

# Long-term Safety and Efficacy of 50 mg of Etanercept Twice Weekly in Patients With Psoriasis

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**Objective:** To evaluate the safety and efficacy of long-term treatment of psoriasis with etanercept, 50 mg twice weekly.

**Design, Setting, and Patients:** A phase 3, randomized, double-blind trial with an open-label extension. A total of 618 adult patients with moderate to severe plaque psoriasis were studied at 39 medical centers in the United States and Canada from May 23, 2003, through June 22, 2005.

**Interventions:** Patients were randomized to receive placebo or etanercept for 12 weeks. Beginning with week 13, all patients (N=591) received etanercept.

**Main Outcome Measures:** Exposure-adjusted adverse event rates were calculated. Efficacy measures included efficacy and patient global assessment of psoriasis.

**Results:** Exposure-adjusted rates of adverse events, serious adverse events, infections, and serious infections were similar for placebo and etanercept treatments. Nonneutralizing antibodies to etanercept, observed in 18.3% of patients, had no apparent effect on safety or efficacy. Patients responded within 2 weeks to etanercept, with

statistically significant differences in the Psoriasis Area and Severity Index and Dermatology Life Quality Index between the etanercept and placebo groups at week 12. At week 24, after 12 weeks of open-label etanercept treatment, patients in the original placebo group had clinical benefits comparable to those of patients in the original etanercept group. As both groups progressed through the open-label period, the Psoriasis Area and Severity Index response peaked at week 48. At week 96, 51.6% of the original placebo-treated patients and 51.1% of the original etanercept-treated patients had improvements from baseline in the Psoriasis Area and Severity Index of at least 75%.

**Conclusions:** Extended exposure to 50 mg of etanercept twice weekly resulted in exposure-adjusted rates of adverse events and infections similar to those in patients receiving placebo. Improvements in physician- and patient-reported measures of psoriasis severity were observed for up to 96 weeks of continuous etanercept therapy.

**Trial Registration:** [clinicaltrials.gov](http://clinicaltrials.gov) Identifier NCT00111449.

*Arch Dermatol.* 2007;143:719-726

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**P**SORIASIS IS A CHRONIC inflammatory disorder that usually requires long-term therapy. Serum and affected tissue levels of tumor necrosis factor (TNF) are elevated in patients with psoriasis compared with levels in uninvolved skin of patients with psoriasis and in healthy individuals, suggesting that TNF plays an important role in the pathogenesis of the disease.<sup>1</sup>

Etanercept (Enbrel; Immunex Corporation, Seattle, Wash) is a fully human soluble TNF receptor that has been approved by the US Food and Drug Administration for the treatment of various inflammatory diseases, including moderate to severe rheumatoid arthritis (RA), moderate to severe polyarticular-course juvenile RA, psoriatic arthritis, ankylosing spondylitis, and, more recently, moderate to se-

vere plaque psoriasis.<sup>2</sup> The recommended dosage of etanercept for patients with psoriasis in the United States is 50 mg twice weekly (BIW) for 3 months followed by a maintenance dosage of 50 mg/wk.

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In two phase 2<sup>3,4</sup> and two phase 3<sup>5,6</sup> placebo-controlled studies of patients with moderate to severe plaque psoriasis, etanercept provided clinical benefit and had a favorable safety profile. In the blinded portions of both phase 3 studies,<sup>5,6</sup> patients were treated with etanercept for 12 to 24 weeks at dosages ranging from 25 mg/wk to 50 mg BIW; efficacy was dose dependent, but no dose-dependent toxic effects were observed.

The present study explores the long-term use of etanercept, 50 mg BIW, in patients with moderate to severe plaque psoriasis. The primary objective of the study was to determine the effect of the 50-mg BIW dosage of etanercept compared with placebo on the Psoriasis Area and Severity Index (PASI) score at week 12. Results of the 12-week, double-blind portion of the study were reported previously.<sup>7</sup> This article provides results of the subsequent 84-week open-label period.

## METHODS

### STUDY DESIGN

This phase 3, double-blind, placebo-controlled, randomized, multicenter study consisted of a 12-week double-blind period followed by an open-label period. Patients were randomly assigned 1:1 to receive subcutaneous injections of placebo or 50 mg of etanercept BIW for the first 12 weeks. Subsequently, all continuing patients received 50 mg of etanercept BIW in an open-label fashion (n=591). The duration of open-label treatment originally specified in the protocol has since been extended to 132 weeks (ongoing). For the double-blind portion of the study and the initial 84-week, open-label period, the reconstituted investigational product was supplied to patients in syringes. After 48 weeks of open-label treatment, patients were trained and allowed to reconstitute etanercept at home.

### PATIENTS

We studied a total of 618 adult patients with moderate to severe plaque psoriasis at 39 medical centers in the United States and Canada. The institutional review boards of the participating medical centers approved the protocol, and all patients gave written informed consent before beginning any study-related procedures.

Details about the study population and inclusion and exclusion criteria have been published separately.<sup>7</sup> Briefly, patients were eligible if they were at least 18 years of age, had active but clinically stable plaque psoriasis involving at least 10% of the body surface area, had a minimum PASI score of 10, and had received at least 1 previous phototherapy or systemic psoriasis therapy or had been candidates to do so. Concomitant use of systemic therapy or phototherapy was not permitted throughout the study. However, patients were allowed to use topical corticosteroids of moderate strength on the scalp, axillae, and groin and tar compound or corticosteroid-free topical emollients.

### ASSESSMENTS

During the open-label portion of the study, safety and efficacy evaluations were performed every 12 weeks.

Safety evaluations included infectious and noninfectious adverse events, serious infections, serious adverse events, injection-site reactions, clinical laboratory values, and antibodies to etanercept. Adverse events and infections were coded using the Medical Dictionary for Regulatory Activities (<http://www.meddransso.com/MSSOWeb/index.htm>). Laboratory toxicities were graded using a modification of the Common Toxicity Criteria of the National Cancer Institute criteria.<sup>8</sup> The assessment of the relationship between adverse events and the study drug was based on the investigator's judgment. No safety monitoring committee oversaw the conduct of the study. Baseline and postdose samples were tested in 3 validated enzyme-linked immunosorbent assays (screening, titration, and neutralizing) to detect an-

tibodies with the capacity to bind to or to neutralize etanercept.<sup>9</sup> If a sample yielded positive results in a screening assay, a titration assay was performed to evaluate the level of the antibody. Samples that yielded positive results in the titration assay were analyzed in a neutralizing antibody enzyme-linked immunosorbent assay.

Psoriasis severity was assessed using the PASI score,<sup>10</sup> which ranges from 0 (no disease) to 72 (maximal disease). Improvements in the PASI score of at least 50%, 75%, and 90% (PASI50, PASI75, and PASI90, respectively) were calculated. The primary efficacy end point was the achievement of PASI75 at week 12. Patient-reported measures included the Dermatology Life Quality Index (DLQI)<sup>11</sup> and patient global assessment of psoriasis. The DLQI is a validated patient-reported outcome questionnaire, with scores ranging from 0 (no impairment) to 30 (maximal impairment). The DLQI responders were prospectively defined as patients who improved from baseline by at least 5 points or achieved a score of 0. Patient global assessment of psoriasis was reported using a 6-point scale ranging from 0 (good) to 5 (severe).

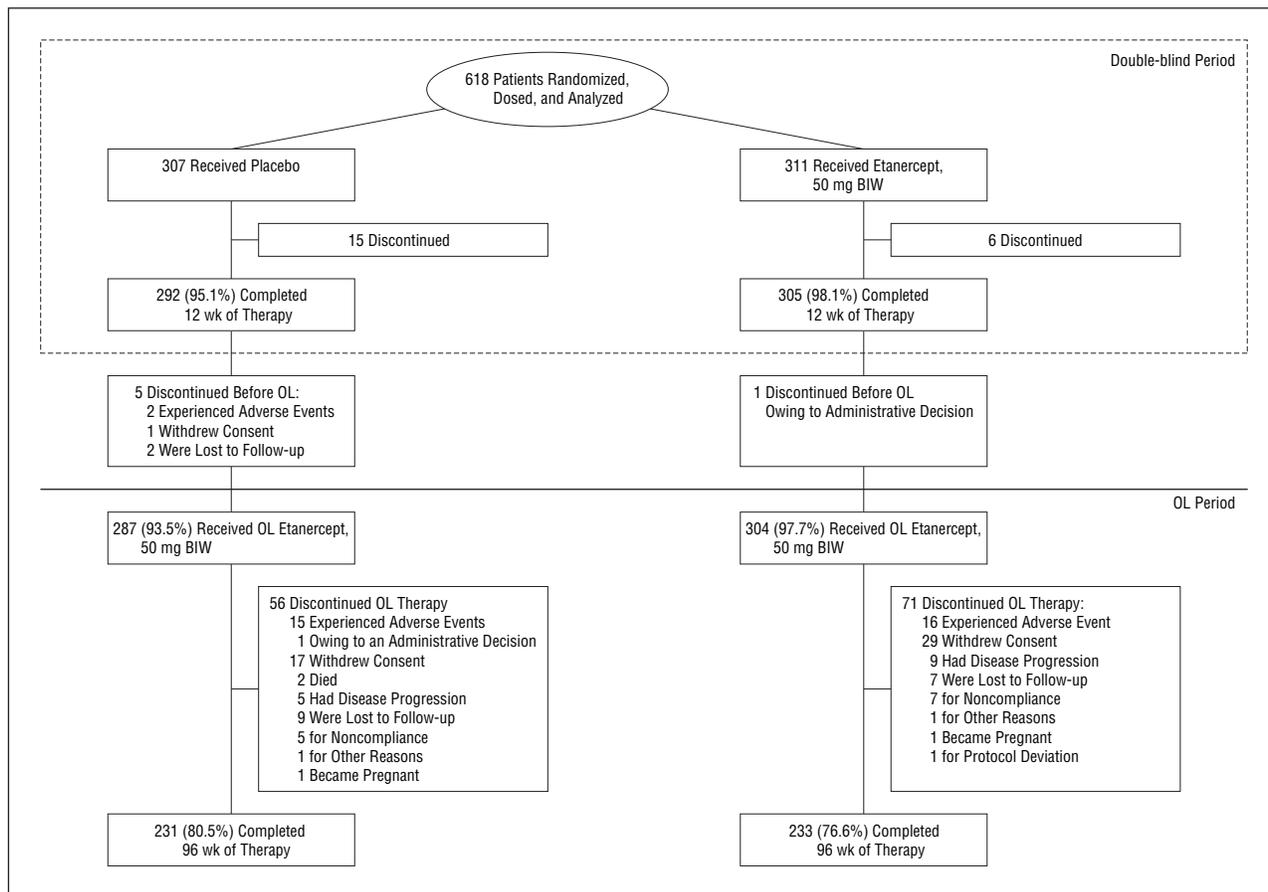
### STATISTICAL ANALYSES

The planned sample size of 600 patients was chosen primarily to provide adequate data for evaluation of safety end points. Open-label data were analyzed after all patients completed the week-96 assessments. During the open-label portion, no formal statistical hypotheses were tested. Descriptive statistics were calculated without statistical inferences and included all randomized patients who received at least 1 dose of investigational product. Safety analyses were based on the actual treatment received, without any imputation of missing data. Exposure-adjusted adverse event rates (incidence adjusted for 100 patient-years of exposure) were calculated. Efficacy analyses were based on the original, randomized treatment groups from the double-blind period; missing efficacy data were imputed using last observation carried forward.

## RESULTS

A total of 618 patients were enrolled and randomized to receive placebo (307 patients) or etanercept (311 patients) (**Figure 1**). After the 12-week double-blind treatment, 591 of those patients were treated in the open-label period. The most common reasons for withdrawal from the study during the open-label portion were withdrawal of consent (46 patients) and adverse events (31 patients). Fourteen patients withdrew because of disease progression, although only 1 met the protocol definition of worsening of disease (increase in PASI score  $\geq 50\%$  from baseline and an absolute increase in PASI score of  $\geq 8$  points after  $\geq 4$  weeks of treatment). Of the 591 open-label enrollees, 464 (78.5%) completed 84 weeks of open-label treatment.

Baseline demographics and disease characteristics were generally well balanced between treatment groups and have been reported previously (**Table 1**).<sup>7</sup> Of the total patient population, 67.6% were men, 89.2% were white, and the mean age among patients was 45.7 years. On average, the duration of psoriasis was 19.9 years, 27.2% of the body surface area was affected, and the baseline PASI score was 18.2. Overall, 34.3% of patients had a history of psoriatic arthritis.



**Figure 1.** Patient flow diagram. BIW indicates twice weekly; OL, open label. Reprinted with permission from Tyring et al,<sup>7</sup> copyright 2006, with permission from Elsevier.

**Table 1. Baseline Demographics and Disease Characteristics\***

Characteristic	Patient Groups		
	Placebo/ Etanercept (n = 307)	Etanercept/ Etanercept (n = 311)	All (N = 618)
No. (%) of men	215 (70.0)	203 (65.3)	418 (67.6)
No. (%) white	270 (87.9)	281 (90.4)	551 (89.2)
No. (%) aged ≥65 y	22 (7.2)	27 (8.7)	49 (7.9)
Mean age, y	45.5	45.8	45.7
Mean weight, kg	91.0	92.6	91.8
Mean height, cm	172.2	171.9	172.1
Mean % of psoriasis-affected BSA	27.2	27.2	27.2
Mean duration of psoriasis, y	19.7	20.2	19.9
Mean PASI score	18.1	18.3	18.2
No. (%) with a history of psoriatic arthritis	101 (32.9)	111 (35.7)	212 (34.3)

Abbreviation: BSA, body surface area; PASI, Psoriasis Area and Severity Index.

\*Adapted from Tyring et al,<sup>7</sup> copyright 2006, with permission from Elsevier.

## SAFETY

Total exposure to 50 mg of etanercept BIW was 908.9 patient-years for the first 96 weeks of this study. With the

**Table 2. Exposure-Adjusted Summary of Adverse Events Through Week 96**

Type of Events	Exposure-Adjusted Rate, No. of Events per 100 Patient-Years	
	Placebo Exposure (n = 306)*†	Etanercept Exposure (n = 598)‡
All noninfectious adverse events	418.8	158.0
All infections	130.5	103.9
Serious noninfectious adverse events	6.1	7.7
Death	0.0	0.2
Serious infections	1.5	1.2
All injection-site reactions	6.1	12.2

\*After data were unblinded, it was discovered that 1 placebo-treated patient received 1 dose of etanercept during the double-blind period. This patient was included in the etanercept group for analyses of adverse events.

†Total number of exposure years was 65.9.

‡Total number of exposure years was 908.9.

exception of injection-site reactions, which occurred more frequently in patients treated with etanercept, exposure-adjusted event rates (EARs) for etanercept were similar to those for placebo (**Table 2**). The EARs of noninfectious adverse events for placebo and etanercept exposures were 418.8 and 158.0 events per 100 patient-years, respec-

**Table 3. SIRs of Malignancies by Major Organ Site for All Etanercept Exposure Through Week 96\***

Malignancy Comparison Databases	No. of Events		SIR (95% CI)
	Observed	Expected†	
All malignancies, excluding nonmelanoma skin cancers compared with general population in SEER database	9	4.77	1.89 (0.86-3.58)
SCC compared with general population			
Arizona database	4	2.51	1.59 (0.43-4.08)
Minnesota database	4	1.02	3.91 (1.07-10.01)
BCC compared with general population in the Arizona database	7‡	10.14	0.69 (0.28-1.42)
All malignancies, including nonmelanoma skin cancers compared with severe psoriatic population in Medicaid claims database	23	26	0.88 (0.56-1.33)

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; SCC, squamous cell carcinoma; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio.

\*Data represent 907.3 total patient-years of exposure.

†Expected number of events for malignancies excluding nonmelanoma skin cancers for the general population were based on the SEER database.<sup>12</sup> Expected number of nonmelanoma skin cancers in the general population was based on the Minnesota<sup>13</sup> and Arizona<sup>14</sup> databases. Events reported in Arizona and Minnesota SCCs were the same events. Expected number of events for malignancies, including nonmelanoma skin cancers, for the psoriatic population was based on a cohort of 1101 patients with severe psoriasis in the Medicaid claims database, as reported by Margolis et al.<sup>15</sup>

‡One patient experienced 4 BCCs at 4 different locations.

tively, and the EARs for serious noninfectious adverse events were 6.1 and 7.7 events per 100 patient-years, respectively. The most frequently observed noninfectious adverse events for placebo exposure and etanercept exposure were headache (36.4 vs 9.2 events per 100 patient-years, respectively), injection-site hemorrhage (24.3 vs 5.8 events per 100 patient-years, respectively), arthralgia (19.7 vs 4.8 events per 100 patient-years, respectively), and back pain (4.6 vs 5.2 events per 100 patient-years, respectively). The most common serious noninfectious adverse events reported for etanercept exposure were myocardial infarction (0.4 event per 100 patient-years), basal cell carcinoma (BCC) (0.3 event per 100 patient-years), and depression (0.3 event per 100 patient-years). None of these common serious noninfectious adverse events were reported after placebo exposure. The EARs of infections (130.5 and 103.9 events per 100 patient-years) and serious infections (1.5 and 1.2 events per 100 patient-years) were similar between placebo and etanercept exposures. The most frequent type of infection was upper respiratory tract infection for placebo (24.3 events per 100 patient-years) and etanercept exposures (20.2 events per 100 patient-years). Ten patients reported serious infections during the open-label period, including 2 patients with cellulitis. One patient had cellulitis after a dog bite and the other had it after a puncture wound. Both cases resolved after surgical procedures and antibiotic treatment. Serious events of gangrene, infection of unknown origin, viral meningitis, diverticulitis, infectious enteritis, gastroenteritis, gas-

trointestinal tract infection, and localized staphylococcal infection were each reported in 1 patient. Viral meningitis was the only serious infection considered possibly related to the investigational product by the investigator.

For patients randomized to etanercept, the EARs of adverse events did not increase with longer-term exposure. The EARs of adverse events (465.9 events per 100 patient-years at week 12 vs 274.1 events per 100 patient-years at week 96) and infections (183.4 events per 100 patient-years at week 12 vs 103.9 events per 100 patient-years at week 96) were comparable at week 12 and at week 96.

Two deaths occurred during the study. One patient died of cardiac arrest approximately 11 months after starting etanercept therapy, with coronary artery disease as the probable cause. He was obese and had a history of hypercholesterolemia and type 2 diabetes mellitus. Concomitant medications included zolpidem tartrate, celecoxib, acetaminophen (paracetamol), glibomet, multivitamin combinations, aspirin for cardiac prophylaxis, and atorvastatin calcium. The investigator reported there was not a reasonable possibility that the death may have been caused by the investigational product. The second patient died of a suspected myocardial infarction approximately 10 months after initiation of etanercept therapy. He had a history of hyperlipidemia and intermittent indigestion and a familial history of unspecified cardiac disease. Concomitant medications included aspirin and an agent to reduce serum lipid levels (rosuvastatin calcium). The investigator reported that there was a reasonable possibility the event was related to the investigational product.

Nine malignancies (excluding nonmelanoma skin cancers and in situ carcinomas) and 14 nonmelanoma skin cancers were reported during the study (**Table 3**). The 9 malignancies were reported in 9 patients who received at least 1 dose of etanercept. Two patients had breast cancer and 1 patient each had tonsil cancer, B-cell chronic lymphocytic leukemia/small cell lymphocytic lymphoma, colon cancer, adenocarcinoma (colon polyp), lymphocyte predominance type Hodgkin's disease (stage unspecified), pancreatic carcinoma, and metastatic lung adenocarcinoma.

Standardized incidence ratios (SIRs) were calculated for expectations in age- and sex-matched cohorts from the general population using the National Cancer Institute Surveillance, Epidemiology, and End Results database.<sup>12</sup> Observed numbers of total malignancies were not statistically significantly different from the expected numbers of total malignancies (SIR, 1.89; 95% confidence interval [CI], 0.86-3.58). The SIRs for body site-specific malignancies had wide 95% CIs because of the small number of cancers observed. Three of the malignancies (tonsil cancer, breast cancer, and Hodgkin's disease) were considered possibly related to the investigational product by the investigator.

Fourteen nonmelanoma skin cancers in 10 patients (6 with BCC, 3 with squamous cell carcinoma [SCC], and 1 with both) were observed. One patient reported BCC in 4 different sites. Five of the 10 patients had received previous UV-B phototherapy and/or psoralen and long-wave UV-A radiation therapy, and 1 patient had a history of BCC. Expected numbers of incident cases of SCC and BCC were calculated for age- and sex-matched co-

horts from the general population using data from the Rochester Epidemiology Project in Minnesota<sup>13</sup> and the Southeastern Arizona Skin Cancer Registry.<sup>14</sup> The incidence of SCC was consistent with the Arizona-based data (SIR, 1.59; 95% CI, 0.43-4.08) but significantly higher than the Minnesota-based data (SIR, 3.91; 95% CI, 1.07-10.01). We observed BCCs less frequently than expected from the Arizona-based data, although the difference was not statistically significant (SIR, 0.69; 95% CI, 0.28-1.42). One BCC was considered possibly related to the investigational product.

The rate of malignancy, including nonmelanoma skin cancers, in this study was also compared with rates reported by Margolis et al<sup>15</sup> for a cohort of patients with severe psoriasis from the Medicaid claims database (Table 3). The observed number of malignancies in this study was not significantly different (SIR, 0.88; 95% CI, 0.56-1.33) from the expected number seen in the psoriatic population who had severe disease, defined as patients who were receiving systemic therapy.

One case of leukemia and 1 case of lymphoma were also reported as serious adverse events during the study. A case of B-cell chronic lymphocytic leukemia/small cell lymphocytic lymphoma that was positive for a gene mutation in a 72-year-old patient was detected 8 months after initiating etanercept therapy. The patient had a history of tobacco use and a family history of ovarian and thyroid cancer. The investigator did not consider this event as possibly related to etanercept use. A case of lymphocyte predominance type Hodgkin's disease in a 50-year-old patient was detected 11 months after initiating etanercept therapy. The patient had psoriatic arthritis in addition to his psoriasis and a history of spherocytosis. The investigator considered the serious event of Hodgkin's disease to be possibly related to the investigational product.

Other medically important events that have been reported with anti-TNF therapies include demyelinating diseases, congestive heart failure, opportunistic infections, and tuberculosis.<sup>2,16,17</sup> A serious adverse event was reported in a 54-year-old patient who experienced worsening of congestive cardiac failure, which occurred 20 months after initiating etanercept therapy. The patient had a history of myocardial infarction, congestive heart failure, smoking, and depression. In addition, 1 nonserious adverse event (exacerbation of congestive heart failure) was reported in a 59-year-old patient approximately 17 months after initiating etanercept therapy. The patient's medical history included myocardial infarctions, congestive cardiac failure, and arterial bypass and cardiac pacemaker operations. The investigator considered the serious event of congestive heart failure to be possibly related to the investigational product. No events of demyelination, tuberculosis, or opportunistic infection were reported.

Laboratory measurements outside the normal range were occasionally observed, but these were rarely considered clinically relevant. One patient had a grade 4 elevation in alanine aminotransferase levels approximately 8 months after beginning etanercept therapy; the patient was subsequently diagnosed as having hepatitis B virus infection. Eight grade 3 abnormalities (4 high alanine aminotransferase levels, 2 high aspartate amino-

transferase levels, 1 low hemoglobin level, and 1 high hemoglobin level) were observed during the open-label period. Six of these laboratory abnormalities were transient and returned to levels of grade 2 or lower.

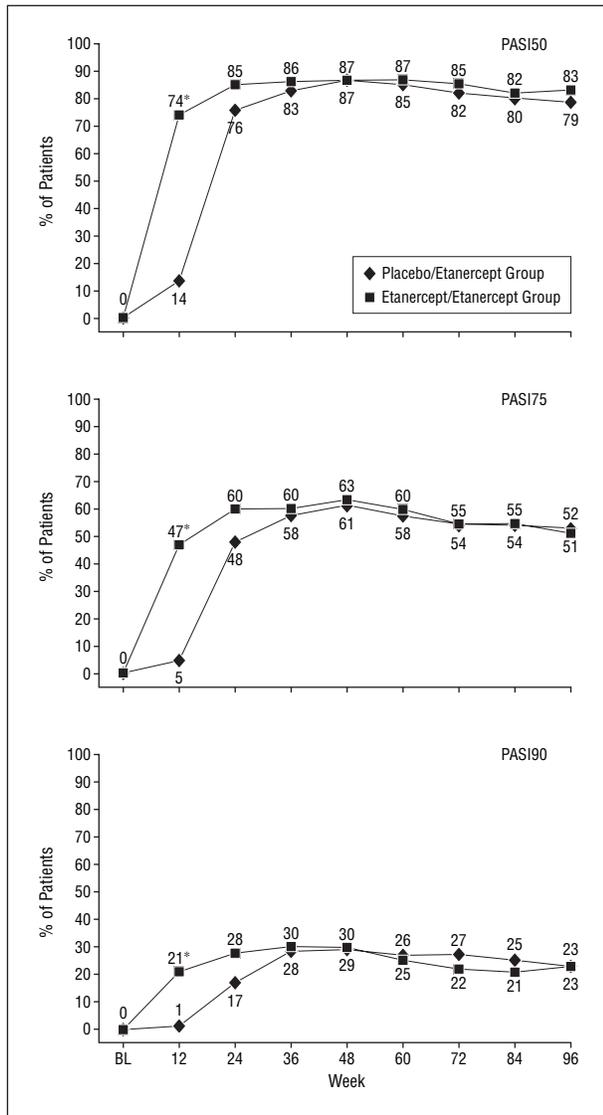
## EFFICACY

During the open-label period, patients in the etanercept/etanercept group continued to maintain clinically meaningful improvements in the PASI response for up to 96 weeks. In the placebo/etanercept group, etanercept administration starting at week 13 was accompanied by improvement in PASI scores by week 24, similar to that seen in the etanercept/etanercept group during weeks 1 through 12. At week 24, PASI50, PASI75, and PASI90 response rates in the placebo/etanercept group were 75.8%, 47.7%, and 16.7%, respectively, which were comparable with results of the first 12 weeks in the etanercept/etanercept group (73.6%, 47.3%, and 20.9%, respectively).<sup>7</sup> By week 96, PASI50, PASI75, and PASI90 response rates were 79.1%, 51.6%, and 22.8%, respectively, for the placebo/etanercept group and 82.6%, 51.1%, and 23.2%, respectively, for the etanercept/etanercept group (**Figure 2**).

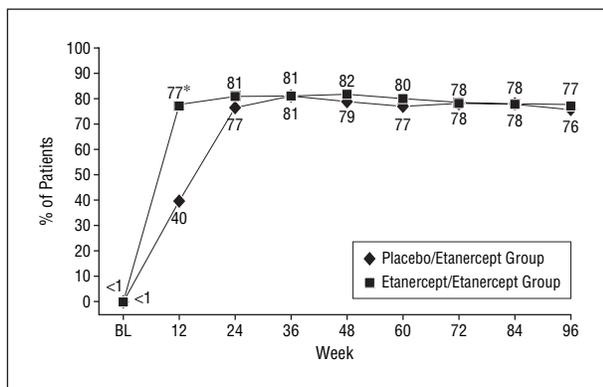
Although PASI75 response rates were sustained from weeks 12 to 96, these rates peaked at week 48, when 63.0% of the etanercept/etanercept group and 61.1% of the placebo/etanercept group achieved a PASI75 response. Of the 320 patients who achieved a PASI75 response at week 48 and were available for evaluation at weeks 48 and 96, 238 (74.4%) maintained a PASI75 response and 82 (25.6%) lost their PASI75 response at week 96. Mean PASI scores for patients who lost their PASI75 responses decreased from baseline scores of 20.0 (placebo/etanercept group) and 18.9 (etanercept/etanercept group) to 3.0 at week 48 (both treatment groups), and increased to 6.7 (placebo/etanercept group) and 7.2 (etanercept/etanercept group) at week 96. Conversely, 132 patients did not achieve a PASI75 at week 48. Of these, 23 (17.4%) were PASI75 responders at week 96.

Patient compliance with self-administration of etanercept was explored as a potential reason for loss of efficacy. *Compliance* was defined as the number of doses actually administered of the number of scheduled doses from weeks 48 to 96. In a post hoc analysis, patients who were at least 90% compliant from weeks 48 to 96 were compared with those who were not at least 90% compliant in the same period. In the cohort who were less than 90% compliant, the PASI75 response declined by more than 20% from week 48 to 96. Patients who were at least 90% compliant showed a decline of about 10%.

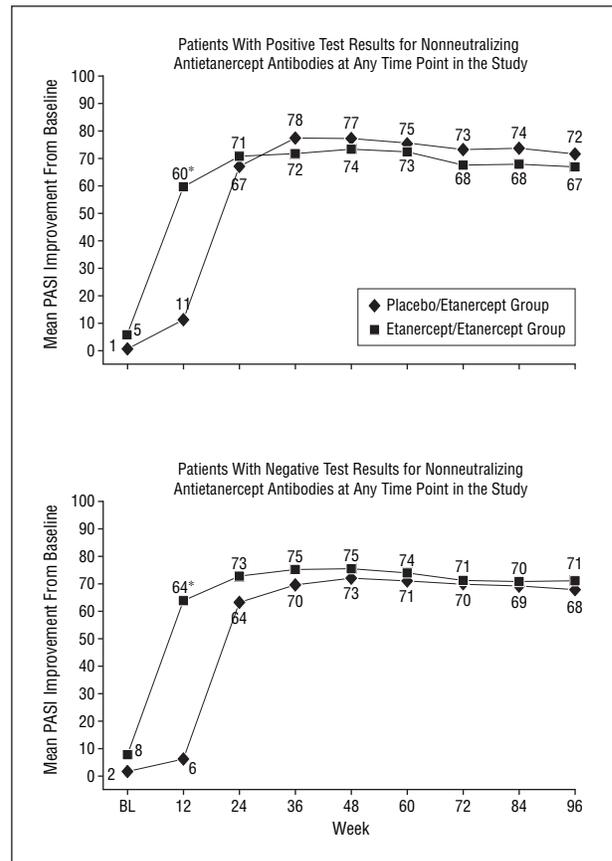
Mean baseline DLQI scores for the placebo/etanercept and etanercept/etanercept groups were 12.5 and 12.1, respectively. At week 12, 39.6% of patients in the placebo/etanercept group and 76.6% of the etanercept/etanercept group were categorized as DLQI responders ( $P < .001$ ). At week 96, DLQI responses were observed in 75.7% of patients in the placebo/etanercept group and in 77.0% of patients in the etanercept/etanercept group (**Figure 3**). Mean DLQI scores at week 96 were 3.7 and 3.5 for the placebo/etanercept and etanercept/etanercept groups, respectively. The distribution of scores on the patient global assessment of psoriasis was balanced between the treatment



**Figure 2.** Improvements in the Psoriasis Area and Severity Index scores of at least 50% (PASI50), 75% (PASI75), and 90% (PASI90) over time. \* $P < .001$ , 50 mg of etanercept twice weekly vs placebo at week 12 (2-sided van Elteren test stratified by previous therapy) based on an intent-to-treat analysis using last observation carried forward. BL indicates original study baseline.



**Figure 3.** Percentage of Dermatology Life Quality Index responders (defined as those with a  $\geq 5$ -point improvement or a score of 0) over time. \* $P < .001$ , 50 mg of etanercept twice weekly vs placebo at week 12 (2-sided Cochran-Mantel-Haenszel test stratified by previous psoriasis therapy) based on an intent-to-treat analysis using last observation carried forward. BL indicates original study baseline.



**Figure 4.** Mean percentage of improvement in the Psoriasis Area and Severity Index (PASI) score by antietanercept antibody status. \* $P < .001$ , 50 mg of etanercept twice weekly vs placebo at week 12 (2-sided van Elteren test stratified by previous psoriasis therapy) based on an intent-to-treat analysis using last observation carried forward. BL indicates original study baseline.

groups at baseline, with approximately 95% of patients in each group scoring 3 to 5 points. At week 12, 73.6% of etanercept-treated patients achieved scores of 0 to 2, compared with 21.2% of patients in the placebo group ( $P < .001$ ). At week 96, approximately 78% of patients in each group achieved scores of 0 to 2.

Of the patients who had baseline and postbaseline samples available for analysis, antietanercept antibodies were observed at least once in 18.3% of patients, with 5.7% of patients having positive test results at 3 or more of 8 time points by our current assay methods. The antietanercept antibodies detected were determined to be nonneutralizing. Efficacy results appeared independent of the presence of these antibodies, with the PASI response, percentage of improvement in PASI scores over time (**Figure 4**), and DLQI scores showing similar profiles between the antibody-positive and antibody-negative cohorts. In addition, the presence of antietanercept antibodies had no apparent impact on the safety profile of etanercept (**Table 4**).

#### COMMENT

In this study, extended exposure to 50 mg of etanercept BIW for up to 96 weeks was generally well tolerated. Interpretation of the safety data is limited by the open-

**Table 4. Exposure-Adjusted Adverse Event Rates by Anti-tumor Necrosis Factor Receptor-1 Inhibitor Antibody Status Through Week 96**

Type of Events	Anti-tumor Necrosis Factor Receptor-1 Inhibitor Antibody Status, Exposure-Adjusted Rate per 100 Patient-Years			
	All Negative Results (n = 470)*	≥1 Positive Result (n = 111)†	1 or 2 Positive Results (n = 76)‡	≥3 Positive Results (n = 35)§
All noninfectious adverse events	182.9	191.2	175.8	222.0
All infections	109.0	125.0	123.3	128.5
Serious noninfectious adverse events	9.9	2.2	3.3	0.0
Death	0.3	0.0	0.0	0.0
Serious infections	1.5	1.1	1.7	0.0
All injection-site reactions	12.7	15.0	14.2	16.7

\*Total number of exposure years was 687.2.

†Total number of exposure years was 179.9.

‡Total number of exposure years was 120.0.

§Total number of exposure years was 59.9.

label nature of the study and the fact that the total number of exposure years for placebo was much lower than that for etanercept. Exposure-adjusted rates of noninfectious and infectious adverse events were similar for the etanercept/etanercept group at weeks 12 and 96, indicating that extended exposure to etanercept did not increase the drug's toxicity. In addition, the safety profile observed in this study is consistent with results previously reported for the lower etanercept dosage of 25 mg BIW.<sup>3-6,18,19</sup> In those studies, the maximum length of time that patients with psoriasis received continuous etanercept therapy was 60 weeks.<sup>18</sup>

Although the observed incidence of SCC in this study was higher than that expected for the general population of the Minnesota-based registry, patients with psoriasis are at increased risk for SCC. The degree of risk correlates with the severity of psoriasis,<sup>15</sup> and this risk may be elevated with previous exposure to phototherapy. In patients with RA, etanercept use for as long as 5 years did not seem to be associated with an increase in the incidence of SCC.<sup>20</sup> Adverse events of interest that occurred in the study included 1 occurrence of B-cell chronic lymphocytic leukemia/small cell lymphocytic lymphoma, 1 occurrence of lymphocyte predominance type Hodgkin's disease, and 2 occurrences of worsening of congestive heart failure. There were no reports of demyelination, tuberculosis, or opportunistic infection.

In the current antibody assays that have been used in multiple clinical trials of etanercept, 18.3% of patients had positive test results for antibodies to etanercept at least once during the study. The 18.3% rate is higher than previously reported (approximately 6% of adult patients with RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis).<sup>2</sup> However, consistent with results from previous clinical trials, the anti-tumor necrosis factor receptor-1 antibodies observed in this study were all found to be non-neutralizing and had no apparent effect on the efficacy or safety profiles of etanercept.

Extensive long-term data are available in etanercept-treated patients with disease-modifying antirheumatic drug-refractory RA, some of whom have been treated with etanercept for as long as 8.2 years.<sup>21</sup> With a total of 3139 patient-years of exposure to etanercept (mostly at a dosage of 25 mg BIW), safety analyses have shown no new

safety signals with long-term etanercept use. The rates of serious noninfectious adverse events and serious infections observed in the present study (7.7 and 1.2 events per 100 patient-years, respectively) are lower than the range observed in the long-term RA study (14.8 and 4.2 events per 100 patient-years, respectively).

Patients showed high levels of response in a wide variety of psoriasis severity measures, including the PASI, DLQI, and patient assessments of psoriasis, for up to 96 weeks of therapy. These results confirm and extend the safety and efficacy profiles of this dosage of etanercept observed in studies of shorter duration.<sup>5,6</sup> The PASI75 response observed with 50 mg of etanercept BIW at 12 weeks<sup>7</sup> was consistent with observations at the same dosage in 2 previous phase 3 studies.<sup>5,6</sup> Baseline demographic and disease characteristics in all 3 studies were similar, although 34.3% of patients in the present study had a history of psoriatic arthritis, compared with 23% to 26% in the previous studies. Similar to the published phase 3 studies, most patients in the present study responded maximally within the first 12 to 24 weeks of etanercept therapy.

In this article, we demonstrate that treatment with 50 mg of etanercept BIW led to a marked reduction in disease severity for up to 96 weeks in patients with psoriasis. Although loss of efficacy during long-term etanercept therapy was observed in a small subset of patients, most maintained their high response for up to 96 weeks. It may be speculated that the loss in PASI75 response may be due to a variety of reasons, including noncompliance with etanercept administration from weeks 48 to 96, inherent limitations of the assessments of PASI scores,<sup>22,23</sup> or psoriasis-specific factors that decrease TNF dependency of the disease in patients treated with TNF antagonists. Although some patients lost their PASI75 response, 17.4% of patients who were not PASI75 responders at week 48 achieved a PASI75 response at week 96.

In conclusion, this study represents, to our knowledge, the longest continuous exposure of patients with psoriasis to 50 mg of etanercept BIW and provides further insights into the safety and efficacy of high-dose etanercept therapy for the management of moderate to severe psoriasis.

Accepted for Publication: October 24, 2006.

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**Author Contributions:** All authors had full access to all of the data for this review and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Tyring and Dunn. *Acquisition of data:* Tyring, Gordon, Poulin, Langley, and Gottlieb. *Analysis and interpretation of data:* Tyring, Gordon, Langley, Gottlieb, Dunn, and Jahreis. *Drafting of manuscript:* Tyring, Gordon, and Jahreis. *Critical revision of the manuscript for important intellectual content:* Tyring, Gordon, Poulin, Langley, Gottlieb, Dunn, and Jahreis. *Statistical analysis:* Dunn and Jahreis. *Obtained funding:* Gottlieb. *Administrative, technical, or material support:* Poulin. *Supervision:* Tyring, Gottlieb, and Jahreis.

**Financial Disclosure:** Dr Tyring has been a member of the speaker's bureau and has received research funding from Amgen Inc and has been an investigator for Abbott Laboratories, Leo Pharma, Schering-Plough Corporation, Genentech, Galderma, and GlaxoSmithKline. Dr Gordon has received research support and honoraria from and has been a consultant for Amgen Inc. Dr Gordon has received research support and honoraria from and has served as a consultant for Abbott Laboratories, Amgen Inc, Astellas, Centocor, Connetics, and Genentech. Dr Poulin has received honoraria/funding for research and/or been an advisory board member for Amgen Inc, Wyeth Pharmaceuticals, Centocor Inc, Schering-Plough Corporation, Serono, BiogenIdec Inc, Celgene Corporation, Boehringer-Ingelheim, Leo Pharma, Isotechnika, and Abbott Laboratories. Dr Langley has served on the scientific advisory board for and received research support from Amgen Inc, Wyeth Pharmaceuticals, Centocor Inc, Serono, BiogenIdec Inc, and Abbott Laboratories. Dr Gottlieb has been on the speaker's bureau for Amgen Inc and Wyeth Pharmaceuticals and has been a consultant for Amgen Inc, BiogenIdec Inc, Centocor Inc, Wyeth Pharmaceuticals, Schering-Plough Corporation, Eisai, Celgene Corporation, Bristol Myers Squibb, Beiersdorf Inc, Warner Chilcott, Abbott Laboratories, Roche, Sankyo, Medarex, Kemia, Celera, TEVA, Actelion, UCB, Novo Nordisk, Almirall, and Immune Control. Ms Dunn and Dr Jahreis receive stocks and stock options as employees of Amgen Inc.

**Funding/Support:** This study was supported by Immunex Corporation, a wholly owned subsidiary of Amgen Inc, and by Wyeth Pharmaceuticals.

**Acknowledgment:** Ralph Zitnik, MD, previously of Amgen Inc, was partially responsible for the study concept and design. Roberta Connelly, MS, on behalf of Amgen Inc, and Ting Chang, PhD, of Amgen Inc provided writing assistance.

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