# A Phase 2 Dose-Finding Study of PEGylated Recombinant Methionyl Human Soluble Tumor Necrosis Factor Type I in Patients with Rheumatoid Arthritis

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***ABSTRACT.*** ***Objective.*** In a phase 2 study, to assess the efficacy and safety of pegsunercept, a soluble tumor necrosis factor receptor type I, for the treatment of rheumatoid arthritis (RA).

***Methods.*** Patients were randomized to receive weekly subcutaneous injections of placebo (n = 61) or active drug [400 $\mu$g/kg (n = 67) or 800 $\mu$g/kg (n = 66)] for 12 weeks. The primary efficacy endpoint was American College of Rheumatology 20% response (ACR20) at Week 12. Secondary efficacy measures included ACR50 and ACR70 responses, and changes in individual ACR components at Week 12. Safety assessments included summaries of adverse events including infectious episodes.

***Results.*** Treatment with pegsunercept resulted in a significantly higher ACR20 response at Week 12 in the 800 $\mu$g/kg group (45%) compared with the placebo group (26%; p = 0.020). The treatment effect of pegsunercept (both doses) over the study period showed statistically significant improvement for most ACR components and health related quality of life, with the 800 $\mu$g/kg group showing greater clinical improvements in efficacy measures. The overall incidence of adverse events and infectious episodes was similar among the treatment and placebo groups.

***Conclusion.*** In this 12 week dose-finding study of 194 patients, weekly subcutaneous dosing with pegsunercept showed beneficial effects in improving the signs and symptoms of RA. It appeared to be safe and well tolerated in this small number of patients. Significant clinical improvements were seen in patients in the 800 $\mu$g/kg group; however, this dose may be suboptimal, and further evaluation of this product with higher doses or a more frequent dosing regimen is warranted. (J Rheumatol 2005;32:2303–10)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS
CLINICAL TRIAL
TUMOR NECROSIS FACTOR INHIBITOR
TUMOR NECROSIS FACTOR-RECEPTOR TYPE I

Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune, inflammatory disorder that affects roughly 1% of the population in the United States and is characterized by synovial inflammation that can progress to cartilage destruction, bone erosion, and joint deformity[1,2]. Patients with RA are at risk of becoming severely disabled and having a significantly reduced quality of life, and are more susceptible to diseases that can result in premature death[3,4].

The proinflammatory cytokine tumor necrosis factor (TNF) has been shown to play a pivotal role in mediating acute and chronic inflammation by binding to specific cell-surface receptors[5-7]. Soluble TNF receptors (sTNF-R) are naturally-occurring monomeric fragments that make up the extracellular portion of the cell-surface receptors. Increased concentrations of sTNF-R have been found circulating in the blood of patients with RA[7-9]. Current treatment of active RA includes therapeutic agents that reduce biologically active concentrations of TNF: infliximab (Remicade®)[10] and adalimumab (Humira™)[11], which are monoclonal antibodies to TNF, and etanercept (Enbrel®)[12], a p75 type II TNF soluble receptor developed with recombinant technology. Pegsunercept, a p55 type I TNF receptor, is evaluated here.

Pegsunercept, also known as r-metHu-sTNF-RI or PEG sTNF-RI, is a truncated form of the original natural receptor molecule with a high molecular weight 30 kDa polyethylene

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glycol (PEG) molecule attached at the N-terminus (met-1) position[13]. Preclinical studies to date suggest that pegsunercept is efficacious in several well characterized, predictive rodent models of established and developing arthritis[14,15]. In both adjuvant and collagen induced arthritis models, treatment with pegsunercept significantly inhibited the amount of joint swelling. Histopathological analysis showed reduced inflammation, pannus, cartilage damage, and bone damage.

In addition to the efficacy observed in animal models, a multicenter, randomized, double blind, placebo controlled, dose escalation trial of subcutaneously administered pegsunercept in patients with RA showed that the molecule is well tolerated[16,17]. Although seroreactivity to PEG sTNF-RI was observed in a small number of patients (4 of 133 patients; 3%), it was not dose- or time-dependent, and no neutralizing antibodies were observed. The pharmacokinetics of pegsunercept did not change after multiple administrations[16]. This trial suggested that pegsunercept is pharmacologically active in RA based on reductions in the number of swollen and tender/painful joints[16,17].

The objective of the phase 2, multicenter, dose-finding study reported here was to assess the efficacy and safety of 2 doses of pegsunercept (400 or 800 $\mu$g/kg) administered weekly for 12 weeks for the treatment of RA.

## MATERIALS AND METHODS

*Patients*. The ethics committee at each of the 15 US sites approved the study protocol, and patients gave written informed consent before any study related procedures were conducted. Eligibility was determined from assessments performed at a screening visit (14 to 28 days before baseline) and at baseline.

Patients were at least 18 years of age at the time of RA diagnosis. All patients had RA defined by American College of Rheumatology (ACR) 1987 criteria, with a disease duration ≥ 6 months and American Rheumatism Association anatomical stage II or III disease. Patients had at least 10 swollen and 12 tender/painful joints, not including distal interphalangeal joints, at screening and baseline, based on a 66/68 joint count. In addition to the joint count requirement, patients had morning stiffness with a duration of at least 45 minutes, C-reactive protein (CRP) ≥ 1.5 mg/dl, or erythrocyte sedimentation rate (ESR) ≥ 28 mm/h. In addition, patients had radiographic evidence of at least one bone erosion in their hands, wrists, or feet. Patients had to have previously taken one or more disease modifying antirheumatic drugs (DMARD); doses of background DMARD had to be stable for at least 8 weeks before initiating study drug treatment. The following combinations of background DMARD were permitted during the study: methotrexate (MTX) plus sulfasalazine, MTX and hydroxychloroquine, or all 3 (MTX, sulfasalazine, and hydroxychloroquine). The addition of new RA medications during the study was not permitted. The use of intraarticular injections (e.g., corticosteroids, hyaluronic acid) or analgesics other than acetaminophen, nonsteroidal antiinflammatory drugs (NSAID), codeine, oxycodone, propoxyphene, tramadol, and hydrocodone was not permitted. Rescue analgesics, such as acetaminophen, codeine, and/or propoxyphene, were not permitted within 12 hours before a scheduled study evaluation.

Patients receiving NSAID and/or low doses of corticosteroids (up to 10 mg/day of prednisone or equivalent) for symptomatic relief of RA were eligible for screening, and they were required to be taking stable doses for 4 weeks before starting study drug treatment. In addition to the requirements for stable doses of NSAID, corticosteroids, and DMARD before enrollment, patients were required to continue their background RA medications at the same doses during the study. However, the use of background DMARD was not required during the study.

Exclusion criteria were pregnancy or breast-feeding, previous treatment with any protein-based TNF inhibitors, and injection of intraarticular or systemic corticosteroids within the previous 4 weeks. Patients were also excluded if they had: diabetes mellitus requiring insulin; any uncontrolled, clinically significant systemic disease (e.g., chronic obstructive pulmonary disease, congestive heart failure, or stroke); a malignancy (other than basal cell carcinoma or *in situ* carcinoma of the cervix within the past 5 years); a history of drug or alcohol abuse (within the previous 6 months); or other chronic inflammatory disease (e.g., spondyloarthropathy or inflammatory bowel disease). Patients with infections requiring systemic antiinfective therapy, a history of frequent acute or chronic infections (within the past 3 months), and patients known to be positive for hepatitis B surface antigen, hepatitis C virus, or human immunodeficiency virus were excluded.

*Study design*. Patients who met the inclusion criteria were randomized equally to one of 3 treatment groups: placebo, 400 $\mu$g/kg pegsunercept, or 800 $\mu$g/kg pegsunercept. A weekly dosing regimen was chosen because the pharmacokinetic half-life of pegsunercept is 82 ± 17 hours, determined in a previous study[16]. Pegsunercept (Amgen Inc., Thousand Oaks, CA, USA) and placebo were supplied as lyophilized powder and were reconstituted with sterile water. Subcutaneous injections of study drug were administered weekly by healthcare professionals. Patients and study staff were blinded to treatment assignment.

All patients who received at least one dose of study drug were included in the analyses of efficacy and safety. Efficacy was assessed using the ACR composite score and individual components. Joint evaluations were based on assessment of 68 joints for tenderness or pain, and 66 joints for swelling and effusion. The physician and patient global assessments of disease activity and patient assessment of pain were measured using visual analog scales. Function was assessed using the Health Assessment Questionnaire (HAQ). Health related quality of life (HRQOL) was examined using the Short-Form Health Survey (SF-36) questionnaire, which assesses overall physical and psychosocial status of patients[18]. The 8 domains in this questionnaire were summarized using physical and mental component summary scores.

*Efficacy endpoints*. The primary efficacy endpoint in this study was the proportion of patients achieving ≥ 20% improvement in signs and symptoms of RA at Week 12 compared with baseline (ACR20 response). Secondary efficacy measures included ACR50 and ACR70 responses, HAQ, and HRQOL.

While not specified as an endpoint, it was hypothesized that treatment with pegsunercept would result in a clinically relevant improvement in the signs and symptoms of RA, prospectively defined as a delta of 25% in the ACR20 response at Week 12 compared with placebo, i.e., the ACR20 response for the treatment group would be at least 25 percentage points higher than the response in the placebo group. The clinical significance of improvements in HAQ scores from baseline were described as a minimally clinically important difference (MCID) for changes greater than 0.22 and a clinically important difference for changes greater than 0.4 units[19].

*Safety evaluation*. Safety evaluations included assessment of adverse events, serious adverse events, infectious episodes, serious infections, injection site reactions, antibodies to PEG sTNF-RI, and patient withdrawals from study. Adverse events were grouped according to body systems affected and by preferred term within the body system according to a modified World Health Organization adverse reaction term dictionary[20].

Plasma samples for determining anti-PEG sTNF-RI antibody levels were collected before study drug administration at baseline and at study weeks 4, 8, and 12. Antibody levels were assessed using microtiter plates coated with capture antigen and blocked with 2% bovine serum albumin blocking buffer. Samples and controls were diluted and added to the assay plates. An alkaline phosphatase anti-human immunoglobulin M (IgM) or biotin chicken anti-human immunoglobulin G (IgG) secondary antibody

was added to detect captured antibodies. A substrate system was used for color development and the optical density was read using a plate reader spectrophotometer at 450 and 490 nm. To be considered seropositive, the mean optical density of the postdose sample had to be at least twice the mean optical density of the predose sample.

*Statistical analysis*. The primary analysis of ACR20 response at Week 12 consisted of individual pairwise comparisons of each pegsunercept dose group to placebo. Sample size estimates were calculated for this analysis: 60 patients per treatment group provided an 80% chance of detecting a clinically relevant treatment effect of at least 25% for at least one pegsunercept treatment group. Adjustments for multiple comparisons were made using Dunnett's multiple comparison procedure with a 1-tailed alpha level of 0.027. This analysis was a nonresponder imputation in which patients were considered to be ACR nonresponders if their ACR criteria could not be evaluated because of missing data, if they discontinued drug before the evaluation point, or if they received new or increased doses of corticosteroids or DMARD while on study.

A test for dose-response of ACR20, ACR50, and ACR70 responses was conducted using the Jonckheere-Terpstra test adjusted for center, with a 0.025 significance level. For each of the ACR components, the average change from baseline at Weeks 4 and 12 was assessed using a repeated-measures, mixed-model analysis of covariance.

## RESULTS

*Patient population*. Patient disposition is shown in Figure 1. One hundred ninety-five patients were randomized into the study, of whom 133 were allocated to pegsunercept and 62 were allocated to placebo. One hundred ninety-four patients (133 pegsunercept, 61 placebo) received study drug and were included in the modified intent-to-treat analysis (all randomized patients who received at least one dose of study drug). The rate of discontinuation was 4.8% in the placebo group, 10.4% in the 400 $\mu$g/kg group, and 3.0% in the 800 $\mu$g/kg group, and did not appear to be dose related. Twelve patients did not complete the study. Six patients withdrew because of non-serious adverse events, 5 patients withdrew consent, and one patient withdrew from the trial because of lack of efficacy.

Patient demographics and disease severity are shown in Table 1. Sixty-nine percent of the placebo group were female, whereas over 80% in each of the pegsunercept groups were female. Mean duration of RA at baseline across all treatment groups was 12.7 to 15.4 years.

Background medication use was similar among the treatment groups at baseline (Table 1). More than half the patients were receiving MTX alone or in combination with other DMARD at baseline (placebo 52%, 400 $\mu$g/kg group 64%, and 800 $\mu$g/kg group 55%). About 20% of patients were taking a single DMARD other than MTX. Previous DMARD use was similar across the treatment groups. Baseline values for ACR components were similar across the treatment groups and were typical for patients with active RA (Table 2).

*Efficacy results*. The ACR20 response at Week 12 was significantly higher in the 800 $\mu$g/kg group (45%) than in the placebo group (26%; p = 0.020; Figure 2); however, the difference in ACR20 response between the 800 $\mu$g/kg group and the placebo group was 19 percentage points, less than the hypothesized criterion for clinically relevant improvement of 25 percentage points. The ACR20 response rate for patients in the 400 $\mu$g/kg group was not significantly higher than that of the placebo group (31% vs 26%; p = 0.556). After adjustment for center, the ACR20 response indicated a statistically significant dose-response trend across placebo and the 2 pegsunercept dose groups (p = 0.017).

ACR50 scores at Week 12 for the 400 and 800 $\mu$g/kg groups were 11% and 22%, respectively, compared with an ACR50 response of 8% in the placebo group. ACR70 scores at Week 12 were comparable among the 3 treatment groups (placebo 3%; 400 $\mu$g/kg group 1%; 800 $\mu$g/kg group 5%).

Absolute values for baseline ACR components are given in Table 2, and changes from baseline over time are given in Figure 3. The treatment effect of pegsunercept over the study period was statistically significant, with improvement

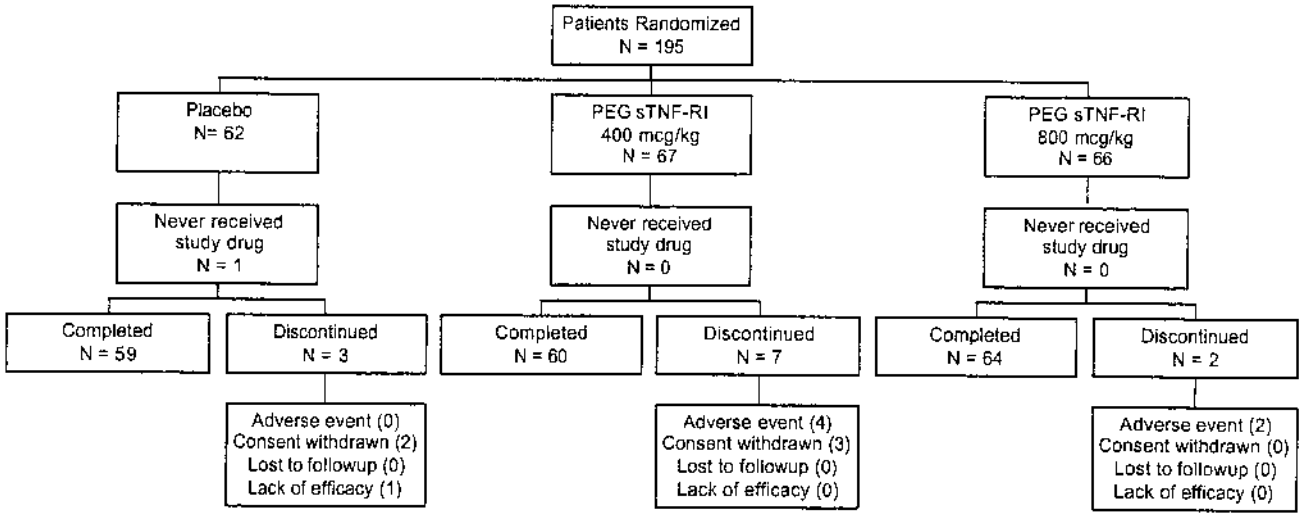


*Figure 1*. Patient disposition during the study.

*Table 1.* Baseline demographics, disease severity, and medication use.

| | Placebo (N = 61) | Pegsunercept 400 μg/kg (N = 67) | Pegsunercept 800 μg/kg (N = 66) |
|---|---|---|---|
| Baseline demographics and disease severity* | | | |
| Sex female, n (%) | 42 (69) | 57 (85) | 55 (83) |
| Race Caucasian, n (%) | 53 (87) | 61 (91) | 54 (82) |
| Age, yrs, mean (SD) | 53.7 (11.2) | 55.4 (11.3) | 55.9 (12.5) |
| Weight, kg, mean (SD) | 81.2 (23.0) | 77.8 (22.0) | 73.8 (19.8) |
| Rheumatoid factor-positive, n (%) | 48 (79) | 48 (72) | 50 (76) |
| Duration of RA, yrs, mean (SD) | 12.7 (9.0) | 15.4 (10.2) | 13.6 (9.6) |
| Baseline medication use* | | | |
| NSAID use, n (%) | 49 (80) | 51 (76) | 52 (79) |
| Corticosteroid use, n (%) | 39 (64) | 34 (51) | 39 (59) |
| DMARD use, n (%) | | | |
| No DMARD | 15 (25) | 11 (16) | 18 (27) |
| MTX alone | 21 (34) | 28 (42) | 29 (44) |
| A single DMARD other than MTX** | 14 (23) | 13 (19) | 12 (18) |
| MTX and 1 other DMARD | 11 (18) | 11 (16) | 6 (9) |
| MTX and 2 other DMARD | 0 (0) | 4 (6) | 1 (2) |
| No. of previous DMARD, mean (SD) | 2.8 (2.0) | 2.7 (1.9) | 2.6 (1.9) |

* For patients who received at least 1 dose of study drug. ** Includes 2 patients who had 2 baseline DMARD with no MTX. N: number of subjects randomized who received at least 1 dose of study drug; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease modifying antirheumatic drug; MTX: methotrexate.

*Table 2.* Baseline disease characteristics.

| | Placebo (N = 61) mean ± SD | Pegsunercept 400μg/kg (N = 67) mean ± SD | Pegsunercept 800μg/kg (N = 66) mean ± SD |
|---|---|---|---|
| Tender/painful joint count (0–68) | 30 ± 14 | 30 ± 13 | 29 ± 13 |
| Swollen joint count (0–66) | 25 ± 12 | 24 ± 13 | 24 ± 12 |
| Physician global assessment (0–100) | 65 ± 17 | 65 ± 15 | 60 ± 16 |
| Patient global assessment (0–100) | 56 ± 21 | 58 ± 19 | 56 ± 23 |
| Patient assessment of pain (0–100) | 59 ± 19 | 59 ± 18 | 57 ± 20 |
| Health Assessment Questionnaire (0–3) | 1.6 ± 0.5 | 1.5 ± 0.5 | 1.5 ± 0.6 |
| C-reactive protein, mg/dl | 2.8 ± 2.4 | 3.2 ± 3.4 | 3.7 ± 5.1 |
| Erythrocyte sedimentation rate, mm/h | 35 ± 22 | 37 ± 26 | 41 ± 30 |
| Duration of morning stiffness, min/day | 143 ± 171 | 137 ± 183 | 148 ± 245 |
| SF-36 HRQOL | | | |
| Mental component summary | 48.9 ± 11.4 | 47.9 ± 12.0 | 48.6 ± 9.9 |
| Physical component summary | 26.7 ± 7.0 | 27.3 ± 7.2 | 28.5 ± 8.8 |

N: number of subjects randomized who received at least 1 dose of study drug.

in all individual ACR components except tender/painful and swollen joint count and CRP (p values ranged from < 0.001 to 0.031). Pairwise comparisons of change from baseline between each dose of pegsunercept and placebo at Week 12 showed statistically significant improvements in all individual ACR components (p values ranged from < 0.001 to 0.037; Figure 3) except for CRP (in the 400 μg/kg and 800 μg/kg groups) and tender/painful joint counts (in the 400 μg/kg group). Pairwise comparisons of ESR changed from baseline at Weeks 4 and 12 between the placebo group and the 400 and 800 μg/kg pegsunercept dose groups, respectively, showing statistically significant reductions (Figure 3).

Significant reductions in the duration of morning stiffness compared with placebo were seen at Week 12 for the 400 μg/kg pegsunercept group (75 vs 35 min/day; p = 0.012) and the 800 μg/kg pegsunercept group (94 vs 35 min/day; p < 0.001).

The mean HAQ values at baseline were 1.6 (of 3.0) in the placebo group and 1.5 in both pegsunercept groups. After 12 weeks the mean HAQ score in the placebo group decreased by 0.2, whereas mean HAQ score in the 400 μg/kg group decreased by 0.3 (p = 0.073 compared with placebo). The mean HAQ score for the 800 μg/kg group decreased by 0.4 (p = 0.005 compared with placebo) at Week 12. This

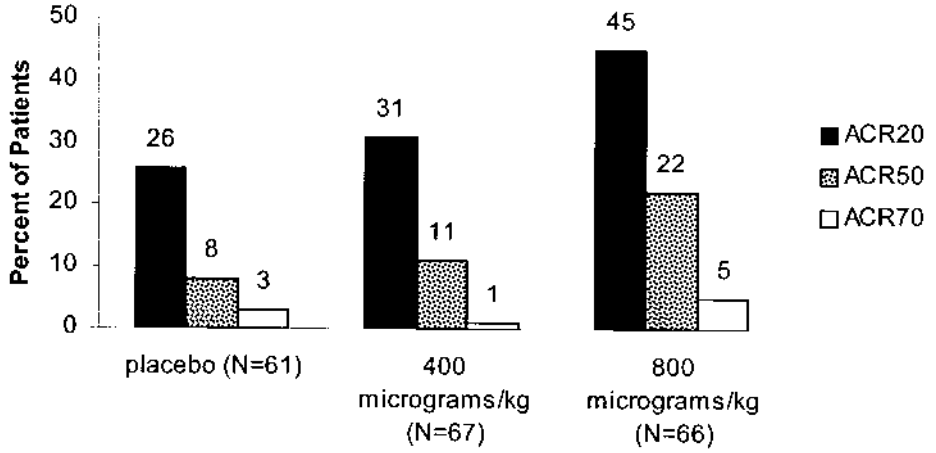


*Figure 2*. Proportion of patients achieving an ACR response by visit week using nonresponder imputation. N: number of subjects randomized who received at least one dose of study drug. The ACR20 score for the 800 $\mu$g/kg group is significantly greater than in the placebo group (p = 0.02).

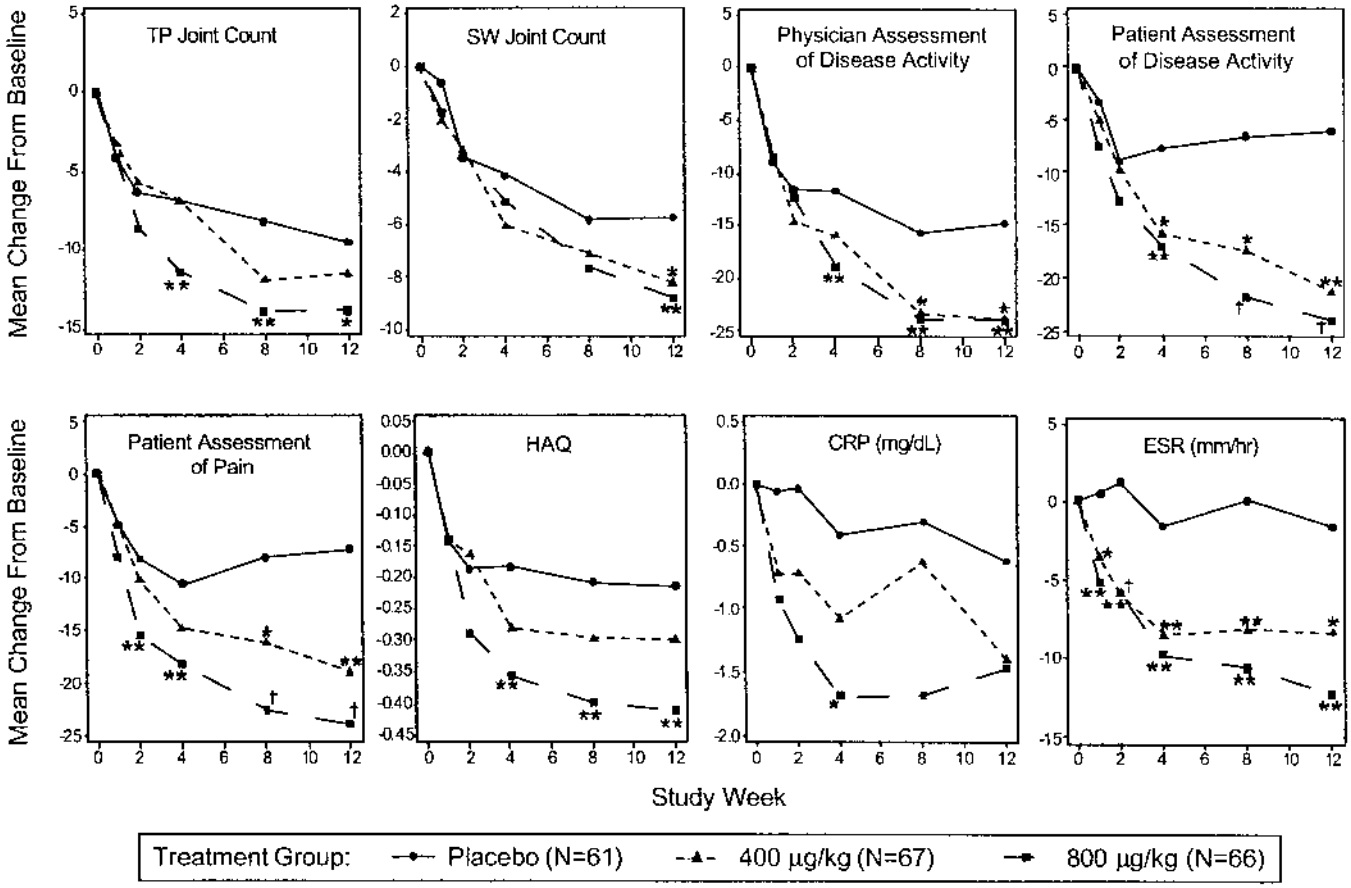


*Figure 3*. ACR component scores. •p < 0.05, **p < 0.01, †p < 0.001 compared with placebo. TP: tender/painful, SW: swollen, HAQ: Health Assessment Questionnaire, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate. Absolute baseline values are given in Table 2.

improvement borders on the accepted criterion for clinically important difference in HAQ score of > 0.4.

HRQOL showed a significant treatment effect with PEG sTNF-RI for all 8 domains over the study period (p values ranged from < 0.001 to 0.047). At Week 12, pairwise comparisons of change from baseline in HRQOL domains for the 400 $\mu$g/kg group versus the placebo group showed statistically significant improvement (p values ranged from 0.001 to 0.024) in role physical, bodily pain, general health, vitality, social functioning, mental health, and the mental

component summary. Pairwise comparisons of the 800 μg/kg group with the placebo group showed statistically significant improvements (p values ranged from < 0.001 to 0.029) for all HRQOL domains except general health. The physical component summary change from baseline at Week 12 was 3.1 (1.1 standard error) for the placebo group, 6.1 (1.1 SE) for the 400 μg/kg group (p = 0.058), and 7.3 (1.1 SE) for the 800 μg/kg group (p = 0.006). The mental component summary change from baseline at Week 12 was –0.3 (1.2 SE) for the placebo group, 4.8 (1.3 SE) for the 400 μg/kg group (p = 0.003), and 4.4 (1.2 SE) for the 800 μg/kg group (p = 0.005).

*Safety.* The overall incidence of adverse events was similar across treatment groups and did not show a dose-dependent effect. Adverse events were reported in 72% of patients in the placebo group and 400 μg/kg groups and 68% of the patients in the 800 μg/kg group (Table 3). The most frequently reported adverse events, by preferred term, were diarrhea (8% for the 400 μg/kg group, 8% for the 800 μg/kg group, 3% for the placebo group); injection site erythema (8% for the 400 μg/kg group, 8% for the 800 μg/kg group, 2% for the placebo group); urinary tract infection (7% for the 400 μg/kg group, 8% for the 800 μg/kg group, 2% for the placebo group); and upper respiratory infection (4% for the 400 μg/kg group, 8% for the 800 μg/kg group, 12% for the placebo group). Most adverse events were mild to moderate in severity. Severe adverse events were experienced by 7% of patients in the placebo group, 5% of patients in the 400 μg/kg group, and 3% of patients in the 800 μg/kg group. There was no apparent dose-response effect in rates of adverse events, with the exception of injection site reactions.

Injection site reactions were reported in 6 of 61 (10%) patients in the placebo group, 12 of 67 (18%) in the 400 μg/kg group, and 14 of 66 (21%) in the 800 μg/kg group, illustrating a dose-response trend. The most frequent injection site reaction in the placebo group was injection site pain, which was reported by 8% of patients, versus 3% and 5% of patients in the 400 and 800 μg/kg groups, respectively. Injection site erythema and pruritus were the most common type of injection site reaction in the pegsunercept groups (erythema occurred in 8% and 8% of patients in the 400 μg/kg and 800 μg/kg groups, respectively; pruritis occurred in 5% and 6% in the 400 μg/kg and 800 μg/kg groups, respectively). All injection site reactions were mild (aware of sign or symptom but easily tolerated) to moderate (discomfort enough to cause interference with usual activity) in severity, and none was considered a serious adverse event by the regulatory definition. Four patients withdrew from the study due to injection site reactions related to pegsunercept: 2 from the 400 μg/kg group and 2 from the 800 μg/kg group.

The overall incidence of infectious episodes was comparable across treatment groups: 26% in the placebo group, 27% in the 400 μg/kg group, and 30% in the 800 μg/kg group. The most frequently reported infectious episodes were urinary tract infection (8% for the 400 μg/kg group, 8% for the 800 μg/kg group, 2% for the placebo group) and upper respiratory tract infection (5% for the 400 μg/kg group, 8% for the 800 μg/kg group, 12% for the placebo group). No opportunistic infections were reported.

Two patients experienced serious adverse events during the study: a 58-year-old man in the 800 μg/kg pegsunercept group was hospitalized with hypoxia secondary to chronic obstructive pulmonary disease, and a 51-year-old woman taking placebo was hospitalized with acute cholecystitis. Both serious adverse events resolved with treatment and were deemed unrelated to study drug, and neither resulted in premature withdrawal from the study.

Seropositivity to pegsunercept was observed in 4 patients (2.1%) during the study. At Week 4, 2 patients (one in each pegsunercept dose group) were pegsunercept (IgM) seropositive and one (in the 400 μg/kg group) was pegsunercept (IgG) seropositive. The IgM seropositive patient in the 800 μg/kg group withdrew from the study due to an injection site reaction. The other 2 patients were seronega-

*Table 3.* Summary of adverse events (AE).

| | Placebo (N = 61) n (%) | Pegsunercept 400μg/kg (N = 67) n (%) | Pegsunercept 800μg/kg (N = 66) n (%) |
|---|---|---|---|
| Overall AE | 44 (72) | 48 (72) | 45 (68) |
| Deaths | 0 | 0 | 0 |
| Serious AE | 1 (1.6) | 0 | 1 (1.5) |
| Severe AE* | 4 (6.6) | 3 (4.5) | 2 (3.0) |
| Withdrawal due to AE | 0 | 4 (6) | 2 (3) |
| Infectious episodes | 16 (26) | 18 (27) | 20 (30) |
| Serious infections | 1 (1.6) | 0 | 0 |
| Injection site reactions | 6 (10) | 12 (18) | 14 (21) |

* Includes severe, life-threatening adverse events. N: number of subjects randomized who received at least 1 dose of study drug. n: number of patients with event type.

tive by Week 8. A fourth patient (in the 800 μg/kg dose group) was pegsunercept (IgG) seropositive at Week 12. This patient subsequently entered the extension study, and none of the samples collected in that study exhibited evidence of neutralizing antibodies.

## DISCUSSION

Phase 2 studies are generally designed to identify the best dose to use in larger, well controlled studies in phase 3 of a drug's development. In this study, the ACR20 response at Week 12 for the 800 μg/kg dose group of pegsunercept showed statistically significant improvements compared with the placebo group, while the 400 μg/kg dose group did not show an ACR20 response that was substantially different from placebo. Further, clinical improvements were seen in a greater number of efficacy measures in the 800 μg/kg dose group than in the 400 μg/kg dose group compared with the placebo group.

Pairwise comparisons of changes from baseline for the 800 μg/kg dose group showed significant improvements for ACR components (except tender/painful joint count and CRP) and morning stiffness compared with placebo at Week 12. In addition, improvements in HAQ exceeded the MCID and were considered to be clinically important differences from baseline. HRQOL showed statistically significant improvements in changes from baseline at Week 12 for 9 of 10 domains (all domains except general health). The ACR50 response was 22% and ACR70 response was 5% in the 800 μg/kg group at Week 12; however, this timepoint may be too early to see more robust improvements.

Although the hypothesized specification for clinically relevant improvement (at least a 25 percentage point difference compared with placebo) was not achieved, treatment with 800 μg/kg of pegsunercept once weekly nevertheless resulted in statistically significant improvements, illustrating that this is an effective, although possibly not the best, dose.

Direct comparison of efficacy responses from patients taking different TNF inhibitors is difficult, in part, because of intrinsic differences between the p55 type I TNF receptor and p75 type II TNF receptor. Both receptors function as TNF buffers but exhibit different kinetics of binding to TNF-α and may have fundamentally different functions; the type II receptor may serve to deliver TNF-α to the type I receptor for enhanced signaling at low TNF-α concentrations[7,21].

Moreover, patient groups from clinical trials differ with respect to background RA medications and duration of treatment with TNF inhibitors. In this study, more than half of the patients in each treatment group received MTX with or without other DMARD (Table 1). Although this subgroup of RA patients might be considered to be less likely to respond to therapy (they had had RA for 12 or more years, they had taken 2.8 previous DMARD on average, and they still had active disease at study entry), they did show a reasonable response to treatment with pegsunercept. In this study, a trend toward a dose-dependent efficacy response was evident with pegsunercept treatment with respect to some variables (including ACR20, ACR50, HAQ, and the physical component summary of the SF-36); treatment with the 800 μg/kg dose resulted in the highest responses.

Rates of serious adverse events and infectious episodes in patients treated with pegsunercept for 12 weeks ranged from 0% to 2% and did not exceed those of placebo. Injection site reactions were seen in 21% of patients receiving 800 μg/kg pegsunercept (vs 10% in the placebo group). This compares with 42% of patients receiving etanercept plus MTX (vs 7% placebo plus MTX)[21] and 15% of patients receiving adalimumab plus MTX (vs 3% placebo plus MTX)[11] in other studies. The withdrawal rate for injection site reactions related to pegsunercept treatment in this study was low (3%).

In summary, weekly administration of 800 μg/kg pegsunercept for 12 weeks demonstrated a beneficial treatment effect in improving signs and symptoms of RA. The ACR20 response at Week 12 was statistically significantly higher for patients in the 800 μg/kg group compared with the placebo group. However, the difference in ACR20 response compared with placebo was less than the predefined requirement of 25%; thus, the study did not achieve this efficacy goal. Patients in the 800 μg/kg group had clinically significant improvements in most secondary efficacy endpoints compared with the placebo group, and Health Assessment Questionnaire scores showed clinically relevant improvements at both the 400 μg/kg and 800 μg/kg dose levels. No clinically significant safety concerns were identified with use of pegsunercept in the treatment of RA.

Pegsunercept, a soluble TNF receptor type I, appeared to be safe and well tolerated in this 12 week dose-finding study. Further evaluation of this product with higher doses or a more frequent dosing regimen is warranted.

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