2014

Efficacy and Safety of Abatacept in Lupus Nephritis A Twelve-Month, Randomized, Double-Blind Study

R. Furie
Zucker School of Medicine at Hofstra/Northwell

K. Nicholls

T. T. Cheng

F. Houssiau

R. Burgos-Vargas

See next page for additional authors

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 2, February 2014, pp 379–389
DOI 10.1002/art.38260

Efficacy and Safety of Abatacept in Lupus Nephritis

A Twelve-Month, Randomized, Double-Blind Study

Richard Furie,[1] Kathy Nicholls,[2] Tien-Tsai Cheng,[3] Frederic Houssiau,[4] Ruben Burgos-Vargas,[5] Shun-Le Chen,[6] Jan L. Hillson,[7] Stephanie Meadows-Shropshire,[7] Michael Kinaszczuk,[7] and Joan T. Merrill[8]

Objective. **To compare the efficacy and safety of intravenous (IV) abatacept, a selective T cell costimulation modulator, versus placebo for the treatment of active class III or IV lupus nephritis, when used on a background of mycophenolate mofetil and glucocorticoids.**

Methods. **This was a 12-month, randomized, phase II/III, multicenter, international, double-blind study. A total of 298 patients were treated in 1 of 3 IV treatment arms: placebo, abatacept at the standard weight-tiered dose (approximating 10 mg/kg), or abatacept at 30 mg/kg for 3 months, followed by the standard weight-tiered dose (abatacept 30/10). The primary end point, time to confirmed complete response, was a composite measure that required maintenance of glomerular filtration rate, minimal proteinuria, and inactive urinary sediment over the 52-week treatment period.**

Results. **There were no differences among treatment arms in the time to confirmed complete response or in the proportion of subjects with confirmed complete response following 52 weeks of treatment. Treatment with abatacept was associated with greater improvements from baseline in anti–double-stranded DNA antibody, C3, and C4 levels. Among 122 patients with nephrotic-range proteinuria, treatment with abatacept resulted in an ~20–30% greater reduction in mean urinary protein-to-creatinine ratio compared with placebo. Abatacept was well tolerated; rates of deaths, serious adverse events, and serious infections were similar across treatment arms. Gastroenteritis and herpes zoster occurred more frequently with abatacept treatment.**

Conclusion. **Although the primary end point was not met, abatacept showed evidence of biologic activity and was well tolerated in patients with active class III or IV lupus nephritis.**

Lupus nephritis (LN) is characterized by the activation and persistence of autoreactive T and B cells and the presence of potentially pathogenic autoantibodies (1). Abatacept is a fusion protein comprising

ClinicalTrials.gov identifier: NCT00430677.
Supported by Bristol-Myers Squibb.
[1]Richard Furie, MD: North Shore–LIJ Health System, Great Neck, New York; [2]Kathy Nicholls, MD: Royal Melbourne Hospital and University of Melbourne, Parkville, Victoria, Australia; [3]Tien-Tsai Cheng, MD: Chang Gung Memorial Hospital–Kaohsiung Medical Center and Chang Gung University, Kaohsiung, Taiwan; [4]Frederic Houssiau, MD, PhD: Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [5]Ruben Burgos-Vargas, MD: Hospital General de México and Universidad Nacional Autonoma de México, Mexico City, Mexico; [6]Shun-Le Chen, MD: Shanghai Jiao Tong University School of Medicine, Shanghai, China; [7]Jan L. Hillson, MD, Stephanie Meadows-Shropshire, BS, Michael Kinaszczuk, RPh: Bristol-Myers Squibb, Princeton, New Jersey; [8]Joan T. Merrill, MD: Oklahoma Medical Research Foundation, Oklahoma City.

Dr. Furie has received consulting fees from Bristol-Myers Squibb (less than $10,000). Dr. Houssiau has received consulting fees, speaking fees, and/or honoraria from Human Genome Sciences, GlaxoSmithKline, and UCB (less than $10,000 each). Dr. Burgos-Vargas has received consulting fees, speaking fees, and/or honoraria from Abbvie, Bristol-Myers Squibb, Jannsen, Pfizer, Roche, and UCB (less than $10,000 each). Dr. Hillson, Ms. Meadows-Shropshire, and Mr. Kinaszczuk own stock or stock options in Bristol-Myers Squibb. Dr. Merrill has received consulting fees, speaking fees, and/or honoraria from Bristol-Myers Squibb (less than $10,000).

Address correspondence to Richard Furie, MD, Division of Rheumatology and Allergy–Clinical Immunology, North Shore–LIJ Health System, 865 Northern Boulevard, Suite 302, Great Neck, NY 11021. E-mail: furie@nshs.edu.

Submitted for publication May 16, 2013; accepted in revised form October 24, 2013.

CTLA-4 linked to the Fc portion of IgG1 (2). It selectively modulates the CD28–CD80/86 signaling pathway, thereby inhibiting costimulatory events, including T cell activation (3,4). Inhibition of costimulation is effective in murine models of LN (5–7). Abatacept is currently approved for the treatment of rheumatoid arthritis (RA) and juvenile inflammatory arthritis, and is being explored for the treatment of other autoimmune diseases (2,8,9).

Results of a phase II study (ClinicalTrials.gov identifier NCT00119678) of abatacept for the treatment of patients with systemic lupus erythematosus (SLE) presenting with arthritis, serositis, or discoid lesions were previously reported (9). Patients (n = 175) were randomized 2:1 to receive intravenous (IV) abatacept (~10 mg/kg) or placebo, in addition to prednisone (30 mg/day or equivalent for 4 weeks, with subsequent dosage modifications at the discretion of the investigator) and stable background immunosuppressants. The primary efficacy end point, i.e., the proportion of patients without one or more moderate or severe flares (British Isles Lupus Assessment Group [BILAG] B flares or BILAG A flares, respectively) (10) during the 12-month treatment period, was not met. However, post hoc analyses suggested that abatacept treatment was associated with fewer major BILAG A flares, as well as improvements in exploratory quality-of-life measures (Short Form-36 [SF-36] health survey [11], sleep problems, fatigue) and biomarker levels (reductions in mean serum anti–double-stranded [anti-dsDNA] antibody levels from baseline) (9).

The present study (ClinicalTrials.gov identifier NCT00430677) evaluated the efficacy and safety of 52-week treatment with IV abatacept compared with placebo, on a background of mycophenolate mofetil (MMF) and glucocorticoids in patients with SLE and active class III or IV LN (12).

PATIENTS AND METHODS

Study design. This 12-month, international, multicenter, randomized, phase II/III, double-blind, placebo-controlled, parallel-group study was conducted at 85 sites worldwide, including 17 in North America, 13 in Europe, 17 in South America, 20 in Asia, and 18 in the rest of the world (Australia, India, South Africa, and Turkey). To be eligible for enrollment, patients had to be age ≥18 years, have met classification criteria for SLE as defined by the American College of Rheumatology (ACR) (13), and have active class III or IV glomerulonephritis (with or without class V) as defined by the 2003 International Society of Nephrology/Renal Pathology Society criteria (14), excluding class III[C], IV-S[C], or IV-G[C], or the World Health Organization 1982 classification criteria (15), excluding class IIIc or IVd, demonstrated on renal biopsy ≤12 months prior to enrollment. For biopsies performed >3 months prior to enrollment, complement C3 or C4 levels below the lower limit of normal (LLN) or elevated anti-dsDNA antibody titers at the time of screening were further requirements for eligibility, as were a urinary protein-to-creatinine ratio of ≥0.44 mg/mg (50 mg/mmole) at the time of screening, and active urinary sediment (>5 red blood cells [RBCs] or >8 white blood cells [WBCs] per high-power field [hpf] or cylinduria) at the time of screening or during the current flare.

Patients were excluded if there was evidence of severe, rapidly advancing renal insufficiency (i.e., an increase in serum creatinine levels of ≥1 mg/dl within 1 month prior to screening, or a serum creatinine level of >3 mg/dl), or if there was evidence of severe, unstable, and/or progressive central nervous system lupus. Use of immunosuppressive or immunomodulatory agents during the study was prohibited, except for antimalarial agents and protocol-defined MMF and glucocorticoids.

Treatment protocol. Patients were randomized 1:1:1 to one of the following IV infusion treatment regimens: abatacept 30/10 mg/kg (abatacept 30/10), abatacept 10/10 mg/kg (abatacept 10/10), or placebo. Patients assigned to the abatacept 30/10 regimen received abatacept 30 mg/kg on days 1, 15, 29, and 57, followed by abatacept approximating 10 mg/kg (weight tiered: 500 mg for patients weighing <60 kg, 750 mg for patients 60–100 kg, 1,000 mg for patients >100 kg) on days 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337. In the abatacept 10/10 group, patients received weight-tiered doses of abatacept approximating 10 mg/kg on all infusion days. Placebo consisted of dextrose 5% in water or normal saline. In all treatment groups, patients received MMF and prednisone or prednisone equivalent, with MMF initiated at dosages based on race and prior treatment, followed by adjustment or taper in accordance with protocol recommendations and investigator discretion (see Supplementary Tables 1 and 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38260/abstract). Randomization was stratified by prior treatment: 1) naive (not currently receiving MMF and/or glucocorticoid treatment at the screening visit), 2) recent treatment (≤3 months of therapy with MMF and/or glucocorticoids for current episode of LN), or 3) inadequate response (>3 months of therapy with MMF and/or glucocorticoids with persisting evidence of active LN).

Treatment with antiproteinuric agents (e.g., angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors) could not be initiated after randomization, but could be continued at stable, pretreatment dosages. The addition of other antihypertensive medications, such as calcium-channel blockers, to improve blood pressure control was permitted. Antimalarial medications and nonsteroidal antiinflammatory drugs were allowed, providing the dosage was stable throughout the study.

Primary and secondary study end points. The primary efficacy end point during the 12-month double-blind treatment period was the time to confirmed complete response. Complete response was defined as fulfillment of the following criteria: 1) Modification of Diet in Renal Disease (MDRD)

estimated glomerular filtration rate (eGFR) ≥90%* of screening level if normal at screening visit, or eGFR ≥90%* of 6-month, pre-flare value if abnormal at screening, 2) urinary protein-to-creatinine ratio <0.26 gm/gm (30 mg/mmole), and 3) inactive urinary sediment (RBCs and WBCs per hpf within normal limits of central laboratory assessments; no RBC or WBC casts). In order to meet criteria for confirmed complete response, all complete response criteria had to be met once again, 4 weeks after they were initially achieved. The complete response criteria were adopted from the ACR response criteria published at the time of the trial (21), which required a urinary protein-to-creatinine ratio of <0.20 gm/gm, inactive urine sediment, and normal eGFR or a decline of <25% from baseline. The present study requirement of ≤10% decline reflected health authority concerns about the applicability of ACR criteria to a global population.

The key secondary efficacy end point was the proportion of patients in whom confirmed complete response had been achieved at week 52 (complete response on days 337 and 365). Additional secondary efficacy end points included the time to partial response (designated as renal improvement) and the proportion of patients with renal improvement. To be considered as having achieved renal improvement, patients were required to have an inactive urinary sediment regardless of the screening value. Furthermore, patients with abnormal proteinuria at screening must have had a ≥50% improvement in the urinary protein-to-creatinine ratio from the screening visit value. Finally, patients with normal MDRD eGFR or with mild renal insufficiency (eGFR 60–89 ml/minute/1.73 m^2) at screening must have had an eGFR of ≥90% of the screening visit value, and patients with moderate-to-severe renal insufficiency (eGFR 15–59 ml/minute/1.73 m^2) must have had a ≥50% improvement in eGFR based on the screening visit value, or an eGFR of ≥90% of the screening or 6-month pre-flare value.

Other secondary efficacy end points were as follows: durability of complete response (the median number of months a complete response was maintained during the double-blind treatment period), mean change from baseline in renal function over time, mean change from baseline in the Systemic Lupus International Collaborative Clinics/ACR Damage Index (SDI) (22) up to week 52, mean change from baseline in the patient's health-related quality of life at each scheduled assessment (measured using the physical and mental component summary scores and each individual component score of the SF-36 questionnaire), and changes from baseline score at each scheduled assessment in the Fatigue Visual Analog Scale (VAS) and total Krupp Fatigue Severity Scale (FSS) (23).

Exploratory study end points. Prior to database lock and unblinding, a modified set of renal outcome criteria, which incorporated different proteinuria thresholds and serum creatinine–based renal measures and allowed for the assessment of complete and/or partial renal responses, was agreed upon; these modified renal outcomes were evaluated as exploratory end points. The modified renal response criterion, incorporated to evaluate renal response as determined using a less stringent definition, was defined as follows: serum creatinine ≤125% of baseline level and improvement in urinary protein-to-creatinine ratio (<50% of baseline and <3.0 gm/gm [339 mg/mmole] if nephrotic [urinary protein-to-creatinine ratio >339 mg/mmole] at baseline, or <1.0 gm/gm [113 mg/mmole] if non-nephrotic [urinary protein-to-creatinine ratio ≤339 mg/mmole] at baseline). Renal response excluded assessment of urinary sediment. The proportion of patients with renal response (assessed on day 337 and confirmed on day 365 [week 52]) was evaluated. The second exploratory outcome measure was the proportion of patients achieving patient response (assessed on day 337 and confirmed on day 365 [week 52]); this end point was in alignment with the recently released US Food and Drug Administration guidance document for LN (24). Patient response had 3 mutually exclusive categories: complete patient response, partial patient response, and no response. The criteria for complete patient response included normal serum creatinine level, urinary protein-to-creatinine ratio <0.5 gm/gm (56.5 mg/mmole), and inactive urinary sediment. For partial patient response, the criteria included serum creatinine level normal or ≤125% of baseline, urinary protein-to-creatinine ratio <50% of baseline and <3.0 gm/gm if nephrotic at baseline or <1.0 gm/gm (113 mg/mmole) if non-nephrotic at baseline, and inactive urinary sediment or >50% reduction in RBCs/hpf from baseline.

Subgroup analyses. Differences between treatment groups, subclassified by prior treatment status (naive, recent, inadequate response) and race (Asian versus non-Asian), in the proportion of patients in whom confirmed complete response was achieved at week 52 were analyzed. Data were summarized only for subgroups consisting of 10% or more of the total study population. As a post hoc analysis, the proportion of patients in whom complete response had been achieved at week 52 (not confirmed) was also analyzed by race (Asian versus non-Asian). In a separate post hoc subgroup analysis, change in proteinuria over time among patients with versus those without nephrotic-range proteinuria at baseline was examined.

Biomarker analyses. Pharmacodynamic variables were also examined. Anti-dsDNA antibody and serum complement C3 and C4 levels were determined from blood samples obtained on days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, and 365, or at the time of early discontinuation.

Adverse events. Adverse events (AEs), monitored throughout the study, were defined as any new or worsening illness, sign, symptom, or clinically significant laboratory abnormality, regardless of attribution by the investigator. A serious AE (SAE) was defined as an AE that met any of the following criteria: fatal, life-threatening, cancer, patient hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth defect, or an important medical event.

Statistical analysis. A 1:1:1 randomized sample size yielding ~100 patients per treatment arm provided 90% power to detect a difference in the time to achievement of confirmed complete response if there was an absolute difference of 20%

*The original protocol contained a syntax error in the definition of eGFR that was used to determine complete response and renal improvement. This error, which considered patients with >10% improvement in eGFR as having not met the end point, was reflected in previous presentations of data (12,16–20) but has been corrected in the present report. The error impacts the number of patients reported as having achieved complete response and renal improvement, but does not impact interpretations of treatment effect.

Table 1. Baseline characteristics of the lupus nephritis patients and patient disposition during the study*

Variable†	Abatacept 30/10 (n = 99)	Abatacept 10/10 (n = 99)	Placebo (n = 100)
Age, mean ± SD years	31.0 ± 9.5	30.5 ± 10.6	31.8 ± 9.0
Female	84 (84.8)	86 (86.9)	81 (81.0)
Geographic region‡			
North America	12 (12.1)	9 (9.1)	13 (13.0)
South America	15 (15.2)	19 (19.2)	18 (18.0)
Europe	9 (9.1)	21 (21.2)	16 (16.0)
Rest of world	63 (63.6)	50 (50.5)	53 (53.0)
Race§			
Asian	60 (60.6)	49 (49.5)	55 (55.0)
White	28 (28.3)	45 (45.5)	38 (38.0)
Black/African American	6 (6.1)	3 (3.0)	5 (5.0)
Other	5 (5.1)	2 (2.0)	2 (2.0)
Class IV glomerulonephritis	76 (76.8)	76 (76.8)	68 (68.0)
Duration of current flare, median (range) months (n = 99, 99, 96)	1.0 (0–143)	1.0 (0–49)	1.0 (0–36)
Baseline creatinine, median (range) mg/dl	0.9 (0.4–2.7)	0.8 (0.4–2.5)	0.8 (0.5–2.0)
Baseline UPCR, mg/mmole (n = 99, 99, 99)			
Mean ± SD	445.7 ± 380.8	482.8 ± 953.8	403.1 ± 329.4
Median (range)	339 (57–2,458)	285 (50–9,400)	312 (14–1,668)
Baseline UPCR >3 gm/gm (339 mg/mmole)	39 (39.4)	38 (38.4)	45 (45.0)
Prestudy treatment status			
Naive (no treatment for current flare)	12 (12.1)	12 (12.1)	12 (12.0)
Recent treatment (≤3 months MMF/GCs)	51 (51.5)	51 (51.5)	51 (51.0)
Inadequate response (>3 months MMF/GCs)	36 (36.4)	36 (36.4)	37 (37.0)
Baseline prednisone or oral prednisone equivalent daily dose, mean ± SD mg (n = 98, 99, 99)	39.5 ± 18.6	41.6 ± 14.1	43.1 ± 17.6
Concomitant treatment with ACE inhibitors/angiotensin receptor blockers	48 (48.5)	42 (42.4)	49 (49.0)
Premature discontinuation	23 (23.2)	25 (25.3)	22 (22.0)
Death	1 (1.0)	1 (1.0)	5 (5.0)
Adverse event	15 (15.2)	13 (13.1)	9 (9.0)
Lack of efficacy	5 (5.1)	6 (6.1)	4 (4.0)
Withdrew consent	1 (1.0)	1 (1.0)	2 (2.0)
No longer met study criteria	1 (1.0)	1 (1.0)	2 (2.0)
Poor compliance/noncompliance	0	1 (1.0)	0
Pregnancy	0	2 (2.0)	0

* No formal statistical comparisons were made for the 2 abatacept treatment groups versus placebo. Except where indicated otherwise, values are the number (%). UPCR = urinary protein-to-creatinine ratio; MMF = mycophenolate mofetil; GCs = glucocorticoids; ACE = angiotensin-converting enzyme.
† For variables with missing data in 1 or more of the groups, n values in the abatacept 30/10, abatacept 10/10, and placebo groups, respectively, are specified.
‡ Mexico was included among the South American sites. Rest of world includes Asia; the majority of the rest-of-world patients were in China and India.
§ Race was self-identified; therefore, patients of Hispanic descent may have identified as white, black/African American, or other.

in response rates between an abatacept regimen and placebo at a significance level of 0.05. This power estimate, based on the log rank test, assumed a background confirmed complete response rate of 20%, a response rate of 40% in the abatacept treatment group, and a constant hazard ratio. The testing of the 2 abatacept dose regimens for the primary measurement of the time to confirmed complete response was performed using the Hochberg multiple testing procedure in order to maintain the overall type I error rate at ≤5%. Only the primary efficacy end point was formally tested for statistical significance; descriptive statistics are provided for all subsequent analyses. The proportion of patients with confirmed complete response at week 52 was assessed using sequential testing in a hierarchical manner within each treatment group, and assessment of all other secondary efficacy end points was performed in a nonhierarchical manner without correction for multiplicity.

All efficacy analyses were based on the intent-to-treat population, defined as all randomized patients for whom study medication data on the electronic case report form indicated that at least 1 infusion of study medication was administered. The primary efficacy end point was analyzed using a Cox proportional hazards model with randomization strata and treatment group as covariates. The exploratory variable of patient response at week 52 was analyzed with a cumulative logit model that included treatment group and randomization strata as covariates. Point estimates and 95% confidence intervals (95% CIs) for differences in proportions between each abatacept treatment group and placebo for all other

secondary prespecified and exploratory efficacy end points were computed using the minimum risk weights method to account for randomization strata. All safety analyses were based on the all-treated analysis population, which included all patients who had received at least 1 infusion of study medication during the double-blind treatment period.

RESULTS

Patient disposition and baseline characteristics. Of the 423 patients screened for the study, 300 were randomized and 298 were treated (1 died prior to treatment; 1 discontinued due to deviation from enrollment criteria). Demographic and baseline disease characteristics were well balanced across treatment groups (Table 1), with the following exceptions: fewer patients randomized to the placebo group had class IV disease, and the placebo group exhibited a lower mean urinary protein-to-creatinine ratio and a narrower range of urinary protein-to-creatinine ratio values compared with the abatacept-treated groups.

The numbers of patients who prematurely discontinued study participation during the 12-month treatment period were similar across groups: 23 (23.2%), 25 (25.3%), and 22 (22.0%) in the abatacept 30/10, abatacept 10/10, and placebo groups, respectively. Reasons for premature discontinuation are summarized in Table 1.

Efficacy end points. The primary end point, time to achievement of a confirmed complete response, was not met. Confirmed complete response was achieved in few patients at any time during treatment (22.2%, 27.3%, and 20.0% in the abatacept 30/10, abatacept 10/10, and placebo groups, respectively), and the time to confirmed response was not statistically significantly different across treatment arms (Figure 1A). The time to achievement of partial response (based on renal improvement) was also similar among treatment groups (Figure 1B).

The proportions of patients who met the criteria for confirmed complete response at week 52 were similar across treatment groups (9.1%, 11.1%, and 8.0% in the abatacept 30/10, abatacept 10/10, and placebo groups, respectively) (Table 2). Renal improvement response rates at week 52 were higher in the abatacept 30/10 group (38.4%) and the abatacept 10/10 group (37.4%) compared with the placebo group (31.0%) (Table 2). The point estimates for the absolute differences in renal improvement between the abatacept groups and the placebo group were 8.3 (95% CI –5.1, 21.7) for abatacept 30/10 and 7.3 (95% CI –6.1, 20.7) for abatacept 10/10. Other secondary efficacy end points (durability of complete response, mean change from baseline in renal function, mean change from baseline in SDI, SF-36, Fatigue VAS, and FSS scores) consistently showed no differences between the abatacept and placebo groups (see Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38260/abstract).

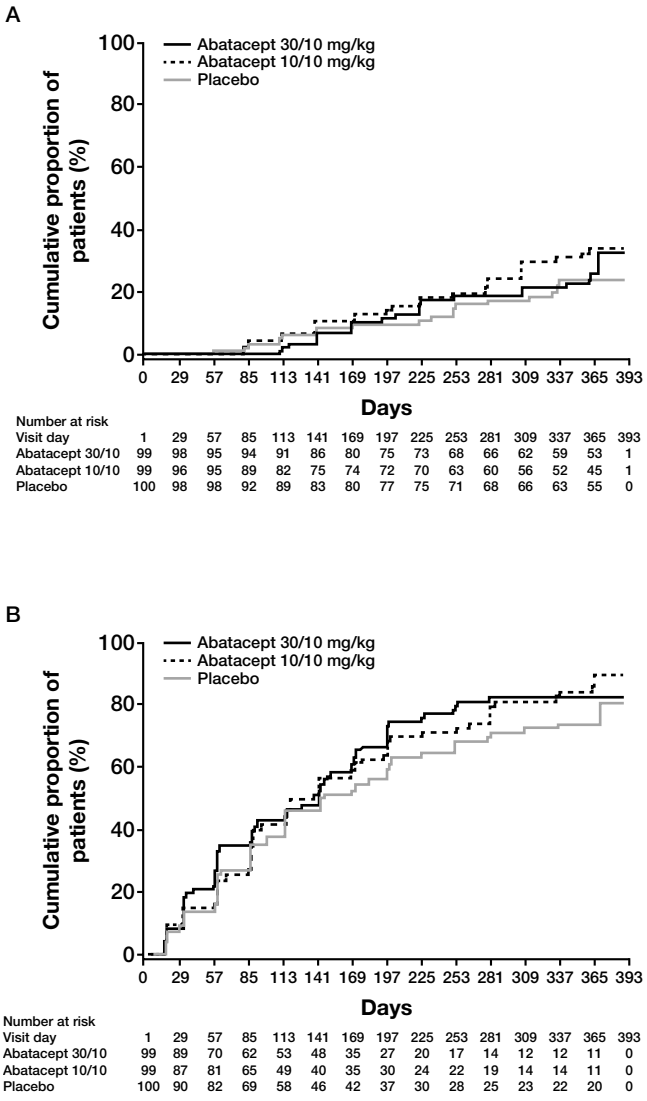


Figure 1. **A**, Time to achievement of confirmed complete response, by treatment group. **B**, Time to achievement of renal improvement, by treatment group. No formal statistical comparisons were made for the analysis of time to achievement of renal improvement.

Due to the stringent nature of the confirmed complete response end point, few patients met the criteria at any time point, and minor fluctuations in eGFR led to variations in the numbers of patients classified as having achieved confirmed complete re-

Table 2. Percentage of patients with responses at week 52*

End point	Abatacept 30/10 (n = 99)	Abatacept 10/10 (n = 99)	Placebo (n = 100)
Prespecified end points			
Complete clinical response at week 52, no. (%) [95% CI]†	9 (9.1) [3.4, 14.8]	11 (11.1) [4.9, 17.3]	8 (8.0) [2.7, 13.3]
Renal improvement at week 52, no. (%) [95% CI]‡	38 (38.4) [28.8, 48.0]	37 (37.4) [27.8, 46.9]	31 (31.0) [21.9, 40.1]
Additional renal end points			
Patient response at week 52			
Patients with response, no. (%) [95% CI]	38 (38.4) [28.8, 48.0]	30 (30.3) [21.3, 39.4]	34 (34.0) [24.7, 43.3]
Complete response, no. (%)§	24 (24.2)	21 (21.2)	20 (20.0)
Partial response, no. (%)¶	14 (14.1)	9 (9.1)	14 (14.0)
No response, no. (%)	61 (61.6)	69 (69.7)	66 (66.0)
Renal response at week 52, no. (%) [95% CI]#	45 (45.5) [35.6, 55.3]	39 (39.4) [29.8, 49.0]	33 (33.0) [23.8, 42.2]
Prespecified subanalyses			
Complete clinical response at week 52 by prior treatment status, no. with response/no. analyzed (%) [95% CI]**			
Naive	1/12 (8.3) [0.2, 38.5]	2/12 (16.7) [2.1, 48.4]	3/12 (25.0) [5.5, 57.2]
Recent	6/51 (11.8) [2.9, 20.6]	7/51 (13.7) [4.3, 23.2]	5/51 (9.8) [1.6, 18.0]
Inadequate response	2/36 (5.6) [0.7, 18.7]	2/36 (5.6) [0.7, 18.7]	0/37 (0) –
Complete clinical response at week 52 by race, no. with response/no. analyzed (%)**			
Asian	9/60 (15.0)	6/49 (12.2)	6/55 (10.9)
Non-Asian	0/39 (0)	5/50 (10.0)	2/45 (4.4)
Post hoc subanalysis			
Complete clinical response at week 52 by race, no. with response/no. analyzed (%)††			
Asian	13/60 (21.7)	12/49 (24.5)	8/55 (14.5)
Non-Asian	2/39 (5.1)	10/50 (20.0)	4/45 (8.9)

* No formal statistical comparisons were made for the 2 abatacept treatment groups versus placebo. 95% CI = 95% confidence interval.

† Defined as follows: for renal function, if normal at screening, estimated glomerular filtration rate (eGFR) ≥90% of screening value and if abnormal at screening, ≥90% of 6-month, pre-flare value; urinary protein-to-creatinine ratio (UPCR) <0.26 gm/gm (30 mg/mmole); inactive urinary sediment; for confirmation, assessed on day 337 and confirmed on day 365 (week 52).

‡ Defined as follows: for renal function, if normal or 60–89 ml/minute/1.73m^2 at screening, eGFR ≥90% of screening value and if 15–59 ml/minute/1.73 m^2, ≥50% improvement or ≥90% of 6-month, pre-flare value; UPCR ≥50% improvement over screening value if abnormal at screening; inactive urinary sediment; confirmation not required.

§ Defined as follows: for renal function, serum creatinine level normal; UPCR <0.5 gm/gm (56.5 mg/mole); inactive urinary sediment; for confirmation, assessed on day 337 and confirmed on day 365.

¶ Defined as follows: for renal function, serum creatinine level normal or ≤125% of baseline; UPCR <50% of baseline and <3.0 gm/gm (339 mg/mmole) if nephrotic, or <1.0 gm/gm (133 mg/mmole) if non-nephrotic; urinary sediment inactive or >50% reduction in red blood cells/high-power field from baseline; for confirmation, assessed on day 337 and confirmed on day 365.

Defined as follows: for renal function, serum creatinine level normal or ≤125% of baseline; UPCR <50% of baseline and <3.0 gm/gm if nephrotic, or <1.0 gm/gm if non-nephrotic; urinary sediment not included in definition; for confirmation, assessed on day 337 and confirmed on day 365.

** Same definition as for the prespecified end point of complete clinical response at week 52.

†† Same definition as for the prespecified end point of complete clinical response at week 52, except confirmation not required.

sponse or renal improvement. Therefore, two less stringent definitions of outcome were proposed and assessed as exploratory measures. The respective proportions of patients with complete, partial, or no response were similar across groups (24.2%, 14.1%, and 61.6% in the abatacept 30/10 group; 21.2%, 9.1%, and 69.7% in the abatacept 10/10 group; and 20.0%, 14.0%, and 66.0% in the placebo group). Because minor fluctuations in urinary sediment can confound interpretation, a definition of response without urinalysis (renal response) was also assessed. Similar to the results obtained using the definition of renal improvement, renal response was achieved in fewer patients in the placebo group at week 52 (45.5% in the abatacept 30/10 group, 39.4% in the

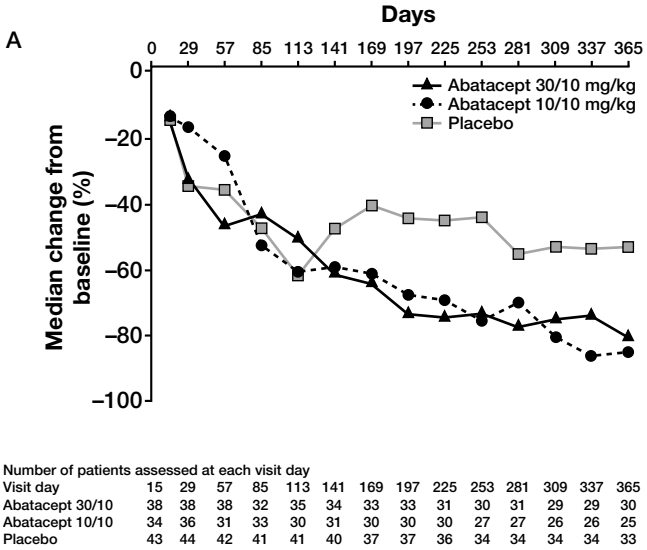
abatacept 10/10 group, and 33.0% in the placebo group) (Table 2). Estimates of the treatment differences in renal response relative to placebo were 12.6% (95% CI –1.1, 26.2) for the abatacept 30/10 group and 6.2% (95% CI –7.1, 19.4) for the abatacept 10/10 group.

Subanalyses of patients stratified according to prior treatment, race, and baseline nephrotic-range proteinuria. Patients were stratified at randomization according to variables in background therapy (naive, recent, inadequate response), and achievement of a prespecified efficacy end point, i.e., the percentage of patients with confirmed complete response at week 52, was performed. The analysis revealed no significant differences among the treatment groups in achievement of the efficacy end point (Table 2).

Subgroup analysis of confirmed complete response at week 52 by race (Asian versus non-Asian) also showed no significant differences among treatment groups (Table 2). In all treatment groups, response rates were higher among Asian patients compared with non-Asian patients. Similar results were observed in a post hoc subgroup analysis, by race, of the proportion of patients in whom complete response (unconfirmed) had been achieved at week 52. Due to the small number of enrolled patients of African descent, separate subanalyses could not be performed for this group.

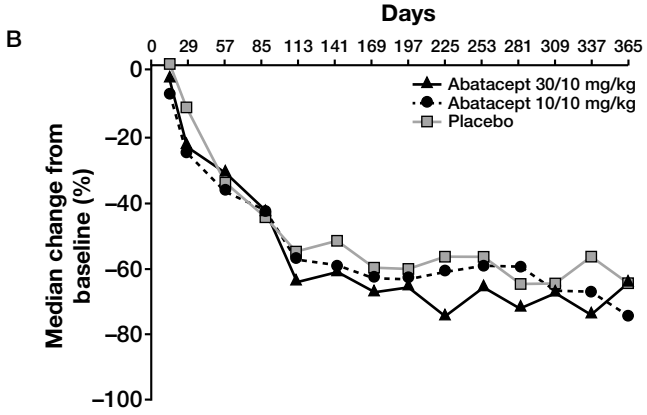
In a subgroup analysis of patients with nephrotic-range proteinuria at baseline (urinary protein-to-creatinine ratio >339 mg/mmole) (n = 122), there was an ~20–30% greater reduction in the mean urinary protein-to-creatinine ratio among those randomized to receive abatacept versus placebo (Figure 2A). This difference first became evident at week 24 and was maintained through week 52. In contrast, among patients who did not have nephrotic-range proteinuria at baseline, reduction in the urinary protein-to-creatinine ratio over time was comparable across treatment groups (Figure 2B).

Anti-dsDNA and complement levels. Greater improvements from baseline in anti-dsDNA antibody levels and complement C3 and C4 levels were seen in both abatacept groups compared with placebo. In the abatacept groups, decreases in mean anti-dsDNA antibody levels were achieved during the induction period (days 0–28) and maintained during the glucocorticoid taper (after day 28) (Figure 3A). The proportion of patients with a shift in the C3 or C4 level from low (below the LLN) at baseline to above the LLN with treatment was higher in both abatacept groups than in the placebo group. For C3, this difference was apparent as early as day 29 and persisted through day 365 (Figure 3B). The difference between the abatacept groups and the placebo group in the proportion of patients with a change in the C4 level from below the LLN at baseline to above the LLN with treatment became apparent on day 57 and persisted through day 365 (Figure 3C).



Number of patients assessed at each visit day

Visit day	15	29	57	85	113	141	169	197	225	253	281	309	337	365
Abatacept 30/10	38	38	38	32	35	34	33	33	31	30	31	29	29	30
Abatacept 10/10	34	36	31	33	30	31	30	30	30	27	27	26	26	25
Placebo	43	44	42	41	41	40	37	37	36	34	34	34	34	33



Number of patients assessed at each visit day

Visit day	15	29	57	85	113	141	169	197	225	253	281	309	337	365
Abatacept 30/10	60	59	57	57	57	55	51	51	52	49	45	47	44	45
Abatacept 10/10	58	59	56	59	53	52	53	52	51	49	51	49	47	49
Placebo	53	53	54	52	51	51	48	48	48	46	45	45	46	45

Figure 2. A, Median change from baseline in the mean urinary protein-to-creatinine ratio among patients who had nephrotic-range proteinuria at baseline, by treatment group. **B**, Median change from baseline in the mean urinary protein-to-creatinine ratio among patients who did not have nephrotic-range proteinuria at baseline, by treatment group. No formal statistical comparisons were made for these subgroup analyses.

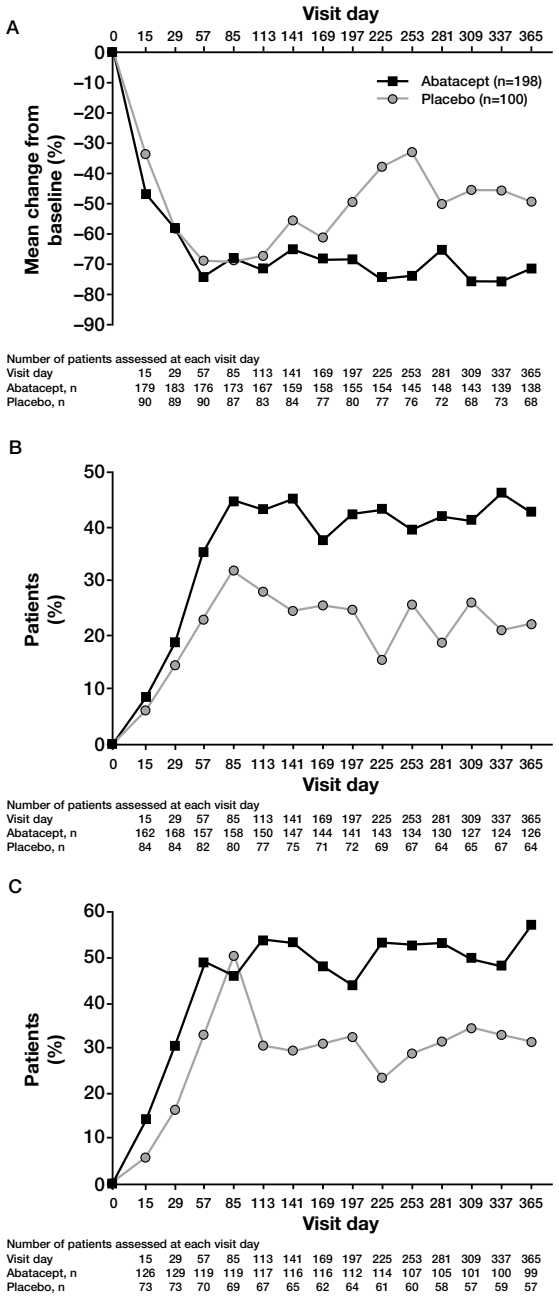


Figure 3. Biomarker levels through week 52. **A**, Changes in anti–double-stranded DNA antibody levels from baseline, as assessed by enzyme-linked immunosorbent assay. **B**, Percentage of patients with low complement C3 levels at baseline whose C3 levels normalized. **C**, Percentage of patients with low complement C4 levels at baseline whose C4 levels normalized. No formal statistical comparisons were made for the biomarker analyses.

Safety. Safety findings were similar with abatacept 30/10, abatacept 10/10, and placebo (Table 3). AEs, regardless of attribution to study drug, were reported at comparable frequencies in the abatacept and placebo treatment groups. Table 3 shows the number of discontinuations due to AEs considered by the investigator to be at least possibly related to the study drug.

Fourteen patients died during the double-blind treatment period (5 [5.1%], 2 [2.0%], and 7 [7.0%] in the abatacept 30/10, abatacept 10/10, and placebo groups, respectively). In 5 patients (3 placebo-treated, 2 abatacept 30/10–treated), the cause of death was ascribed to their underlying disease (acute renal failure, worsening SLE, and multiple organ failure, respectively, in the 3 placebo-treated patients; multiple organ failure in each of the 2 abatacept 30/10–treated patients). Seven deaths were related to infection (bronchopneumonia, sepsis, malaria, pneumonia [accompanied by cardiac failure], respectively, in 4 patients in the placebo group; pneumonia/lung abscess and bacterial peritonitis, respectively, in 2 patients in the abatacept 30/10 group, and interstitial pneumonia in 1 patient in the abatacept 10/10 group).

The proportions of patients with SAEs were similar among the 3 treatment groups (Table 3), with infections being the most commonly reported events. Pneumonia was the most common serious infection, and was reported in a similar percentage of patients in each group. Herpes zoster occurred at higher rates in both

Table 3. Summary of adverse events (AEs)*

	Abatacept 30/10 (n = 99)	Abatacept 10/10 (n = 99)	Placebo (n = 100)
All AEs	93 (93.9)	89 (89.9)	94 (94.0)
Related AEs	61 (61.6)	53 (53.5)	55 (55.0)
Discontinued due to AEs†	14 (14.1)	13 (13.1)	9 (9.0)
Deaths‡	5 (5.1)	2 (2.0)	7 (7.0)
Serious AEs	33 (33.3)	28 (28.3)	31 (31.0)
Infections	23 (23.2)	18 (18.2)	17 (17.0)
Pneumonia	4 (4.0)	4 (4.0)	3 (3.0)
Herpes zoster	3 (3.0)	6 (6.1)	0
Gastroenteritis	5 (5.1)	1 (1.0)	2 (2.0)
Urinary tract infection	0	2 (2.0)	2 (2.0)
Renal failure§	3 (3.0)	2 (2.0)	3 (3.0)
Related serious AEs	20 (20.2)	19 (19.2)	15 (15.0)
Discontinued due to serious AEs	14 (14.1)	12 (12.1)	7 (7.0)
Peri-infusional AEs	23 (23.2)	18 (18.2)	17 (17.0)
Acute infusional AEs	4 (4.0)	4 (4.0)	3 (3.0)

* No formal statistical comparisons were made for the 2 abatacept treatment groups versus placebo. Values are the number (%).
† According to the Action Taken Regarding Study Drug field on the Adverse Event Case Report form.
‡ All deaths reported during the double-blind period, including those that occurred >56 days after the last dose of study treatment.
§ Includes acute and chronic renal failure.

abatacept-treated groups compared with the placebo group, and rates of gastroenteritis were highest in the abatacept 30/10 group. SAEs considered by the investigator to be at least possibly related to the study drug were more frequent in the abatacept groups; of these, "infections and infestations" were the most common (18.2%, 15.2%, and 12.0% in the abatacept 30/10, abatacept 10/10, and placebo groups, respectively). Rates of study discontinuation due to SAEs were also higher in the abatacept groups compared with the placebo group (Table 3).

Prespecified and prospectively defined peri-infusional AEs (reported within 24 hours after the start of study medication infusion) were reported in similar numbers of patients in all treatment groups (Table 3). Two peri-infusional events were serious (1 in a patient receiving abatacept 30/10; 1 in a patient receiving placebo), but none resulted in study discontinuation. Acute infusional AEs—a subset of peri-infusional AEs defined as those occurring within 1 hour of infusion—were reported in a small percentage of patients in each group. None of the acute infusional AEs was serious or resulted in discontinuation of study medication.

DISCUSSION

Treatment of active LN includes high-dose glucocorticoids, together with prolonged treatment with immunosuppressants. Deaths and treatment failures are common in the first year of therapy, and complete response is often delayed or not achieved (25–29). Several agents have been investigated as add-on therapies for LN. In the Lupus Nephritis Assessment with Rituximab (LUNAR) study (ClinicalTrials.gov identifier NCT00282347), rituximab failed to demonstrate additional efficacy, and the ocrelizumab and atacicept programs were prematurely terminated because of toxicity (30–32).

The rationale for considering abatacept for the treatment of LN included not only preclinical evidence that CTLA-4Ig is effective in treating and preventing nephritis in the NZB × NZW mouse model (5–7), but also observations in a study of extrarenal lupus indicating favorable effects on anti-dsDNA antibody levels (9). The consistent safety profile of abatacept in combination with immunosuppressants in patients with RA (33–35) or SLE (9) provided additional support for investigations of abatacept as combination treatment in LN.

The present study is the first randomized, placebo-controlled trial of the efficacy and safety of IV abatacept added to background therapy in adult patients with LN. Overall, the safety profile for IV abatacept in patients with active LN was comparable to that of MMF and glucocorticoids alone, with the exception of higher frequencies of moderate-to-severe herpes zoster infections (grades II and III). The safety profile generated from this study is consistent with the results of previous studies comparing abatacept with placebo in patients with RA (33–35).

The study did not meet its prespecified primary efficacy end point of time to confirmed complete response. However, treatment with IV abatacept was associated with improved levels of anti-dsDNA antibodies, complement, and urinary protein. As has also been reported previously (17,20), a post hoc review indicated several limitations relevant to the present study that may have obscured treatment effects measured using the primary end point and some secondary end points. These include the disproportionate allocation of patients with lower levels of urinary protein in the placebo arm, unrestricted use of glucocorticoids during the treatment period, and a stringent definition of confirmed complete response that may have failed to capture some clinically and prognostically significant end points.

The definition of confirmed complete response, which required that the eGFR was $\geq$90% of the reference value (confirmed at 2 time points), led to the exclusion of patients experiencing minor fluctuations in creatinine levels and reduced the confirmed complete response rates in all groups (to 8.0–11.1%—levels far lower than those observed in other clinical trials) (25,31). For example, in the LUNAR study, the definition of complete response required a serum creatinine level within 15% of the baseline level and did not require confirmation of response on a consecutive visit. Although the primary end point was not met in that trial, the proportion of patients achieving the trial-specified definition of complete response in the LUNAR study ranged from 26.4% to 30.6% (31).

Noting the variation among primary end points in LN trials, Wofsy et al (19) explored the impact of different definitions of a complete response end point on the results in subsets of patients from the present data set. The analysis considered only patients who met the entry criteria for the given trial whose end point criteria were being applied, and required a successful taper of glucocorticoids to $\leq$10 mg/day for the patient to be considered to show response. The week 52 complete response rates were as follows for the abatacept 30/10, abatacept 10/10, and placebo groups, respectively: ACR-recommended end point 13.0%, 14.0%, and 6.0%;

LUNAR trial end point 24.0%, 22.0%, and 6.0%; Aspreva Lupus Management Study (ClinicalTrials.gov identifier NCT00377637) end point 28.0%, 25.0%, and 13.0%, and the end point being used in the Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study (an ongoing National Institutes of Health–sponsored trial; ClinicalTrials.gov identifier NCT00774852) 33.0%, 36.0%, and 19.0%. In this exploratory analysis, the choice of primary efficacy measure had substantial impact on the results of the current study (19,20), demonstrating that the stringent definition of confirmed complete response used in the present study was the least discriminating among end points tested.

Study end points may also have been affected by use of glucocorticoids. Although it was recommended in the protocol that glucocorticoids be tapered over a 12-week period, glucocorticoid administration, including by IV pulse, was permitted throughout the study period for safety reasons. The proportion of patients receiving IV pulse glucocorticoids was similar across treatment arms (44.4%, 44.4%, and 45.0% in the abatacept 30/10, abatacept 10/10, and placebo groups, respectively); however, the proportion receiving pulse glucocorticoids after the first 3 months differed across groups (17.2%, 9.1%, and 18.0%, respectively). Confirmed complete response was achieved in few patients who were treated with pulse glucocorticoids (4.0%, 5.0%, and 3.0%, respectively). Thus, although the imbalance may not have affected confirmed complete response substantially, pulse glucocorticoids could have had an impact on partial responses and other estimates of response. Therefore, in future clinical studies, background use of glucocorticoids should be carefully controlled.

Findings of the present study illustrate the importance of applying appropriate end points in LN trials. In patients with active class III or IV LN who were receiving background MMF and glucocorticoids, treatment with IV abatacept was associated with an acceptable safety profile and with improvement in anti-dsDNA antibody levels and complement levels. In those with nephrotic-range proteinuria at baseline, greater reductions in proteinuria were observed in the abatacept treatment groups than in the placebo group. Although the primary efficacy end point was not met, the findings of the exploratory and post hoc analyses support further evaluation of abatacept for the treatment of LN.

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. Furie 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. Chen, Kinaszczuk, Merrill.

Acquisition of data. Furie, Nicholls, Cheng, Houssiau, Burgos-Vargas, Kinaszczuk, Merrill.

Analysis and interpretation of data. Furie, Houssiau, Burgos-Vargas, Hillson, Meadows-Shropshire, Merrill.

ROLE OF THE STUDY SPONSOR

Bristol-Myers Squibb facilitated the study design and reviewed and approved the manuscript prior to submission. The authors had full access to the study data, contributed to the interpretation of the results, and had ultimate control over the decision to publish and the final version of the manuscript submitted for publication. Professional medical writing and editorial assistance were provided by Sarah Funderburk, PhD (Caudex Medical), and were funded by Bristol-Myers Squibb.

REFERENCES

1. Foster MH. T cells and B cells in lupus nephritis. Semin Nephrol 2007;27:47–58.
2. Orencia (abatacept) prescribing information. Princeton (NJ): Bristol-Myers Squibb; 2013. URL: http://packageinserts.bms.com/pi/pi_orencia.pdf.
3. Davis PM, Abraham R, Xu L, Nadler SG, Suchard SJ. Abatacept binds to the Fc receptor CD64 but does not mediate complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity. J Rheumatol 2007;34:2204–10.
4. Weisman MH, Durez P, Hallegua D, Aranda R, Becker JC, Nuamah I, et al. Reduction of inflammatory biomarker response by abatacept in treatment of rheumatoid arthritis. J Rheumatol 2006;33:2162–6.
5. Daikh DI, Finck BK, Linsley PS, Hollenbaugh D, Wofsy D. Long-term inhibition of murine lupus by brief simultaneous blockade of the B7/CD28 and CD40/gp39 costimulation pathways. J Immunol 1997;159:3104–8.
6. Daikh DI, Wofsy D. Reversal of murine lupus nephritis with CTLA4Ig and cyclophosphamide. J Immunol 2001;166:2913–6.
7. Schiffer L, Sinha J, Wang X, Huang W, von Gersdorff G, Schiffer M, et al. Short term administration of costimulatory blockade and cyclophosphamide induces remission of systemic lupus erythematosus nephritis in NZB/W F1 mice by a mechanism downstream of renal immune complex deposition. J Immunol 2003;171:489–97.
8. Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis Rheum 2011;63:939–48.
9. Merrill JT, Burgos-Vargas R, Westhovens R, Chalmers A, D'Cruz D, Wallace DJ, et al. 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. Arthritis Rheum 2010;62:3077–87.
10. Isenberg DA, Rahman A, Allen E, Farewell V, Akil M, Bruce IN, et al. BILAG 2004: development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology (Oxford) 2005;44:902–6.
11. Ware JE Jr, Snow KK, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. 2nd ed. Lincoln (RI): QualityMetric; 2000.
12. Furie R, Nicholls K, Cheng TT, Houssiau F, Burgos-Vargas R, Chen SL, et al. Efficacy and safety of abatacept over 12 months in

patients with lupus nephritis: results from a multicenter, randomized, double-blind, placebo-controlled phase II/III study [abstract]. Arthritis Rheum 2011;63 Suppl:S962–3.
13. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
14. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004; 15:241–50.
15. Churg J, Sobin H. Renal disease: classification and atlas of glomerular disease. Tokyo: Igaku-Shoin; 1982.
16. Furie R, Nicholls K, Cheng TT, Houssiau F, Burgos-Vargas R, Chen SL, et al. Efficacy and safety of abatacept in lupus nephritis [abstract]. Ann Rheum Dis 2012 Suppl 3;71:534.
17. Wofsy D, Meadows Shropshire S, Hillson JL, Diamond B. Abatacept for lupus nephritis: alternative outcome measures support opposing interpretations of data from a multicenter, randomized, double-blind, placebo-controlled phase II/III study [abstract]. Arthritis Rheum 2011;63 Suppl:S964–5.
18. Wofsy D, Meadows-Shropshire S, Hillson JL, Diamond B. Comparative analysis of alternative outcome measures for use in lupus nephritis trials [abstract]. Ann Rheum Dis 2012 Suppl 3;71:535.
19. Wofsy D, Hillson JL, Diamond B. Abatacept for lupus nephritis: alternative definitions of complete response support conflicting conclusions. Arthritis Rheum 2012;64:3660–5.
20. Wofsy D, Hillson JL, Diamond B. Comparison of alternative primary outcome measures for use in lupus nephritis clinical trials. Arthritis Rheum 2013;65:1586–91.
21. Renal Disease Subcommittee of the American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria. The American College of Rheumatology response criteria for proliferative and membranous renal disease in systemic lupus erythematosus clinical trials. Arthritis Rheum 2006;54:421–32.
22. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.
23. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–3.
24. US Food and Drug Administration. Guidance for industry. Systemic lupus erythematosus—developing medical products for treatment. June 2010. URL: URL:http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072063.pdf.
25. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103–12.
26. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, et al, for the Hong Kong-Guangzhou Nephrology Study Group. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. N Engl J Med 2000;343:1156–62.
27. Chan TM, Tse KC, Tang CS, Mok MY, Li FK, for the Hong Kong Nephrology Study Group. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol 2013;16: 1076–84.
28. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med 2005;353:2219–28.
29. Houssiau F, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–31.
30. Ginzler EM, Wax S, Rajeswaran A, Copt S, Hillson J, Ramos E, et al. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. Arthritis Res Ther 2012;14:R33.
31. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al, for the LUNAR Investigator Group. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012;64:1215–26.
32. Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. Arthritis Rheum 2013;65:2368–79.
33. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. N Engl J Med 2005;353: 1114–23.
34. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006;144:865–76.
35. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 2009;68:1870–7.