

Advisory Committee Briefing Document

HUMIRA™ **(Adalimumab)**

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ABBOTT LABORATORIES

This document contains fully releasable information.

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1.0 Executive Summary

Rheumatoid arthritis (RA) is a common, chronic, inflammatory disorder of the joints that results in substantial morbidity and increased mortality.¹ Both preclinical and clinical data support the use of tumor necrosis factor (TNF)-antagonists as an effective approach to the treatment of RA. However, TNF antagonism carries a risk of rare serious side effects including infections (particularly granulomatous infections such as tuberculosis [TB]), demyelinating disorders, and autoimmunity. RA is associated with an increased risk of lymphoma. The role of immunomodulators such as TNF-antagonists in this risk is uncertain.

Adalimumab (HUMIRA™) is a human monoclonal antibody to TNF developed through phage display technology containing solely human sequences. Adalimumab binds specifically to TNF (and not lymphotoxin) and has a half-life of approximately 2 weeks. The efficacy and safety of this antibody have been characterized in a series of adequate and well-controlled double-blind and open-label extension studies providing the largest and most robust database available for this class of agents.

The data from this database support the following efficacy and safety conclusions with respect to adalimumab:

- Adalimumab is effective in reducing signs and symptoms, improving the quality of life, and inhibiting the progression of structural damage in adult patients with moderately to severely active RA.
- Adalimumab is effective in rapidly inducing an ACR20 response (within 1 to 2 weeks) and this response is maintained with continued use.
- Adalimumab is effective given alone or in combination with methotrexate (MTX) or other disease-modifying anti-rheumatic drugs (DMARDs).
- The recommended dose of adalimumab for adult patients with RA is 40 mg given every other week (eow) subcutaneously. Some patients not using concomitant MTX may derive additional benefit from increasing the dose to 40 mg weekly.

- Adalimumab treatment is associated with an incidence of serious infections comparable to the RA population in general.
- TNF-antagonists, including adalimumab, are associated with an increased risk of TB that is related to the role of TNF in innate immunity. Screening is an effective means to reduce the incidence of this serious adverse effect.
- Rare cases of autoimmunity and central nervous system (CNS) demyelination have been observed with TNF-antagonists, including adalimumab, and are possibly related to TNF biology.
- The overall incidence and types of malignancies observed in the adalimumab clinical development program were similar to those observed in the general population.
- The risk of lymphoma in the overall clinical development program was commensurate with the increased risk expected in our RA patient population, but increased relative to the general population.

In summary, the available data on adalimumab show this therapy to be an effective approach to the treatment of RA with a large benefit to risk ratio. The most serious adverse effects observed with adalimumab such as serious infections, TB, demyelinating disorders and autoimmunity have been seen with TNF-antagonists and are possibly related to TNF biology. RA patients have been shown to have an increased risk of lymphomas. At this point in time, there is no clear, pervasive evidence of an added increase in lymphoma risk due to adalimumab therapy. Guidance regarding these risks is included in the adalimumab Package Insert (PI) and the Patient PI. In order to assess these risks with increasing duration of treatment, Abbott Laboratories is committed to the continued assessment of safety in patients treated with adalimumab.

2.0 Introduction

In December 2002, adalimumab was approved for reducing signs and symptoms and inhibiting progression of structural damage in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. Adalimumab can be used alone or in combination with MTX or other DMARDs.

The purpose of this document is to review the essential data on efficacy and safety with respect to adalimumab. Accordingly, this document will describe the clinical development program, the efficacy and safety profile for adalimumab, and the post-marketing surveillance plan Abbott Laboratories has put in place for evaluating and reducing any future, potential risks. The discussion of safety will focus on those safety concerns of primary concern with TNF-antagonist treatment, namely, infections, autoimmune diseases, demyelination, and malignancy with particular attention to the occurrence of lymphoma.

3.0 Overview of Adalimumab Clinical Development Program

To date, the safety and efficacy of adalimumab has been assessed in 17 completed and 3 ongoing open-label clinical trials in RA. A Biologic License Application (BLA) was filed and updated through 31-Aug-2002, from all US and non-US (Europe, Australia, and Canada) sources.

The clinical trials were conducted in patients who received adalimumab via both intravenous (iv) and/or subcutaneous (sc) routes of administration, either alone or in combination with MTX or other DMARDs. These patients came from a variety of geographic territories and have, in some cases, received up to 5 years of adalimumab therapy.

There were four adequate and well-controlled studies in the adalimumab program. Study DE009 was a Phase II/III study that examined different doses of adalimumab administered sc eow in patients with background MTX. Study DE011 confirmed the results of a prior Phase II study (DE007) and also explored eow dosing with adalimumab as monotherapy. Study DE019 confirmed the results of Study DE009 in patients with background MTX. In addition, Study DE019 addressed whether adalimumab inhibited the progression of structural damage in RA patients. Study DE031 was a Phase III study in which adalimumab was added to pre-existing rheumatologic care. The study design for DE031 was chosen to mimic typical outpatient rheumatologic care and had safety as the primary endpoint.

During the development program, all patients who completed a predefined portion of a clinical study were given the option to continue treatment in an open-label continuation study to provide extensive data on the long-term safety and tolerability of adalimumab. Study DE019X is an open-label continuation of the adequate and well-controlled Study DE019. Studies DE018 and DE020 are open-label continuation studies consisting of the patients that rolled over from multiple European and North American studies.

Overall, there were a total of 2468 unique RA patients who received adalimumab in the clinical development program in completed studies (with ongoing extensions) through 31-Aug-2002. This number of patients represents an increase in the exposure as presented in the BLA and as reflected in the PI. As of the above update, 4870 patient-years (pt-year) of experience have been collected. There were 2070 patients in adequate and well-controlled studies, of which 1380 received adalimumab, representing 785 pt-year of experience. In addition, there were 4006 pt-year of experience in open-label extension studies (the residual patient exposure being in clinical pharmacology trials). Table 1 summarizes the duration of exposure to adalimumab through 31-Aug-2002 for the 2468 RA patients.

Table 1 **Summary of the Duration of Exposure to Adalimumab in All RA Patients through 31-Aug-2002**

Duration of exposure	All adalimumab (N=2468) N
≥0 year	2468
≥1 year	1990
≥2 years	1258
≥3 years	331
≥4 years	142
≥5 years	41

The baseline characteristics of patients on adalimumab enrolled in the adequate and well-controlled clinical studies are provided in Table 2. All patients had a definitive diagnosis of RA. Baseline disease activity of patients enrolled in the adalimumab adequate and well-controlled clinical studies is provided in Table 3. Baseline disease activity was similar between trials except for DE011 in which patients generally exhibited a higher degree of disease activity and disability (i.e., higher tender joint count, Health Assessment Questionnaire [HAQ], and C-reactive protein [CRP]). Baseline characteristics and disease activity of the placebo-treated patients were similar to the adalimumab-treated patients for these studies.

Table 2 Baseline Characteristics in All Adalimumab-Treated Patients Enrolled in the Controlled Studies

Study	Sex (% female)	Age (mean ± SD years)	Duration RA (mean ± SD years)	Previous DMARDs (mean #)	Concomitant MTX (% patients)	Corticosteroids (% patients)	Rheumatoid factor positive (% patients)
DE009	76	55 ± 12	13 ± 10	3	100	48	79
DE011	77	53 ± 12	11 ± 8	4	0	72	82
DE019	76	56 ± 12	11 ± 9	2	100	47	81
DE031	80	55 ± 13	9 ± 9	1	56	51	77

Table 3 Baseline Disease Activity in All Adalimumab-Treated Patients in the Controlled Studies

Study	Tender Joint Count (Mean ± SD)	Swollen Joint Count (Mean ± SD)	HAQ (Mean ± SD)	CRP (Mean ± SD)
DE009	29 ± 14	17 ± 8	1.5 ± 0.6	26 ± 27
DE011	34 ± 15	20 ± 10	1.9 ± 0.6	50 ± 42
DE019	28 ± 13	20 ± 10	1.4 ± 0.6	16 ± 19
DE031	27 ± 13	21 ± 11	1.4 ± 0.6	16 ± 20

4.0 Efficacy

The clinical development of adalimumab focused on establishing the therapeutic indications of:

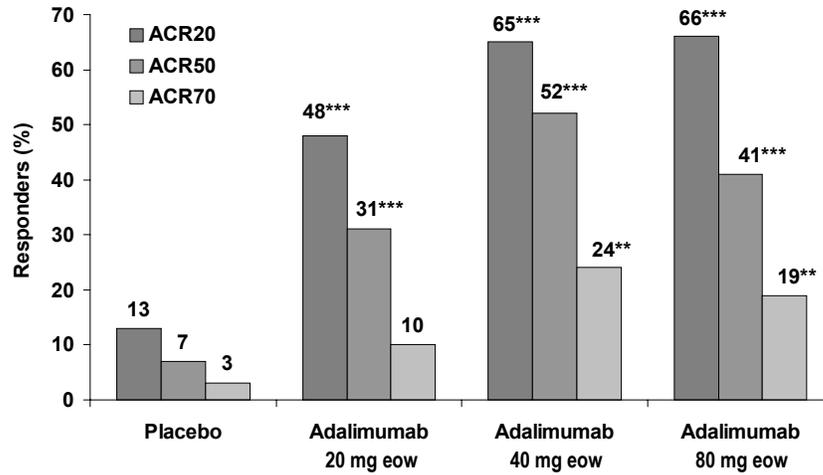
- 1) reducing the signs and symptoms, and
- 2) inhibiting the progression of structural damage in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs.

In addition, other efficacy assessments were investigated including multiple quality of life instruments (HAQ, Medical Outcomes Short Form 36 questionnaire [SF-36], Functional Assessment of Chronic Illness Therapy [FACIT], and Health Utilities Index [HUI]).

4.1 ACR Responses

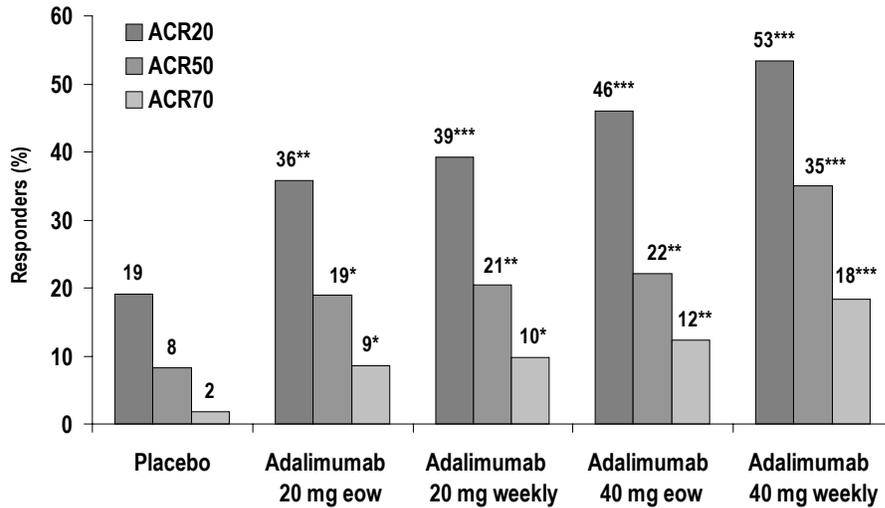
4.1.1 Primary Efficacy Assessment

Each of the four adequate and well-controlled studies independently demonstrated the efficacy of adalimumab on the primary endpoint of ACR20 response at Weeks 24 or 26 (Figures 1a to 1d). Across the four studies, ACR20 response rates were statistically significantly superior to placebo for all doses tested. In addition at the recommended dose of 40 mg eow, higher order responses at Weeks 24 or 26 were also attained by patients across all four studies with ACR50 and ACR70 response rates statistically superior to placebo.



*p≤0.05 vs. placebo; **p≤0.01 vs. placebo; ***p≤0.001 vs. placebo
Observed data, non-completer imputation

Figure 1a Study DE009 ACR Responses at 24 Weeks



*p≤0.05 vs. placebo; **p≤0.01 vs. placebo; ***p≤0.001 vs. placebo
Observed data, non-completer imputation

Figure 1b Study DE011 ACR Responses at 26 Weeks

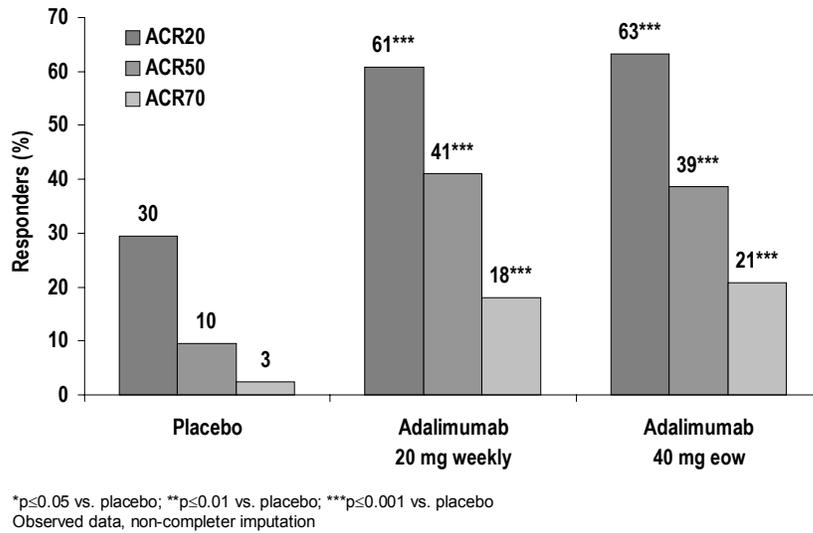


Figure 1c Study DE019 ACR Responses at 24 Weeks

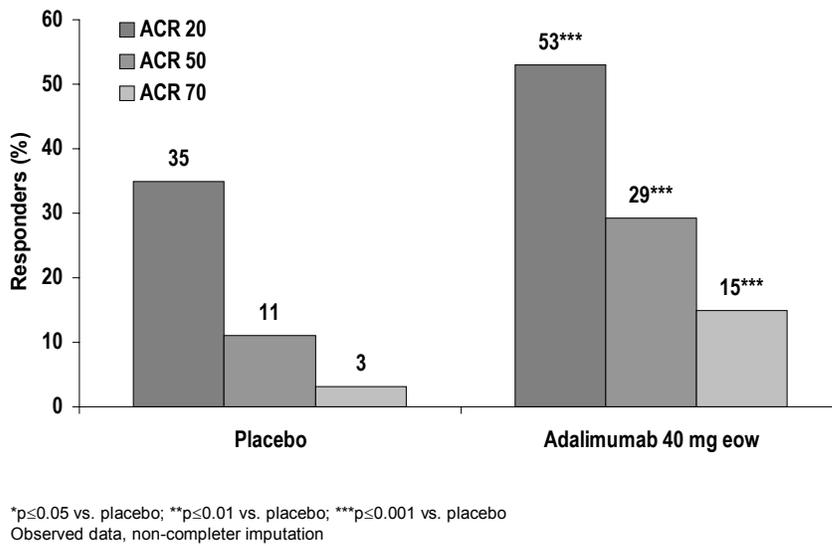


Figure 1d Study DE031 ACR Responses at 24 Weeks

4.1.2 Time-Course of ACR Responses

In all four adequate and well-controlled studies, adalimumab-treated patients achieved ACR20 responses faster and more often than placebo-treated patients. In Study DE009, 26% of patients treated with adalimumab achieved an ACR20 response by the first study visit (Week 1), compared to only 5% of placebo-treated patients ($p \leq 0.001$). In Studies DE011, DE019, and DE031, a similar rapid onset of response was seen with 36%, 29%, and 34%, respectively, of adalimumab-treated patients achieving ACR20 responses by the first study visit (Week 2), compared to only 7%, 13%, and 9%, respectively, of placebo-treated patients ($p \leq 0.001$). A similar pattern of the time to first ACR50 and ACR70 responses was noted in all four studies.

ACR20 responses were maintained over time. In Study DE019, 85% of patients with ACR20 responses at week 24 maintained the response at 52 weeks.

4.1.3 Selection of Recommended Dose

A relationship between adalimumab dose and efficacy was demonstrated in the adequate and well-controlled studies. Based on these analyses, 40 mg adalimumab eow by sc administration is the recommended dose for all patients.

Study DE009 established that the highest ACR20, ACR50, and ACR70 response rates were obtained with the 40 mg eow dose of adalimumab in patients taking concomitant MTX.

Study DE011 also demonstrated that the 40 mg eow recommended dose of adalimumab as monotherapy was statistically significantly better than placebo. In addition, Study DE011 (along with support from Phase II Study DE007) also suggests that patients who have an incomplete clinical response to adalimumab 40 mg eow may derive additional benefit from an increase in dosing frequency to 40 mg weekly when adalimumab is administered as monotherapy.

4.2 Quality of Life Assessment

Health related quality of life assessments were performed in all the adequate and well-controlled studies in the adalimumab clinical development program through the use of a number of validated instruments, including the disability index of the HAQ and SF-36.

At Week 24/Week 26 across all doses in all four studies, mean changes in the disability index of the HAQ following the administration of adalimumab were statistically superior to placebo ($p \leq 0.01$), ranging from -0.3 to -0.6, which exceeded the 0.22 unit decrease reported to represent minimum clinically important improvement.² The mean change in the HAQ scores from baseline to Week 52 for both doses in Study DE019 was -0.6. In addition, both of these values were statistically superior to placebo ($p \leq 0.001$).

Across the four adequate and well-controlled studies and all adalimumab treatment groups, mean values for the different quality of life measures showed consistent associations with each other. Clinically important mean changes (≥ 5 points) from baseline to Week 24/Week 26 in SF-36 physical component summary (PCS) scores of 5.5 to 8.8 were shown in the adalimumab groups across studies. These changes were associated with relatively large decreases in the disability index of the HAQ of -0.3 to -0.6. The association of positive PCS scores and negative HAQ scores suggests that as physical functioning, physical role, and other physical attributes measured by PCS improve, disability measured by HAQ is reduced.

4.3 Core Components of the ACR Response and Additional Quality of Life Measurements

The core components of the ACR responder calculation and additional quality of life data in the four adequate and well-controlled studies supported the effectiveness of adalimumab in treating the signs and symptoms of RA as summarized in Table 4. The individual components of the ACR measures were statistically superior following the administration of the recommended adalimumab dose of 40 mg eow across all four studies compared to placebo.

Table 4 Response Rates of ACR Core Set Components and Additional QoL Measurements for the Controlled Studies (Mean Changes ± SD)

Variable	DE009		DE011		DE019		DE031	
	40 mg eow	Placebo						
Swollen Joint Count	-10 ± 10***	-3 ± 10	-9 ± 11***	-2 ± 10	-10***	-6 ± 11	-10 ± 11***	-6 ± 9
Tender Joint Count	-13 ± 18***	-5 ± 12	-14 ± 19***	-7 ± 17	-16 ± 12***	-10 ± 15	-14 ± 14***	-9 ± 13
HAQ	-0.6 ± 0.6***	-0.2 ± 0.5	-0.5 ± 0.5***	-0.1 ± 0.5	-0.6 ± 0.5***	-0.2 ± 0.5	-0.5 ± 0.6***	-0.3 ± 0.5
C-reactive protein	-16 ± 16***	0.9 ± 24	-21 ± 38***	-4 ± 39	-10 ± 29***	-2 ± 19	-5 ± 18**	-2 ± 17
Physician Assessment of Disease Activity	-30 ± 25***	-5 ± 24	-27 ± 29***	-11 ± 25	-37 ± 21***	-21 ± 25	-32 ± 24***	-18 ± 24
Patient Assessment of Disease Activity	-29 ± 32***	-8 ± 24	-28 ± 31***	-11 ± 28	-27 ± 27***	-11 ± 28	-24 ± 27***	-9 ± 28
Patient Assessment of Pain	-23 ± 33***	-7 ± 22	-28 ± 31***	-11 ± 27	-28 ± 26***	-13 ± 26	-23 ± 29***	-9 ± 29
SF-36 PCS	9 ± 11***	2 ± 9	8 ± 10***	2 ± 6	9 ± 10***	3 ± 9	8 ± 9***	4 ± 9
SF-36 MCS	5 ± 10	4 ± 12	6 ± 12***	-0.0 ± 11	4 ± 10*	2 ± 10	4 ± 11*	2 ± 9
SF-36 - Bodily Pain	24 ± 26***	8 ± 22	24 ± 23***	10 ± 18	23 ± 20***	8 ± 20	20 ± 23***	11 ± 20
SF-36 - Vitality	18 ± 27***	6 ± 24	18 ± 20***	3 ± 21	17 ± 21***	9 ± 21	16 ± 22***	8 ± 20
FACIT-F	8 ± 11**	3 ± 10	NA	NA	8 ± 10***	5 ± 9	7 ± 10***	3 ± 9

Data are from Full Analysis Set at 24-Week/26-Week Endpoint, LOCF.

For ACR measures - Comparison vs. placebo (Pearson's chi-square test): *p≤0.05, **p≤0.01, ***p≤0.001.

For all others - Comparison vs. placebo (ANCOVA [treatment group and baseline]): *p≤0.05, **p≤0.01, ***p≤0.001.

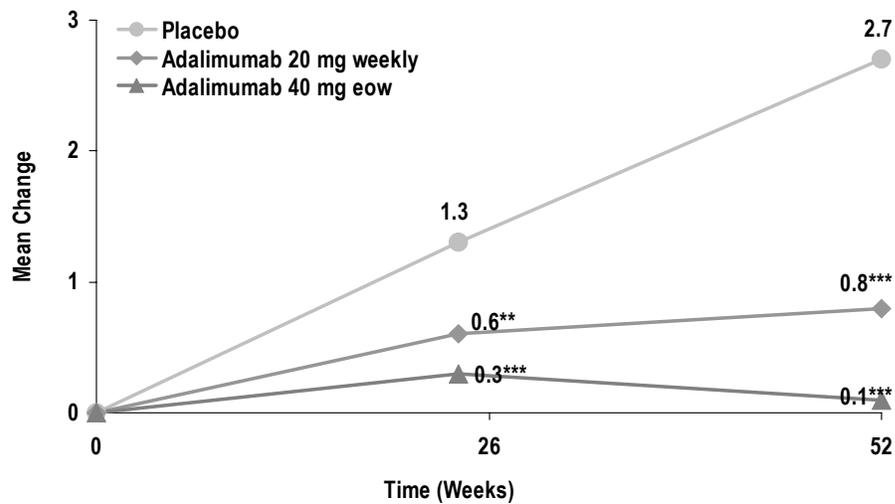
QoL = Quality of Life HAQ = Health Assessment Questionnaire PCS = Physical Component Summary Score MCS = Mental Component Summary Score

FACIT = Functional Assessment of Chronic Illness Therapy

Note: The adalimumab PI presents median analyses.

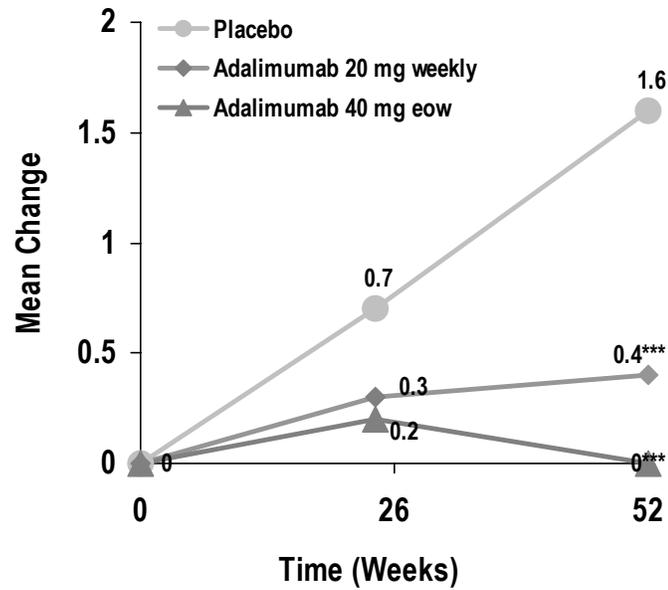
4.4 Inhibition of the Progression of Structural Damage

Adalimumab was associated with a statistically significant inhibition of the progression of joint destruction based on the Total Sharp Score at 24 and 52 weeks compared to placebo (Figure 2). Additionally as demonstrated in Figure 3, the mean change of joint erosion scores at 52 weeks was statistically significantly lower in the patients receiving adalimumab compared to those receiving placebo. Joint space narrowing was likewise significantly less in the 40 mg eow adalimumab group compared to the placebo group. Given the fact that RA is a life long disease, this reduction in the rate of joint destruction is expected to slow or prevent the onset of deformities and disability that are hallmarks of RA.¹



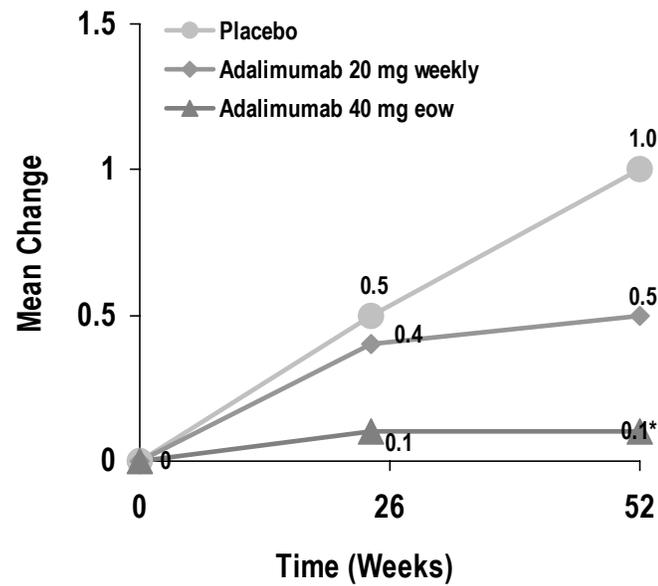
**p ≤ 0.01 vs. placebo
***p ≤ 0.001 vs. placebo
Observed data

Figure 2 Study DE019 Modified Total Sharp Score Changes



* $p \leq 0.05$ vs. placebo; ** $p \leq 0.01$ vs. placebo; *** $p \leq 0.001$ vs. placebo
LOCF

Figure 3a Study DE019 Joint Erosions Changes



* $p \leq 0.05$ vs. placebo; ** $p \leq 0.01$ vs. placebo; *** $p \leq 0.001$ vs. placebo
LOCF

Figure 3b Study DE019 Joint Space Narrowing Changes

4.5 Efficacy Conclusions

Adalimumab consistently demonstrated a robust response across the efficacy measures tested in each of the adequate and well-controlled studies. Specific efficacy conclusions are:

- Adalimumab is effective in reducing signs and symptoms, improving the quality of life, and inhibiting the progression of structural damage in adult patients with moderately to severely active RA.
- Adalimumab is effective in rapidly inducing an ACR20 response (within 1 to 2 weeks) and this response is maintained with continued use.
- Adalimumab is effective given alone or in combination with MTX or other DMARDs.
- The recommended dose of adalimumab for adult patients with RA is 40 mg given eow subcutaneously. Some patients not using concomitant MTX may derive additional benefit from increasing the dose to 40 mg weekly.

5.0 Safety

TNF is a central mediator of inflammation and immunity, and plays a crucial role in host defense. Inhibition of TNF clearly predisposes to certain infections, such as granulomatous infections like TB.³ Inhibition of TNF may also play a role in autoimmunity although the pathophysiologic mechanisms are uncertain.⁴

The role TNF plays in tumor development is unclear and the preclinical data are conflicting. Early literature supports the role of TNF in the body's defense against the formation of tumors.^{5,6} However, TNF-deficient mice are not predisposed to the development of spontaneous tumors.⁷ Additionally, TNF-deficient mice are resistant to skin carcinogenesis^{8,9,10} and TNF has been shown to induce proliferation of human lymphoma and leukemia cell lines *in vitro*.¹¹

Abbott Laboratories' large clinical database collected during the trials in RA patients allows for a robust analysis for potential safety signals. The information presented below will discuss data related to the following adverse events (AEs) associated with TNF-

antagonist use: infections, demyelinating disorders, autoimmunity, and malignancies including lymphomas.

5.1 Infections

Patients with RA are at an increased risk for infection compared to the age- and sex-matched general population. The underlying immune dysregulation of RA is one factor associated with this increase in infections. Other risk factors in RA patients include increased age, male sex, smoking, various comorbidities, disease activity, level of disability and use of corticosteroids¹² or other immunosuppressive agents.¹³ Overall, a 50% or higher increase in the frequency of infections has been noted in RA patients with the greatest risk being associated with bone, joint, skin, soft tissues and respiratory tract infections.¹⁴

During all adalimumab clinical trials, most patients had moderately to severely active RA and had received or were receiving immunosuppressive therapy including corticosteroids. Thus, these patients had multiple contributing factors putting them at increased risk for infections.

During the pivotal trials (DE009, DE011, DE019 and DE031), the rate of all infections was 1.0/pt-year and 0.9/pt-year for adalimumab- and placebo-treated patients, respectively. The overall rate of infections for adalimumab-treated patients in all trials was 1.5/pt-yr (as of 31-Aug-2001).

During the pivotal trials, the rate of serious infections (requiring hospitalization or iv antibiotics) was 0.04/pt-year and 0.02/pt-year for adalimumab- and placebo-treated patients, respectively. The overall rate of serious infections for adalimumab-treated patients in all trials was 0.04/pt-year (as of 31-Aug-2002). These rates are similar to the rates reported in the literature of 0.03-0.10/pt-year^{13,14} for traditional DMARDs or 0.05/pt-year for TNF-antagonists.¹⁵

The most common sites for serious infection in the adalimumab program were the respiratory system, skin/soft tissue, urinary tract and bone, which are similar to those

reported in the literature for patients with RA. No dose-response was observed with the possible exception of TB.

Information regarding infections is in the adalimumab PI (**Warnings and Adverse Reactions**).

5.1.1 Tuberculosis

TNF is involved in the innate immune response to intracellular bacteria such as *Mycobacterium tuberculosis*.¹⁶ Preclinical studies have demonstrated increased susceptibility to development of primary TB in TNF- or lymphotoxin- α -deficient mice,^{17,18} TNF receptor-deficient mice,¹⁹ mice with adenoviral or transgenic expression of soluble TNF-receptor Fc constructs,^{20,21} and animals treated with anti-TNF antibodies¹⁶ or other TNF-antagonists such as pentoxifylline.²² In addition, neutralization of TNF also results in reactivation of TB in a model of latent TB.²³

In addition, cases of TB have been reported in patients treated with TNF-antagonists.^{24,25} A quantitative assessment of risk due to TNF-antagonist use is not available as the cases to date have been reported through passive surveillance. The risk for TB in RA patients is associated with multiple other factors including age, country of origin or current residence, exposure history to persons with TB, concomitant therapy with other immunomodulators including corticosteroids, and disease activity.

Thirteen cases of TB have been reported during the clinical development program for adalimumab (up to 31-Aug-2002). During the Phase I-II development program when supra-therapeutic doses of adalimumab were examined and before screening was instituted, eight cases of TB were seen. During Phase III studies, the currently recommended doses were used and screening with prophylaxis was instituted. One case of TB was seen on adalimumab demonstrating a reduction in risk. In long-term follow-up, four additional cases of TB have been observed. Two of these cases had evidence of latent TB upon enrollment, reactivation of which may have been prevented under current screening and prophylaxis recommendations.

TB cases typically occurred after 3-8 months of therapy, and many were extrapulmonary in nature. All patients responded to standard anti-tuberculous therapy and no deaths associated with TB were reported. The eight cases that occurred early in the adalimumab clinical development program were from Europe including regions with a known high prevalence of latent TB in the age group being studied in the adalimumab clinical trials (mean age = 55 years).

Information regarding TB is in the adalimumab PI (**Warnings, Precautions, and Adverse Reactions**).

5.2 CNS Demyelinating Disorders

CNS demyelinating disorders have been seen with patients treated with TNF-antagonists although a causal relationship has not been conclusively established.^{26,27,28} During the adalimumab clinical development program two cases of a demyelinating disorder, one case of optic neuritis and one case of exacerbation of pre-existing multiple sclerosis were seen. The label for adalimumab presently warns the treating physicians about this possible relationship.

Information regarding demyelinating disorders is in the adalimumab PI (**Warnings – Neurologic Events**).

5.3 Autoimmunity

TNF-antagonists have been associated with an increase in the percentage of RA patients with positive serologies (ANA and anti-ds-DNA) and lupus-like syndromes.²⁹ In the adalimumab controlled trials, 12% of patients treated with adalimumab and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. One patient on adalimumab developed a lupus-like syndrome as of 31-Aug-2002, which resolved upon discontinuation of therapy. This patient developed neither nephritis nor CNS inflammation.

Information regarding autoimmunity is in the adalimumab PI (**Precautions – Autoimmunity and Adverse Reactions - Autoantibodies**).

5.4 Malignancy

5.4.1 Introduction

RA patients have a chronically dysregulated immune system, and this defect may lead to an increased risk for cancers particularly of the lymphoproliferative type. The overall incidence of cancers in the RA population has not been shown to be consistently increased.^{30,31,32} However, several epidemiology studies have demonstrated that the risk of lymphoproliferative cancers is increased several-fold over the general population (Table 5), with the upper boundary of the relative risk as high as 26-fold for patients with severe RA.³⁰⁻³⁵

Factors that may contribute to this increased risk of lymphoproliferative malignancies include use of immunosuppressive drugs (e.g., MTX, azathioprine and corticosteroids), infection with Epstein-Barr virus (EB virus), disease activity, widespread joint involvement, advanced age, poor functional class, and duration of RA.³⁰⁻³⁵

The range of odds ratios seen in Table 5 may reflect differences between RA populations studied with respect to these factors. At this time, it is not possible to determine which of these factors is pre-eminent as they are not independent (e.g., use of immunosuppressive drugs is a covariate with disease activity).

Cancer incidence was evaluated in a population of patients receiving adalimumab for treatment of RA. Standardized incidence ratios (SIRs) were calculated to compare the cancer incidence in the RA patients with the cancer incidence rates of men and women in the general US population.

Table 5 Risk of Lymphoma in RA Patients As Reported in the Literature

Study	Country	Number of RA Patients	Years of follow-up	SIR for Cancer	SIR for Lymphomas
Gridley 1993 ³¹	Sweden	11,683	20	1.0	2.4
Mellenkjaer 1996 ³²	Denmark	20,699	14	1.1	2.4
Isomaki 1978 ³⁰	Finland	46,101	7	1.1	2.7
Wolfe* 1994 ³³	US and Canada	3501	35	0.3	8.0
Matteson** 1991 ³⁵	Canada	530	7	1.5	8.0
Baecklund 1998 ³⁴	Sweden	11,683	18	--	1 (low disease activity) 5.4 (medium disease activity) 25.8 (high disease activity)

* lymphomas and leukemias, ** DMARD registry data

5.4.2 Methods for Standardized Incidence Ratio

Patient demographics, treatment assignments, and AEs collected on all patients enrolled in trials of adalimumab were evaluated. Malignancies were grouped together under major headings used by the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) registry.³⁶ The SEER Program currently collects and publishes cancer incidence data including patient demographics, primary tumor site, morphology, stage at diagnosis, first course of treatment, and follow-up for vital status. Information on over 3.5 million invasive cancer cases is included in the SEER database. Cancers were excluded from the SIR analysis if they were classified as *in situ* or metastases from cancers at other sites. Metastases are not included in the cancer incidence rates calculated by SEER, and *in situ* tumors are more likely to be diagnosed in a carefully followed clinical trial population than in the general population. Thus inclusion of metastases and *in situ* cancers observed in RA patients in the SIR analysis would lead to an overestimate of cancer risk in the RA patients in the adalimumab trials. The adalimumab trials included in this analysis began in April 1997 and the cut-off date for this analysis was August 31, 2002; any patient that received a dose of adalimumab was used for the calculation. Only the first cancer was included in the SIR analysis.

Five-year age, sex and race-specific incidence rates (from years 1992-99) for men and women were obtained from SEER for all cancers (except non-melanoma skin cancers for which normative data in SEER do not exist). These age-, race and sex-adjusted rates were

used to calculate the expected incidence of each specific type of cancer. The SIR was calculated as the ratio of the observed number of cancers to the expected number of cancers for each cancer site. Confidence intervals (95%) for the SIRs were calculated using Byar's approximation to exact confidence limits.³⁷ SIRs were calculated for the most commonly occurring cancers in the US population, as well as for any site (organ) at which more than one cancer was observed among RA patients taking adalimumab.

5.4.3 Results

The 2,468 RA patients used in this cancer incidence analysis were enrolled in the 17 completed and 3 ongoing clinical trials in RA in the United States (50%), Canada (13%), Europe (34%), and Australia (3%). Of the patients included in this analysis, 77% were female (N=1892) and 94% were white (N=2316). The mean age at entry into the adalimumab trials was 55 years old (range 19 to 87 years). The mean length of follow-up for cancer incidence was 2 years with a range of 11 days to 5.4 years.

A total of 46 cancers (excluding non-melanoma skin cancers, *in situ* cancers, and metastases for the reasons noted above) were analyzed (see Table 6). The only case of multiple cancers (a patient with bilateral breast cancer) was analyzed as one cancer. In addition, two cases of cancer shown in the adalimumab PI are not included in this analysis (studies remain blinded and exposure is unknown).

For all cancer types combined (excluding non-melanoma skin cancer), there was no evidence of an excess of diagnosed cancers (45.8 expected cancers; SIR=1.01, 95% CI=0.7-1.3). The SIRs for all cancers besides lymphoma were not significantly greater than 1.0. The cancers expected to occur most frequently based on general population rates, breast cancer and lung cancer, had SIRs of 0.6 (95% CI=0.3-1.3) and 0.2 (95% CI=0.0-0.8), respectively.

Table 6 Results from Cancer Incidence Analysis With Follow-up Through August 2002

Cancer type	Observed	Expected*	SIR	95% CI
All Sites	46	45.54	1.01	(0.7 - 1.3)
All Lymphomas	10	1.81	5.52	(2.6 - 10.0)
Breast	7	11.00	0.64	(0.3 - 1.3)
Colon	5	4.76	1.05	(0.3 - 2.4)
Lung	1	6.63	0.15	(0.0 - 0.8)
Melanoma	3	1.45	2.07	(0.4 - 6.0)
Prostate	5	4.49	1.11	(0.4 - 2.6)
Uterine	4	2.25	1.78	(0.5 - 4.6)
Other Sites	11	13.14	0.84	(0.4 - 1.5)

* Cancer rates used were 1992-1999 SEER Rates

The adalimumab clinical trials enrolled patients with moderately to severely active RA, with a long duration of disease and who had previously failed DMARD therapy (see Table 2 and Table 3). This closely resembles the population with medium to high disease activity (SIR of 5.4 to 25.8) reported in the publication of Baecklund et al.³⁴ The SIR for lymphomas in the RA patients taking adalimumab (SIR=5.5, 95% CI=2.6-10.1) was thus comparable to what might be expected from RA patients with moderately to severely active RA (see Table 5).³⁰⁻³⁵

The histology of the lymphomas and the clinical characteristics of the patients are reported in Table 7 below. The histologic subtypes of lymphomas observed in patients that received adalimumab treatment was consistent with that observed in prior RA patients³⁸ and RA patients treated with TNF-antagonists.³⁹ There was no predilection for

any unexpected type of lymphoma. One of the non-Hodgkin's lymphomas (NHL) was a MALT lymphoma, a type of lymphoma known to be strongly associated with autoimmune disorders. As shown, patients had multiple risk factors for the development of lymphoma (long-standing disease, high disease activity, previous and/or concomitant immunosuppressive therapy, and older age).

Table 7 Histology of Lymphomas Seen During the Clinical Trials for Adalimumab

Histology	Sex	Age	Duration of RA (years)	No. Days on Adalimumab Therapy	Prior/Concomitant MTX	No. of Previous DMARDs	Baseline SJC	Baseline TJC	Baseline HAQ
Mantle Cell type B cell	M	58	13.2	1265	Yes/Yes	5	13	46	0.3
High Grade Large B Cell	F	56	4.3	769	Yes/No	3	15	6	0.2
MALT Lymphoma of parotid (possible Sjögren's Syndrome) B Cell	F	39	6.6	716	Yes/No	4	31	42	1.9
Follicular B cell with sclerosis	F	71	29.9	467	Yes/Yes	2	29	34	1.6
Diffuse Large B cell	F	75	2.8	265	No/No	1	17	16	0.4
Mixed Large and Small B cell	F	62	7.3	147	Yes/Yes	2	18	50	1.4
Low-intermediate grade T-cell	M	64	2.9	57	Yes/Yes	1	32	24	0.1
Mixed small and large cell B cell lymphoma	F	68	20.8	796	Yes/Yes	4	9	17	1.3
Large B cell	M	59	17.0	675	Yes/Yes	1	29	25	1.4
Mixed cellularity Hodgkin's	M	75	19.9	612	Yes/Yes	3	50	54	0.5

EB Virus status undetermined in all cases.

SJC = swollen joint count TJC = tender joint count HAQ = Health Assessment Questionnaire

Therefore at this point in time, there is no clear, pervasive evidence of an added increase in lymphoma risk due to adalimumab therapy. Further data collection is ongoing (see section 6.0).

Information regarding lymphoma is included in the adalimumab PI (**Warnings and Adverse Reactions - Malignancies**).

5.5 Safety Conclusions

The safety of adalimumab has been assessed in 17 completed and 3 ongoing clinical trials in RA. The clinical safety database includes 2468 patients with 4870 years of exposure. The most serious adverse effects observed with adalimumab such as serious infections, TB, demyelinating disorders and autoimmunity have been seen with TNF-antagonists and are possibly related to TNF biology. RA patients have been shown to have an increased risk of lymphomas. At this point in time, there is no clear, pervasive evidence of an added increase in lymphoma risk due to adalimumab therapy. Guidance regarding these risks is included in the adalimumab PI and the Patient PI.

Specific safety conclusions are:

- Adalimumab treatment is associated with an incidence of serious infections comparable to the RA population in general.
- TNF-antagonists, including adalimumab, are associated with an increased risk of TB that is related to the role of TNF in innate immunity. Screening is an effective means to reduce the incidence of this serious adverse effect.
- Rare cases of autoimmunity and CNS demyelination have been observed with TNF-antagonists, including adalimumab, and are possibly related to TNF biology.
- The overall incidence and types of malignancies observed in the adalimumab clinical development program were similar to those observed in the general population.
- The risk of lymphoma in the overall clinical development program was commensurate with the increased risk expected in our RA patient population, but increased relative to the general population.

6.0 Post-Marketing Assessments

6.1 Introduction

The safety database that supported the approval of adalimumab was based primarily on adequate and well-controlled clinical trials and open-label extensions of these trials in adult patients with moderately to severely active RA who had failed one or more prior DMARDs. Despite the fact that the safety database collected from these studies under controlled and well structured conditions is large, ongoing safety vigilance is nonetheless warranted. Abbott Laboratories is committed to the ongoing collection and analysis of safety data to more fully understand the safety profile of adalimumab. The methods for collecting and analyzing these data will include:

- 1) the continued conduct of monitored open-label extensions of randomized clinical trials,
- 2) the conduct of new controlled clinical trials in RA and for other indications,
- 3) the conduct of large simple trials in RA, and
- 4) post-marketing surveillance of spontaneously reported AEs.

Each of these methods is described below.

6.2 Conduct of Monitored Open-Label Extensions of Studies in the BLA

As part of its post-marketing commitments, Abbott Laboratories will extend the three ongoing studies currently in their open-label follow-up period, so that patients will have been monitored for 5 years of exposure to adalimumab. Approximately 1700 patients are currently included in this cohort. Events of particular interest include: deaths, serious infections, malignancies, and autoimmune disease. Because these studies are monitored, precise determination of the event rates can be determined (i.e., case capture is complete and the exposed population is well-defined).

6.3 Conduct of Controlled Clinical Trials in RA and New Indications

Currently, adalimumab is licensed for adult patients with moderately to severely active RA who have failed one or more prior DMARDs. Studies are currently under way or planned to support registration for adult RA in other countries. In addition, controlled trials in patients with juvenile RA, early RA, Crohn's disease, psoriatic arthritis, psoriasis and ankylosing spondylitis are either enrolling patients, under way, or scheduled to start. These controlled trials will address any disease-specific safety issues.

6.4 Conduct of Large Simple Trials in RA

To collect additional safety data in a population that is broader than that from the initial clinical development program, a large simple trial is currently enrolling RA patients in a number of countries. It is anticipated that a cohort of these patients will be continued in a registry designed to facilitate reporting of safety data even after adalimumab is licensed for sale in their respective countries. The target enrollment is approximately 5000 patients with the majority of patients to be followed long-term in a subsequent registry.

6.5 Post-Marketing Surveillance of Spontaneously Reported Adverse Events

Abbott Laboratories is committed to the timely collection, analysis and reporting of spontaneously reported AE data through its international pharmacovigilance systems. Because adalimumab has only been commercially available for a short time, there is limited data from that system at present. Nonetheless, since the FDA approval of adalimumab, there have been no post-marketing reports received that differ qualitatively from the AE profile observed during clinical trials. Thus, the limited number of spontaneous post-marketed reports received to date suggests no new safety issues.

6.6 Rationale for the Ongoing Collection of Safety Data

Despite the development of a large safety database during the clinical development program, collection of additional safety data during the post-marketing period is important for many reasons. Adalimumab may be used in patient populations different than those studied in the clinical development program. Different schedules of follow-up,

different concomitant medications, and different means of treating AEs may occur outside of clinical trials. Rare events may not have been detected and for those that have, additional experience will provide better incidence data and, perhaps, avenues for prevention.

With respect to the development of malignancies and, in particular, malignant lymphomas, this ongoing surveillance effort will be especially important. The monitored studies will provide the most complete data compared to spontaneous reporting methods. Specifically, these studies will provide reliable numerators and denominators for the calculation of incidence rates. Furthermore, the close relationship Abbott Laboratories has with the reporting sites will facilitate the request for follow-up data, such as tumor histology, staging, risk factors, and treatment outcome that can be difficult to obtain with spontaneous reports. In addition, the long follow-up periods will help detect if there is any relationship between exposure time and cancer rates. The facilitated and spontaneous reporting mechanisms, while subject to well-known limitations, offer additional value. For example, these methods will detect qualitative shifts in AEs (e.g., changes in the histologic types of cancer seen) and changes in incidence patterns in populations different from those in the clinical trials. Taken together, these efforts will refine the knowledge of risks associated with adalimumab over time.

7.0 Conclusions and Overall Assessment

7.1 Efficacy Conclusions

- Adalimumab is effective in reducing signs and symptoms, improving the quality of life, and inhibiting the progression of structural damage in adult patients with moderately to severely active RA.
- Adalimumab is effective in rapidly inducing an ACR20 response (within 1 to 2 weeks) and this response is maintained with continued use.
- Adalimumab is effective given alone or in combination with MTX or other DMARDs.

- The recommended dose of adalimumab for adult patients with RA is 40 mg given eow subcutaneously. Some patients not using concomitant MTX may derive additional benefit from increasing the dose to 40 mg weekly.

7.2 Safety Conclusions

- Adalimumab treatment is associated with an incidence of serious infections comparable to the RA population in general.
- TNF-antagonists, including adalimumab, are associated with an increased risk of TB that is related to the role of TNF in innate immunity. Screening is an effective means to reduce the incidence of this serious adverse effect.
- Rare cases of autoimmunity and CNS demyelination have been observed with TNF-antagonists, including adalimumab, and are possibly related to TNF biology.
- The overall incidence and types of malignancies observed in the adalimumab clinical development program were similar to those observed in the general population.
- The risk of lymphoma in the overall clinical development program was commensurate with the increased risk expected in our RA patient population, but increased relative to the general population.

7.3 Overall Assessment

Adalimumab is a human monoclonal antibody to TNF containing solely human sequences. Adalimumab therapy is effective for the treatment of patients with moderately to severely active RA. It has demonstrated its effectiveness in improving the signs and symptoms, inhibiting joint destruction and improving the health-related quality of life in treated patients.

The safety of adalimumab has been assessed in 17 completed and 3 ongoing clinical trials encompassing 2468 patients with 4870 years of exposure. Serious AEs associated with TNF-antagonists, such as infections, TB, demyelinating disorders, and autoimmunity have been reported. The risk for overall malignancies is the same as for the general population. The risk for lymphomas is within the range reported for RA patients who are

known to have an increased risk of lymphomas. Guidance regarding these risks is included in the adalimumab PI and Patient PI. In order to assess these risks with increasing duration of treatment, Abbott Laboratories has made a long-term commitment to the continued assessment of safety over 5 years of adalimumab exposure.

Taken together these data support the finding of a strong benefit-risk ratio for the use of adalimumab in adult patients with moderately to severely active RA.

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