# The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis

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**Objectives**

*To evaluate the immunogenicity, safety, and efficacy of 50 mg/mL liquid etanercept.*

**Methods**

*In a multicenter, open-label study, adults with active rheumatoid arthritis (RA) received 50 mg/mL liquid etanercept subcutaneously once weekly for 24 weeks. Immunogenicity was assessed at baseline and weeks 24 and 28, safety at all study visits, and efficacy at baseline and weeks 12 and 24.*

**Results**

*Of 222 treated patients, 88% completed the study; 81% were women; 84% were white; mean age was 53 years; mean RA duration was 10 years. Antibodies to etanercept, all non-neutralizing, were detected in 12 of 214 patients; 7 of the 12 were borderline positive (antibody titers <1:50). The presence of non-neutralizing anti-etanercept antibodies did not appear to affect clinical safety or efficacy. Few patients reported serious adverse events (6.3%), serious infections (2.3%), or withdrew because of adverse events (4.5%). Most adverse events were mild or moderate. The most common event, injection site reaction, occurred in 29.3% patients. At week 24, 63% of patients achieved an ACR20 response, 36% an ACR50 response, and 14% an ACR70 response. Similar responses were apparent by week 12. Week 24 mean improvement in the Health Assessment Questionnaire disability index scores was 0.6 points; improvement in the Short Form-36 Physical Component Score was 10.0 points.*

**Conclusion**

*The 50 mg/mL liquid etanercept formulation administered once weekly was well tolerated. The incidence of anti-etanercept antibodies, the nature and frequency of adverse events, and improvements in signs and symptoms of RA and patient physical function were similar to those in previous etanercept studies.*

**Key words**

Etanercept, tumor necrosis factor, rheumatoid arthritis, immunogenicity, liquid formulation, prefilled syringes.

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*This study was funded by Immunex Corporation, Seattle, Washington, a wholly owned subsidiary of Amgen Inc., Thousand Oaks, California.*

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*Received on March 15, 2006; accepted in revised form on June 30, 2006.*



## Introduction

Etanercept, a soluble tumor necrosis factor (TNF) receptor, was first approved for the treatment of rheumatoid arthritis (RA) in the United States in 1998 and has subsequently been approved for the treatment of juvenile RA, psoriatic arthritis, ankylosing spondylitis, and psoriasis. As of May 2005, an estimated 326,000 patients worldwide have received etanercept.

Etanercept was originally introduced in vials containing 25 mg lyophilized powder requiring reconstitution. A recent study showed that the safety and efficacy of a 50 mg etanercept dose (administered subcutaneously once weekly as 2 injections) was comparable to that of 2 separate 25 mg etanercept injections administered 3 to 4 days apart (1). Most patients have received 25 mg reconstituted etanercept twice weekly.

A 50 mg/mL liquid formulation of etanercept, supplied in prefilled syringes for subcutaneous administration, was recently approved for commercial use. This formulation was developed to enhance patient and caregiver convenience and adherence to the treatment regimen. We report the results of a clinical study designed to evaluate the immunogenicity, safety, and efficacy of this 50 mg/mL etanercept formulation.

## Patients and methods

*Patients*

All patients gave written informed consent before any study-related procedures were performed. Men and nonpregnant, nonlactating women at least 18 years of age were eligible for the study if they had active RA (at least 6 swollen joints and 6 tender or painful joints based on 66/68 joints excluding the distal interphalangeal joints) and had adequate hematologic, renal, and hepatic function. Patients who were receiving up to 25 mg per week methotrexate before the study were allowed to continue taking methotrexate if the dose had been stable for at least 28 days before the first dose of etanercept. Patients who were receiving oral corticosteroids (≤10 mg/day prednisone or its equivalent) before the study were allowed to continue corticosteroid dosing if the dose had been stable for 14 days before study drug initiation. Analgesics and nonsteroidal anti-inflammatory drugs were also allowed.

Patients were excluded from participation in the study if they previously received etanercept, infliximab, adalimumab, experimental metalloproteinase inhibitors, or other TNF inhibitors within 90 days before study drug initiation; intra-articular corticosteroids within 14 days before study drug initiation; any disease-modifying anti-inflammatory drugs within 28 days before study drug initiation; or cyclophosphamide within 6 months before study drug initiation. Patients also were excluded if they were receiving other investigational products, were enrolled in another investigational device or drug trial within 30 days before study drug initiation, or had other significant medical diseases.

*Study treatment*

Etanercept liquid was supplied in boxes of 5 prefilled, single-dose syringes with attached sterile needles for subcutaneous injection. Each syringe contained 1.0 mL of a clear, colorless protein solution consisting of 50 mg/mL etanercept, 25 mM sodium phosphate, 25 mM L-arginine HCl, 100 mM sodium chloride, and 1% sucrose per syringe at a pH of 6.3. Product was stored in the refrigerator and was administered at room temperature.

*Study design*

The institutional review boards at the 27 participating U.S. study centers approved the study protocol for this Phase 3, multicenter, open-label study. After a 14-day screening period, all patients received 50 mg/mL liquid etanercept once weekly for 24 weeks in this single-arm study and then entered a 4-week post-treatment observation period. Physical examinations and disease and laboratory assessments were done on day 1 and at weeks 12 and 24 (or upon early termination). Physical examinations and limited laboratory assessments also were done at week 28. Blood samples were tested for anti-etanercept antibodies on day 1 and at weeks 24 and 28. Reports of adverse events, serious adverse events, con-

comitant medication use, and other safety information were recorded at all clinic visits scheduled at 4-week intervals. The American College of Rheumatology (ACR) 20%, 50%, and 70% improvement criteria (ACR 20, 50, and 70 responses) and other efficacy measures were assessed at baseline and at weeks 12 and 24.

*Study endpoints*

The primary endpoint of the study was the proportion of patients who developed serum antibodies to liquid etanercept during the treatment period or by the end of the observation period. Three validated enzyme-linked immunosorbent assays (ELISAs) were used to detect and characterize anti-etanercept antibodies. If a sample was positive in a screening assay (the sample's mean optical density [OD] exceeded its corresponding pretreatment mean OD by > 0.301 units), a titration assay using a 2-fold serial dilution was performed to evaluate the level of antibody and determine endpoint titer (the highest dilution in which the mean OD exceeded the corresponding pretreatment dilution mean OD by > 0.301 units). Samples that were positive in the titration assay were analyzed in a neutralizing antibody ELISA. A sample was positive for neutralizing antibodies if 1 or more post-treatment dilutions showed a 50% or greater reduction in mean OD compared to the corresponding pretreatment sample mean OD.

Secondary safety endpoints included the incidence of patients with serious and nonserious adverse events (including infections) and abnormalities in laboratory measurements and vital signs. Efficacy endpoints in the study included the following: the proportion of patients achieving ACR 20, 50, and 70 responses (2), and the mean change from baseline in the modified Disease Activity Score (DAS28) (3), duration of morning stiffness, Health Assessment Questionnaire (HAQ), and the Short Form 36 (SF-36) Physical Component Score (PCS), and Mental Component Score (MCS). A visual analog scale was used by patients and physicians to assess disease activity and by patients to assess their pain.

*Statistical methods*

Data for the seroreactivity analyses were summarized and presented with 95% confidence intervals for all patients who had at least 1 positive immunoassay response during the treatment or post-treatment observation periods. Seroreactivity data also were stratified and summarized by the covariates of age (< 65 and ≥ 65 years), sex, race, and baseline methotrexate use for all patients who had at least 1 positive immunoassay response during the treatment or post-treatment observation periods.

All patients who received at least 1 dose of etanercept were included in the safety and efficacy analyses. The incidence of infections and noninfectious adverse events, both serious and nonserious; laboratory abnormalities; and adverse events leading to withdrawal from the study were summarized and listed. Serious adverse events included events that were fatal, life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, were a persistent or significant disability or incapacity, or were congenital anomalies or birth defects. Serious infections were events that required hospitalization or treatment with intravenous antibiotics.

The severity of adverse events and infections was graded based on the Common Toxicity Criteria (CTC) of the National Cancer Institute (NCI). Adverse events were coded using the Medical Dictionary for Regulatory Activities (4). Changes in laboratory abnormalities based on NCI's CTC grades were compared with baseline laboratory values.

In the efficacy analyses, the proportion of patients who achieved ACR 20, 50, and 70 improvement responses was summarized. Nonresponder imputation was used for missing values. The changes from baseline in the DAS28, the duration of morning stiffness, and in the SF-36 PCS and MCS were summarized. The proportion of patients who had remission (DAS28 score less than 2.6), low disease activity (DAS28 score of 2.6 to 3.2) (5), and a minimum clinically important difference in the HAQ (improvement of at least 0.22) (6) was calculated.

For categorical endpoints, the summary statistics included frequency and percentage. For continuous endpoints, the summary statistics included the number of observations, mean, 95% confidence interval for the mean, standard deviation, median, minimum, and maximum. The number and percentage of patients who received at least 1 dose of etanercept or who were prematurely discontinued from the study (categorized by the reasons for withdrawal) were summarized.

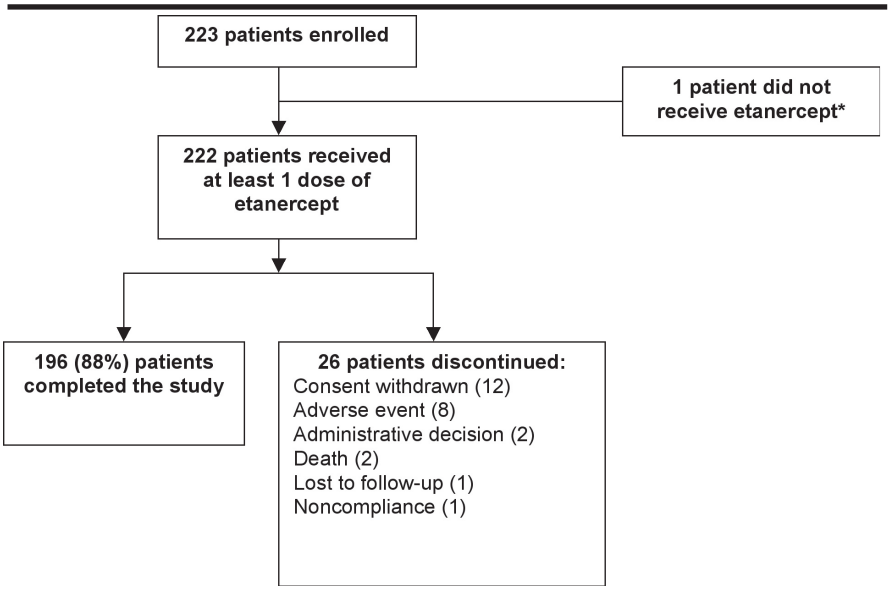


**Fig. 1.** Disposition of patients during the study. *Patient withdrew consent before receiving any study drug.

## Results

*Patients*

Of 222 patients who enrolled in the study and received at least 1 dose of etanercept, 196 (88%) completed the study. (Fig. 1 CONSORT) Twenty-six patients (12%) prematurely withdrew from the study; 12 of the patients (5%) withdrew consent for participation and 8 (4%) withdrew because of adverse events. The majority of patients (84%) were white; 81% were women. The mean age was 53 years, and the mean duration of RA was 10 years. Table I shows the baseline demographic and disease characteristics of the patients.

*Antigenicity of liquid etanercept*

Of the 222 patients who received liquid etanercept, 214 had baseline and post-baseline blood samples available for seroreactivity testing. Twelve patients (5.6%; 95% confidence interval 2.93, 9.59) tested positive for anti-etanercept antibodies in the immunoassay. All antibodies were non-neutralizing, ie, were not capable of neutralizing the biological activity of etanercept. Seven of the 12 patients had low antibody titers (< 1:50) and were considered borderline positive. Four of the 7 patients were receiving concomitant methotrexate.

Transient positive antibody status (positive at some time point and negative at a time point thereafter) was observed in 9 of the 12 patients. In 2 of the 3 patients whose positive antibody status was not transient, 1 patient tested negative for anti-etanercept antibodies at baseline and week 24 and positive at week 28; the other patient tested negative at baseline and positive at weeks 24 and 28. Antibody titers in both patients were less than 1:50. The third patient tested negative at baseline and week 28 and positive with an antibody titer of 1:50 at the end-of-study visit.

Seropositive status did not appear to have an effect on the safety profile of etanercept; rates of adverse events were similar in antibody-positive and antibody-negative patients. Table II summarizes overall adverse events by immunoassay response in the 214 patients who had blood samples tested for antigenicity. None of the 12 patients who tested positive for antibody to etanercept had serious infections or significant laboratory abnormalities. Seven of the patients had nonserious infections, and 1 patient withdrew from the trial because of an infection of the 5$^{th}$ proximal interphalangeal joint.

One of the patients had a femur fracture that was considered by the investigator to be unrelated to etanercept. No deaths occurred among the 214 patients who were tested for antibody status. However, 2 patients for whom postbaseline blood samples were not available for seroreactivity testing died during the study (see Safety section below), and thus, their antibody status is not known.

Because of the small number of patients who tested positive in the antibody immunoassay, no definitive conclusions could be drawn from subgroup analyses (age, sex, race, and baseline methotrexate use).

**Table I.** Baseline demographics and disease characteristics.

| | | 50 mg/mL Etanercept Liquid QW (N = 222) |
|---|---|---|
| Age, yrs | | |
| | Mean (SD) | 53.4 (12.0) |
| | Median (range) | 54.0 (23 - 84) |
| | < 65, n (%) | 179 (80.6) |
| | ≥ 65, n (%) | 43 (19.4) |
| Sex, n (%) | | |
| | Male | 42 (18.9) |
| | Female | 180 (81.1) |
| Race, n (%) | | |
| | White | 186 (83.8) |
| | Black | 15 (6.8) |
| | Hispanic | 11 (5.0) |
| | Other | 10 (4.5) |
| Weight, kg (n = 220) | | |
| | Mean (SD) | 80.9 (18.7) |
| | Median (range) | 77.7 (38.8 - 139.5) |
| Duration of RA, yrs | | |
| | Mean (SD) | 9.9 (9.1) |
| | Median (range) | 7.4 (0.0 - 43.8) |
| Baseline methotrexate use, n (%) | | |
| | Yes | 143 (64.4) |
| | No | 79 (35.6) |
| Baseline corticosteroid use, n (%) | | |
| | Yes | 102 (45.9) |
| | No | 120 (54.1) |
| Baseline NSAID use, n (%) | | |
| | Yes | 200 (90.1) |
| | No | 22 (9.9) |
| Signs and symptoms | | |
| | DAS28, mean score (SD) | 6.2 (1.2) |
| | Duration of morning stiffness, mean minutes/day (SD) | 260 (401) |
| Physical function, mean score (SD) | | |
| | HAQ | 1.5 (0.6) |
| | SF-36 PCS | 28.9 (9.0) |
| | SF-36 MCS | 45.7 (12.2) |

N = Number of patients enrolled who received at least 1 dose of investigational product. % = n/N * 100. QW: once weekly; SD: standard deviation; RA: rheumatoid arthritis; NSAID: nonsteroidal anti-inflammatory drug; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; SF-36 PCS: Short-Form 36 Physical Component Score; MCS: Mental Component Score.

**Table II.** Summary of adverse events by patient immunoassay response.

| | 50 mg/mL Etanercept Liquid QW. Postbaseline Immunoassay Response (N = 214) | |
|---|---|---|
| | Positive (n = 12) n (%) | Negative (n = 202) n (%) |
| Any adverse event | 10 (83.3) | 172 (85.1) |
| Adverse events related to etanercept | 4 (33.3) | 93 (46.0) |
| Severe adverse events | 1 (8.3) | 22 (10.9) |
| Injection site reactions | 3 (25.0) | 60 (29.7) |
| Serious adverse events | 1 (8.3) | 10 (5.0) |
| Infections | 7 (58.3) | 94 (46.5) |
| Serious infections | 0 | 2 (1.0) |
| Adverse events leading to etanercept withdrawal | 1 (8.3) | 7 (3.5) |
| Adverse events leading to study withdrawal | 1 (8.3) | 6 (3.0) |
| Deaths | 0 | 0 |

N: number of patients who received at least 1 dose of etanercept and had at least 1 postbaseline blood sample tested for etanercept seroreactivity. %: n/N *100. QW: once weekly.

*Other safety evaluations of liquid etanercept*

The majority of adverse events were mild or moderate, and no significant trends in laboratory results or vital signs were evident. The most common events were injection site reactions (29.3%), sinusitis (11.3%), upper respiratory infection (10.8%), and headache (7.2%). Table III describes adverse events that occurred in more than 5% of all patients. Ten patients (4.5%) discontinued etanercept treatment because of adverse events. The only event that caused discontinuation of etanercept in more than 1 patient was headache in 2 patients. The rate of serious infections was 0.053 events per patient-year, and the rate of serious adverse events was 0.149 events per patient-year.

Fourteen patients (6.3%) experienced serious adverse events, including 5 (2.3%) who had serious infections [necrotizing fasciitis (1); viral meningitis (1); cellulitis (1); bacteremia (1); and epidural abscess, osteomyelitis, and staphylococcal sepsis (1)]. Two of the 5 patients who experienced serious infections died, 1 from ischemic bowel disease (bacteremia) and the other from septic shock (staphylococcal sepsis); neither event was considered by the investigator to be related to etanercept. All other serious events resolved, except for 1 case of deep venous thrombosis that was unresolved at the patient's last assessment. Three serious events (thrombocytopenia, necrotizing fasciitis, and viral meningitis) in 3 patients were considered by the investigator to be possibly related to etanercept.

**Table III.** Adverse events reported in 5% or more of all patients.

| | 50 mg/mL Etanercept Liquid QW (N = 222) n (%) |
|---|---|
| Number of patients reporting adverse events | 188 (84.7) |
| Injection site erythema | 37 (16.7) |
| Sinusitis | 25 (11.3) |
| Upper respiratory tract infection | 24 (10.8) |
| Injection site pruritus | 21 (9.5) |
| Headache | 16 (7.2) |
| Injection site reaction | 15 (6.8) |
| Worsening of RA | 15 (6.8) |
| Injection site pain | 14 (6.3) |
| Diarrhea | 13 (5.9) |
| Fatigue | 13 (5.9) |
| Nausea | 12 (5.4) |

N: number of patients who received at least 1 dose of etanercept. n: number of patients who reported at least 1 occurrence of an adverse event. n (%): n/N *100. QW: once weekly; RA: rheumatoid arthritis.

*Efficacy of liquid etanercept*

Improvement in disease status was evident by week 12, at which time the majority of patients (62%) had at least a 20% improvement (ACR 20) in signs and symptoms of RA. The improvement remained stable through the 24 weeks of therapy. At week 24, 63% of the patients achieved an ACR 20 response, 36% an ACR 50 response, and 14% an ACR 70 response (Table IV).

Fifty percent of the patients who tested positive for anti-etanercept antibodies at any point during the study achieved an ACR 20 response at week 24, and 17% achieved an ACR 50 response; none of these patients achieved an ACR 70 response. In addition, ACR response rates in patients who were receiving methotrexate at baseline tended to be slightly higher than in patients who did not receive methotrexate, although sample sizes were small (Table V).

Improvements also were seen in the DAS28, patient's duration of morning stiffness, HAQ, and SF-36 PCS and MCS at weeks 12 and 24. Table IV summarizes mean changes from baseline in the above disease activity measurements. The proportion of patients who had remission or low disease activity (DAS28) was 27% at week 12 and 30% at week 24. Seventy percent of the patients had an MCID in the HAQ at week 12 and 74% at week 24.

## Discussion

The immunogenicity, safety, and efficacy profiles of 50 mg/mL liquid etanercept administered once weekly for 24 weeks were comparable to those of the currently approved 25 mg reconstituted formulation, which is administered either as a single dose twice weekly (3 to 4 days apart) or as 2 doses once weekly. The incidence of patients who developed anti-etanercept antibodies in this study (5.6%) was similar to that reported previously for reconstituted etanercept in controlled clinical trials (6%) and cited in the etanercept product label (7). All antibodies were non-neutralizing, i.e., did not neutralize binding of etanercept to TNF. The clinical relevance of the occurrence of these non-neutralizing antibodies is unknown, and no adverse effects on the safety or efficacy profiles were observed with liquid etanercept. While the observed incidence (3%) of patients who developed anti-etanercept antibodies in a recently published study of once weekly dosing with reconstituted etanercept in patients with RA appears lower (1), that rate was reported after only 16 weeks of etanercept exposure versus 24 weeks in this study.

The overall adverse event profile as-

**Table IV.** Efficacy assessments.

| | 50 mg/mL Etanercept Liquid QW (N = 222) | |
|---|---|---|
| | Week 12 | Week 24 |
| Signs and symptoms | | |
| ACR 20, n (%) | 137 (61.7) | 139 (62.6) |
| ACR 50, n (%) | 73 (32.9) | 79 (35.6) |
| ACR 70, n (%) | 33 (14.9) | 32 (14.4) |
| DAS28, mean change from baseline (SD) (CI) | -2.02 (1.3) | -2.24 (1.3) |
| | (-2.2, -1.8) | (-2.4, -2.1) |
| Remission (DAS28) (%) | 15 | 16 |
| Low disease activity (DAS28) (%) | 12 | 14 |
| Duration (minutes) of morning stiffness, mean change from BL (SD) (CI) | -170.8 (389.3) (-223.5, -118.1) | -191.6 (395.6) (-247.7, -135.6) |
| Physical function, mean change from baseline (SD) (CI) | | |
| HAQ | -0.5 (0.6) | -0.6 (0.6) |
| | (-0.6, -0.4) | (-0.7, -0.5) |
| HAQ, MCID (%) | 70 | 74 |
| SF-36 PCS | 7.9 (9.6) | 10.0 (9.8) |
| | (6.6, 9.2) | (8.6, 11.5) |
| SF-36 MCS | 5.3 (11.0) | 5.1 (10.7) |
| | (3.8, 6.8) | (3.6, 6.7) |

Note: For ACR 20, 50, and 70 analyses, nonresponder imputation was used for missing values. Observed values were used for all other analyses.
N = number of patients who received at least 1 dose of etanercept. n (%) = n/N *100. QW: once weekly; ACR: American College of Rheumatology; DAS: Disease Activity Score; SD: standard deviation; CI: 95% confidence interval; MCID: minimum clinically important difference; BL: baseline; HAQ: Health Assessment Questionnaire; SF-36 PCS: Short Form 36 Physical Component Score; MCS: Mental Component Score.

**Table V.** ACR response rates by prior and baseline methotrexate use.

| | | Prior methotrexate use | | Baseline methotrexate use | |
|---|---|---|---|---|---|
| | | Yes (N = 190) | No (N = 32) | Yes (N = 143) | No (N = 79) |
| ACR 20 (%) | Week 12 | 62% | 63% | 62% | 61% |
| | Week 24 | 63% | 59% | 67% | 54% |
| ACR 50 (%) | Week 12 | 33% | 31% | 34% | 30% |
| | Week 24 | 35% | 38% | 41% | 27% |
| ACR 70 (%) | Week 12 | 15% | 16% | 15% | 15% |
| | Week 24 | 14% | 19% | 16% | 11% |

Note: Prior methotrexate use = patients started methotrexate on or before the first dose of etanercept. Baseline methotrexate use = patients were taking methotrexate when they received the first dose of etanercept.
ACR: American College of Rheumatology.

sociated with the 50 mg/mL liquid etanercept formulation was similar to that reported in the product label for the reconstituted formulation. The frequency, severity, and nature of injection site reactions, the most common events, were consistent with those seen with reconstituted etanercept. In controlled studies of patients who received reconstituted etanercept for rheumatoid arthritis, 37% had injection site reactions (mostly mild to moderate in intensity) (7) compared with 29% of patients in this study. Serious infections occurred in 2.3% of the patients in this study compared with 1% in studies with reconstituted etanercept (7). The infection rates are consistent with expectations based on observations from studies of the background rate of serious infections in the RA population. Those estimates range from 0.03 to 0.12 events per patient-year (8-10) compared with 0.053 events per patient-year in this 6-month study.

The improvements in the signs and symptoms of RA and in patient physical functioning that were observed with 50 mg/mL liquid etanercept were similar to the improvements seen with the reconstituted formulation in previous studies. In this study, the percentage of patients who had ACR 20, 50, and 70 responses at week 24 was 63%, 36%, and 14%, respectively. In 2 studies with reconstituted etanercept, the percentage of patients who had ACR 20, 50, and 70 responses at week 24 was 59%, 40%, and 15%, respectively, in a long-term RA study (11) and 65%, 40%, and 21% in a study in patients with early RA (12).

A single, 50 mg/mL liquid etanercept dose administered once weekly for 24 weeks was safe, well tolerated, and effective in patients with RA. This liquid etanercept formulation, conveniently packaged in prefilled syringes, replaces the need for reconstitution and injection of 2 doses of the lyophilized formulation without compromising efficacy or safety.

## Acknowledgements

We thank Marshelle Warren, MD, and Pirow Bekker, MD, PhD, for their contributions to this project; Ellen Lin for statistical programming and analysis, and Julie Wang and Orysia V. Lutz for assistance with writing the manuscript.

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