The Efficacy and Safety of Abatacept in Patients With Non–Life-Threatening Manifestations of Systemic Lupus Erythematosus

Results of a Twelve-Month, Multicenter, Exploratory, Phase IIb, Randomized, Double-Blind, Placebo-Controlled Trial

J. T. Merrill, R. Burgos-Vargas, R. Westhovens, A. Chalmers, D. D'Cruz, D. J. Wallace, S. C. Bae, L. Sigal, J.-C. Becker, S. Kelly, K. Raghupathi, T. Li, Y. Peng, M. Kinaszczuk, and P. Nash

Objective. To evaluate abatacept therapy in patients with non–life-threatening systemic lupus erythematosus (SLE) and polyarthritis, discoid lesions, or pleuritis and/or pericarditis.

Methods. In a 12-month, multicenter, exploratory, phase IIb randomized, double-blind, placebo-controlled trial, SLE patients with polyarthritis, discoid lesions, or pleuritis and/or pericarditis were randomized at a ratio of 2:1 to receive abatacept (10 mg/kg of body weight) or placebo. Prednisone (30 mg/day or equivalent) was given for 1 month, and then the dosage was tapered. The primary end point was the proportion of patients with new flare (adjudicated according to a score of A/B on the British Isles Lupus Assessment Group (BILAG) index after the start of the steroid taper.

Results. A total of 118 patients were randomized to receive abatacept and 57 to receive placebo. The baseline characteristics were similar in the 2 groups. The proportion of new BILAG A/B flares over 12 months was 79.7% (95% confidence interval [95% CI] 72.4, 86.9) in the abatacept group and 82.5% (95% CI 72.6, 92.3) in the placebo group (treatment difference –3.5 [95% CI –15.3, 8.3]). Other prespecified flare end points were not met. In post hoc analyses, the proportions of abatacept-treated and placebo-treated patients with a BILAG A flare were 40.7% (95% CI 31.8, 49.5) versus 54.4% (95% CI 41.5, 67.3), and the proportions with physician-assessed flare were 63.6% (95% CI 54.9, 72.2) and 82.5%

ClinicalTrials.gov identifier: NCT00119678.

Supported by Bristol-Myers Squibb, Princeton, NJ. Bristol-Myers Squibb also funded the editorial assistance provided by Medicus International. Dr. Westhovens holds the UCB Pharma Chair of Rheumatoid Arthritis Care at Katholieke Universiteit Leuven.

J. T. Merrill, MD: Oklahoma Medical Research Foundation, Oklahoma City; R. Burgos-Vargas, MD: Hospital General de México, Mexico City, Mexico; R. Westhovens, MD, PhD: UZ Gasthuisberg, Leuven, Belgium; A. Chalmers, MD, FRCPC: University of British Columbia, Vancouver, British Columbia, Canada; D. D'Cruz, MD, FRCP: The Rayne Institute and St. Thomas' Hospital, London, UK; D. J. Wallace, MD: Cedars-Sinai Medical Center and David Geffen School of Medicine at the University of California, Los Angeles; S. C. Bae, MD, PhD, MPH: Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea; L. Sigal, MD (current address: Novo Nordisk, Princeton, NJ), J.-C. Becker, MD, S. Kelly, MD, T. Li, PhD, M. Kinaszczuk, RPh, BS: Bristol-Myers Squibb, Princeton, New Jersey; K. Raghupathi, MSc, Y. Peng, PhD: Bristol-Myers Squibb, Pennington, New Jersey; P. Nash, MBBS, FRACP: University of Queensland, Brisbane, Queensland, Australia.

Dr. Merrill has received consulting fees from Bristol-Myers Squibb (less than $10,000) and serves as a consultant for investment analysts through vetted sources requiring only disclosure/discussion of public information. Dr. Burgos-Vargas has received consulting fees, speaking fees, and/or honoraria from Schering-Plough, Abbott, Wyeth, Bristol-Myers Squibb, and Roche (less than $10,000 each). Dr. Westhovens has received consulting fees from Roche, Centocor, and Schering-Plough (less than $10,000 each) and consulting and speaking fees from Bristol-Myers Squibb (more than $10,000). Dr. D'Cruz has received consulting fees from Bristol-Myers Squibb and has served as a member of their Advisory Board (less than $10,000). Drs. Sigal, Becker, Kelly, Li, and Peng, Mr. Raghupathi, and Mr. Kinaszczuk own stock or stock options in Bristol-Myers Squibb. Dr. Becker is a named employee of Bristol-Myers Squibb on a patent for abatacept (CTLA-4Ig), for which he receives no royalties. Dr. Nash has received consulting fees, speaking fees, and/or honoraria from Bristol-Myers Squibb (less than $10,000).

Address correspondence and reprint requests to J. T. Merrill, MD, Oklahoma Medical Research Foundation, 825 NE 13th Street, Oklahoma City, OK 73104. E-mail: joan-merrill@omrf.org.

Submitted for publication December 15, 2009; accepted in revised form June 3, 2010.
with SLE pathology. T cells also stimulate B cells and the high-affinity IgG autoantibodies that are associated with B cells plays an important role in the production of immune processes. The interaction of T cells pathogenesis of SLE (7), acting as mediators of down-for the control of SLE. T cells are central to the lymphocyte activation may represent a rational strategy disease activity suggests that targeting mechanisms of immune response that intensifies during periods of high and T cells (6). The involvement of an ongoing cellular domain of human CTLA-4 linked to IgG1, which selectively modulates the CD80/CD86:CD28 co-stimulatory signal. The use of abatacept for up to 5 years in patients with rheumatoid arthritis (RA) is associated with sustained efficacy and acceptable safety (10–12). The efficacy and safety of abatacept in patients with juvenile idiopathic arthritis (JIA) have also been shown (13). Abatacept currently has Food and Drug Administration (FDA) and European Medicines Agency (EMA; formerly the European Medicines Evaluation Agency [EMEA]) approval for the treatment of moderate-to-severe RA, and for JIA. Since abatacept modulates T cell activation and interactions between activated T cells and B cells play a central role in antibody production and other B cell functions, the investigation of this treatment for other autoimmune diseases, such as SLE, seems appropriate.

We present herein the results of the first trial to assess the effects of abatacept on disease flares in patients with non–life-threatening SLE whose primary manifestations were active polyarthritis, chronic cutaneous (discoid) lesions, or serositis (pleuritis and/or pericarditis).

**PATIENTS AND METHODS**

**Study design.** This 12-month, multicenter, exploratory, phase Ib, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov identifier NCT00119678) (14) was approved by the appropriate Institutional Review Boards/Independent Ethics Committees and was performed in accordance with the ethical principles of the Declaration of Helsinki (15).

All patients had SLE (i.e., met 4 of the 11 American College of Rheumatology [ACR] criteria for the classification of SLE at some time during the course of the disease [16]), were ≥18 years of age, and had 1 of the following primary manifestations: active polyarthritis (musculoskeletal organ system), active discoid lesions (mucocutaneous organ system), or active pleuritis and/or pericarditis (cardiovascular/respiratory organ system) (17,18). Disease activity was defined according to the British Isles Lupus Activity Group (BILAG) index (17,18), which consists of 86 questions related to symptoms, examination findings, and laboratory results across 8 organ systems. A score of BILAG A in an organ system represents severe disease activity, reflecting the need for disease-modifying therapy (i.e., high-dose corticosteroids/
immunosuppressants), and a score of BILAG B in an organ system represents moderate disease activity, reflecting the need for symptomatic therapy (i.e., hydroxychloroquine/nonsteroidal antiinflammatory drugs [NSAIDs]/low-to-moderate-dose corticosteroids). Patients were required to have at least BILAG A (severe) or BILAG B (moderate) musculoskeletal, mucocutaneous, and/or cardiovascular/respiratory organ system activity, as defined above. If patients had multiple prespecified active manifestations at study entry, the investigator specified which was the primary manifestation.

Permitted background treatments were NSAIDs, azathioprine, MMF, chloroquine, hydroxychloroquine, or MTX, as well as proteinuria therapies (i.e., angiotensin-converting enzyme inhibitors or angiotensin receptor–blocking agents) and statins. Background treatments must have been maintained at a stable dosage for ≥1 month before the study screening. All other background medications were required to have been discontinued ≥1 month before screening.

Patients were excluded if they had a concomitant illness that was likely to require additional systemic steroid therapy, had organ-threatening features of SLE (e.g., lupus nephritis or central nervous system disease), had received any investigational drug within 28 days of study entry or had taken abatacept or rituximab at any time previously, had received corticosteroids for an SLE flare for >14 days before randomization, had undergone treatment of the entry flare episode at any time with a prednisone dosage ≥30 mg/day (or equivalent), or were pregnant or breastfeeding.

Patients were randomized at a ratio of 2:1 to receive abatacept or placebo plus prednisone or prednisone equivalent, with randomization stratified according to the primary manifestation and BILAG A or B activity within that primary manifestation. Permitted background treatments for SLE (see above) that were being used at study entry were continued at a stable dosage throughout the study. Abatacept was mixed into 0.9% normal saline and administered by intravenous (IV) infusion on days 1, 15, and 29, and every 4 weeks thereafter up to and including day 337. Dosing was 10 mg/kg of body weight according to the patient’s weight range at study entry, as follows: 500 mg for weight <60 kg, 750 mg for weight of 60–100 kg, and 1,000 mg for weight >100 kg. Placebo-treated patients received 0.9% normal saline alone by IV infusion.

The prednisone dosage was increased from a maximum of 20 mg/day (or equivalent) during screening to 30 mg/day (or equivalent) at randomization. The prednisone dosage was then tapered per protocol to a target dosage of 5 mg/day, which was initiated by day 29 or by day 57. If disease activity had subsided on day 29 (BILAG score of C or D [except for duration] in all organ systems), steroid taper was initiated. If disease activity had not subsided, pulse steroid therapy was permitted, and patients were reassessed on day 57. If disease activity had subsided by day 57, steroid taper was initiated. Patients whose SLE activity disallowed steroid taper by day 57 could receive rescue therapy (as deemed appropriate by the investigator); this was recorded as an inception treatment failure.

**Efficacy assessments.** *Clinical assessments of SLE flare.*

**Primary end point.** The primary end point was the proportion of patients with a new flare of SLE (defined as a BILAG score of A or B adjudicated as a flare in any organ system) at any time following the initiation of steroid taper during the 12-month, double-blind period.

A blinded analysis of BILAG A and B flares executed early in the study (prior to unblinding) showed that flare was insufficiently defined on the computer system. For example, if a symptom improves for a month, and then afterwards, it remains present at the same level of partial improvement for the following month, this can be misinterpreted by the computer as a new flare, rather than what it actually represents: partial improvement of ongoing disease. Consequently, during the course of the study, a set of guidelines was developed for use by an independent BILAG Adjudication Committee to adjudicate each new BILAG A or B score picked up by the computer to determine whether it represented a new SLE flare. In all cases, the rules of the validated BILAG scoring system were rigorously observed. These guidelines were endorsed by the study data monitoring committee and by the FDA. The Adjudication Committee comprised 3 BILAG experts who reviewed on a blinded basis the attribution to flare of all new BILAG A and B events. Adjudication was applied to all BILAG-based flare measures, and all BILAG assessments described herein were adjudicated.

**Secondary end points and exploratory analyses.** The secondary efficacy end points were as follows: the proportion of patients with a new SLE flare within the initial 6 months of the double-blind period, the total number of new SLE flares per patient during the double-blind period, the time to occurrence of a new SLE flare, the proportion of patients with no new SLE flares while receiving low-dose steroids (≤7.5 mg) for any 2 consecutive months during the double-blind period, and the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (19) at 12 months as compared with baseline. Prespecified exploratory analyses evaluated the primary end point in subgroups defined according to the primary manifestation at study entry.

**Post hoc exploratory analyses.** Post hoc exploratory analyses, including variant definitions of SLE flare, were conducted to explore the data and to generate hypotheses about optimal trial designs and efficacy measures. Flare was analyzed post hoc as the proportion of patients experiencing at least 1 flare with BILAG score of A or an occurrence of flare according to the physician’s assessment at any point over 12 months. Physician’s assessments were performed at each evaluation, after the BILAG assessments. A yes/no checkbox was completed in response to the question, “Since the last visit, does the patient exhibit symptoms of an acute SLE flare?” As with the primary end point, these alternative definitions of flare were assessed according to the primary manifestation of SLE at study entry. In an additional post hoc analysis, the proportion of patients taking low-dose steroids (mean daily dose of prednisone or equivalent ≤7.5 mg) who experienced no disease flare during months 10–12 (when the minimal possible steroid dosage should have been achieved) was examined.

**Patient-reported outcomes and biomarkers.** A number of prespecified exploratory patient-reported assessments were performed. Health-related quality of life was measured using the Short Form 36 (SF-36). Improvement of ≥3 units in either the physical component summary (PCS) score or the mental
The component summary (MCS) score was considered clinically meaningful (20). Fatigue severity was measured using a 0–100-mm visual analog scale (21). Sleep quality was assessed using the Medical Outcomes Study Sleep Problems Index; the scores range from 0 to 100, with higher scores reflecting more problems (22). A reduction of 10 points in fatigue severity and 6 points in sleep problems is considered to be clinically meaningful (23). Depression was measured using the Center for Epidemiologic Studies Depression (CES-D) Scale, which ranges from 0 to 60, with higher scores indicating greater levels of depression (24). In a prespecified exploratory biomarker analysis, serum levels of anti–double-stranded DNA (anti-dsDNA) antibody, which were measured using the Farr radioimmunoassay method, were assessed.

Safety assessments. Adverse events (AEs) and serious AEs (SAEs) were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 11 (online at http://www.medramosso.com/).

Sample size determination. A 2:1 randomization system was planned, which would result in 120 patients in the abatacept group and 60 in the placebo group. The sample size of this exploratory study provided a 95% 2-sided confidence interval (95% CI) half-width for a difference in flare rate between the 2 study groups of 15% (assuming a control flare rate of 60% and an ~33% relative reduction in the active treatment group).

Statistical analysis. All efficacy assessments were performed using the intent-to-treat population (i.e., all randomized and treated patients). All flare-based end points were summarized in terms of treatment differences and associated 95% CIs, with adjustment for randomization strata using the minimum risk weights method (25). When patients discontinued prematurely without a documented SLE flare, this was recorded as a treatment failure. Data for the SF-36, fatigue, and sleep problems end points were analyzed based on the adjusted mean change from baseline, using an analysis of covariance, with baseline and treatment group as covariates; a last observation carried forward method was used for missing data. Safety analyses were performed on all patients who received at least 1 dose of study medication, and the results are presented as frequencies and percentages of AEs.

Table 1. Baseline demographic and clinical characteristics and concomitant medications in the intent-to-treat population

<table>
<thead>
<tr>
<th>Baseline characteristic*</th>
<th>Abatacept (n = 118)</th>
<th>Placebo (n = 57)</th>
<th>Total (n = 175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD years</td>
<td>39.1 ± 12.4</td>
<td>37.6 ± 11.5</td>
<td>38.6 ± 12.14</td>
</tr>
<tr>
<td>No. (%) female</td>
<td>104 (88.1)</td>
<td>55 (96.5)</td>
<td>159 (90.9)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>74 (62.7)</td>
<td>39 (68.4)</td>
<td>113 (64.6)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>12 (10.2)</td>
<td>4 (7.0)</td>
<td>16 (9.1)</td>
</tr>
<tr>
<td>American Indian/Ak.</td>
<td>1 (0.8)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>28 (23.7)</td>
<td>13 (22.8)</td>
<td>41 (23.4)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.5)</td>
<td>1 (1.8)</td>
<td>4 (2.3)</td>
</tr>
<tr>
<td>Time since first diagnosis, mean ± SD years</td>
<td>7.2 ± 7.3</td>
<td>6.5 ± 6.0</td>
<td>7.0 ± 6.9</td>
</tr>
<tr>
<td>Duration of current SLE episode, mean ± SD days†</td>
<td>12.3 ± 6.9</td>
<td>12.8 ± 7.5</td>
<td>12.4 ± 7.1</td>
</tr>
<tr>
<td>Overall SLICC/ACR Damage Index at screening, mean ± SD</td>
<td>0.5 ± 0.9</td>
<td>0.4 ± 0.7</td>
<td>0.5 ± 0.9</td>
</tr>
<tr>
<td>Primary manifestation at study entry, no. (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymyositis</td>
<td>63 (53.4)</td>
<td>32 (56.1)</td>
<td>95 (54.3)</td>
</tr>
<tr>
<td>Discoid lesions</td>
<td>41 (34.7)</td>
<td>19 (33.3)</td>
<td>60 (34.3)</td>
</tr>
<tr>
<td>Pleuritis and/or pericarditis</td>
<td>14 (11.9)</td>
<td>6 (10.5)</td>
<td>20 (11.4)</td>
</tr>
<tr>
<td>Antibody status, no. positive/no. tested (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANAs</td>
<td>86/114 (75.4)</td>
<td>45/57 (78.9)</td>
<td>131/171 (76.6)</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>65/120 (54.2)</td>
<td>29/58 (50.0)</td>
<td>94/178 (52.8)</td>
</tr>
<tr>
<td>Seronegative for both ANAs and anti-dsDNA</td>
<td>23/118 (19.5)</td>
<td>10/57 (17.5)</td>
<td>33/175 (18.9)</td>
</tr>
<tr>
<td>Concomitant medications over 12 months§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive agents, no. (%)</td>
<td>97 (82.2)</td>
<td>43 (75.4)</td>
<td>140 (80.0)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>20 (16.9)</td>
<td>4 (7.0)</td>
<td>24 (13.7)</td>
</tr>
<tr>
<td>Antimalarial agents</td>
<td>83 (70.3)</td>
<td>37 (64.9)</td>
<td>120 (68.6)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>1 (0.8)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>26 (22.0)</td>
<td>12 (21.1)</td>
<td>38 (21.7)</td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>7 (5.9)</td>
<td>2 (3.5)</td>
<td>9 (5.1)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0</td>
<td>1 (1.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Corticosteroids (prednisone or equivalent), no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>117 (99.2)</td>
<td>57 (100.0)</td>
<td>174 (99.4)</td>
</tr>
<tr>
<td>Injectable</td>
<td>15 (12.7)</td>
<td>4 (7.0)</td>
<td>19 (10.9)</td>
</tr>
<tr>
<td>NSAIDs, no. (%)</td>
<td>61 (51.7)</td>
<td>35 (61.4)</td>
<td>96 (54.9)</td>
</tr>
</tbody>
</table>

* SLE = systemic lupus erythematosus; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology; ANAs = antinuclear antibodies; anti-dsDNA = anti–double-stranded DNA; NSAIDs = nonsteroidal antiinflammatory drugs.
† Length of time that the primary flare manifestation was at the British Isles Lupus Assessment Group study entry score prior to day 1.
‡ Patients may have had multiple manifestations of active disease at study entry.
§ Includes medications taken between the first and the last double-blind dose dates.
RESULTS

Baseline demographic and clinical characteristics, patient disposition, and concomitant medications. One hundred eighty patients were randomized and treated with abatacept (n = 121) or placebo (n = 59). Five patients (3 from the abatacept group and 2 from the placebo group) were enrolled and treated at a site with significant study protocol violations; these patients were discontinued and excluded from the intent-to-treat population. The demographic and baseline clinical characteristics were generally comparable between the 2 treatment groups, with a mean disease duration of 7 years in all patients (Table 1). At study entry, the most common primary manifestation was polyarthritis (54.3%). Discoid lesions were present in 34.3% of the patients and serositis (pleuritis and/or pericarditis) in 11.4%. A BILAG score of A or B in at least 1 additional organ system was present in 35.4%, 21.1%, and 8.6% of patients whose primary manifestations were polyarthritis, discoid lesions, and serositis, respectively.

During the study, 82.2% of the abatacept-treated patients and 75.4% of the placebo-treated patients were receiving other treatments for SLE, the most common of which were antimalarials (chloroquine and hydroxychloroquine). In the abatacept and placebo groups, respectively, the proportions of patients receiving concomitant NSAIDs were 51.7% and 61.4%, and the proportions receiving concomitant azathioprine were 16.9% and 7.0% patients.

Eighty-one patients in the abatacept group (68.6%) and 35 patients in the placebo group (61.4%) completed 12 months of treatment (Figure 1). The most frequent reason for discontinuation was lack of efficacy (21 [17.8%] in the abatacept group and 12 [21.1%] in the placebo group).

Findings of the efficacy assessments. Clinical assessments of SLE flare. Prespecified assessments of SLE flare. The primary and secondary end points of this trial were not met. The proportion of patients with a new flare following the initiation of steroid taper over 12 months (primary end point) was 79.7% in the abatacept group.
Post hoc assessments of SLE flare. The proportion of patients who had at least 1 new flare with a BILAG score of A after initiation of steroid taper was 40.7% in the abatacept group, as compared with 54.4% in the placebo group (treatment difference -13.7 [95% CI -29.5, 2.1]) (Figure 2B). The treatment effect was most pronounced for patients with polyarthritis as the primary manifestation (treatment difference -26.1 [95% CI -47.4, -4.8]).

When the treating physician was asked to record a global assessment of whether a patient did or did not exhibit symptoms of an acute SLE flare, the proportion of patients who were assessed during at least 1 clinical visit as having a flare was 63.6% in the abatacept group versus 82.5% in the placebo group (treatment difference -19.3 [95% CI -30.6, -8.0]) (Figure 2C). The treatment effect for this assessment was also most pronounced for patients who had polyarthritis as the primary manifestation of SLE at study entry (treatment difference -28.3 [95% CI -46.1, -10.5]).

The number of patients who did not experience a new flare and who were receiving low-dose corticosteroids (mean daily dose of prednisone or equivalent ≤7.5 mg) during months 10, 11, or 12 was also examined post hoc in order to generate hypotheses about the potential effect of abatacept on the tapering of the corticosteroid dosage and the duration of flare-free periods at the end of the double-blind period. Using the primary end point definition of flare, the proportion of patients who did not experience a disease flare and who were taking low-dose steroids was 42.4% in the abatacept group and 28.1% in the placebo group (treatment difference 15.8 [95% CI 1.5, 30.1]). When flare was defined by the physician, the proportion of patients who did not experience a disease flare and who were taking low-dose steroids was 49.2% in the abatacept group and
28.1% in the placebo group (treatment difference 21.9 [95% CI 7.1, 36.7]).

Post hoc analyses assessed the primary end point (flare as defined by a BILAG score of A or B) according to seropositivity for antinuclear antibodies (ANAs) and anti-dsDNA antibodies. At baseline, 76.6% of patients were positive for ANAs and 52.8% were positive for anti-dsDNA; 18.9% were negative for both. In patients negative for ANA and anti-dsDNA, flare was observed in 82.6% (95% CI 67.1, 98.1) in the abatacept group and 90.0% (95% CI 71.4, 100.0) in the placebo group. For patients who were positive for ANAs and/or anti-dsDNA, flare was observed in 78.3% (95% CI 69.8, 86.7) in the abatacept group and 80.4% (95% CI 69.0, 91.9) in the placebo group.

**Changes in patient-reported outcomes.** The adjusted mean improvement from baseline to 12 months in the abatacept and placebo groups, respectively, was 6.24 and 2.32 for the PCS score of the SF-36 and 5.81 and 3.57 for the MCS score (treatment difference 3.92 [95% CI 1.22, 6.62] for the PCS score and 2.24 [95% CI –1.19, 5.67] for the MCS score) (Figure 3A). The adjusted mean change in the fatigue score from baseline to 12 months in the abatacept and placebo groups, respectively, was –20.27 and –10.82, and the adjusted mean change in the sleep problems score in the respective groups was –7.84 and –0.25 (treatment difference –9.45 [95% CI –17.65, –1.25] for fatigue and –7.59 [95% CI –12.27, –2.90] for sleep problems) (Figure 3B). Improvements in the SF-36 PCS and MCS, fatigue, and sleep problems scores that were observed in the abatacept-treated patients exceeded the minimum clinically important difference. For MCS and fatigue, improvements in the placebo group also exceeded this threshold.

The adjusted mean change in the CES-D Scale (measuring depression) from baseline to 12 months was –4.10 for abatacept and –1.96 for placebo (treatment difference –2.14 [95% CI –5.60, 1.32]).

**Changes in levels of biomarkers.** Mean reductions in serum levels of anti-dsDNA antibody levels from baseline were numerically greater in the abatacept group as compared with the placebo group at each visit. The median changes from baseline to 12 months were –0.3 units/ml (quartiles 1 and 3 –5.1, –0.5) in the abatacept group (n = 73) and –0.1 units/ml (quartiles 1 and 3 –1.6, –0.6) in the placebo group (n = 33).

**Findings of the safety assessments.** Over 12 months, the percentage of patients with any AEs was comparable between treatment groups, with 90.9% in the abatacept group and 91.5% in the placebo group.
reporting an AE (Table 2). Ten patients in the abatacept group (8.3%) and 3 patients in the placebo group (5.1%) discontinued the study because of AEs.

The most frequently reported AEs (>10% in either group) were upper respiratory tract infection (25 [20.7%] receiving abatacept versus 9 [15.3%] receiving placebo), headache (25 [20.7%] versus 10 [16.9%]), back pain (15 [12.4%] versus 5 [8.5%]), diarrhea (14 [11.6%] versus 4 [6.8%]), nasopharyngitis (3 [2.5%] versus 7 [11.9%]), and urinary tract infection (13 [10.7%] versus 5 [8.5%]).

The proportion of patients with SAEs was higher in the abatacept group than in the placebo group (24 [19.8%] and 4 [6.8%] patients, respectively) (Table 3). The SAEs were considered by the investigator to be treatment-related (or possibly treatment-related) in 7 patients in the abatacept group (facial edema, hand edema, and pyrexia in 1 patient, with alveolitis, polynuropathy, diverticulitis, bronchitis, drug hypersensitivity, and dehydration in 1 patient each) and in 2 patients in the placebo group (angioedema and lupus vasculitis in 1 patient, and lupus peritonitis in 1 patient). Given the higher proportion of SAEs in the abatacept group, further post hoc analyses were performed, which revealed that 17 of the 24 patients in the abatacept group who had SAEs developed the SAEs between the start of the steroid taper and month 6. In the placebo group, 2 of the 4 patients had SAEs that occurred between the start of the steroid taper and month 6. Seven patients in the abatacept group (5.8%) and 1 patient in the placebo group (1.7%) discontinued the study because of SAEs (Table 2).

One malignancy was reported in the abatacept group (basal cell carcinoma). There was 1 death during the study, which occurred in a patient in the abatacept group and was not treatment related. This was a gunshot wound, which was not self-inflicted.

In the category of musculoskeletal and connective tissue disorder SAEs, 3 patients in the abatacept group had worsening of SLE, as compared with 1 in the placebo group; the remaining 3 events were arthritis, costochondritis, and musculoskeletal chest pain, which occurred in 1 patient each in the abatacept group. In the category of general disorders and administration site conditions, events were reported in a total of 4 patients. Pyrexia was reported in 3 abatacept-treated patients; chest pain, facial edema, and peripheral edema were reported in 1 patient each in the abatacept group.

Serious infections were reported in 3 abatacept-treated patients and 1 placebo-treated patient (Table 3). One abatacept patient was admitted to the hospital after developing a nonproductive cough, and on day 134 of the study, this patient was diagnosed as having bronchitis. The bronchitis resolved, and the patient continued...
the study treatment. One abatacept-treated patient developed nausea, vomiting, and abdominal pain, and a presumptive diagnosis of diverticulitis was reported on day 362. This SAE also resolved, and the patient continued in the study. One patient had gastroenteritis on day 333, which the treating physician considered to be of mild intensity; abatacept was discontinued. Bronchopneumonia was reported in 1 patient in the placebo group.

SAEs consisting of glomerulonephritis, mesangio proliferative glomerulonephritis, and lupus nephritis occurred in 1 patient each in the abatacept group and were reported under the category of renal and urinary disorders. The glomerulonephritis and mesangio proliferative glomerulonephritis were considered to be unrelated to the study drug and occurred in patients in whom renal abnormalities had been noted on their baseline medical history. Glomerulonephritis was reported after the patient had discontinued the study because of lack of efficacy (day 147). This patient was subsequently hospitalized on day 172 and was diagnosed as having severe alveolitis due to SLE activity. Proteinuria of 1.3 gm/day was recorded, and a renal biopsy showed mild glomerulonephritis. The patient with mesangioproliferative glomerulonephritis was hospitalized because of “renal flare activities,” and as a consequence, the study drug was discontinued. Results of a renal biopsy supported a diagnosis of mesangial glomerulonephritis, which was moderate in intensity. The presence of lupus nephritis was reported in a patient who had received 3 doses of abatacept (up to day 29). On day 82, the patient was hospitalized because of increased proteinuria, and renal biopsy results confirmed a diagnosis of moderate lupus nephritis (World Health Organization class II). The investigator considered this unlikely to be related to the study treatment.

**DISCUSSION**

This exploratory phase II study evaluated the clinical efficacy and safety of abatacept in patients with SLE with primary manifestations of active polyarthritis, discoid lesions, or pleuritis and/or pericarditis. The predefined primary and secondary efficacy end points for this study were not met; however, certain predefined exploratory analyses and post hoc analyses were performed, and the findings supported the possibility of evidence for abatacept clinical activity and benefit. Additionally, these analyses provided information for alternative trial designs and efficacy measures that may be suitable for use in future studies.

The heterogeneity of clinical symptoms and laboratory abnormalities associated with SLE makes the assessment of disease activity and flare and, consequently, the evaluation of treatments a complex and challenging process. Assessment is further complicated by the fact that some symptoms may improve while others are worsening, or some symptoms may spontaneously regress without treatment. The findings presented here are consistent with those of other recent phase II trials of biologic therapies in SLE that have failed to meet prespecified end points but have shown clinical activity when alternative assessments were applied or when subgroups of patients were examined (26). Although post hoc analyses are inherently more subject to bias and can lead to misinterpretation, there is nevertheless value in examining the results of these completed lupus trials in order to assist in the generation of new hypotheses for future trial designs.

The primary end point of new flare (adjudicated BILAG A or B events) was not met. However, when this end point was reassessed considering only BILAG A flare, a greater treatment difference was observed between the abatacept and placebo groups. Patients meeting this BILAG A end point met a strict definition of severe flare, while those with BILAG B flares (ranging from relatively small changes in disease activity to moderately severe flares) were not considered to have met the end point. In the setting of this clinical trial, the use of the BILAG assessment for the determination of flare was better able to approximate the physician-assessed outcomes when flare events were adjudicated and when only BILAG A events were considered (rather than BILAG A and B events).

The overall rate of physician-assessed flare was lower than that of flare assessed by a BILAG score of A or B. This difference occurred primarily within the abatacept group, resulting in a greater treatment difference for physician-assessed flare versus BILAG-assessed flare. One potential reason for the discrepancy between these 2 measures is that the normal minor waxing and waning of the disease in a known patient may be picked up by the BILAG A or B definition of flare, but would be less likely to be considered as a flare by the patient’s treating physician. However, it is also possible that use of an organ-based system instrument such as the BILAG might miss flares that represent accumulated mild-to-moderate disease in multiple organs, whereas the treating physician may be more likely to detect this.

Approximately one-fifth of the patients included in this study were seronegative for ANAs and anti-dsDNA. In a phase II trial of belimumab, seropositive
patients had a statistically significantly better response to treatment than did seronegative patients (26). Analysis of the primary end point according to seropositivity revealed that the flare rate was lower in seropositive patients in the current trial, although this did not appear to affect the difference between treatment groups.

Treatment differences for post hoc–defined flare rates between the abatacept and placebo groups were greatest in the subgroup of patients whose primary manifestation at entry was polyarthritis. This finding was consistent for both BILAG A–determined flare and physician-determined flare. These findings suggest the possibility that abatacept treatment might be more useful in patients with a primary manifestation of lupus arthritis, a hypothesis that may warrant investigation in future studies.

In prespecified exploratory analyses, greater improvements in the SF-36 PCS, fatigue, and sleep problem scores were observed at 12 months in the abatacept group as compared with the placebo group. This suggests that abatacept can affect some of the major problems experienced by patients with SLE and may improve their ability to perform their activities of daily living as well as their social roles. Analysis of serum biomarkers revealed a reduction in anti-dsDNA levels between baseline and 12 months. This reduction was numerically greater in the abatacept group than in the placebo group.

The frequency of patients with SAEs during the 12 months of study was higher in the abatacept group than in the placebo group (19.8% versus 6.8%). Most SAEs were single events, with no discernible pattern; SLE and pyrexia (reported in 3 patients each) and pericarditis (2 patients) were the only SAEs reported in more than 1 abatacept-treated patient. The majority of SAEs could be attributed to underlying SLE disease, and most occurred during the first 6 months of the study, including the 2-month steroid taper period. The proportion that occurred within this timeframe was higher in the abatacept group than in the placebo group. It should be noted that the forced steroid taper in this trial is not representative of normal clinical practice. Whether the combination of abatacept, background treatments, and forced steroid taper poses an unacceptable safety risk in this context warrants further study. It is unclear whether the 3 nephritis flares in the abatacept group suggest an untoward incidence in this population, but further immunologic characterization of patients with these types of events is also warranted. However, data from 2 ongoing nephritis trials in which abatacept is added to standard of care (27,28) should illuminate this issue.

The results presented herein should be interpreted within the context of the trial and its limitations. Although patients were randomized in a blinded manner, there were some differences in NSAID and azathioprine use between the treatment groups, which may have affected the study outcomes. Post hoc analyses must be interpreted with caution with respect to their known limitations, such as regression to the mean bias and the potential for suggesting differences where none exist. In addition, subanalyses of data according to primary manifestation at study entry results in relatively low numbers of patients per group, which limits the conclusions that can be drawn due to lack of precision with respect to estimation of the treatment effect. Despite these limitations, the post hoc analyses presented here do provide some useful insight into better understanding the clinical effects of abatacept in SLE as well as potential assessment measures that could be used in future studies.

In summary, this study of abatacept in patients with SLE with primary manifestations of polyarthritis, discoid lesions, or pleuritis and/or pericarditis did not meet its primary or secondary objectives. The findings presented here suggest the possibility of clinical activity of abatacept, although an increased incidence of SAEs was observed in abatacept-treated patients, and this requires further characterization. We conclude that further evaluation of this agent in different clinical contexts is warranted. Assessments of the efficacy and safety of abatacept in lupus nephritis are ongoing.

**ACKNOWLEDGMENT**

Professional medical writing support was provided by Helen Clarke, an employee of Medicus International, and was funded by Bristol-Myers Squibb.

**AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Merrill had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Merrill, Westhovens, Wallace, Sigal, Becker, Raghupathi, Li, Kinaszczuk.

**Acquisition of data.** Merrill, Burgos-Vargas, Westhovens, Chalmers, D'Cruz, Wallace, Baé, Sigal, Becker, Raghupathi, Li, Peng, Kinaszczuk, Nash.

**Analysis and interpretation of data.** Merrill, Burgos-Vargas, Westhovens, Chalmers, Wallace, Baé, Sigal, Becker, Kelly, Raghupathi, Li, Peng, Nash.

**ROLE OF THE STUDY SPONSOR**

Bristol-Myers Squibb was involved in the study design, the collection, analysis, and interpretation of the data, and provided
Efficacy and Safety of Abatacept in Non-Life-Threatening SLE

REFERENCES


