma observed during the adalimumab clinical development program by type and concomitant therapy. Lymphomas that have occurred in the setting of impaired immune function have most often been large B cell, Non Hodgkin's lymphomas.[8] Similarly, the lymphoma type most often reported in this clinical development program was the large B cell, Non Hodgkin's lymphoma. Ninety percent of the lymphoma patients had received MTX (seven were receiving concomitant MTX and two had received prior MTX), and 80% were receiving concomitant corticosteroids.

[8] Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the FDA. *Arthritis and Rheumatism* 2002;**46**: 3151-3158

Table 21: Summary of Lymphoma Cases By Type and Concomitant Therapy

Subject/Study	Type of Lymphoma	Family History	Concomitant Therapy		
			Azathioprine/ Cyclophosphamide	MTX	CSTD
2204/DE007	Mantle zone B cell	Sister-leukemia		X	X
69/DE001	Diffuse Large B cell			X [P]	
1414/DE011	MALT cell B cell		X [P]	X [P]	X
8911/DE019	Follicular B cell			X	
10509?DE031	Large B cell				X
1705/De019	Mixed small and large B cell			X	
11601/DE031	T cell			X	X
8208/DE019	Small and large B cell			X	X
14605/DE031	Large B cell			X	X
4404/DE019	Hodgkin's			X	X
Total = 10		1	1	9	8

P = previous CSTD = Corticosteroids

Available data are insufficient to determine whether adalimumab increases the incidence of lymphomas. Continued monitoring of adalimumab-treated patients is necessary to quantify the role of adalimumab, if any, in contributing to the observed higher incidence of lymphomas than in the general population.

To reflect the observed higher rate of lymphomas compared to the general population and the uncertainties in interpretation, the following language was included in the **WARNINGS** section of the package insert:

> Malignancies
>
> Lymphomas have been observed in patients treated with TNF blocking agents including HUMIRA. In clinical trials, patients treated with HUMIRA had a higher incidence of lymphoma than the expected rate in the general population (see **ADVERSE REACTIONS-Malignancies**). While patients with rheumatoid arthritis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the role of TNF blockers in the development of malignancy is not known[4,5].

And the following in the Adverse Reactions section:

> **Malignancies**
>
> Among 2468 rheumatoid arthritis patients treated in clinical trials with HUMIRA for a median of 24 months, 48 malignancies of various types were observed, including 10 patients with lymphoma. The Standardized Incidence Ratio (SIR) (ratio of observed rate to age-adjusted expected frequency in the general population) for malignancies was 1.0 (95% CI, 0.7, 1.3) and for lymphomas was 5.4 (95% CI, 2.6, 10.0). An increase of up to several fold in the rate of lymphomas has been reported in the rheumatoid arthritis patient population[4], and may be further increased in patients with more severe disease activity[5] (see **WARNINGS-Malignancies).** The other malignancies observed during use of HUMIRA were breast, colon-rectum, uterine-cervical, prostate, melanoma, gallbladder-bile ducts, and other carcinomas.

VI. Data comparing TNF blockers to other DMARDs

In order to make reasoned decisions about treatment, physicians and patients need data comparing the various available options. Unfortunately, only limited data are available on the relative safety and efficacy of the approved TNF blockers and other available DMARDs. The agency has encouraged sponsors to conduct comparative trials to address this important issue and hopefully, additional data will become available in the future.

Only one randomized controlled trial has been reviewed by FDA comparing a TNF blocking agent with another DMARD, the ERA trial of etanercept in early RA. This

study was reviewed at a meeting of the Arthritis Advisory Committee in April 2000. The ERA trial enrolled approximately 600 patients with RA for under 3 years who had never

received MTX. Patients were randomized to receive etanercept 10 mg or 25 mg biw sc or MTX. MTX was begun at a dose of 7.5 mg weekly and increased to 20 mg weekly unless patients experienced toxicity or had a complete clinical response.

As shown in Table 22, 65% of patients receiving etanercept 25 mg had ACR20 responses at 6 months, 40% had ACR 50 responses and 21% had ACR 70 responses at 6 months. Slightly higher proportions of subjects had ACR 20, 50 and 70 responses at 12 months. The point estimates for MTX treated subjects were similar however, for each comparison, the response rates for subjects receiving etanercept 25 mg was higher than for the MTX comparator group. The difference in the proportion of patients with an ACR20 response between etanercept and MTX was not statistically significant. The area under the curve for ACR-N was higher for etanercept 25 mg than for MTX (Figure 2).

Table 22: ACR 20, 50 and 70 responses at 3, 6 and 12 months

	MTX	Etanercept	
		10 mg	25 mg
	N = 217	N = 208	N = 207
Time	N (%)	N (%)	N (%)
20% ACR			
Month 3	116 (56)	108 (53)	123 (62)
Month 6	121 (58)	115 (59)	130 (65)
Month 12	129 (65)	115 (61)	138 (72)
50% ACR			
Month 3	50 (24)	56 (28)	57 (29)
Month 6	67 (32)	64 (33)	79 (40)
Month 12	85 (43) †	61 (32)	95 (49)**
70% ACR			
Month 3	15 (7)	16 (8)	26 (13)*
Month 6	28 (14)	26 (13)	42 (21)*
Month 12	44 (22)	31 (16)	49 (25)

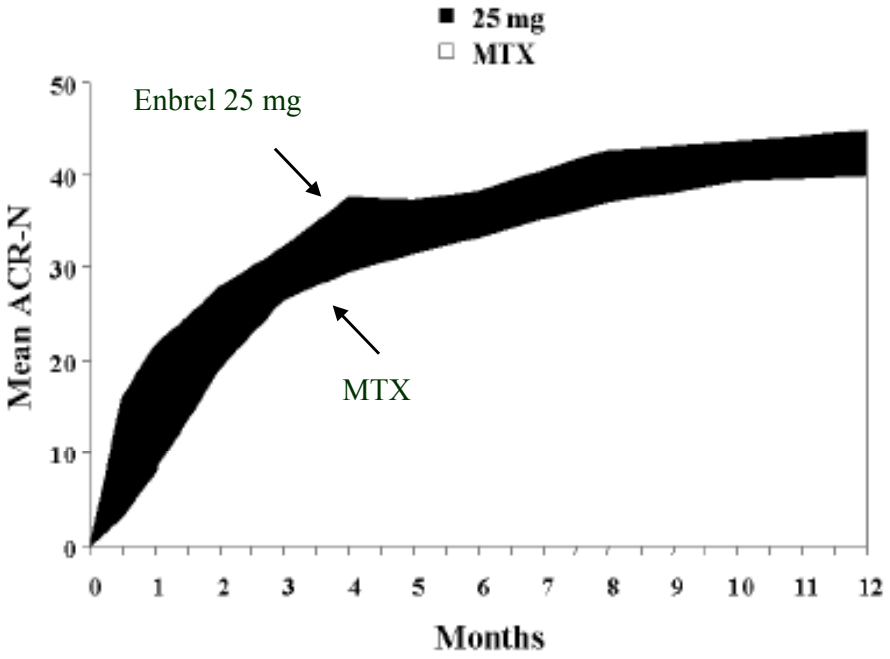

Figure 2: ACR-N over time during the study

During the course of trial 16.0012, two deaths occurred. There was one death of lung cancer in a subject in the Enbrel 10 mg arm diagnosed after two months of dosing. The other death was in the Enbrel 25 mg arm and arose from non-infectious complications of an aortic aneurysm repair.

A similar number of SAE's were observed in the MTX arm and the etanercept 25 mg arms of the ERA trial (Table 23). A similar number of infectious SAE's were seen with etanercept and MTX. Three malignancies were seen in the etanercept 25 mg arm compared to 1 in the MTX arm. Three cases of interstitial pneumonitis were seen in the MTX arm and none in the two etanercept arms. Two cases each of thromboembolic SAE's were seen in the etanercept arms and none in the MTX arms.

A higher proportion of subjects in the Enbrel 25 mg arm completed 12 months of dosing with assigned study drug than in the methotrexate arm. A total of 21 subjects discontinued study drug in the methotrexate arm compared to 10 in the Enbrel 25 mg arm and 9 in the Enbrel 10 mg arm ($p = 0.016$, MTX vs. all Enbrel). The reasons for discontinuation due to adverse events are shown in Table 24. The most common adverse events leading to discontinuation were alopecia, oral/nasal ulcers and vomiting, adverse events associated with methotrexate use. These events occurred in 9 subjects in the methotrexate arm and none in the Enbrel arms. Infection led to discontinuation in 3 subjects in the methotrexate arm and 3 and 1 in the Enbrel 10 mg and 25 mg arms, respectively. A diagnosis of a malignancy led to discontinuation in 1 subject in the methotrexate arm and two each in the Enbrel arms. MTX pneumonitis was observed in 3 subjects in the methotrexate and none in the Enbrel arms. Finally, injection site reaction

(ISR) led to discontinuation in one subject in the Enbrel 25 mg arm. Other adverse events leading to discontinuation were evenly distributed in the 3 arms of the trial.

Adverse events were reported by a higher proportion of subjects in the methotrexate arm than the two Enbrel arms: 95% vs. 90% and 89% in the Enbrel 10 mg and 25 mg arms respectively ($p = 0.010$, methotrexate vs combined Enbrel arms). The ten most common adverse events were headache, nausea, rash, rhinitis, diarrhea, bleeding at injection site, asthenia, dyspepsia, abdominal pain and dizziness. Of these, the only adverse event occurring at least 2% more commonly in the Enbrel 25 mg arm than the methotrexate arm was bleeding at injection site (14% vs. 10%).

One laboratory abnormality, low absolute neutrophil count (ANC), was seen more frequently in the subjects receiving Enbrel than subjects in the methotrexate arm: 16% of subjects in the Enbrel 25 mg arm vs. 8% in the methotrexate arm. The majority of these cases were grade 1 or 2. Grade 3 cases (ANC of 500-1000 cells/mm^3) of low ANC were seen in 3 subjects in the Enbrel 25 mg arm and 2 in the methotrexate arm. In none of three cases of low ANC were there associated infectious adverse events. Low ANC counts recovered spontaneously within 8 weeks while continuing Enbrel. No grade 4 cases were observed.

Laboratory abnormalities observed at a higher frequency in the methotrexate arm than the Enbrel arms of the trial are shown in Table 25. Elevated liver enzymes (SGOT, SGPT) were observed more frequently in the MTX arm than in the Enbrel arms. However, there were 4 cases of elevated liver enzymes in Enbrel-treated subjects, all in the 10-mg arm. One subject, #0106, had mildly elevated liver enzymes at screening which increased 1 week after beginning Enbrel. Study drug was discontinued. Liver biopsy showed fatty liver ascribed to obesity and prednisone. Another subject, #2001, had chronically elevated liver enzymes with grade 2 and grade 1 elevation of SGOT and SGPT, respectively, at baseline. During the study, liver enzymes increased to 5x the upper limit of normal and study drug was discontinued. Elevated liver enzymes were ascribed to autoimmune hepatitis or acetaminophen toxicity. A third subject, #2088, had normal liver enzymes at baseline, but developed elevations during the trial with an SGPT of 35 at 2 months, and at 9 mo SGOT 53 and SGPT 80. Study drug was discontinued and liver enzyme elevations returned to the normal range. The fourth subject, #6703, had a single set of elevated liver enzymes, SGOT 43 and SGPT 178. Liver enzymes 4 weeks before and 6 weeks after were within the normal range.

Table 23: SAEs occurring in trial 16.0012

	MTX	10 mg	25 mg
Infections	4	4	5
Malignancy (excl. skin)	1	2	3
DVT, pulm. Embolus	0	2	2
Interstitial pneumonitis	3	0	0
Angina, MI	4	3	0
Other	9	3	8
Total cases (patients):	21 (17)	14 (9)	18 (15)

Table 24: Adverse events leading to discontinuation of study drug

	MTX	Enbrel 10	Enbrel 25
Alopecia, oral/nasal ulcers, vomiting	9	0	0
Infection	3	3	1
Malignancy	1	2	2
MTX pneumonitis	3	0	0
ISR	0	0	1
Other AEs	5	4	6

Table 25: Abnormal laboratory values

	MTX	Enbrel 10	Enbrel 25
Higher in Enbrel:			
Low ANC	18 (8%)	21 (10%)	34 (16%)
Higher in MTX:			
Hi SGOT	70 (32%)	31 (15%)	34 (16%)
Hi SGPT	96 (44%)	47 (23%)	49 (24%)
Lo lymphs	172 (79%)	142 (68%)	115 (56%)
Lo albumin	104 (48%)	89 (43%)	88 (43%)
Lo Hb	83 (38%)	79 (38%)	53 (26%)

VI. Summary

The three licensed TNF-blocking products have all been shown to be effective in patients with rheumatoid arthritis; they have also been associated with certain types of serious adverse events. As expected, much of the information on serious events have accumulated during the post-marketing period, where causality assignment and precise quantification of the event rates are more difficult. Since the initial product approvals, the agency has made frequent changes to product labels and used other methods to communicate safety information to health care professionals and patients. Long term follow up of patients enrolled in registry studies is ongoing, where a particular emphasis is on all reports of malignancies and serious infections. The safety profile of these products will continue to be developed through use of the registry, periodic safety updates from the passive surveillance program, and safety data from controlled trials of TNF blocking therapy for other diseases.

Because the clinical trial designs and patient populations studied differ among the three approved TNF-blocking agents and have not been studied in head to head trials, direct comparisons cannot be made among the products and between the various studies.

Nonetheless, certain generalizations can be made. First, certain serious, but uncommon, adverse events have been observed with all three products, including 1) Serious

infections, including serious bacterial infections, TB and certain opportunistic infections; demyelinating syndromes; and lupus-like reactions. These data suggest that these adverse reactions may be related to blockade of TNF-α and may, therefore represent class effects of these agents. However, the severity and degree of risk may not be the same with all three agents. Second, because these serious adverse reactions are so uncommon, they were not fully appreciated in the initial safety database available at the time of approval of Enbrel and Remicade, even though those safety databases met minimum ICH guidelines. However, all of these serious adverse events were observed in the safety database submitted for approval of Humira. These findings indicate that for agents of this type, a larger safety database than the minimum ICH guidelines may be warranted.

The large size of the Humira database presented certain challenges in interpretation of the data. Because the number of patients treated and the duration of observation was extensive, it is expected that there would be deaths and malignancies, as there were. Yet because much of the period of exposure was in open-label extension studies, there is no internal control to allow an objective assessment of risk attributable to the study drug. Assessment of the deaths that were observed indicate that the mortality rate with Humira was not increased over that expected in the general population. This finding is reassuring, especially since the rate of mortality has been reported to be increased in patients with RA, including a recent study of patients diagnosed between 1955 and 1994 in Rochester MN.[9]

More complicated is the interpretation of the malignancies observed in the Humira database. While the rate of malignancies overall was not found to be increased over that seen in the general US population, the rate of lymphomas was increased, with a standardized incidence rate of 5.4. The rate of lymphomas has been reported to be increased in patients with RA compared to the general population and the rate is reported to be increased still further in patients with highly active disease, such as the patients evaluated in the Humira clinical development program. The standardized incidence ratio for lymphomas with Humira is in the range reported for RA patients with moderately active disease. Analysis of the rate of lymphomas relative to the general US population with the other two approved TNF blockers indicates a rate that is in the same range. It is difficult to reach firm conclusions about whether TNF blockers increase the risk of lymphomas because the patient populations studied are different from those studied in the epidemiologic studies and because of the lack of a concurrent control for most of the data.

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[9] Gabriel, SE, Crowson CS *et al*. Arthritis & Rheumatism, 48(1):54-58, 2003.

The agency addressed the issue of lymphomas observed in patients receiving Humira by including all the available information in the package insert and including a warning

about lymphomas. It could be argued that similar information should be included in the package inserts of the other TNF-blocking agents. The agency is interested in hearing discussion from the advisory committee about the best approach to studying the issue of lymphomas with TNF-blocking agents and the best way to report this information in product labels.

VII. Appendices

Appendix A. Medical officer review of BLA STN #125057 – Adalimumab for use in the treatment of Rheumatoid Arthritis.

Appendix B.

Other analyses for infliximab claim of improvement in physical function

Table 26: Landmark analysis at one year: Improvement from baseline in HAQ ≥ 0.3 at weeks 30 and 54

Methods of Handling Missing Data	Placebo (N=88)	3 mg/kg q8 wks (N=86)	3 mg/kg q4 wks (N=85)	10 mg/kg q8 wks (N=87)	10 mg/kg q4 wks (N=81)
Missing as nonresponder					
#Improvement (%)	20 (23%)	31 (36%)	41 (48%)	48 (55%)	33 (41%)
P-value vs. placebo		0.054	<0.001	<0.001	0.012
Multiple Imputations#					
#Improvement (%)	26 (30%)	34(40%)	45(53%)	49 (56%)	35 (43%)
P-value vs. placebo		0.17	0.002	<0.001	0.065
Modified Worst Case*					
#Improvement (%)	24 (27%)	31 (36%)	41 (48%)	49 (56%)	35 (43%)
P-value vs. placebo		0.213	0.004	<0.001	0.030
Worst Case					
#Improvement (%)	33 (38%)	31 (36%)	41 (48%)	48 (55%)	33 (41%)
P-value vs. placebo		0.84	0.15	0.19	0.66

Table 27: Number of infliximab patients with HAQ improvement of ≥0.3 at week 54 who also had improvement of ≥0.3 at week 102 (non-responder imputation)

	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	86	86	87	81	340
All patients					
Pts with improvement at week 54	48	46	54	41	189
Pts with improvement ≥ 0.3 at week 102	32 (67%)	41 (89%)	43 (80%)	35 (85%)	151 (80%)
Pts blinded through 102 weeks					
Pts with improvement at week 54	33	33	44	36	146
Pts with improvement ≥ 0.3 at week 102	19 (58%)	29 (88%)	34 (77%)	31 (86%)	113 (77%)
Pts unblinded at/or prior to 102 weeks					
Pts with improvement at week 54	15	13	10	5	43
Pts with improvement ≥ 0.3 at week 102	13 (87%)	12 (92%)	9 (90%)	4 (80%)	38 (88%)

Table 28: Landmark analysis at 2 years. Number of patients with improvement in HAQ ≥0.3 units at weeks 30, 54, 78 and 102

Methods of Handling Missing Data	Placebo (N=88)	3 mg/kg q8 wks (N=86)	3 mg/kg q4 wks (N=85)	10 mg/kg q8 wks (N=87)	10 mg/kg q4 wks (N=81)
Missing as nonresponder					
#Improvement (%)	11 (13%)	21 (24%)	36 (42%)	34 (39%)	28 (35%)
P-value vs. placebo		0.043	<0.001	<0.001	<0.001
Multiple Imputations#					
#Improvement (%)	22 (25%)	28 (33%)	37 (44%)	37 (43%)	31 (38%)
P-value vs. placebo		0.27	0.010	0.014	0.063
Modified Worst Case*					
#Improvement (%)	22 (25%)	21 (24%)	36 (42%)	34 (39%)	28 (35%)
P-value vs. placebo		0.93	0.016	0.046	0.173
Worst Case					
#Improvement (%)	31 (35%)	21 (24%)	36 (42%)	34 (39%)	28 (35%)
P-value vs. placebo		0.12	0.34	0.60	0.93

Appendix C – Briefing materials from August 17, 2001 Safety update on anti-TNF products

Appendix D Medical Officer review of Etancercept in CHF

Appendix E Medical Officer Review of Infliximab in CHF

Appendix F – selected publications