Arthritis Advisory Committee Meeting

Briefing Document for ENBREL® (etanercept)

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Amgen Inc.

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1. Introduction

Immunex Corporation, a wholly owned subsidiary of Amgen Inc., developed ENBREL® in partnership with Wyeth and certain predecessors of Wyeth. In this report, Immunex will be referred to as Amgen.

This Briefing Document is submitted to facilitate discussion regarding the safety of tumor necrosis factor (TNF) antagonist therapies and focuses attention on lymphoma. Given limitations in our current understanding of the natural history of rheumatoid arthritis (RA), the contributions of RA disease severity, prior and concurrent immunosuppressive therapies, and the interaction of these elements with TNF antagonist therapies, Amgen and Wyeth welcome the opportunity for review and commentary from the Arthritis Advisory Committee.

ENBREL® is a protein comprised of the extracellular domains of two human TNF receptors attached to a portion of a human IgG immunoglobulin (Mohler et al, 1993). ENBREL® acts primarily by binding and neutralizing both soluble and cell-bound TNF. The conformation and binding specificity of the human TNF receptor reflect evolutionary selection and may have distinct advantages over other TNF antagonists. ENBREL® contains an entirely human amino acid sequence and is therefore only rarely immunogenic. ENBREL® does not bind complement and is not associated with complement-mediated cell lysis. These product-specific attributes may be relevant to the ENBREL® safety profile.

In November 1998, ENBREL® was approved by the Food and Drug Administration (FDA) for reducing signs and symptoms of moderately to severely active rheumatoid arthritis (RA), as monotherapy or in combination with methotrexate, in patients who had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). The current label includes information describing the safety and efficacy in patients with RA treated over the course of 3 years. The indications for ENBREL® have since expanded to include polyarticular-course juvenile rheumatoid arthritis (JRA, May 1999); inhibition of structural damage in patients with moderately to severely active RA, including those who have not previously failed prior DMARD therapy (June 2000); and reduction of signs and symptoms in psoriatic arthritis either as monotherapy or in combination with methotrexate (January 2002). ENBREL® is the only TNF antagonist approved as an initial DMARD in RA, and is approved for application in children with JRA and in patients with psoriatic arthritis.

The safety information included in this document, unless otherwise noted, is from the worldwide ENBREL® safety database, including patients who have received ENBREL® in clinical trials since 1993 and 4 years of commercial experience with ENBREL® through November 2, 2002.

2. ENBREL® Experience

ENBREL® has been the subject of extensive investigation and safety evaluations since 1991, starting with cell culture toxicity studies, animal tolerability studies, through studies evaluating safety in normal human volunteers and patients with a variety of different medical conditions.

2.1 Clinical Trials in Patients with Rheumatic Diseases

The ENBREL® clinical trial database through 2002 includes 3389 patients who have received ENBREL® in Amgen- and Wyeth-sponsored rheumatic disease clinical trials for currently approved indications. In open-label extension studies, the efficacy and the safety profile associated with longer-term administration of ENBREL® (up to 6 years) remain stable over time. The following table reflects worldwide trial experience estimated through December 2002.

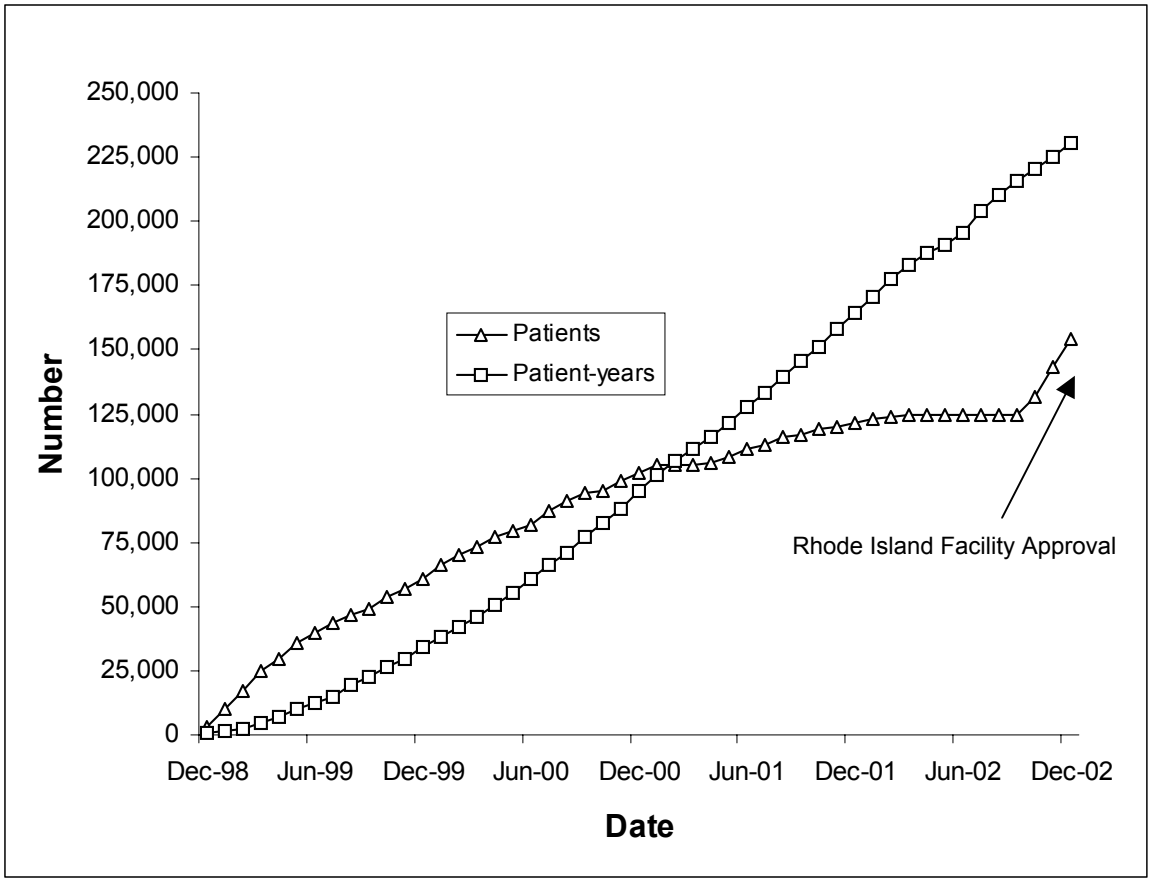
Table 2- 1. Clinical Trial Experience Worldwide

	Patients (n)	Patient-years
North America	2119	5444
Ex-North America	1270	2851
Total	3389	8295

2.2 Post-Marketing Commercial Experience

The post-marketing worldwide commercial experience with ENBREL® through December 2002 includes greater than 150,000 patients treated, representing over 230,000 patient-years of therapy, depicted in Figure 2-1 below. The numbers of patients treated have recently increased substantially with the approval of the new ENBREL® manufacturing facility in Rhode Island.

Figure 2-1. Patients and Patient-Years of ENBREL® Therapy Over Time



3. ENBREL® Pharmacovigilance Program

Establishing the safety profile for a new therapeutic requires analysis and interpretation of safety observations from multiple settings, including controlled clinical trials and longer-term extension studies, surveillance of post-marketing spontaneous (or facilitated) reports, observational registries, epidemiologic studies, and the medical literature.

Because ENBREL® was the first TNF antagonist approved for chronic therapy in patients with RA (1998), Amgen and Wyeth jointly established a comprehensive pharmacovigilance program at the time of approval to advance the following objectives:

- Understand the natural history of treated populations (RA, JRA, and psoriatic arthritis) in patients receiving conventional DMARDs compared to those receiving ENBREL®, and understand the impact of disease severity on health outcomes.

- Determine the relative risk and incidence of adverse events, as power considerations permit, by conducting prospective and retrospective population-based studies in large and diverse patient populations.
- Assess potential adverse events of long latency by performing studies with long-term follow-up.
- Assess potential risks to special patient subpopulations, including children, geriatric patients, and those with comorbidities.

3.1 Post-Marketing Safety Surveillance

The ENBREL® pharmacovigilance program includes evaluation and follow-up of reported adverse events and ongoing surveillance of safety information from the medical literature. Analyses are performed both at the individual case level as well as at the aggregate population level. Although retrospective, anecdotal, and frequently incomplete, post-marketing reports can provide insights into product impact in a broader patient population than clinical trials, including patients with multiple comorbidities and concomitant medications. Amgen believes that post-marketing safety surveillance provides an important window on the "real world" patient and prescriber experience with ENBREL® therapy, and has shared observations from this experience as part of proactive risk communication (Holman et al, 2002; Sabath et al, 2002a), including the post-marketing experience with lymphoma (Sabath et al, 2002b). These authors have also demonstrated that extensive communication with ENBREL® patients facilitates adverse event reporting and when communication increases, adverse event reporting increases in parallel (Sabath et al, 2002c). Amgen and Wyeth believe that facilitated reporting has supported improved collection of adverse events from clinical practice and more rapid characterization of the ENBREL® safety profile.

3.2 Ongoing Clinical Trials

In cooperation with the FDA and the European Agency for the Evaluation of Medicinal Products (EMEA), a significant number of prospective safety studies have been initiated that advance the pharmacovigilance objectives outlined above. Brief descriptions of these multiple safety studies are included in Appendix 1. These programs effectively monitor ENBREL® safety in special subpopulations, including RA patients receiving concomitant

methotrexate, sulfasalazine, hydroxychloroquine, or parenteral gold; RA patients with significant concurrent medical problems; elderly RA patients; and children with JRA and systemic onset JRA. In addition, Amgen and Wyeth have initiated multiple RA observational studies, including a 10,000-patient North American study (RADIUS) which provides additional perspective on clinical practice experience from both patients and physicians.

3.3 Registries

National observational RA registries evaluating the safety and effectiveness of ENBREL® are ongoing in the United Kingdom, Germany, and Sweden (Moreland et al, 2002).

3.4 Epidemiologic Studies

Amgen has initiated a retrospective epidemiologic study with Drs. Alexander Walker and Catherine Johannes of the UnitedHealth Group to assess the incidence of adverse events, including lymphoma, in patients from the general population as well as patients with RA, psoriatic arthritis, and ankylosing spondylitis. This ongoing study includes over 49,000 patients with rheumatic diseases out of more than 9.7 million patients in the general population. Medical records will be reviewed to validate observations, and analyses will be performed to determine if prior exposure to medications are associated with any of the predefined adverse events of interest.

4. FDA Arthritis Advisory Committee 2001: TNF Antagonists Safety Review and Recent Safety Update to the Label

Safety reports of serious infections, tuberculosis, neurological disorders, hematological events, and rashes in conjunction with autoantibodies (lupus-like conditions) have been incorporated into the prescribing information for all approved TNF antagonists. Details regarding these safety issues in patients treated with ENBREL® were presented to the FDA Arthritis Advisory Committee, August 17, 2001 (FDA, 2001). Since that time, ENBREL® pharmacovigilance has continued and the reporting rates for these types of events have been stable over time.

Subsequent to the 2001 meeting, a precaution was added to the product labeling based upon the results of two large clinical trials with ENBREL® in patients with congestive heart failure as well as rare post-marketing reports. The studies were stopped after an independent data monitoring committee indicated that they would be unlikely to demonstrate

benefit, even if carried to completion. One of the two trials revealed a trend toward worse heart failure outcomes in the ENBREL®-treated patients, while the other did not (Coletta et al, 2002). Meanwhile, the results from a controlled trial with another marketed TNF antagonist showed a significant dose-related increase in mortality (Coletta et al, 2002). Because of these observations, language regarding heart failure experience with ENBREL® was added to the prescribing information.

As the events leading to the 2001 FDA Arthritis Advisory Committee TNF Antagonists Safety Review have already been extensively reviewed, and Amgen was asked at this time to focus on the issue of lymphoma, the events outlined above will not be addressed further in this report.

5. TNF and Carcinogenesis

The role of TNF in carcinogenicity and tumor surveillance has not been completely established. Early cell culture studies indicated that TNF is cytotoxic for certain tumor cell lines (Old et al, 1985; Creasey et al, 1986; Palladino et al, 1987), but subsequent studies revealed that, for certain types of malignancies, TNF may act as a growth factor (Filella et al, 1996; Brach et al, 1992; Freedman et al, 1992; Moore et al, 1999; Warzocha et al, 1998; Naylor et al, 1993) and may even enhance the metastatic potential of certain tumors (Malik et al, 1990).

Over-production of TNF in B-cell chronic lymphocytic leukemia and hairy cell leukemia has been associated with more severe disease progression and decreased patient survival (Foa et al, 1990; Barak et al, 1999). Highly metastatic lymphoma cells have been shown to have even greater metastatic potential when co-administered with recombinant TNF (Orosz et al, 1993). These results suggest that therapeutic TNF antagonism could potentially be beneficial in patients with lymphoproliferative disorders.

Early studies evaluating the effect of ENBREL® on cultured cells revealed no increase in the frequency of gene injury or gene mutations that may be predictive of greater cancer risk. In addition, animal studies with ENBREL® have not revealed findings to suggest a higher than background risk for the development of malignancies. Please refer to BLA 98-0286.

6. Lymphoma in Rheumatoid Arthritis

There are multiple risk factors for the development of lymphoma. These include underlying disease, disease severity and medication exposures.

Appendix 2 summarizes epidemiologic studies of lymphoma incidence in various RA populations, compared to the incidence expected (observed/expected, or standardized incidence ratio, SIR). Although the observed RA SIRs vary, most studies reveal an increased incidence of lymphoma in RA. In a review of all published literature between 1966 and 1998 evaluating the incidence of cancer associated with RA therapies, Beauparlant et al (1999) conclude that the increased risk of lymphoma in patients with RA is generally recognized to be two to three times that observed in the general population.

Reports of juxta-articular lymphoma in patients with RA suggest a link between inflammation and transformation (Goodlad et al, 1999). Both Prior et al (1985) and Wolfe (1998) reported that the risk for development of lymphoma in RA increases with severity of disease. Baecklund et al (1998) performed a case control analysis indicating that lymphoma risk increases substantially with greater RA disease activity.

The contribution of DMARDs to the incidence of hematologic malignancies in RA patients remains controversial. Lymphomas (some reversible) have been described in patients receiving both methotrexate (Georgescu et al, 1997; Sibilia et al, 1998) and azathioprine (Larval et al, 1994), but Wolfe (1998) suggested that methotrexate therapy is not clearly associated with increased lymphoma risk. Cyclosporine has also been associated with lymphoma (Penn, 1987) and the Epstein-Barr virus has also been implicated in methotrexate-associated lymphomas (Kamel et al, 1993).

In conclusion, there are multiple factors that augment lymphoma risk including underlying disease, disease severity, and medication exposures. These risk factors are particularly pertinent to the patient population treated with ENBREL® and need to be considered when interpreting lymphoma incidence.

7. Lymphoma Observations from Pharmacovigilance

7.1 Clinical Trial Observations

Lymphoma reports from clinical trials with ENBREL® will be represented by the standardized incidence ratio (SIR, the ratio of observed to expected cases). All "expected" numbers were calculated using the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database (11 Registries, 1992-99) using age, gender, and race-specific rates to predict the number of cases within the cohort of patients in clinical trials. Note that these expected numbers represent expectations for the United States general population and do not account for potential variations in rates that may exist among patients in diverse geographical regions, nor do they account for the increased risk known to exist in the RA population as described in Section 6.0. The confidence intervals were calculated under the assumption of a Poisson distribution for the observed cases (Breslow et al, 1987). The following data represent worldwide Amgen and Wyeth rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriatic arthritis clinical studies performed with ENBREL®. The vast majority of the clinical experience is from rheumatoid arthritis clinical trials.

The only precise representation of lymphoma incidence can be determined in clinical trials as there is complete accounting for observed cases in the numerator, and total patient-year experience in the denominator is accurately available. The expected number of cases takes into consideration the age, gender, and race distribution of the treated population. In calculating the SIR, the numerator (observed cases) includes all cases observed during ENBREL® clinical trial experience (including 30 days after discontinuation of study drug) through December 31, 2002. The denominator (expected cases) is calculated from an estimation of the total experience in ENBREL® clinical trials to the end of December 2002 (representing 8295 patient-years of therapy, Table 7-1).

Table 7-1. SIR for Lymphoma Cases in ENBREL® Clinical Trials

Number of Cases	Expected*	SIR	95 % Confidence Intervals
6	2.59	2.31	0.85-5.03

*Expected in the US general population and does not account for increased risk in RA patients.

Three additional cases of lymphoma have been reported in patients previously exposed to ENBREL® in clinical trials, but the events occurred beyond 30 days after discontinuation of

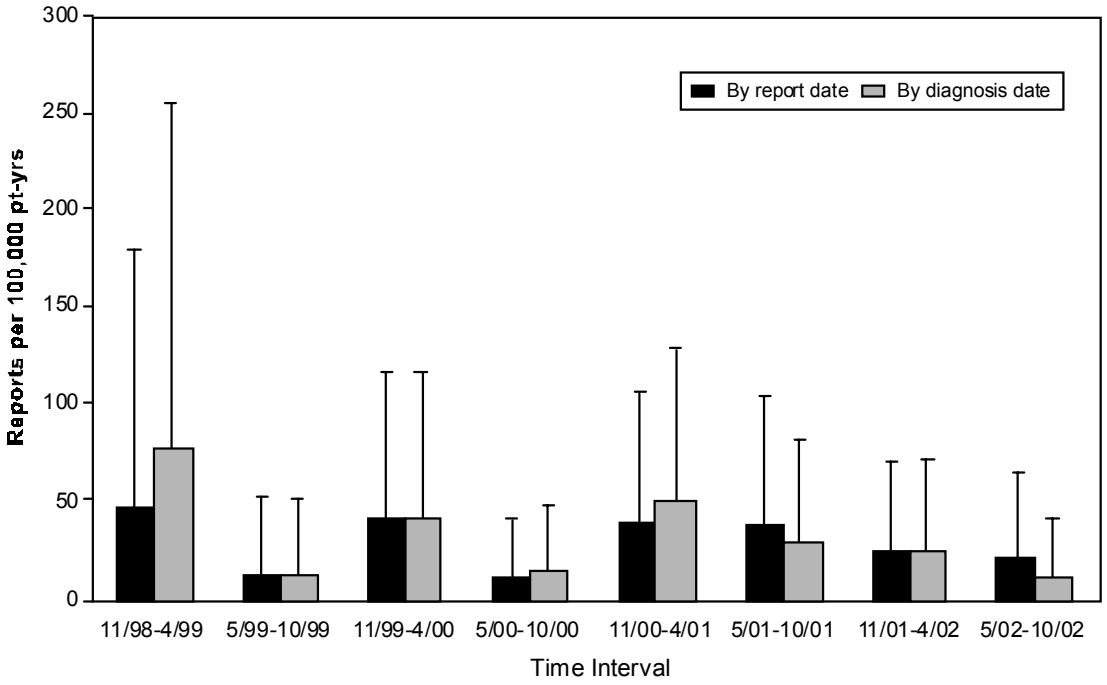
ENBREL®. As it is not possible to accurately estimate the additional time exposure represented by these events, one cannot perform an SIR analysis.

The calculations above demonstrate that the SIR for lymphoma (comparing patients in ENBREL® in clinical trials to the general U.S. population) is 2.31, which is comparable to the reported SIR of 2–3 in all rheumatoid arthritis patients relative to the general population (Beauparlant et al,1999).

7.2 Post-Marketing Safety Surveillance

Through November 2, 2002, after four years of worldwide commercial experience, over 150,000 patients have received over 230,000 patient-years of ENBREL® therapy, and the observed worldwide lymphoma reporting rate is 0.3 per 1000 patient-years of therapy. Some of these cases were described in a recent publication (Brown et al, 2002). Analysis of the reporting rate (reports per patient year of therapy) at each six-month interval since ENBREL® approval indicates that the reporting rate is stable over time, with no increase over the course of four years (Figure 7-1).

Figure 7-1. Lymphoma Reporting Rates by Time Interval for U.S. Post-Marketing Experience



All reported cases of lymphoma from 11/98 to 10/02. Error bars represent the upper limit of exact 95% Confidence Intervals.

Many of the previously described risk factors for lymphoma have been noted in ENBREL® patients. The majority of patients who have reported lymphoma have confounding risk factors including severe RA, Sjögren's syndrome, and medication exposures such as methotrexate, azathioprine and cyclosporine.

7.3 Lymphoma Histopathologic Subtypes Compared to RA and Non-RA Controls

Analysis of the distribution of Hodgkin's disease and non-Hodgkin's lymphoma (NHL) from both ENBREL® clinical trials and post-marketing reports reveals that 86% of cases were NHL and 14% were Hodgkin's disease, a proportion similar to that observed in the SEER database.

Further characterization of all non-Hodgkin's lymphomas reports (Table 7-2) reveals that the distribution of histopathologic subtypes is consistent with that previously reported in the general population and in the RA population (Kamel et al, 1999). This contrasts with the

increased proportion of large B-Cell lymphomas and large T-cell lymphomas associated with immunosuppression after transplantation (Oertel et al, 2002).

Table 7-2. Distribution of Histologic Subtypes of Non-Hodgkin's Lymphoma: Comparison of Reports in Patients Receiving ENBREL® with RA and Non-RA Controls

	Lymphoma Cases From:		
REAL Classification*	Patients Receiving ENBREL®** (%)	RA Controls*** (%)	Non-RA Controls*** (%)
Diffuse large B-cell	43%	38%	43%
Mantle	5%	0%	2%
Peripheral T-cell	8%	2%	4%
Follicular	16%	33%	27%
Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia	22%	14%	12%
Waldenstrom's Macroglobulinemia	5%	NA	NA
Marginal zone	0%	7%	0%
Mycosis fungoides	0%	2%	10%
Other	NA	2%	2%

* REAL = Revised European-American Lymphoma Classification
**Reports through November 2, 2002
**Kamel, et al. J Rheum 1999; 26:1676-80

8. Communication and Education

Rheumatic diseases are common and frequently severe, and can be associated with unacceptable discomfort, progressive disability, and increased mortality. It is widely recognized that ENBREL® has been a substantial contribution to the lives of many patients with rheumatic disorders.

Clinical trial experience for over nine years and practice experience for over four years have consistently demonstrated that, in the great majority of patients treated, ENBREL® acts rapidly and is remarkably effective in reducing clinical signs and symptoms of inflammatory arthritis, even in patients with long-standing disease who have had inadequate responses to methotrexate and other DMARDs (Moreland 1997; Moreland 1999; Weinblatt 1999). ENBREL® frequently permits durable reduction or discontinuation of corticosteroids

(Moreland et al, 2001) and methotrexate (Kremer et al, 2002) and thus may permit avoidance of adverse effects associated with other medications. It is widely recognized that ENBREL®, with its unique mechanism of action, provides substantial benefit to the lives of many patients with rheumatic disorders.

Since approval, there have been reports of adverse events, some serious, in patients who have received ENBREL® therapy. Amgen established a comprehensive pharmacovigilance program to investigate the background rates for many of these events and to further characterize the clinical experience with ENBREL®. The pharmacovigilance program is strengthened by the ENLIVEN program which allows direct communication with over 70,000 patients on an ongoing basis. Comprehensive education and communication efforts are summarized in Table 8-1.

Table 8-1. Summary of ENBREL® Safety Education and Communication Initiatives

- Multiple product label revisions
- Corresponding changes in patient package inserts
- Letters to Health Care Professionals: May 1999, October 2000
- Ongoing ENLIVEN program for patient education and outreach; this periodic newsletter contains safety information
- 1-888-4ENBREL telephone access for product information
- Collaboration with the American College of Rheumatology for “Hotline” announcements
- Collaboration with investigators preparing publications concerning safety issues
- Safety abstracts submitted to national meetings
- RADIUS RA observational study: opportunity for rheumatologists to share observations and analyze practice data with colleagues and investigators

9. Summary and Conclusions

After more than nine years of ENBREL® clinical trial experience and more than four years of commercial experience, with proactive pharmacovigilance of adverse events reports including lymphomas, the numbers and types of lymphomas remain within the range that would be expected for the population considered for ENBREL® treatment. Though a causal

relationship between ENBREL® therapy and lymphoma has not been established, Amgen and Wyeth remain committed to ongoing pharmacovigilance.

To summarize:

- The reporting rates of lymphoma from ENBREL® post-marketing safety surveillance and the SIRs observed in ENBREL® clinical trials are consistent with the background rates expected in rheumatoid arthritis patients.
- The distribution of lymphoma histologic subtypes from reports in the ENBREL® database is consistent with that previously reported in the general population and the RA population.
- Greater disease severity, which confers greater lymphoma risk, may be present in patients receiving biologic therapies.
- Patients receiving biologic therapies may have greater exposure to prior DMARD therapies, which may independently confer greater risk of developing lymphoma.
- The ENBREL® benefit/risk ratio remains strongly favorable.

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APPENDIX 1

Appendix 1. Post-Approval Studies with ENBREL®

Protocol #	Title	Status	No. of Patients	Duration of Study	Comments
016.0018†	Open-label extension treatment for DMARD-refractory RA patients in previous trials (various)	Enrolled	639	≥ 5 years	Includes patients from initial licensing studies who have received ENBREL® continuously for up to 6 years with serial safety and efficacy observations.
016.0023†	Open-label extension treatment for early RA patients (from Protocol 016.0012)	Enrolled	469	≥ 5 years	Patients in this study have received ENBREL® for up to 5 years with serial safety and efficacy observations.
016.0026†	Registry of ENBREL® for patients with JRA	Enrolling	600*	3 years	Safety, including effects on growth and development parameters, among those who receive ENBREL® will be compared to a similar cohort of patients with polyarticular course or systemic JRA who are receiving methotrexate.
016.0029†	Double-blind, randomized, placebo-controlled study of ENBREL® in RA patients with comorbid disorders	Enrolling	1,000*	16 weeks	Patients must have at least 1 documented comorbidity, including diabetes mellitus (at least 200 pts), pulmonary disease (e.g. asthma or COPD), pneumonia within previous year, history of recurrent bronchitis, sinusitis, or UTI. Study monitored by a data safety monitoring board.
016.0031†	Safety and efficacy study of ENBREL® in children with systemic onset JRA	Enrolling	75*	≤ 13 months	Safety of ENBREL® in pediatric patients with systemic onset JRA. Patients may be eligible for registry (016.0026).
016.0034	RA DMARD intervention and utilization study (RADIUS 1)	Enrolled	5,000*	≥ 5 years	Prospective, observational; RADIUS 1 is designed to systematically collect and document use patterns, effectiveness, and safety of DMARD treatments currently used in the management of RA.

† post-approval commitment with the FDA

* enrollment goal

Appendix 1. Post-Approval Studies with ENBREL® (Continued)

Protocol #	Title	Status	No. of Patients	Duration of Study	Comments
016.0035	RA DMARD intervention and utilization study (RADIUS 2)	Enrolling	5,000*	≥ 5 years	Prospective, observational; RADIUS 2 is designed to systematically collect and document use patterns, effectiveness, and safety profile of ENBREL® in the management of RA in clinical practice. Will compare experience with ENBREL® use in Radius 2 to experience with other DMARDs in RADIUS 1.
016.0620†	Three month open label safety trial of ENBREL® plus hydroxychloroquine, sulfasalazine, or injectable gold in patients with RA	Enrolled	120*	3 months	Prospective study to evaluate the safety of ENBREL® in combination with other DMARDs.
0881A1–301-EU‡	Open-label safety study of etanercept in patients with rheumatoid arthritis	Enrolled	549	Up to 4 years	Includes patients from initial European double-blind studies.
EU registry‡	European RA patient registry	Enrolling	2000*		Prospectively collects both safety and efficacy information with registries conducted in the United Kingdom, Sweden, and the Netherlands

† post-approval commitment with the FDA

‡ post-approval commitment with the EMEA

* enrollment goal

Appendix 1. Post-Approval Studies with ENBREL® (Continued)

Protocol #	Title	Status	No. of Patients	Duration of Study	Comments
0881A1-308-EU‡	A double-blind study evaluating the efficacy and safety of the combination of etanercept and methotrexate in comparison to etanercept and methotrexate alone in rheumatoid arthritis	Enrolled	686	12 months with double-blind extension	This study will compare the combination of ENBREL® and methotrexate to ENBREL® alone and methotrexate alone with respect to efficacy and safety in RA patients who have failed previous DMARD therapy. Radiographic progression of disease will be evaluated. Standard safety and efficacy assessments will be performed.
0881A1-309-EU‡	A 6-month, double-blind comparison of etanercept, sulphasalazine, and the combination of etanercept and sulphasalazine in patients with active rheumatoid arthritis receiving sulphasalazine	Enrolled	260	6 months with double-blind extension	This study will compare the combination of ENBREL® and sulphasalazine to ENBREL® alone and sulphasalazine alone with respect to efficacy and safety in RA patients who have failed previous DMARD therapy. Standard safety and efficacy assessments will be performed.

‡ post-approval commitment with the EMEA

APPENDIX 2

Appendix 2. Epidemiologic Studies of Lymphoma in RA

Study	Country	n (patients)	Patient-years	Observed		Standardized Incidence Ratio		Comment
1978 Isomaki	Finland	46,101	213,911	NHL (m) NHL (f) HD (m) HD (f)	13 25 5 14	NHL (m) NHL (f) HD (m) HD (f)	2.69 2.68 2.19 3.08	National RA patient registry
1985 Katusic	USA	521	7,389	All Lymph (m) All Lymph (f)	2 1	All Lymph (m) All Lymph (f)	4.00 0.48	Population-based cohort
1985 Prior	UK	489	N/A	NHL HD	7 2	NHL HD	24.0 12.5	Clinic-associated RA patients
1985 Symmons	UK	Study 1. 489 RA pts Study 2. 30 RA pts who developed lymphoproliferative malignancies	Study 1. 5,468	Study 1. NHL HD (Also 1 CLL, which the authors do not count as NHL) Study 2.	 7 2 30	Study 1. NHL HD	 24.1 12.5	Study 1. Cohort seen by one physician Study 2. 10 from Study 1, and 20 from various UK hospitals
1993 Gridley	Sweden	11,683	101,000	NHL HD	36 12	NHL HD	1.88 2.34	Hospitalized RA patients

CLL = Chronic lymphocytic leukemia; HD = Hodgkin's disease; Lymph = Lymphoma; MM = Multiple myeloma; N/A = Not available; NHL = Non-Hodgkin's lymphoma; RA = Rheumatoid arthritis

Appendix 2. Epidemiologic Studies of Lymphoma in RA (Continued)

Study	Country	n (patients)	Patient-years	Observed	Standardized Incidence Ratio	Comment
1993 Tennis	Canada	13,333	N/A	N/A	Lymph/MM RA (all) 2.2 Lymph/MM RA-RH 4.1	*Hospitalized RA patients. RA-RH= RA patients. Hospitalized by a rheumatologist
1996 Mellemkjaer	Denmark	20,699	144,421	NHL 85 HD 14	NHL 2.4 HD 3.4	Hospitalized RA patients
1997 Cibere	Canada	862	14,998	NHL 3 HD 0	NHL 0.55 HD 0	University-based rheumatic disease unit
2000 Thomas	UK	124,143	652,133	NHL (m) 30 NHL (f) 71 HD (m) 84 HD (f) 90	NHL (m) 2.39 NHL (f) 2.04 HD (m) 5.49 HD (f) 3.04	Scottish national cohort
2002 Mariette	France	27,000-30,000	81,000-90,000	NHL (m) 6 NHL (f) 12 HD (m) 5 HD (f) 2	NHL (1.07-1.2) HD (7.4-8.2) (Depends on which n used)	National study from 61 French departments of rheumatology

CLL = Chronic lymphocytic leukemia; HD = Hodgkin's disease; DLBCL: Diffuse large B-cell lymphoma, Lymph = Lymphoma; MM = Multiple myeloma; N/A = Not available; NHL = Non-Hodgkin's lymphoma; RA = Rheumatoid arthritis

Appendix 2. Epidemiologic Studies of Lymphoma in RA (Continued)

Study	Country	n (patients)	Patient-years	Observed	Standardized Incidence Ratio	Comment
2002 Baecklund	Sweden	N/A	N/A	296 Total NHL 277 DLBCL 52% HD 19	N/A	Swedish Hospital Inpatient Register and Swedish Cancer Register study
2002 Watterson	US	Non-RA 557,242 RA 10,700	Non-RA 1,967,956 RA 32,979	Non-RA 1,386 RA 28 NHL 23 HD 5	1.01 (95% CI = 0.69-1.47)	Tennessee Medicaid Cohort

CLL = Chronic lymphocytic leukemia; HD = Hodgkin's disease; DLBCL: Diffuse large B-cell lymphoma, Lymph = Lymphoma; MM = Multiple myeloma; N/A = Not available; NHL = Non-Hodgkin's lymphoma; RA = Rheumatoid arthritis