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Two-Year Maintenance of Efficacy and Safety of Infliximab in the Treatment of Ankylosing Spondylitis

J Braun,^{1,2} J Brandt,¹ J Listing,³ A Zink,³ R Alten,⁴ G Burmester,⁵ W Golder,¹
E Gromnica-Ihle,⁶ H Kellner,⁷ M Schneider,⁸ H Sörensen,⁹ H Zeidler,¹⁰ J
Reddig,¹¹ J Sieper^{1,3}

¹University Medicine Berlin, Campus Benjamin Franklin, Germany;

²Rheumatology Medical Center Ruhrgebiet, Herne, Germany; ³German
Rheumatism Research Center, Berlin, Germany; ⁴Schlosspark Clinic, Berlin,
Germany; ⁵Charité Hospital, Humboldt University, Berlin, Germany; ⁶Berlin-
Buch Hospital, Berlin Germany; ⁷Ludwig-Maximilians-University, Munich,
Germany; ⁸Heinrich-Heine-University, Düsseldorf, Germany; ⁹Immanuel
Hospital, Berlin, Germany; ¹⁰Medical University, Hannover, Germany; ¹¹Essex
Pharma, Munich, Germany

The first two authors have equally contributed to this paper.

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Contact Information for Corresponding Author and Reprint Requests:

Prof. Dr. J. Braun

Rheumazentrum Ruhrgebiet

Landgrafenstr. 15,

44652 Herne,

Germany

Telephone: 0049/2325/592-131

Fax: 0049/2325/592-136

e-mail: J.Braun@Rheumazentrum-Ruhrgebiet.de

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ABSTRACT

Objective: This report provides results of the second-year extension of the original 3-month randomized, placebo-controlled trial (and the 1-year extension study) assessing the use of infliximab, a monoclonal antibody to tumour necrosis factor alpha (TNF- α), for the treatment of patients with ankylosing spondylitis (AS).

Methods: Of the 54 AS patients who completed the first year of the study, 52 continued to receive infliximab 5 mg/kg every 6 weeks through week 102. The primary endpoint was the proportion of patients achieving at least 50% improvement from baseline in the Bath AS Disease Activity Index (BASDAI) at week 102. Other assessments included patient and physician global assessments, quality of life as assessed by Short Form-36, Bath AS Functional Index, Bath AS Metrology Index, and C-reactive protein (CRP).

Results: Improvement in signs and symptoms of AS observed during the first year of the study was sustained during the second year. Forty-nine patients (71%, 49/69, of enrolled patients and 94%, 49/52, of patients who started year 2) completed the study through week 102. Thirty patients (58%) achieved at least 50% improvement from baseline in the BASDAI score at week 102. Scores for other efficacy assessments were similar at weeks 54 and 102. Median CRP levels remained low at weeks 54 and 102 (3.9 and 4.3 mg/L, respectively). The side effect profile during the second year of the study was similar to that of the first year of treatment with infliximab.

Conclusions: AS patients treated for 2 years with infliximab 5 mg/kg exhibited a good and durable clinical response.

Key words: ankylosing spondylitis, TNF α , infliximab

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, immune-mediated, inflammatory disease that involves the sacroiliac joints, axial skeleton, entheses, and, occasionally, peripheral joints. Until recently, treatment of AS has typically consisted of a chronic regimen of nonsteroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. Although NSAIDs can relieve pain to allow for increased spinal movement, they appear to have little effect on the underlying inflammatory process unless used daily as indicated by one recent study [1]. Disease modifying antirheumatic drugs (DMARDs) that are used successfully in patients with rheumatoid arthritis are only partially effective in treating patients with AS [2].

Agents that target the proinflammatory cytokine tumor necrosis factor alpha (TNF- α) have recently been identified as a possible alternative to existing therapies for AS [3]. In 2002, we reported the results of a 12-week, double-blind, placebo-controlled study of infliximab in patients with AS [4]. Patients receiving infliximab showed significant improvement in measurements of disease activity, physical function, and quality of life compared with those receiving placebo [4]. This response was shown to be durable for up to a full year in an open-label extension, during which patients in the placebo group crossed over at week 12, and all patients subsequently received infusions of infliximab 5 mg/kg every 6 weeks [5]. This open-label phase of the study was extended for a second year to further assess the long-term efficacy and safety of infliximab. Here, we present findings from the second year of the study.

METHODS

Patients and Study Protocol

The eligibility criteria and the study design of the 12-week, randomized, placebo-controlled phase of the study [4] and the 1-year extension study [5] have been reported previously. Sixty-nine patients with active AS participated in the original study. Active AS was defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of at least 4 and a spinal pain assessment score of at least 4 (on a numerical rating scale [NRS] ranging from 0 to 10). Throughout the 2-year study, concomitant DMARDs and oral corticosteroids were not permitted. NSAID use was permitted, and the dosages of NSAIDs could have been reduced during the study. However, NSAID dosages could not have been increased over the baseline level.

Patients who completed the first year of the study were eligible to continue with the extension study through week 102. Patients who chose to participate in the second year of the study received open-label infusions of infliximab 5 mg/kg every 6 weeks beginning with the week-54 infusion. Study medication was manufactured by Centocor, Inc. and was packaged and labeled for the study by Essex Pharma (Munich, Germany).

The study was conducted at eight centers in Germany, all of which had patients who participated in the second year of the study. The local independent ethics committees approved the original study protocol and the second-year extension. All patients who chose to participate in the second year of the study provided written informed consent.

Assessments

Disease activity was assessed using the BASDAI, which consists of six questions relating to fatigue, spinal pain, peripheral arthritis, enthesitis, and morning stiffness [6]. The Bath AS Functional Index (BASFI), a 10-item questionnaire used to assess the patient's ability to conduct daily activities, was used to measure physical function [7]. The Bath AS Metrology Index (BASMI [8]) was used to grade mobility of the spine and hip by measuring tragus to wall, lumbar flexion, cervical rotation, lumbar side flexion, and intermalleolar distance on a scale of 1 to 10. Patient and physician global disease assessments and assessments of spinal pain were measured using a NRS ranging from 0 to 10. Health-related quality of life was assessed using the Short Form (SF)-36 instrument [9]. The scoring algorithm of the Medical Outcome Trust [10] was used to calculate the SF-36 physical and mental component summary scores.

Partial remission was assessed by using the criteria of the Assessment in Ankylosing Spondylitis (ASAS) Working Group [11]. Furthermore, the ASAS 40%' and ASAS 5 out of 6' criteria recently proposed were applied [12]. ASAS 40% improvement is defined as an improvement of at least 40% and an absolute improvement of at least 2 units (on a 0 to 10 scale) in at least three domains and no deterioration in the fourth remaining domain. The four following domains were used in the assessment: patient's global assessment, pain, function (represented by the BASFI score), and inflammation (represented by the mean of the two morning stiffness scales of the BASDAI). To meet the ASAS 5 out of 6 criteria a 20% improvement in any five of the following six domains is required: the four domains used for ASAS 40% and

the following two domains: acute phase reactants (assessed by C-reactive protein [CRP]), and spinal mobility (assessed by BASMI score).

Statistical Analysis

Two different analysis populations, intent-to-treat (ITT) and the second year study population, were used in the analyses. In the ITT analysis, data for all patients randomized who fulfilled the inclusion criteria (n=69, Figure 1) were included. In analysis based on the second year study population, data for 52 patients who participated in the second year of follow up were included (Figure 1). The primary efficacy endpoint was the proportion of patients achieving at least 50% improvement from baseline to week 102 in the BASDAI score. Secondary endpoints were the proportion of patients at week 102 achieving 20% or 70% improvement from baseline in the BASDAI score, the proportion of patients achieving the ASAS 40% and ASAS 5 out of 6 criteria as well as change from baseline to week 102 in spinal pain, BASDAI score, BASFI score, BASMI score, SF-36 physical and mental component summary scores, CRP, and erythrocyte sedimentation rate (ESR). Patients who withdrew were considered to be BASDAI/ASAS nonresponders for every missing visit. To calculate the means for the second year study population, data for the last observation was carried forward to the endpoint for patients who discontinued prematurely. To compare mean differences between time points (week 0 versus week 102, week 54 versus week 102), the paired t-test was applied. In the case of skewed distributions (CRP, ESR) the corresponding nonparametric test (Wilcoxon test) was used. The McNemar test was used to compare frequencies between different points in time. Furthermore, a recently proposed nonparametric dropout test was applied to

investigate if the dropout could be considered as a random sample from the ITT study population in respect to selected parameters [13].

RESULTS

Results of the first 3 months [4] and the first year [5] of this study have been reported previously. Fifty-four patients (78%) completed the study through week 54. Of the patients who completed the first year of the study, 52 patients (96%) chose to continue with the second year (second year study population). Two patients withdrew from the study. One patient withdrew because of personal reasons (wanted a pregnancy) and one reported lack of efficacy. Sixty-four percent of the patients were men, the mean age was 38.8 years, and the mean weight was 73.0 kg. Forty-nine of the original 69 patients (71%) completed the entire 102-week study, representing 94% of the patients who started year 2. Three patients discontinued the study during the second year of treatment because of adverse events (Figure 1).

Efficacy

ITT analysis. Similar and stable response rates over two years were observed in the analysis of the data of the complete ITT population (Figure 2). Although each patient who discontinued was counted as nonresponder, no significant decrease in the response rates of the primary efficacy endpoint (BASDAI 50% response) was observed for the two treatment groups as well as for the total group (Figure 2a). At week 54, 47% of the patients in the infliximab and 51% of the patients in the placebo infliximab group achieved a 50% improvement in the BASDAI score from baseline. At week 102 these figures were 41% and 49%, respectively (Figure 2a). The evaluation of the ASAS 40% criteria and the ASAS 5 out of 6 criteria among the 69 patients who fulfilled the inclusion

criteria also showed comparable levels of response at each time point over 2 years of follow up (Figure 2b and 2c).

Analysis of the second year study population. Thirty patients (58%, 30/52) achieved the primary efficacy endpoint of at least a 50% reduction of the BASDAI score from baseline to week 102. This level of response was similar to that observed at week 54 when 33 patients (63%) achieved at least 50% improvement in the BASDAI score. The BASDAI 50% response was consistent over the entire second year of the study, with 30 or more patients achieving at least 50% improvement at each assessment point. Forty-nine (94%) and 44 (85%) patients achieved at least 20% improvement in BASDAI at weeks 54 and 102, respectively. The proportions of patients achieving at least a 70% reduction in BASDAI score from baseline were the same at weeks 54 and 102 (22 patients, 42%).

The sustained response observed for the BASDAI was consistent with results obtained for the other clinical assessments of AS (Table 1, Figure 3). Almost all parameters showed a statistically significant change from baseline to week 102 ($p < 0.0001$); as expected, changes from week 54 to week 102 were not significant (Table 1). Specifically, the mean BASFI score was 3.0 at both weeks 54 and 102. The mean BASMI scores were 2.4 and 2.7 at weeks 54 and 102, respectively (Table 1, Figure 3). The individual parameters of the BASMI showed no substantial changes during the study period (Table 2). Patients' and physicians' global disease assessments and physical and mental components summary scores of the SF-36 were similar between weeks 54 and 102 (Table 1). The median ESR remained stable (≤ 8.0 mm/hr)

between weeks 54 and 102; the median CRP serum level showed a minor increase from 3.9 mg/L at week 54 to 4.3 mg/L at week 102 (Table 1).

Notably, the median CRP remained well below the mean baseline value of 21.5 mg/L.

At week 102, 13 patients (25%) achieved partial remission, two additional patients in comparison to those who had achieved remission at week 54.

Enthesitis was evident in seven patients, which was consistent with findings at previous time points. Peripheral arthritis was reported in six patients, which represented an increase of five patients in comparison to with the number reported at week 54 ($p > 0.05$; Table 3).

Through week 54, 17 patients dropped out of the study (mean infliximab treatment of 30 ± 14.4 weeks). The baseline disease characteristics of these patients were similar to those of patients who remained in the study (Table 4). At their last visit these patients had, on average, higher values for BASDAI, physician global, and CRP than those who participated in the second year of follow up. For this reason, results for the complete ITT study population are also provided (Figures 2a, 2b, 2c).

Adverse Events

During the second year of this study, 47 patients (90%) reported adverse events (Table 5). The most frequently reported events were upper respiratory tract infections (17%), rhinitis (13%), and herpes simplex (12%).

Six patients (12%) reported serious adverse events that were considered to be clinically relevant. The events for four of these patients were considered by the investigator to be unrelated to study medication (osteoporosis, euphoria/syncope, pancreatitis, and menorrhagia; each in one patient). The patient with osteoporosis, a 32-year-old man, was diagnosed by dual-energy x-ray absorptiometry (DXA) in the 1st year of the study by a routine examination. It could not be ascertained whether the bone density had changed during the study. The patient continued to receive infliximab after the diagnosis. Two serious adverse events (infusion-associated symptoms and musculoskeletal pain, each in one patient) were considered to be possibly related to study medication. Five other patients reported surgical procedures or rehabilitation measures that were considered to be clinically irrelevant and unrelated to study medication (e.g., correction of the nasal septum, plastic surgery of the patella, treatment at a health resort [two patients], foot operation, and thyroid surgery).

Three patients (6%) discontinued infliximab due to the adverse events reported above. Two of these patients had infusion-associated reactions that led to discontinuation. The third patient discontinued therapy after reporting an exacerbation of pre-existing pancreatitis, which the investigator considered to be unrelated to study treatment.

DISCUSSION

These data for the 2-year open-label extension study of infliximab in patients with AS suggest sustained efficacy and safety of this biologic. The original randomized, controlled, clinical trial conducted over 3 months [4] and the 1-year open-label phase [5] were extended for a second year to further investigate the efficacy and safety of this therapy in patients with severe AS. The high level of response observed during the first year of the study was maintained throughout the second year, with similar proportions of patients achieving the primary endpoint of at least 50% improvement in the BASDAI score at week 54 (63%) and week 102 (58%). It is especially relevant that patients remained in a state of low disease activity through week 102, as evidenced by the clinical assessments made, including BASDAI, BASFI, BASMI, the global scores and quality of life (SF-36). Scores for these parameters were similar at the 1- and 2-year assessment time points, indicating continuous improvement of clinical symptoms and a durable clinical response to infliximab. Thus, in patients with AS who were treated continuously using a maintenance regimen with infusions at regular intervals, we did not observe the reduction in efficacy that was reported in patients with Crohn's disease who received infusions at irregular intervals [14].

Infliximab was generally well tolerated by patients with AS participating in this study. The adverse events observed during the second year of treatment were similar to those reported for the first year and were consistent with the known safety profile of infliximab. There were no more reports of lupus-like syndrome, serious infections, or tuberculosis. Few patients discontinued treatment during the second year, and only two patients did have infusion-

related reactions that led to discontinuation. Additionally, the overall discontinuation rate (8%) during the second year of the study was lower than that observed during the first year of the study (22%) and also lower than that observed during the second year of the anti-TNF trial in rheumatoid arthritis (RA) with Concomitant Therapy (ATTRACT) (17%, 43/259), the pivotal phase 3 trial of infliximab in RA [15].

To our knowledge, this is the longest treatment and follow-up experience described in the literature for an anti-TNF agent in patients with AS. The results show maintenance of the clinical benefit observed during the first year of the study throughout the second year and that infliximab therapy was generally well tolerated through 2 years of treatment. Additional long-term studies of infliximab in AS are warranted using larger patient populations.

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Tables:

Table 1. Assessment of response to all clinical parameters after 54 and 102 weeks of therapy for all 52 patients who participated in the second year study population.

| Assessment | Baseline | Week 54 | Week 102 | p- value wk. 0 vs. wk. 102 | p-value wk. 54 vs. wk. 102 |
|---------------------------------|-----------|-----------|-----------|----------------------------------|----------------------------------|
| Global disease assessment (VAS) | | | | | |
| Patient (0 – 10 cm) | 6.9 ± 1.9 | 2.8 ± 1.9 | 2.6 ± 2.0 | <0.0001 | 0.39 |
| Physician (0 – 10 cm) | 6.3 ± 1.6 | 2.2 ± 1.5 | 2.0 ± 1.4 | <0.0001 | 0.14 |
| BASDAI | 6.4 ± 1.4 | 2.5 ± 1.7 | 2.6 ± 2.0 | <0.0001 | 0.61 |
| BASFI | 5.2 ± 1.9 | 3.0 ± 2.2 | 3.0 ± 2.2 | <0.0001 | 0.88 |

| | | | | | |
|--------------------|-----------------|--------------|--------------|---------|-------|
| BASMI | 3.8 ± 2.0 | 2.4 ± 2.0 | 2.7 ± 2.1 | <0.0001 | 0.038 |
| CRP median (range) | 21.5 (0.9-74.0) | 3.9 (0-17.8) | 4.3 (0-42.7) | <0.0001 | 0.51 |
| ESR median (range) | 25.0 (3-88) | 8.0 (1-70) | 7.5 (2-70) | <0.0001 | 0.39 |
| SF-36 | | | | | |
| Physical component | 29.3 ± 7.0 | 40.6 ± 10.6 | 40.9 ± 11.1 | <0.0001 | 0.73 |
| Mental component | 42.3 ± 12.2 | 50.9 ± 8.9 | 50.2 ± 9.5 | <0.0001 | 0.47 |

Table 2. The individual aspects of the BASMI, as assessed for the second year study population at baseline, week 54, and after two years (week 102).

| BASMI n (%) | Baseline | Week 54 | Week 102 | p- value wk. 0 vs. wk. 102 | p- value wk. 54 vs. wk. 102 |
|----------------------------------|-----------|-----------|-----------|----------------------------------|-----------------------------------|
| Tragus wall distance < 15 cm | 41 (78.8) | 43 (82.7) | 39 (75.0) | 0.73 | 0.13 |
| Lumbar flexion > 4 cm | 4 (7.7) | 17 (32.7) | 12 (23.1) | 0.021 | 0.18 |
| Cervical rotation > 70° | 7 (13.5) | 25 (48.1) | 20 (38.5) | 0.002 | 0.18 |
| Lateral lumbar flexion > 10 cm | 23 (44.2) | 32 (61.5) | 32 (61.5) | 0.012 | 1.0 |
| Intermalleolar distance > 100 cm | 30 (57.7) | 38 (73.1) | 38 (73.1) | 0.021 | 1.0 |

Table 3. Partial remission, enthesitis and arthritis for the 52 patients who participated in the second year of the study at baseline, week 54, and week 102, with data about the 95% confidence interval for each assessed parameter.

| Assessment | Baseline | Week 54 | Week 102 | p- value wk. 0 vs. wk. 102 | p- value wk. 54 vs. wk. 102 |
|--------------------------|-----------|-----------|-----------|----------------------------------|-----------------------------------|
| Partial remission | | | | | |
| n (%) | 0 | 11 (21.2) | 13 (25.0) | 0.0002 | 0.73 |
| 95% CI | | (12-34) | (15-38) | | |
| Enthesitis | | | | | |
| n (%) | 23 (42.2) | 7 (13.5) | 7 (13.5) | 0.0004 | 1.00 |
| | (32-58) | (7-25) | (7-25) | | |

| | | | | | |
|-------------|-----------|-----------|-----------|---------|-------|
| 95% CI | | | | | |
| Arthritis | | | | | |
| n (%) | 18 (34.6) | 1 (1.9) | 6 (11.5) | 0.004 | 0.063 |
| 96% CI | (23-48) | (0-10) | (5-23) | | |
| CRP ≤6 mg/L | | | | | |
| n (%) | 12 (23.1) | 43 (82.7) | 41 (78.8) | <0.0001 | 0.79 |
| 95% CI | (14-36) | (70-91) | (66-88) | | |

Table 4. Disease characteristics at baseline and at the last visit of the drop out; patients not included in the 2-year-analysis (n=17).

| Assessment | Mean±SD | p-value* | Mean±SD | p-value* |
|-------------------------------|-------------|----------|---------------|----------|
| | At baseline | | At last visit | |
| Physician global (VAS 0 – 10) | 6.4 ± 1.3 | 0.85 | 4.0 ± 1.9 | 0.03 |
| BASDAI | 6.3 ± 11 | 0.60 | 5.0 ± 2.0 | 0.02 |
| BASFI | 5.5 ± 2.4 | 0.61 | 4.3 ± 3.0 | 0.12 |
| CRP, mg/L (median,range) | 19 (3-131) | 0.88 | 6 (1-91) | 0.04 |

* In comparison to the n=52 patients included in the primary analyses.

Table 5. Summary of the adverse events reported for all 52 patients who participated in the second year of the study.

| Assessment | Year 2 study population (n = 52) |
|---|-------------------------------------|
| Patients reporting at least 1 adverse event | 47 (90%) |
| Patients who discontinued the study due to an adverse event | 3 (6%) |
| Patients reporting at least 1 clinically relevant serious adverse event | 6 (12%) |
| Patients reporting at least 1 treatment-related* serious adverse event | 2 (4%) |
| Most frequently reported adverse events (≥ 5% of patients) | |
| Upper respiratory tract infections | 9 (17%) |
| Rhinitis | 7 (13%) |
| Herpes simplex | 6 (12%) |
| Influenza-like symptoms | 5 (10%) |
| Pulmonary infection | 5 (10%) |
| Antinuclear factor test positive | 4 (8%) |
| Infusion-associated symptoms | 4 (8%) |
| Hepatic enzymes increased | 4 (8%) |
| Bronchitis | 4 (8%) |
| Headache | 3 (6%) |

| | |
|--------------------|--------|
| Fatigue | 3 (6%) |
| Dry eyes | 3 (6%) |
| Allergy | 3 (6%) |
| Accidental injury | 3 (6%) |
| SGPT increased | 3 (6%) |
| Menorrhagia** | 1 (5%) |
| Fungal vaginitis** | 1 (5%) |

*The determination of an event's relationship to treatment was made by the investigator.

**Percentage is based on the population of women only.

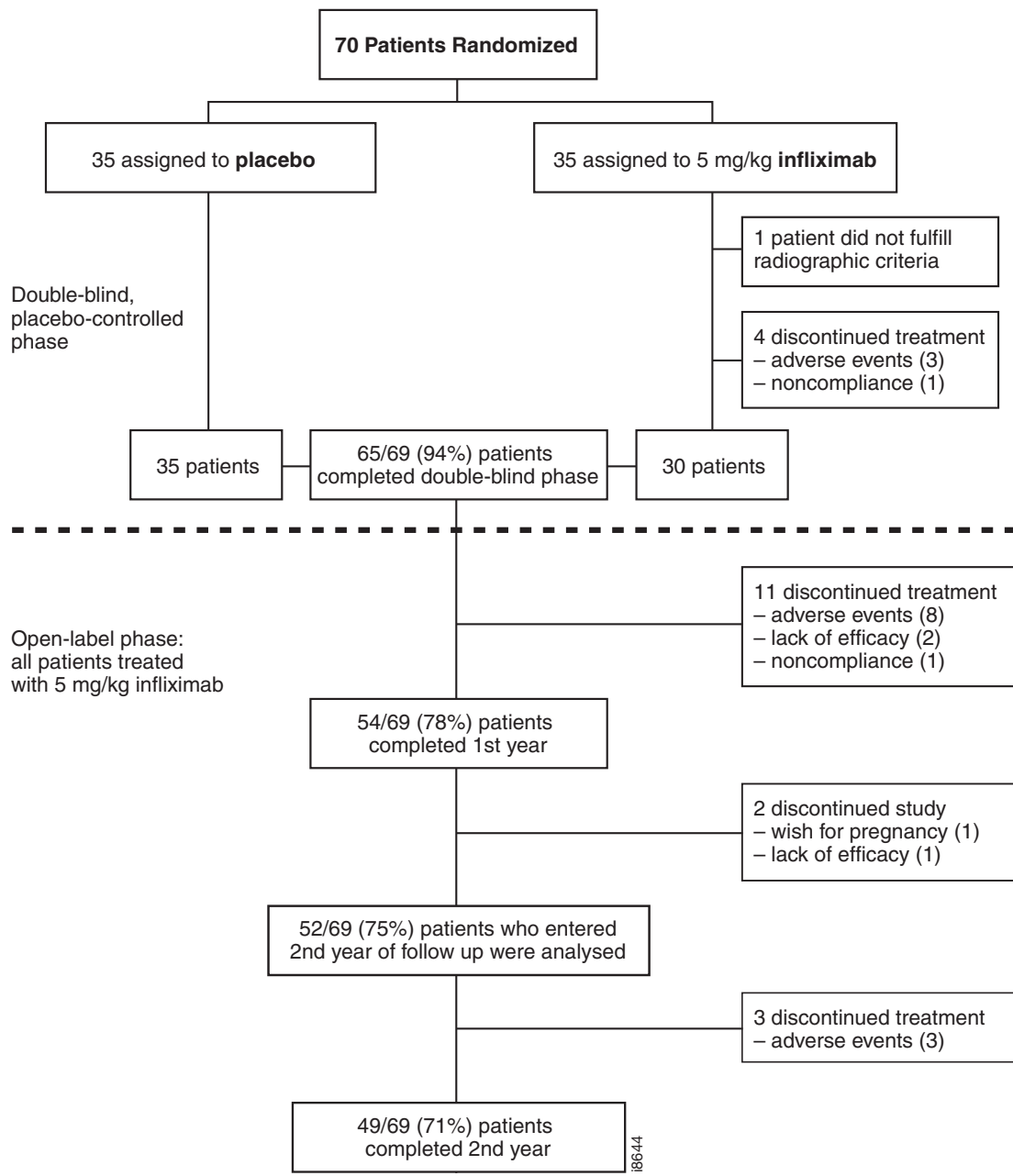
Figure Legends

Figure 1. Summary of Patient Disposition through week 102.

Figure 2 a-c. Maintenance of response to infliximab treatment (ITT study population), as assessed by Figure 2a: at least 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Figure 2b: at least 40% improvement in the criteria of the Assessment in Ankylosing Spondylitis (ASAS) working group and Figure 2c: improvement of at least 20% in the 'ASAS 5 out of 6' criteria for ankylosing spondylitis.

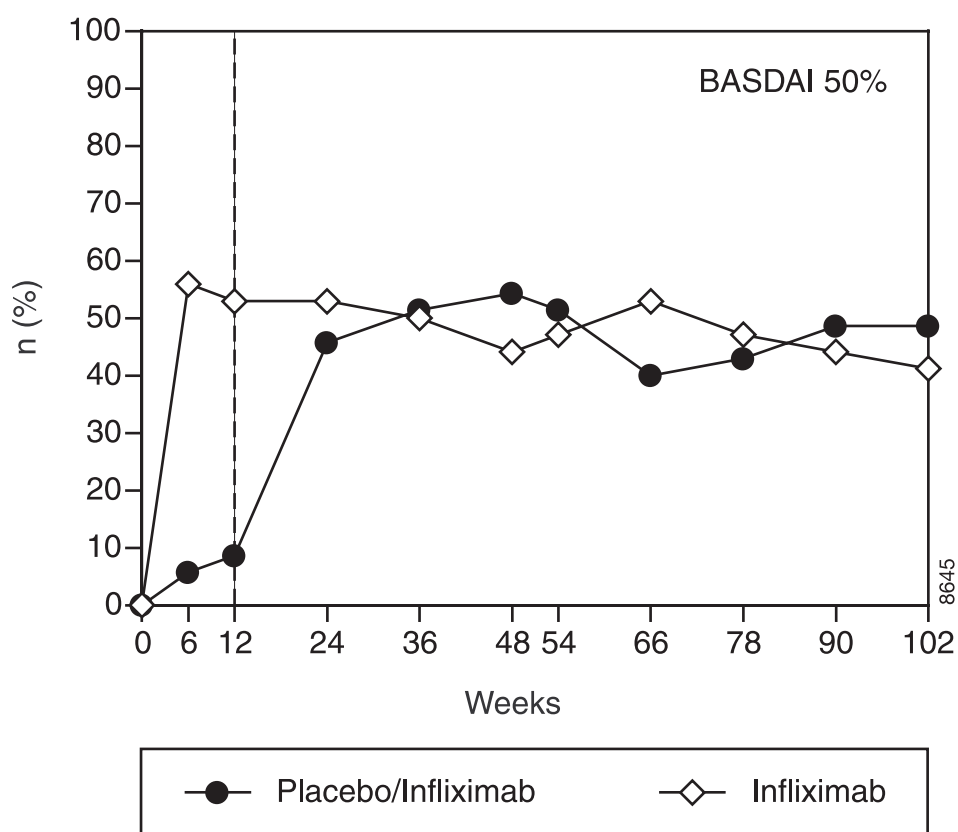
Figure 3. Sustained improvement of patients of the second year study population over 2 years of follow up, as assessed by the mean BASDAI, mean BASFI and mean BASMI.

Figure 1



18644

Figure 2a



8645

Figure 2b

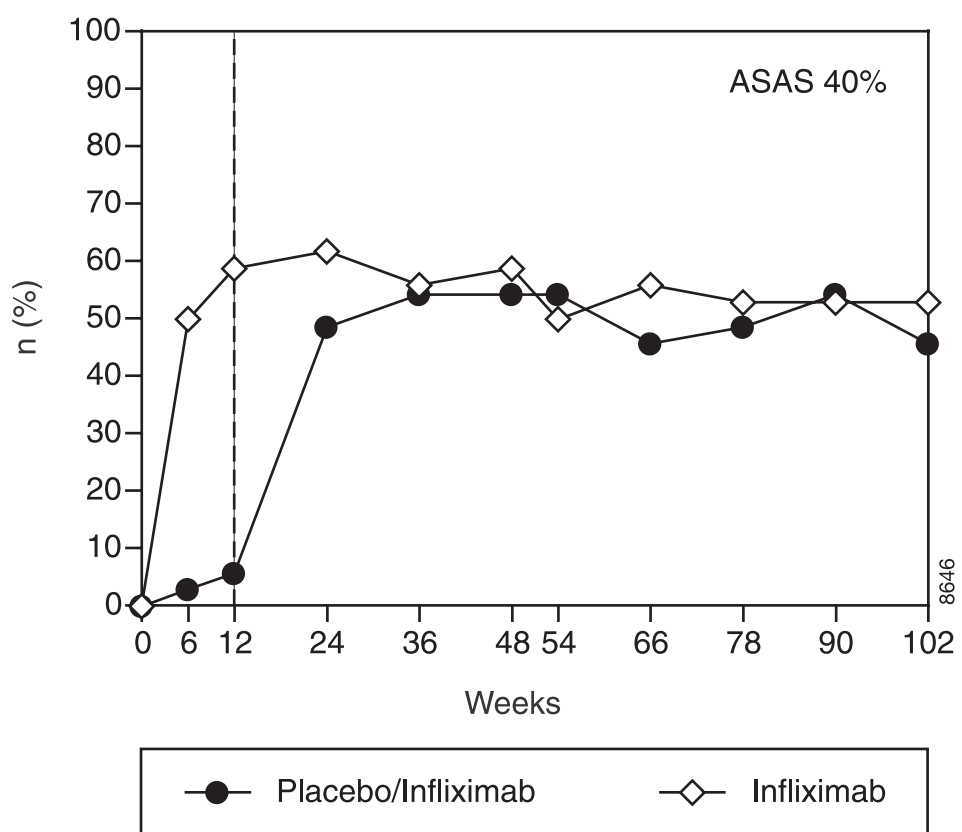


Figure 2c

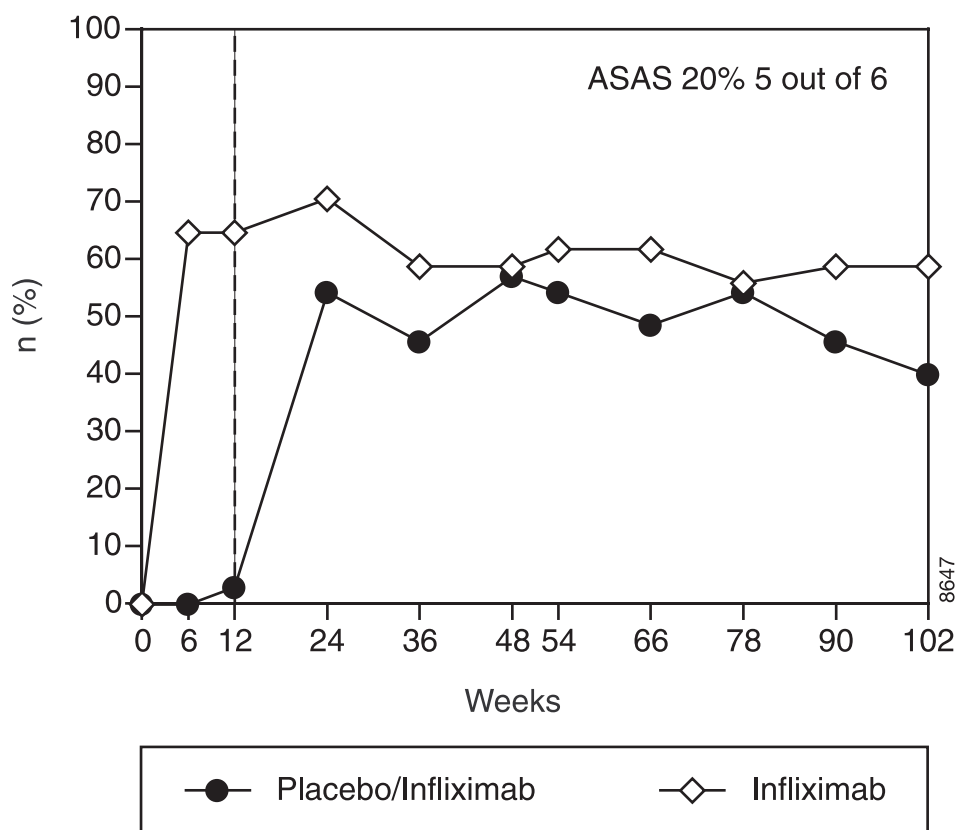
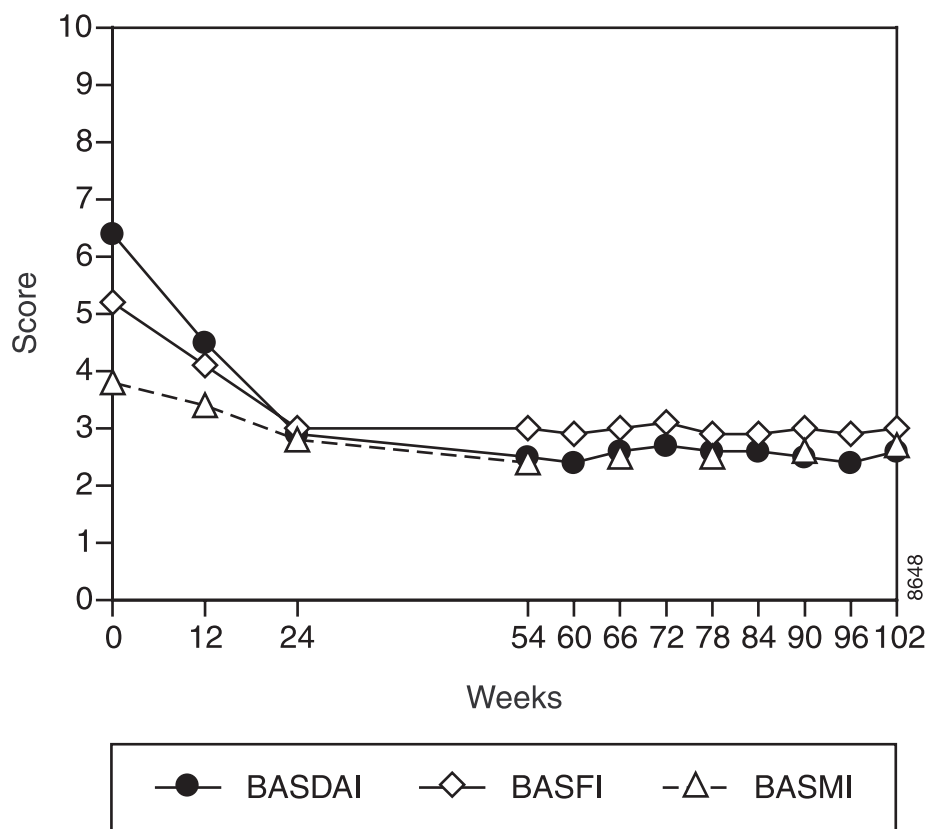


Figure 3



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