Efficacy of Abatacept in Inflammatory Polyarthritis of Systemic Lupus Erythematosus (SLE)

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PROTOCOL SYNOPSIS

Protocol Title:	
Site Numbers & Names:	001: UCLA Rheumatology 002: UCSD Rheumatology
Research Hypothesis:	Primary: Abatacept will improve lupus inflammatory polyarthritis in patients by 16 weeks of treatment.
Study Rationale	Inflammatory polyarthritis is common in people with SLE, with swollen, tender joints occurring in up to 88% of patients [1]. Inflammatory arthritis often improves on aggressive therapies, including glucocorticoids, mycophenolate, and cyclophosphamide [2], sometimes with azathioprine, and occasionally with methotrexate or leflunomide. The use of abatacept by the subcutaneous route is a highly attractive alternative for treatment of lupus arthritis for the following reasons. 1) Abatacept is effective in rheumatoid arthritis, which lupus arthritis resembles [3], 2) The synovitis of SLE depends on activated innate and adaptive immunity, with antigen-presenting cells (APC) activating effector T cells, which activate B cells. Together, these cells secrete pro-inflammatory cytokines including IFN type 1, IFNgamma and IL-17 [4]. Interruption of CD80/86-CD28 interactions by abatacept should block APC/T cell signals that drive inflammation, without blocking regulatory cell generation that is anti-inflammatory. 3) A prospective controlled trial of abatacept in SLE showed a lower flare rate in patients with polyarthritis who received abatacept compared to patients with polyarthritis who received placebo [5]. 4) A recently published retrospective study of 6 patients with rhupus (satisfying ACR criteria for both rheumatoid arthritis and systemic lupus erythematosus) showed that all responded to abatacept with decrease in Clinical Disease Activity Index (a validated measure of disease activity in rheumatoid arthritis) and minimal adverse events[6].

Study Objectives:	**Primary:** Improvement of lupus inflammatory polyarthritis measured by ≥20% improvement in tender and swollen 28 joint counts at 16 weeks. **Secondary:** 1. Mean and median joint counts in treated vs placebo patients at 16 weeks, compared to baseline scores. 2. Proportion of patients who achieve improvement in SLEDAI 2K at 16 weeks of >3 points. 3. Mean and median changes in CDAI comparing abatacept to controls at 16 weeks. 4. Changes in a) synovitis, b) tenosynovitis and c) erosions measured by high-energy ultrasound with Doppler flow at zero and 16 weeks. 5. Proportion of patients with BILAG A in any system other than musculoskeletal at week 16. 6. Proportion of patients with no significant increase in physician global assessment (defined as <0.8 on a 1-10 scale) at 16 weeks. 7. Steroid sparing effect of abatacept, measured as ability to taper prednisone to ≤10mg/day by week 16. 8. Effects on fatigue at 16 weeks as measured by the FACIT fatigue score instrument 9. Effects on quality of life at 16 weeks as measured by the SF 36 10. Safety, measured in standard methods as AE and SAE, including likelihood that the AE/SAE was related to the study biologic. 11. Time to response, measured as time to ≥20% decrease in joint counts (sum of tender and swollen joints) at zero, 4, 8, 12, and 16 weeks. 12. Change in peripheral blood T cell compartments indicating decline in pro-inflammatory profiles, i.e., we expect decrease in CD4+ effector T cells that make IFNgamma (TH1) and IL-17 (TH17) and increase in ratio of Treg to Teff, as well as decreased function of Thelper and increased functions of Tregs. CD4+CD25+ Foxp3+ and CD8+Foxp3+ will be the definition of regulatory T cells. These will be measured at zero and 16 weeks. 13. Change in anti-DNA and total IgG levels, as well as rise in serum complement levels as disease improves and fewer B cells are activated: measure these at zero, 8 and 16 weeks. 14. Effects of abatacept on serum levels of BLyS (BAFF) at baseline, 8 and 16 weeks. As numbers of activated B cells and plasmablasts fall, we expect an increase in BLyS levels .

Study Design:	Randomized trial of 32 SLE patients treated with subcutaneous abatacept 125mg sq once a week vs. 32 placebo treated subjects over a 16 week period. Patients will be seen every 4 weeks from baseline. One half of patients will be recruited at UCLA and one-half at UCSD. We expect 30 patients in each group to complete the 16 week study.
Study Schema **Drugs / Doses / Length of Treatment)**	Abatacept 125 mg or placebo will be administered subcutaneously once a week for 16 weeks. There will be a telephone follow up 2 months after the last injection to capture post-treatment adverse events.
Accrual Goal: (Total number of subjects)	64 (32 at UCLA and 32 at UCSD)
Accrual Rate: (Number of subjects expected per month)	2-3 subjects per month at each site
FPFV: April 1, 2015 **LPFV: March 31, 2018** **Follow Up: 16 weeks per patient plus 8 weeks of observation for adverse events**	
Correlative Studies: These will be performed at the UCLA site only	1) Biomarkers: a) T cell numbers and phenotypic and functional characteristic in PBMC measured at week 0 and 16. These will include for T cells CD4+, CD3+, CD25+, CD8+, Foxp3+ and cytoplasmic stains for IFNgamma, IL2, IL-17, IL21 and IL-10. b) B cell numbers and subsets, including naïve, activated and plasmablasts. c) Ability of autologous CD4+CD25hi T cells to suppress proliferation of CD4+CD25- T cells. d) Cytokines in serum: IFNgamma, IL-6, IL-10, IL-17, IL23 and BLyS 2) Ultrasound with power Doppler of joints assessing synovitis, tenosynovitis (18 joints) and erosions at week 0 and 16.

Inclusion Criteria	1. Meet at least 4 of the 11 American College of Rheumatology (ACR) 1997 criteria for classification of SLE (see Appendix 1).OR meet the recent classification recommended by SLICC (Appendix 2) [6] 2. ≥3 swollen and tender joints on 2 examinations at least 2 weeks apart and no more than 8 weeks apart. 3. SLEDAI2K score ≥4 indicating active disease. 4. Documented positive ANA (≥1:80) and/or anti-dsDNA during course of SLE. 5. Men and women, at least 18 years of age. Women of childbearing potential must use adequate method(s) of contraception to avoid pregnancy throughout the study and for up to 2 months after last study drug dose. They must have a negative serum or urine pregnancy test prior to the start of study medication. 6. Background therapies allowed: antimalarials (dose constant for ≥ one month before study entry and during 16 weeks of trial), methotrexate (same criteria as for antimalarials), azathioprine (same criteria), mycophenolate (same criteria), leflunomide (same criteria). During the screening period and for up to 6 weeks after randomization, a daily prednisone (or equivalent) regimen of up to 20 mg daily may be initiated to treat the moderate to severe disease activity present at screening. The initial steroid regimen is not required if investigators or patients believe that the risks would outweigh the potential benefits. Patients who do not take any glucocorticoids during the study will be included in the treatment groups and analysis. *Steroids should be tapered to a target dose of no more than 10 mg/day of prednisone (or equivalent) by the end of Week 8 (Day 56). The steroid regimen should be tapered as quickly as safely possible. Prednisone dose requirements higher than 10 mg daily at the 8 week visit will cause the patient to be ruled a non-responder for the abatacept treatment arm.

Exclusion Criteria:	1. Subjects with active infection requiring oral or IV antibiotics within one month of first dose of study medication. 2. Subjects with BILAG A in any system outside the musculoskeletal system. 3. Subjects with positive quantiferon Gold test in the absence of treatment for tuberculosis. 4. Subjects with positive tests for active infection with hepatitis B or C during the past 6 months. Any confirmed positive test for HIV at any time prior to entry into this study. 5. Subjects with active glomerulonephritis (>3 g protein/24h and/or active urine sediment). 6. Subjects with active CNS disease. 7. Subjects with any other serious disease that would require immunosuppressive or parenteral anti-microbial therapy outside the study protocol. 8. Inability to self-administer subcutaneous injections, to comply with instructions, or to keep appointments for study visits. 9. Treatment with rituximab within the past 6 months (B cells must be detectable in peripheral blood at onset of treatment with study biologic), belimumab within the past 3 months, cyclophosphamide within the past 3 months. 10. Treatment with any other immunomodulatory biologic or cyclophosphamide during treatment with abatacept is not allowed. 11. Patients requiring >20 mg of prednisone daily. 12. Women who are pregnant or breast feeding. 13. Women of child bearing potential unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 2 months after last study drug. 14. Subjects with a history of cancer within the last five years (other than non-melanoma skin cell cancers cured by local resection). 15. Any laboratory test results that, in the opinion of the Investigator, might place the subject at unacceptable risk for participation in this study.
Criteria for Evaluation: (Efficacy, safety, stopping rules, etc.)	See text
Statistics:	See text

1 INTRODUCTION

1.1 Research Hypothesis

Abatacept via subcutaneous injection will induce clinical response in inflammatory polyarthritis in patients with systemic lupus erythematosus.

1.2 Product Development Rationale

Abatacept is a recombinant fusion protein consisting of the extracellular domain of human CTLA4 and a fragment (hinge- CH2-CH3 domains) of the Fc domain of human IgG1 that has been modified to prevent complement fixation and antibody-dependent cellular cytotoxicity.

Abatacept is the first drug in a new class of agents termed "selective costimulation modulators." Abatacept binds specifically to the CD80 and CD86 molecules, proteins prominently displayed on the surface of antigen-presenting cells (APCs). Activation of naive T cells during an immune response requires two stimuli from APCs. The first signal is antigen-specific; antigens are presented by APCs, with the signal transmitted to the T cell through the T cell's antigen receptor. The second, or costimulatory, signal is not antigen-specific and is delivered following the engagement of a costimulatory ligand on the APC with a cognate receptor on the T cell.

A key costimulatory receptor on T cells is CD28. CD28 is constitutively expressed on resting T cells and binds to both CD80 (B7-1) and CD86 (B7-2) on the APC [7-10]. A costimulatory signal is required not only for the full activation of naive T cells, but also may be required for the survival of memory and autoimmune effector cells [11, 12]. At 24 to 48 hours following T cell activation, the T cell expresses CTLA4 on its surface, which engages the CD80 and CD86 molecules on the APC surface interfering with CD28's ability to bind to its ligands on the APC; CD80 and CD86 preferentially bind to CTLA4 with a much higher avidity than with CD28. Although the precise mechanisms are as yet unclear, CTLA4 expression is associated with a decrease in T cell activation.

After the T cell activity has been dampened, the CTLA4 recycles into the T cell's cytoplasm. The CTLA4 section of abatacept binds specifically to CD80 and CD86 (B7-1 and B7-2, respectively) and down-modulates the CD28-mediated costimulation of T cells. Thus, abatacept uses a segment of a molecule that is part of the normal immune homeostatic mechanism to suppress T cell activity involved in the immunopathogenesis of autoimmune diseases. The FC region of abatacept was engineered with several point mutations designed to inactivate it. Because of these changes, abatacept does not mediate pathways such as antibody-dependent cell cytotoxicity or complement-dependent cytotoxicity [13].

1.2.1 Overview of Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is an autoimmune disease with unknown etiology. It is of great clinical variation as it can affect virtually all body systems including musculoskeletal, mucocutaneous, cardiovascular, neurological, respiratory, renal, ophthalmic, hematological and gastrointestinal systems.

1.2.2 Polyarthritis in Lupus Patients

Inflammatory polyarthritis is common in systemic lupus patients, with swollen, tender joints occurring in up to 88% [1]. Although SLE arthritis is generally less destructive than rheumatoid

arthritis, joint deformities similar to rheumatoid arthritis can occur in 25-35% of SLE patients. Erosions detectable on standard x-rays occur in approximately 4%. However, in multiple studies[16-19], high-resolution ultrasound and/or power Doppler of the wrists, MCPs and PIPs in SLE patients with hand arthritis showed synovitis in 70-95% depending on joint studied (synovitis was most abundant in wrists), erosions in approximately 50% (particularly in MCPs) and tenosynovitis in 65%.

Lupus arthritis can cause pain, stiffness, swelling, tenderness, and warmth of joints in a waxing and waning pattern. Several joints may be involved at the same time and all major and minor joints may be affected.

There is no definitive treatment or cure for lupus polyarthritis. Standard of care for patients with lupus such as corticosteroids, NSAIDs, anti-malarials, and immunosuppressive drugs and biologics treat lupus polyarthritis as well as other SLE symptoms. These treatments, however, especially immunosuppressive medications, have many side effects, including infectious complications.

The PI recently reviewed 10 patients with lupus arthritis she examined serially. On a 66-joint tender/swollen joint count, the average score was 21. In two patients who had just completed 12-week-long open clinical trials and who reported improvement, counts dropped from 22-31 to zero-4. Thus, arthritis is an important component of SLE and can easily be quantitated by experienced investigators to assess benefits of interventions. We are proposing here to use a standard 28 joint count, which includes the joints most frequently involved in SLE (hand 1-5 PIPs, 1-5 MCPs, wrists, elbows, knees). Reliability of these joint counts (28 joints) has been well documented in patients with rheumatoid arthritis, the 28 joint count is standard in clinical investigations in RA, and the ultrasound examination for synovitis proposed here will examine the hand (PIP2-5, MCP 2-5) and wrist joints. Change in joint counts can be evaluated as a dichotomous variable (as we are proposing for the primary outcome measure), or as a continuous measure to increase sensitivity. In addition, as a secondary outcome we are proposing use of the Clinical Disease Activity Measure (CDAI)[7,20] which is also a continuous variable. We have not used CDAI in studies of lupus arthritis, but a recent publication[6] reports that the CDAI responded favorably to abatacept therapy in 6 of 6 patients with rhupus – an overlap syndrome between rheumatoid arthritis and systemic lupus. In RA, CDAI (a sum of swollen joints, tender joints, physician global assessment and patient global assessment) correlates well with DAS28, ACR response rates 20/50/70, HAQ scores and radiographic changes over time[7]. It has the advantage of not requiring laboratory assessments and thus can be done at the patient visit.

1.2.3 Role of T cells in Systemic Lupus Erythematosus

The arthritis of SLE, like RA, is an inflammatory synovitis. Histology, cell infiltrates and gene expression in synovial specimens from patients with SLE, RA and osteoarthritis were compared in a recent study[4]. SLE arthritis was characterized by proliferation of synovial lining cells (less than in RA), diffuse mononuclear cells infiltrating into the synovium, and perivascular mononuclear cell infiltrates. Infiltrating cells include CD3+ T cells, CD8+ T cells, CD20+ B cells, CD68+ macrophages and CD138+ plasma cells. Nearly half of the genes dysregulated in RA synovial tissue related to T and B cell functions; nearly half in SLE were interferon-regulated genes and STAT1 (in the IFN pathway). Since clinical disease in SLE is initiated by autoantibodies and immune complexes which deposit in target tissues, activate complement, and initiate inflammation, the role of B cells is central in the disease. Increases in circulating mature B cell subsets, such as

memory B cells, activated B, plasmablasts and short-lived plasma cells are characteristic[21]. Since most pathogenic autoantibodies and immune complexes contain IgG, and T cell help is required for Ig switch from IgM to IgG, T cell help is critical for sustaining many autoreactive B cells and promoting their differentiation to autoantibody-secreting plasma cells [22]. Helper CD4+ T cells can secrete IFNgamma or IL-17. Therefore, interfering with T cell activation and thus T cell help by administering abatacept should reduce B cell stimulation and therefore reduce quantities of autoantibodies and possibly of total IgG. In this study, we propose to determine biological consequences of treatment with abatacept, which might include 1) decrease in numbers of activated CD4+CD25- T cells and in those cells that stain for IFNgamma or IL-17; 2) increased numbers (measured as CD4+CD25+Foxp3+ and CD8+Foxp3+ peripheral blood cells) and/or function of Tregs (measured as ability of CD4+CD25hi T cells to suppress proliferation of autologous CD4+CD25- T cells); 3) decreased plasma levels of IFNgamma, IL17 and IL23, with increased levels of IL10 and TFGbeta. 4) decreased numbers of activated B cells and plasmablasts; 5) decreased quantities of total IgG, and IgG anti-DNA; 6) increased plasma levels of BLyS in response to lower numbers of activated/mature B cells and plasmablasts. Any of these features would indicate a biologic effect of abatacept, whether or not those effects correlate with clinical outcomes.

Recent data, published in abstract form, from other institutions performing clinical trials of abatacept in SLE suggest that responders can be differentiated from non-responders by 1) transcriptome differences in mononuclear cells at baseline, and 2) interferon signatures at baseline, based on changes in expression of genes induced by interferons (Bandyopadhyay S et al, De-convolution of whole blood transcriptomic data from a phase IIb, randomized, double-blind, placebo-controlled trial of abatacept in systemic lupus erythematosus. 2015 ACR/ARHP Annual Meeting, abstract number 2067.)

Most importantly, the treatment should suppress disease activity. In the published phase III trial of abatacept in SLE (without active nephritis), overall disease activity suppression occurred in both placebo and abatacept groups, but the group with polyarthritis had a significantly fewer flares with abatacept than with placebo [5].

1.3 Summary of Results of Investigational Program in Rheumatoid Arthritis

The initial efficacy and safety of abatacept (previously known as CTLA4-Ig and BMS-188667) was established in clinical studies of RA, psoriasis, and multiple sclerosis. The subsequent registrational program was in juvenile idiopathic arthritis (JIA), with data being collected from the ongoing long-term extension portion. Current active registrational programs for abatacept include studies in systemic lupus erythematosus (SLE) including lupus nephritis, and psoriatic arthritis.

A full development program conducted in adult RA led to regulatory approval in the United States for this indication in December 2005, in Canada in June 2006, and in Europe in May 2007. In the US, abatacept now has two indications: (1) treatment of moderate to severe active RA in adults, and (2) treatment of moderate to severe juvenile idiopathic arthritis (JIA) in patients who have failed prior therapy with disease-modifying anti-rheumatic drugs (DMARDs).

1.3.1 Core Efficacy Studies of Abatacept in Rheumatoid Arthritis

The RA clinical program consisted of five core studies: IM101-100, IM101-101, IM101-102, IM101-029, and IM101-031 (N=2944) [23-27]. Each study had a double-blind placebo-controlled period of 6 months or 1 year. In Study IM101-100, subjects received abatacept 2 mg/kg, 10 mg/kg, or placebo. In the other studies, subjects received abatacept 10 mg/kg or a fixed dose that approximated 10 mg/kg or placebo.

Subjects who completed the double-blind period were offered entry into an uncontrolled, open-label period, in which all subjects received abatacept (in a fixed dose that approximated 10 mg/kg). A total of 2624 subjects in the core RA studies received the approved abatacept dose (10 mg/kg or a fixed dose that approximated 10 mg/kg) in the combined double-blind and open-label periods, representing 4603 person-years of exposure[28].

The efficacy of abatacept at a weight-tiered dose approximating 10 mg/kg was demonstrated in placebo-controlled studies in adult subjects with active RA and an inadequate response to methotrexate (IM101-100, IM101-102, and IM101-043), and in one study in adult subjects with active RA and an inadequate response to at least one TNF-blocking agent (etanercept and/or infliximab; IM101-029) [23-27,29-33] Other studies have provided additional supportive evidence of efficacy. Abatacept (10 mg/kg or a fixed dose approximating 10 mg/kg) was significantly more effective than placebo in reducing the signs and symptoms of RA, including induction of major clinical response, improving physical function, slowing the progression of structural damage, and improving the quality of life in subjects with moderately to severely active RA.

In Studies IM101-102 and IM101-029, improvement in signs and symptoms assessed by the American College of Rheumatology (ACR) 20 response rate versus placebo was observed after administration of the first dose, as measured at Day 15, and it was maintained through the double-blind study phase and for up to 3 years (in IM101-029 and IM101-102) and up to 5 years (in IM101-100)[30,31]. In the open-label extensions of IM101-100, IM101-102, and IM101-029, durable and sustained ACR20, ACR50, and ACR70 responses have been observed through 48, 24, and 18 months, respectively, of abatacept treatment [30,32,33].

1.3.2 Pharmacokinetics of Subcutaneous Formulation

Subcutaneous (SC) formulation in adult population

Single SC doses of abatacept (50 to 150 mg) demonstrated approximately dose proportional PK in healthy adult subjects[34]. Following administration of single doses of 50 to 150 mg of abatacept, the mean Cmax increased from 3.5 to 10.7 μg/mL and the geometric mean AUC(INF) increased from 1490 to 4270 μg·hour/mL. The median time to occurrence of Cmax (Tmax) following SC administration ranged between 48 and 168 hours. Mean $T_{1/2}$ values in healthy subjects ranged from 11.2 to 14.7 days. $T_{1/2}$ values from this study were comparable with the $T_{1/2}$ values obtained with abatacept administered IV to subjects with RA (13 to 14 days) 30. The fact that $T_{1/2}$ values following SC dosing were comparable to $T_{1/2}$ values obtained after IV dosing suggests that the elimination characteristics of abatacept were not altered following SC administration.

A double-blind, randomized, placebo-controlled, parallel-group, multiple-dose study (IM101063) assessed the steady-state trough serum concentrations of abatacept following SC administration in

subjects with RA[35]. Subjects were randomized to receive either abatacept or placebo in 1 of 5 parallel groups based on body weight obtained at the screening visit (Table 1.3.2). The SC dose regimens were selected to target trough levels between 10-30 ug/ml, which was associated with efficacy with the IV formulation.

Table 1.3.2A IM101063 Treatment Groups Based on Body Weight

Treatment Group	Subject weight (kg)	IV dose on Day 1 (mg)	SC dose weekly for 12 weeks (mg)	SC injection volume (mL)
1	< 60	500	75	0.6
2	< 60	500	125	1
3	60 - 100	750	125	1
4	> 100	1000	125	1
5	> 100	1000	200	0.6 + 1.0

Source: IM101063 CSR

On Day 1, subjects received a single IV infusion (loading dose) of abatacept or placebo, based on their weight range. Approximately 1 hour after the completion of the IV infusion, subjects received their assigned SC dose of abatacept or placebo. Abatacept or placebo was administered weekly by the SC route, at the same dose as the SC dose on Day 1, for a total of 12 SC injections. Blood samples for PK analysis were collected on Day 1 prior to and at the end of the IV infusion. In addition, blood samples were collected prior to each weekly SC dose of abatacept.

Steady-state trough serum concentrations were achieved after ~ 4 to 5 weeks following the combined regimen of a single IV loading dose and weekly SC injections. With the exception of Treatment group 4 (abatacept 125 mg SC weekly dose for subjects weighing > 100 kg), the mean steady-state trough concentrations across all other treatment groups appeared to be comparable.

However, to truly represent the steady-state serum levels from SC administration without the contribution of the IV loading dose, Cmin values on Days 71-85 were selected, since contribution from IV was expected to be negligible. Comparison of mean steady-state trough concentrations on Day 71, 78 and 85 indicated that abatacept did not appear to accumulate following weekly dosing (Table 1.3.2B).

Table 1.3.2B: Summary Statistics for Abatacept Steady-State Cmin Values on Days 71, 78, and 85 - IM101063

Treatment Group	Study Day	n	Cmin (μg/mL) Geometric Mean (CV%)	Cmin (μg/mL) Median (Min, Max)
1 (500 mg IV / 75 mg SC)	71	7	22.64 (20.13)	20.92 (17.06, 29.84)
	78	7	21.66 (19.99)	22.40 (16.01, 28.93)
	85	7	23.62 (31.63)	21.91 (18.24, 39.60)

Table 1.3.2B: Summary Statistics for Abatacept Steady-State Cmin Values on Days 71, 78, and 85 - IM101063

Treatment Group	Study Day	n	Cmin (μg/mL) Geometric Mean (CV%)	Cmin (μg/mL) Median (Min, Max)
2 (500 mg IV / 125 mg SC)	71	4	28.03 (42.13)	32.57 (13.73, 43.30)
	78	3	34.17 (29.49)	33.10 (25.97, 46.40)
	85	3	36.73 (31.64)	37.50 (26.26, 50.30)
3 (750 mg IV / 125 mg SC)	71	26	24.05 (40.65)	26.53 (7.97, 54.11)
	78	23	24.41 (52.35)	27.54 (5.40, 68.90)
	85	25	24.93 (38.42)	26.01 (9.57, 53.80)
4 (1000 mg IV / 125 mg SC)	71	3	16.22 (24.39)	15.15 (13.37, 21.07)
	78	5	11.57 (32.25)	13.20 (6.89, 16.33)
	85	5	13.01 (41.35)	13.30 (6.66, 22.73)
5 (1000 mg IV / 200 mg SC)	71	5	26.52 (56.53)	26.20 (8.68, 55.20)
	78	5	29.21 (52.96)	40.40 (8.04, 57.10)
	85	5	27.53 (58.87)	29.01 (8.74, 62.00)

Source: IM101063 CSR, Supplemental Table S.8.2.2

n=number of observations

Steady-state pharmacokinetic parameters of abatacept after weekly SC administration were determined between the SC dosing interval from Day 71 to 78. Cmax and AUC(TAU) appear to be comparable in Treatment Groups 1, 3 and 5 (Table 1.3.2C).

Table 1.3.2C Summary Statistics for Abatacept Steady-State Pharmacokinetic Parameters - IM101063

Treatment Group	Pharmacokinetic Parameter	
	Cmax (µg/mL) Geometric Mean (CV%)	AUC(TAU) (µg*h/mL) Geometric Mean (CV%)
1 (500mg IV / 75mg SC)	n = 7 26.3 (29.5)	n = 7 4066 (22.2)
2 (500mg IV / 125mg SC)	n = 4 34.9 (46.6)	n = 3 6699 (20.7)
3 (750mg IV / 125mg SC)	n = 26 31.9 (42.8)	n = 24 4607 (38.6)
4 (1000mg IV / 125mg SC)	n = 5 14.7 (44.3)	n = 4 2555 (30.1)
5 (1000mg IV / 200mg SC)	n = 5 41.7 (41.2)	n = 5 5849 (40.5)

Source: IM101063 CSR, Supplemental Table S.8.2.3

n = number of subjects, TAU = 7 days

Cmax and AUC(TAU) were calculated between a SC dosing interval from Day 71 to Day 78 profile.

SC formulation in pediatric population

Data are not available for clinical pharmacokinetic parameters of SC abatacept in children.

1.3.3 Safety of Abatacept in Core Rheumatoid Arthritis Studies

The clinical safety data for abatacept (IV formulation) in subjects with RA is derived from:

- the open-label, long term (LT) periods of the 5 core RA studies, plus LT data from 3 supportive studies (IM101043, IM101064, and IM101015) and ST and LT data from IM101023 [36]
- the double-blind period of the JIA study (IM101033)
- the post marketing experience with abatacept and
- the data collected for post-marketing commitments to regulatory authorities.

The safety data from the open label LT periods of the clinical studies were analyzed in 2 ways; one to assess the LT safety profile of abatacept (Integrated Population) and another to assess the safety profile of abatacept across 3 prior therapy populations (Prior Therapy Population). Collectively, the Integrated Population safety experience covers the LT periods of the RA clinical studies from the methotrexate inadequate-responders (MTX-IR) and tumor necrosis factor inadequate responders TNF-IR studies, which includes up to 8 years of continued exposure (11,658 person-years [p-y] experience with 1030 subjects with at least 5 years of exposure); new data from an earlier population of MTX-naïve subjects followed for 2 years including assessments at 1 and 2

years; as well as data from pharmacovigilance monitoring under the conditions of market usage (~32,187 p-y experience). For the Prior Therapy Population, there were 4,632 subjects (12,375 p-y) treated with abatacept in combination with MTX,

- 1,280 MTX-IR subjects, representing 4,465 p-y of exposure, who were treated for up to total of 8 years; and
- 1419 TNF-IR subjects, representing 1,986 p-y of exposure, who were treated for up to total of 5.5 years;

The remaining 483 MTX-naive subjects represented 717 p-y of exposure and were treated with abatacept for up to 2 years [36].

1.3.4 Safety of SC Formulation

SC formulation in adult population

IM101013

In Study IM101013[34], a double-blind, randomized (within dose), placebo-controlled, parallel-group, single-dose study in healthy subjects weighing ≤ 100 kg, single SC doses of abatacept were well-tolerated by healthy adult subjects. There were no deaths, no discontinuations, and no SAEs reported. All AEs were mild to moderate in intensity. In general, there was no difference between the frequency and types of AEs reported by the abatacept (all abatacept groups combined, n = 40) and placebo (all placebo groups combined, n = 8) groups. The most common type of AEs reported by abatacept and placebo subjects were injection site reactions including erythema, swelling, and tenderness. Infections were commonly reported by both the abatacept and placebo groups and were not more common in abatacept-treated subjects than in placebo-treated subjects. One (1) abatacept-treated subject had laboratory abnormalities (increases in alanine aminotransferase and gamma-glutamyl transferase levels) that were considered by the investigator to be clinically significant and were reported as AEs.

Overall, 11 of the 40 subjects (27.5%) developed antibodies to the CTLA4 region of the abatacept molecule, with endpoint titers in healthy subjects followed for 71 days ranging from Day 33 to Day 872. Only 1 of the 11 subjects developed antibodies that had abatacept neutralization activity. The earliest onset of seroconversion was at Day 43 (seen in 1 subject), after approximately 3 to 4 half-lives of abatacept and accounting for over 94% of the drug being eliminated from the vascular system.. The presence of an immune response resulted in increased clearance of abatacept from the vascular system. This resulted in a shorter $T_{1/2}$ (range = 3.2 to 7.5 days) compared with the $T_{1/2}$ for subjects who did not exhibit an immune response to abatacept (range = 11.2 to 14.7 days). The incidence rate of seroconversion in subjects receiving a single SC dose of abatacept (27.5%) was higher compared with subjects who discontinued IV abatacept treatment (7.4%) in the Phase 2/3 development program of IV abatacept for RA. The development of immunogenicity did not appear to be associated with adverse safety outcomes; the safety profile of abatacept in subjects with and without an immune response was comparable.

IM101063

Study IM101063, a double-blind, randomized, placebo-controlled, parallel-group, multiple-dose study in subjects with active RA who are on background DMARDs (MTX or MTX plus no more than 1 additional oral DMARD) was designed to evaluate the safety and immunogenicity of several doses of SC abatacept. No deaths were recorded during the short-term 12-week phase of the study. Safety evaluations from the 51 abatacept-treated subjects and 17 placebo-treated subjects showed that abatacept administered by SC injections weekly was safe and well tolerated. The most common infections observed in both abatacept-treated and placebo-treated subjects were upper respiratory and urinary tract infections. There were 7 SAEs (diastolic dysfunction/chest discomfort/dyspnea/COPD/sleep apnea in 1 subject; wound infection in 1 subject; and drug overdose in 1 subject) reported during the short-term phase of the study. All the SAEs were reported to be unrelated or unlikely related to study drug by the investigator. In addition, injection site reactions from the weekly SC injections were uncommon and predominantly mild in intensity. Overall, the safety profile for SC abatacept was observed to be consistent with that for IV abatacept[35,36].

IM101173

IM101173 [37], a multi-center open-label study in adults with active RA requiring a new therapeutic intervention, was designed to evaluate SC abatacept in a monotherapy setting and to assess if the use of background MTX influences the development of immunogenicity. An initial IV abatacept loading dose was not given in this study in order to maximize the potential for immunogenicity following SC administration of abatacept. In addition, this study was designed to assess whether the development of immunogenicity following SC abatacept impacted the PK, safety, or effectiveness of the drug. Safety and exploratory efficacy data for subjects treated for 4 months with SC abatacept in Study IM101173 were available.

A total of 100 subjects with RA and requiring a new therapeutic intervention were stratified based on their current MTX use to 4 months of open-label treatment with SC abatacept monotherapy (N = 49) or to SC abatacept in combination with MTX (N = 51). Subjects in both cohorts received weekly SC injections of abatacept 125 mg (dosing irrespective of body weight).

The safety profile for SC abatacept in adults with RA in this study appeared favorable overall. Treatment with SC abatacept 125 mg/week, with or without background MTX, and in the absence of an IV loading dose, was well tolerated by subjects with RA in this study. During the 4-month short-term treatment period, there were no deaths, SAEs assessed as at least possibly related to study treatment were reported in only 2 subjects, and AEs resulted in treatment discontinuation for 4 (4%) subjects. Local injection site reactions, a common finding for SC-injected drugs, were infrequent (7%); all were mild and did not result in treatment discontinuation. Similarly, systemic injection site reactions occurring within 24 hours following SC injection of abatacept were also infrequent (8%) and mostly mild in intensity. One subject experienced angioedema following the initial SC injection of abatacept, which was moderate in intensity, serious and led to treatment discontinuation. The angioedema resolved the same day. The rate of systemic injection reactions with SC abatacept was consistent with the rates of peri-infusional AEs reported for IV abatacept [38,39].

Consistent with the experience with IV abatacept, infections and infestations were the most commonly reported AEs in subjects receiving SC abatacept (32% in short-term period). Fewer than

3% of treated subjects had an infection AE(s) that was serious or required discontinuation of abatacept treatment.

In IM101173, one previously un-labelled SAE was reported: severe grade 4 Pneumocystis jiroveci pneumonia [37]. The subject had been on study for 3 months, receiving 125 mg of abatacept SC once a week and developed bilateral pneumonia with severe respiratory failure. The subject was hospitalized to receive treatment for the infection and severe respiratory failure; the subject recovered and was discharged 1 month later.

STUDY IN SYSTEMIC LUPUS ERYTHEMATOSUS

In NCT 001 10678, A phase IIb study in SLE was conducted and published [5]. 118 patients were treated with 10mg/kg abatacept i.v. in the standard RA dose, and 57 with placebo. 65% completed 12 months of study. The primary outcome, rate of flare beginning after prednisone taper, over a total of 12 months, measured by adjudicated BILAG A and B, did not show significant differences between the groups. However, patients with lupus polyarthritis at entry had significantly fewer flares compared to placebo in both BILAG A flare (36.5% in placebo vs 12.5% in abatacept) and physician-identified flares. The incidence of serious adverse events was higher in abatacept (19.8%) vs placebo (6.8%) without any particular type of SAE identified.

In a recent study in patients with lupus nephritis[40], 198 individuals were treated with abatacept i.v.. for 12 months (one group with a loading dose of 30 mg/kg once a month x3 followed by 10 mg/kg monthly; a second with 10 mg/kg monthly i.v. for the entire 12 month period). At 12 months, there were no statistically significant differences in response rates (defined as complete renal response or partial- plus- complete renal responses) between the group that received placebo infusions plus standard care compared to either of the groups that received abatacept plus standard care. The occurrence of severe adverse events did not differ significantly between the groups: SAEs occurred in 28-33.3% of the abatacept groups and 31% of the placebo group. There were 7 deaths in the abatacept groups (one of which was a gunshot wound) for a rate of 2.5%, with 7 deaths in the placebo group for a rate of 7%. Treatment related SAEs occurred in 19-20% of the abatacept groups and 15% of the placebo groups.

To summarize, there are published data on abatacept, administered i.v., to 316 patients with SLE for 12 months[5,40]. In the patients most comparable to the subjects to be studied here (no active nephritis or CNS disease), SAEs occurred in approximately 20%. We expect the SAE rate to be lower in the study proposed here because the treatment duration is 16 weeks rather than 52 weeks. Another difference is that the treatments will be administered subcutaneously instead of intravenously. Perhaps more relevant to this proposal is study IM101173 described above, in which patients with rheumatoid arthritis on methotrexate received 125 mg of abatacept weekly for 16 weeks; SAEs in that study occurred in 2%. One individual had pneumocystis pneumonia requiring hospitalization.

SC formulation in pediatric population

Data are not available for the safety of SC abatacept in the pediatric population.

1.4 Overall Risk/Benefit Assessment

Lupus is an autoimmune disorder that involves inflammatory polyarthritis that can lead to deformity, significant physical disability, and poor quality of life.

In the past decade, the success of abatacept and other biologic immune/inflammation modifiers such as TNF inhibitors in suppressing rheumatoid arthritis have led to testing of some of these products in patients with SLE. To date, TNFalpha inhibitors have been disappointing in that a high infection rate has cause early stopping of some trials[41]. Although the efficacy, tolerability, and safety profile of abatacept was demonstrated in the RA clinical development program, the two trials to date using abatacept in SLE did not identify an overall benefit. However, the subset of patients with active lupus polyarthritis at entry had significant benefit, shown as a significant reduction in flares of SLE. Abatacept, a biologic DMARD with a unique mechanism of action, has demonstrated a good efficacy/safety profile in RA. Abatacept has been on the market in the US since January 2006 and in Europe since May 2007.

Abatacept, a selective costimulation modulator, is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte (T-cell)-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). An intravenous (IV) formulation of abatacept is approved in several countries including the United States and in the European Union (EU) for the treatment of moderate to severe rheumatoid arthritis (RA) in adults. The subcutaneous preparation is currently approved in the United States for rheumatoid arthritis in adults. Based on the clinical trial experience in adults, the risks that may be associated with the use of abatacept include infections, some of which may be serious or fatal, infusion related reactions, and an increase in respiratory adverse events and infections in patients with chronic pulmonary obstructive disease (COPD). Other potential risks may include the development of malignancies or autoimmune disorders, but an increased risk of these types of events has not been observed. As with the use of any protein therapeutic, antibodies against abatacept (immunogenicity) may develop. The rate of immunogenicity has generally been low and there has not been an apparent effect on safety, efficacy, or pharmacokinetics (PK). Abatacept intravenous is also currently approved for the treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in pediatric patients 6 years of age or older in several countries including the USA for patients aged 6 - 17 years old. Abatacept was generally safe and well tolerated in subjects with JIA.

For the period from the fourth quarter of 2005 to the third quarter of 2009 inclusive, the total number of patients exposed to abatacept is estimated to be equivalent to 60,225 patient-years of exposure. The overall pattern of safety reporting raises no new safety concerns. A subcutaneous (SC) formulation of abatacept is being studied for the treatment of a number of immune mediated disorders; results from 3 completed clinical studies in RA are included in this document.

Within the clinical studies, there were no reports of progressive multifocal leukoencephalopathy (PML). In the post-marketing experience, there was 1 healthcare professional report of recurrent PML that involved a 44-year-old female with previous history of PML while receiving methotrexate (10 years ago). The patient received 6 doses of abatacept prior to hospitalization due to status epilepticus. A brain magnetic resonance image scan was atypical for PML; a cerebral spinal fluid analysis was negative for the JC virus. At the time of the report, the patient was

recovering from hemiparesis and expressive dysphasia. The overall pattern of safety reporting raises no new safety concerns.

The ongoing efficacy of abatacept is robust and persistent, based on ongoing clinical study data and confirmed by clinical practice in the marketplace. The long term safety profile of abatacept, in the context of maintained efficacy, is reassuring and confirms the positive benefit/risk of abatacept in the treatment of rheumatoid arthritis.

In treatment of lupus nephritis patients with Abatacept over 12 months, it has been reported that abatacept had a similar safety profile compared to mycophenolate mofetil and steroids[35]. Abatacept may have been more effective than placebo in that study, depending on the stringency of criteria used to define renal response[36]. In the phase IIb trial published, serious adverse events were more common with abatacept (19.8%) than with placebo (6.8%) but no particular type of adverse event emerged as more common with abatacept, such as infection[5,35,40]. Therefore, abatacept has been shown to have acceptable safety.

1.5 Study Rationale

SLE is a systemic autoimmune disease with life-threatening manifestations. Currently, there are limited approved treatments for SLE and none (except high dose glucocorticoids) have been shown to prolong survival or permanently reverse the course of the disease. SLE remains a disease with unmet medical need, especially for patients with active and life-threatening manifestations, and for the many with adverse effects from chronic glucocorticoid use.

Lupus arthritis is a common manifestation of lupus. It can cause a debilitating and disabling condition in lupus patients resulting in poor quality of life. Currently, the therapies in treating lupus arthritis such as glucocorticoids, NSAIDs, hydroxychloroquine, belimumab or MMF are far from optimum, inducing complete remission in fewer than 50% of affected patients.

Thus, there is an unmet need in patients with lupus arthritis for more effective and safe therapy. Rationale for abatacept to work in treating lupus arthritis is based on abatacept's mechanism of action, evidence of its safety in lupus nephritis patients and experience in Rheumatoid arthritis.

2 STUDY OBJECTIVES

2.1 Primary Objective

Improvement of lupus inflammatory polyarthritis measured by proportion of patients who achieve >=20% improvement in tender and swollen 28 joint counts at 16 weeks.

Secondary Objectives:

1. Mean and median joint scores in treated vs placebo patients at 16 weeks, compared to baseline scores.
2. Proportion of patients who achieve improvement in SLEDAI 2K at 16 weeks of >3 points, comparing abatacept to placebo.
3. Proportions of patient who do not worsen by PGA score (≤0.8 change from initial PGA score on 3 point line).
4. Mean and median changes in CDAI comparing abatacept to controls at 8, 12 and 16 weeks.

5. Changes in a) synovitis, b) tenosynovitis and c) erosions measured by high-energy ultrasound with Doppler flow at zero, and 16 weeks, compared to placebo.
6. Steroid sparing effect of abatacept, measured as ability to taper prednisone to <10mg/day by week 16 comparing abatacept-treated subjects to placebo-treated subjects.
7.Change in fatigue from baseline to 16 weeks as measured by the FACIT fatigue score instrument
8.Change in quality of life comparing baseline to 16 weeks as measured by the SF 36.
9.Safety, measured in standard methods as AE and SAE, including likelihood that the AE/SAE was related to the study biologic.
10.Time to response, measured as joint counts (sum of tender and swollen joints) at zero, 4, 8, 12, and 16 weeks.
11.Change in peripheral blood T cell compartments indicating decline in pro-inflammatory profiles, i.e., we expect decrease in CD4+ effector T cells that make IFNgamma (TH1) and IL-17 (TH17) and increase in ratio of Treg to Teff, as well as decreased function of Thelper and increased functions of Tregs. CD4+CD25+ Foxp3+ and CD8+Foxp3+ will be the definition of regulatory T cells. These will be measured at baseline and 16 weeks
12.Change in anti-DNA and total IgG levels, as well as rise in serum complement levels as disease improves and fewer B cells are activated: measure these at zero, 8 and 16 weeks.
13.Effects of abatacept on serum levels of BLyS (BAFF). As numbers of activated B cells and plasmablasts fall, we expect an increase in BLyS levels. Measure at baseline and 16 weeks.
14. Changes in transcriptome in whole blood and/or purified mononuclear cells in peripheral blood, and changes in interferon-induced gene expressions at baseline that may predict response or non-response at 16 weeks. Measure at baseline and last study visit.

3 3. ETHICAL CONSIDERATIONS

2.3 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

All potential serious breaches must be reported to Bristol-Myers Squibb (BMS) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

3.1 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.2 Informed Consent

Investigators must ensure that subjects (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) before clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study. An additional informed consent form will be signed by subjects willing to supply DNA and RNA for research to predict response to abatacept.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3.4 Stopping Rules

The study will be put on hold if 1) there are two deaths thought to be possibly, probably or definitely related to the treatment, or 2) there are 3 patients with SAEs thought to be probably or definitely related to the treatment. If either of these occurs, the study will be suspended until the DSMB determines whether it is safe for patients to continue on the therapy. This determination will be made within two weeks of the events described so that patients will hold their doses of abatacept or placebo for no longer than two weeks if the reviewers determine it is safe to continue. A data safety monitoring board (one to-be-named Rheumatology faculty member plus one to-be-named statistician) will review the SAEs quarterly and issue a report to the IRB and to the investigators regarding AEs and SAEs, reported according to patient assignments to groups A or B (the double-blind code will not be broken); these reports will also be supplied to the sponsor

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

This is a randomized placebo-controlled double-blind study for the 16 weeks, in patients with SLE whose active lupus manifestation is primarily arthritis. The study consists of a baseline visit, a 16-week treatment period (with visits every 4 weeks), and a telephone follow up 8 weeks after the last dose of study drug. Patients are expected to participate in the study for up to approximately 26 weeks (including screening visit).

Informed consent will be obtained at the Screening Visit, prior to patients undergoing any study procedures. Eligibility criteria will be assessed and medical history will be reviewed prior to

patient's participation in this study. Starting at the baseline visit, patients will receive 125 mg sc of abatacept or placebo every week for 16 weeks. Patients may continue on their stable background standard of care medications (according to the protocol) throughout the study. In the first dose visit, patients will be monitored for systemic symptoms for at least 1 hour after abatacept has been administered.

Subjects who discontinue the trial early, i.e. prior to Week 16 should come to a follow-up study completion visit within 1 week of treatment termination.

Unscheduled visits for safety or for any other reason may be conducted at any time during the study.

During the study period, at 4 week intervals, swollen and tender joint counts (28 joints), the British Isles Lupus Assessment Group (BILAG) score, SLE Disease Activity Index (SLEDAI 2K), Physician Global Assessment Score and Patient Global Assessment will be assessed in addition to routine safety laboratory and physical tests. Disease related immunology tests/biomarkers will be taken at baseline and 16 weeks.

Bilateral Posterior-Anterior (PA) Hand X-rays (including wrists) will be performed at baseline for all subjects. Ultrasound examination of the PIP (2-5), MCP (2-5), and wrist joints designated below will be performed at baseline and at 16 weeks. At baseline and 16 weeks, synovitis (18 joints), tenosynovitis and erosions will be assessed.

Please see Time and Events Schedule in Section 6.

SLE patients with 3 or more swollen and tender joints and moderate or severe lupus activity (SLEDAI 2K score 4 or greater) will be eligible for this study. In addition, patients must have current or historical documented positive Antinuclear Antibody (ANA) and/or anti-double stranded deoxynucleotide antibody (anti-dsDNA).

The established SLE therapy (as allowed by the study) at study entry will be continued as background therapy. Background therapy should be kept stable throughout the study, although increase in prednisone to not more than 30 mg a day, which much be tapered to $\leq$ 10 mg daily by 8 weeks, will be permitted. Tapering of prednisone dose at any time will be permitted. Dosage increases in antimalarial, or any other non-glucocorticoid immunosuppressives, or introduction of any of these or a biologic agent as a new therapy (not allowed by the protocol) will be regarded as a treatment failure. Subjects requiring prednisone or equivalent doses >10 mg a day at/after the 8 week visit will be regarded as treatment failures.

The US will be performed by a rheumatologist with expertise in musculoskeletal ultrasound and images will be digitally saved. US will be performed at UCLA only, for the 32 patients enrolled there. Each UCLA patient will have ultrasounds performed on the same machine by the same ultrasonographer at baseline and 16 weeks.

18-Joint US Scoring System (bilat wrists, bilat MCPs 2-5, bilat PIPs 2-5)

JOINT	VIEW	Power Doppler Synovitis	B-mode Synovial Hypertrophy	Tendons	Erosions
Wrists	Dorsal Longitudinal Midline (Radio carpal, intercarpal)	X	X		
MCPs (2-5)	Dorsal Orthogonal	X	X		X (MCP 1,2,and 5)
	Volar Longitudinal	X	X	X	
	Dorsal Paratendon	X	X	X	
PIPs/IP (2-5)	Volar Longitudinal	X	X	X	

US assessments will be performed using the 18-joint US score. To date, no single US scoring system has been determined as the prevailing method. However, several US scoring systems have demonstrated that power Doppler synovitis and B-mode synovial hypertrophy scores are sensitive to change. For this proposal, selection of the specific 18 joints was based on maximizing precision, reliability, and feasibility for ultrasonography. Most US scoring systems weigh heavily on the hands and wrists. Some studies demonstrate the presence of normal amounts of fluid at the 1st metarsophalangeal (MTP) joints primarily as well as with 2-5 MTPs. In addition, these joints frequently demonstrate the presence of deformities such as hammer toes. Thus, these joints were excluded[42,43]. Grey-scale synovial hypertrophy and power doppler will be assessed for bilateral wrists (dorsal), MCPs 2-5 (dorsal and volar), and PIPs/IPs 2-5 (volar). In addition, MCP 2, and 5 will be assessed for erosions. All the above areas will be examined with B-Mode and power Doppler mode sonography (Table above). Standard OMERACT definitions will be used for effusion and synovial hypertrophy.

Assessment of the extensor and flexor tendons (grey-scale and power doppler) of the MCPs bilaterally will be obtained as well for further exploratory analyses.

4.2 Study Population

For entry into the study, the following criteria MUST be met. Any exceptions must be approved by the Principal Investigator and/or IRB/IEC before enrollment.

4.2.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.

Target Population

b) SLE as defined by meeting at least 4 of the 11 classification criteria of the American College of Rheumatology for the classification of Systemic Lupus Erythematosus. The 4 criteria need not be present at the time of study entry.

OR

Patients meet the new SLICC criteria for SLE[8]. Patients must fulfill at least 4 criteria, including at least one clinical and one immunologic. Clinical criteria are acute cutaneous lupus, chronic cutaneous lupus, oral or nasal ulcers, nonscarring alopecia, synovitis (2 or more joints with swelling, or tenderness in 2 or more plus at least 30 min of morning stiffness), serositis, renal disease, neurologic, hemolytic anemia, leucopenia or lymphopenia, thrombocytopenia. Immunologic criteria are ANA above laboratory reference range, anti-dsDNA, anti-Sm, antiphospholipid, low complement and direct Coomb's test.

c) Active arthritis, as defined by:

1) At least 3 or more swollen and tender joints

2) Moderate or severe lupus activity - SLEDAI 2K score 4 or greater

d) Patients must have documented positive Antinuclear Antibody (ANA) and/or anti-double stranded deoxynuclear antibody (anti-dsDNA). Presence/absence of anti-CCP and rheumatoid factor will be measured but results will not exclude patients from the trial.

e) No active nephritis, active central nervous system disease, or other life-threatening manifestations of SLE

Age and Sex

f) Men and women, ≥ 18 years of age

g) Women of childbearing potential (WOCBP) must use highly effective methods of birth control [for up to 4 weeks after the last dose of abatacept] to minimize the risk of

pregnancy. WOCBP must follow instructions for birth control for the entire duration of the study including a minimum of 28 days after dosing has been completed.

- Acceptable methods of highly effective birth control include:
- Condom with spermicide
- Hormonal contraceptives
- Diaphragm and spermicide
- Cervical cap and spermicide
- Intrauterine device

Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 48 hours prior to the start of investigational product.

c) Women must not be breastfeeding

Sexually active fertile men must use highly effective birth control if their partners are WOCBP. Men that are sexually active with WOCBP must follow instructions for birth control for the entire duration of the study and a minimum of 28 days after dosing has been completed.

d) Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile; see Section 3.3.3 for the definition of WOCBP) and men may be included in the study.

e) Exclusion Criteria

Individuals to be excluded if:

a) WOCBP who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for at least 4 weeks after the last dose of study drug.

b) Women who are pregnant or breastfeeding.

c) Women with a positive pregnancy test on enrollment or before administration of abatacept.

d) Sexually active fertile men not using effective birth control if their partners are WOCBP.

Medical History and Concurrent Diseases

e) Subjects who are impaired, incapacitated, or incapable of completing study-related assessments.

f) Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease,

whether or not related to SLE and which, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study.

g) Female subjects who have had a breast cancer screening that is suspicious for malignancy and in whom the possibility of malignancy cannot be reasonably excluded by additional clinical, laboratory, or other diagnostic evaluations.

h) Subjects with a history of cancer in the last 5 years, other than non-melanoma skin cell cancers cured by local resection, or carcinoma in situ. Existing non-melanoma skin cell cancers should be removed, the lesion site healed, and residual cancer ruled out before administration of the study drug.

i) Subjects who currently abuse drugs or alcohol.

j) Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral infections at the time of potential enrollment, including subjects with evidence of human immunodeficiency virus (HIV), hepatitis B or hepatitis C detected at any time prior to screening for this study

k) Subjects with herpes zoster or cytomegalovirus (CMV) that resolved less than 2 months before the informed consent document was signed.

l) Subjects who have received any live vaccines within 3 months of the anticipated first dose of study medication.

m) Subjects with any serious bacterial infection within the last 3 months, unless treated and resolved with antibiotics, or any chronic bacterial infection (eg, chronic pyelonephritis, osteomyelitis, or bronchiectasis).

n) Subjects at risk for tuberculosis (TB). Specifically excluded from this study will be subjects with a history of active TB within the last 3 years, even if it was treated; a history of active TB greater than 3 years ago, unless there is documentation that the prior anti-TB treatment was appropriate in duration and type; current clinical, radiographic, or laboratory evidence of active TB; and latent TB that was not successfully treated (≥ 4 weeks).

o) Subjects with concomitant illness that in the opinion of the investigator, is likely to require additional high dose oral glucocorticosteroid therapy (i.e. >30 mg prednisone or equivalent per day) during the study (e.g. severe asthma)

Physical and Laboratory Test Findings

p) Subjects must not be positive for hepatitis B surface antigen.

q) Subjects who are positive for hepatitis C antibody if the presence of hepatitis C virus was also shown with polymerase chain reaction or recombinant immunoblot assay.

r) Subjects with any of the following laboratory values

i) Hemoglobin < 8.5 g/dL

ii) WBC < 2000/mm^3 (< 3 x 109/L)

iii) Platelets < 100,000/mm^3 (< 3 x 109/L)

iv) Serum creatinine > 2 times the ULN

v) Serum ALT or AST > 2 times the ULN

s) Any other laboratory test results that, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study.

Prohibited Treatments and/or Therapies

t) Subjects who have at any time received treatment with any investigational drug within 28 days (or less than 5 terminal half-lives of elimination) of the Day 1 dose.

u) Any concomitant biologic DMARD, such as anakinra.

v) Treatment with rituximab within the past 6 months (B cells must be detectable in peripheral blood at onset of treatment with study biologic); belimumab within the past 3 months, cyclophosphamide within the past 3 months prior to study baseline visit.

w) Previous treatment with abatacept

Prednisone or equivalent at doses higher than 20 mg daily.

Other Exclusion Criteria

x) Prisoners or subjects who are involuntarily incarcerated.

y) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

4.2.2 Women of Childbearing Potential

Women of childbearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), and who is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or

NOTE: FSH level testing is not required for women ≥ 62 years old with amenorrhea of ≥ 1 year

Women who are using oral or other hormonal contraceptives, such as vaginal products, skin patches, or implanted or injectable products, or mechanical products, such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides), to prevent pregnancy or who are practicing abstinence or who have a sterile (eg, vasectomy) partner should be considered to be of childbearing potential.

4.2.3 Discontinuation of Subjects from Treatment

If a study subject is found to have worsening disease activity during the duration of the study, the choice of using a rescue medication (e.g.increase prednisone dose but not to >20 mg daily) will be considered. However, if significant worsening of disease activity is found at 8 weeks in comparison to baseline disease activity, the investigator will consider the discontinuation of the subject from the study after discussing in detail with the patient alternative SLE treatment strategies. Throughout the duration of the study, background allowed standard of care therapies (prednisone, MMF, leflunomide, hydroxychloroquine) will be continued at the baseline dosage.

Subjects MUST discontinue study treatment and withdraw from the study for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
    - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
    - The investigator must immediately notify BMS if a study subject becomes pregnant. The mechanism for reporting pregnancy is described in Section 7.6.
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

4.3 Concomitant Treatments

4.3.1 Prohibited and/or Restricted Treatments

Initiation of therapy with any of the following medications or treatments during the study is not allowed:

- Methotrexate
- Azathioprine
- Cyclophosphamide
- Leflunomide
- Rituximab
- Belimumab
- Cyclosporine
- Tacrolimus
- Gammaglobulin
- Experimental therapies for treatment of SLE
- Plasmapheresis
- Prednisone or equivalent at doses >20 mg daily.

The prescribing label of all concomitant medications used as subject's background therapy should be evaluated by the investigator for continued administration during subject's participation in this study (e.g. known toxicities, drug-drug interactions).

Change in SLE standard of care (SOC) therapy after 12 weeks will not be permitted to allow assessment of efficacy of abatacept.

4.3.2 Other Restrictions and Precautions

Due to risk of infection, vaccination of subjects with any live vaccine is absolutely contraindicated for 3 months before and during the course of the study. In view of the long half-life of abatacept, study subjects should not receive a live virus vaccine for a minimum of 3 months following the last dose of abatacept.

4.4 Discontinuation of Subjects from Treatment

Subjects MUST discontinue study treatment and withdraw from the study for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

- Pregnancy
  - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
  - The investigator must immediately notify BMS if a study subject becomes pregnant. The mechanism for reporting pregnancy is described in Section 7.6.
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

5 TREATMENTS

5.1 Study Treatment: Abatacept

An investigational product, also known as investigational medicinal product in some regions, is defined as follows: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. In this protocol, the investigational product is abatacept.

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care are considered noninvestigational products.

5.1.1 Identification

Abatacept Injection, 125 mg/Syringe (125 mg/mL), is a sterile solution for SC administration, which contains approximately 126 mg abatacept, 171 mg sucrose, 8 mg Poloxamer 188, 0.28 mg monobasic sodium phosphate, monohydrate, and 0.84 mg dibasic sodium phosphate, anhydrous, in Water for Injection. It is packaged in 1 mL long glass syringe barrel staked with a 29 gauge stainless steel needle and stoppered with a 7.1 mm rubber stopper. The composition of this solution has a ratio of monobasic sodium phosphate, monohydrate, and dibasic sodium phosphate, anhydrous, used to achieve the target pH of 7.2.

5.1.2 Storage, Handling, and Dispensing

The investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations.

All investigational product supplies that will be used in the study must be maintained securely under the direct responsibility of the investigator or delegated by the investigator to the hospital pharmacist, or other personnel licensed to store and dispense drugs. All drugs shall be dispensed in accordance with the investigator's responsibility to ensure that an accurate record of drugs issued and returned is maintained.

The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity), as determined by the sponsor and defined by the Investigator Brochure or SmPC/ reference label. If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product and contact the sponsor immediately. Care should be taken when handling the injectable drug products that are used in this protocol. Proper aseptic techniques must be used when preparing and administering sterile parenteral products such as abatacept. Parenteral drug products should be inspected visually for particulate matter prior to administration. Refer to the Investigator Brochure for additional information regarding handling, preparation, and storage of abatacept.

5.1.3 Additional Information for the Handling, Dispensing, and Storage of Abatacept

ABATACEPT INJECTION FOR SUBCUTANEOUS (SC) ADMINISTRATION:ABATACEPT INJECTION, 125 MG/ML, AND PLACEBO FOR SC ADMINISTRATION ARE READY TO USE SOLUTIONS PROVIDED IN PRE-FILLED SILICONIZED SYRINGES. NO ADDITIONAL DRUG PREPARATION IS REQUIRED PRIOR TO ADMINISTERING TO PATIENTS. A SUFFICIENT AMOUNT OF ABATACEPT OR PLACEBO SOLUTION IS INCORPORATED INTO EACH SYRINGE SO THAT EACH SYRINGE CAN DELIVER LABELED AMOUNT UPON ADMINISTRATION.

5.1.4 RECOMMENDED STORAGE AND USE CONDITIONS

ABATACEPT INJECTION FOR SC ADMINISTRATION: ABATACEPT SC FORMULATIONS (PREFILLED SYRINGES) AND CORRESPONDING PLACEBO SHOULD BE STORED UNDER REFRIGERATION (APPROXIMATELY 2□C TO 8□C). DO NOT USE BEYOND THE LABELED EXPIRATION DATE ON THE PRODUCT. PROTECT FROM LIGHT BY STORING IN THE ORIGINAL PACKAGE UNTIL TIME OF USE. DO NOT ALLOW THE PREFILLED SYRINGE TO FREEZE.

5.2 Method of Assigning Subjects to a Treatment

5.3 Selection and Timing of Dose for Each Subject

Subjects will receive SC dose of Abatacept (125mg) or placebo at baseline for 16 weeks. Study drug will be provided for subjects to take at home. Qualified study personnel will teach subjects the proper administration of the study drug at baseline visit and teach subjects proper storage of the syringes to be taken home (see section 5.1.4 above.

5.3.1 Dose Modifications for Adverse Events

If there is evidence of toxicity, as determined by laboratory tests or by clinical assessment that could place the subject at increased risk in the judgment of the investigator, administration of abatacept should be interrupted and the investigator should notify BMS. Subjects may be considered eligible to continue with abatacept treatment only if full resolution of the adverse event is documented. If the adverse event completely resolves and the next dose of abatacept cannot be

administered within 14 days of the target date, then that scheduled dose should be skipped. The next dose of abatacept should then be administered on the next targeted day for administration.

5.4 Blinding/Unblinding

No data will be unblinded until the conclusion of the study, unless a serious adverse event cannot be treated effectively without the information, or unless 2 or more deaths that may be related to the therapy occur.

5.5 Concomitant Treatments

5.5.1 Prohibited and/or Restricted Treatments

The following medications are prohibited throughout the 24 week study period:

- Any biologic DMARD (such as but not limited to: anakinra, infliximab, etanercept, adalimumab, rituximab, belimumab or any other investigational biologic).
- Live vaccines.
- Use of any investigational drug other than study medication.
- Corticosteroid use higher than the equivalent of prednisone 10 mg/day is not permitted after week 8.

The following rescue medications may be used:

- Nonsteroidal antiinflammatory drugs (NSAIDS) or Aspirin
- Acetaminophen
- Combination products, including acetaminophen and narcotic analgesics (eg, acetaminophen with codeine phosphate or propoxyphene napsylate or oxycodone hydrochloride or hydrocodone bitartrate).
- Tramadol
- Morphine.
- Prednisone at doses not to exceed 20 mg a day in the first 4 weeks of the study, but not more than 10 mg daily after 8 weeks

5.5.2 Other Restrictions and Precautions

Immunizations

There is limited information available regarding the effectiveness of immunizations in non-human primates and humans that have been treated with abatacept. Limited data are available on the effect of therapeutic vaccinations in subjects receiving abatacept.

Due to the risk of infection, vaccination of subjects with any live vaccine is absolutely contraindicated during the treatment phase of the study (that is, at any time after entry into the induction period), as is the administration of LIVE oral polio vaccine to household contacts. The

Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (CDC-ACIP) recommends that subjects should not be administered a live virus vaccination for at least 3 months after discontinuing high-dose corticosteroid therapy (defined as more than 20 mg of prednisone per day for more than 2 weeks). In view of the long half-life of abatacept, study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of abatacept.

5.6 Management of Possible Acute Hypersensitivity Reactions to Abatacept

Hypersensitivity or acute allergic reactions may occur as a result of the protein nature of abatacept. The following information is provided to assist in the recognition of hypersensitivity reactions and in the management of those reactions should they occur during or after the administration of study drug. Care should be taken to treat any acute toxicities expeditiously, should they occur.

Signs and management of potential acute hypersensitivity reactions:

Sign	Management
Symptomatic Hypotension	Discontinue the abatacept injection if it has not been completed. Pplace the subject in the Trendelenburg position and administer IV fluid. Administer epinephrine, glucocorticoids, antihistamines, and pressor agents as indicated. Since injections will be self-administered after the initial dose, the subject will have emergency contact information for all the physician investigators participating in this trial. We will also ensure that patients have immediate emergency access to a local physician (if they live more than 20 miles away from the UCLA Medical Center) and Emergency Room.
Dyspnea	Discontinue the abatacept injection. Observe the subject for worsening of the event and for the appearance of additional signs and symptoms of anaphylaxis. Administer antihistamines, epinephrine, and glucocorticoids as indicated. Since injections will be self-administered after the initial dose, the subject will have emergency contact information for all physicians participating in this trial. We will also ensure that patients have immediate emergency access to a local physician (if they live more than 20 miles away from the UCLA Medical Center) and Emergency Room
Acute Pain in Chest, Back or Extremities	These are potential signs of anaphylaxis. Follow the same treatment regimen as is used to treat dyspnea.
Chills, Fever, Urticaria, or Generalized Erythema	These may be signs of an allergic reaction to protein products. Treat by administration of acetaminophen and antihistamines.

Because abatacept has immunomodulatory activity, subjects may be at increased risk of infectious complications. Significant infectious complications should be treated appropriately. Study medication should be withheld, and restarted only when the infection is clinically resolved.

5.7 Treatment Compliance

During the study, subjects will complete a weekly dosing diary and return the diary to the study personnel to check for compliance.

During the study, all investigational drug (used and unused) and the corresponding accountability forms must be reconciled on an on-going basis.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Time and Events Schedule

The Time and Events Schedule (Section 6, Table 1) summarizes the frequency and timing of various measurements.

Screening Visit

The following assessment and procedures will be performed at screening visit

- Obtain written informed consent
- Inclusion/exclusion criteria review
- Medical history
- Physical examination
- Vital signs (temperature, pulse, systolic and diastolic blood pressure), height and weight
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Serology A (hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab)
- Serology B (anti-dsDNA, , ANA)
- HIV testing
- Beta human chorionic gonadotropic (beta-HCG) on all women of childbearing potential.
- Concomitant medication review
- SLEDAI-2K
- 28- Tender/Swollen Joint Count
- Quantiferon gold assay for tuberculosis

Baseline Visit (Visit 1)

The following procedures/assessments will be performed at Baseline Visit (Visit 1)

- Patient Global Assessment
- SF 36 and fatigue scale questionnaire

- Concomitant medications
- Adverse events
- Physical Examination
- Vital signs (temperature, pulse, systolic, and diastolic blood pressure) and weight
- 28 Tender and Swollen Joint Count
- Urine pregnancy test (beta-hCG) for all women of child-bearing potential. In case of positive result, the subject will not be eligible to participate in the study and will be considered as a Screening failure.
- Review all laboratory assessments for subject safety/clinical significance
- Review all inclusion exclusion criteria including compliance with allowed concomitant medications prior to Baseline and assess subject's final eligibility.
- Bilateral Posterior-Anterior (PA) hand x-rays (including wrists) should be performed for eligible subjects (unless already performed within 4 weeks prior to Baseline)
- Joint Ultrasound (18 joints: 2-5PIPs, 2-5 MCPs and wrists, bilaterally)
- SLEDAI 2K
- BILAG 2004
- Physician Global Assessment
- Safety Laboratory Testing (hematology and biochemistry)
- Urinalysis
- Immunology assessments (C3, C4, IgG)
- Lupus Biomarkers; IFN gamma, IL10, TGFbeta, IL17, IL23 and BLyS levels.
- T and B cell studies
- First dose administration of Study drug. The subject should stay at the study site for 1 hour following the administration of the first dose.
- Subjects will be given all the necessary supplies and detailed instructions for administration of study drug. In addition, subjects will be instructed to contact the study center if any questions or problem arise.
- Instruct subjects to complete study drug dosing diary for accountability and compliance.

Visits 2, 3, and 4 (Weeks 4, 8 and 12 from Baseline Visit) (+/-5 days)

- Patient Global Assessment
- SF 36 and fatigue scale questionnaire
- Concomitant medication
- Adverse events
- Vital signs (temperature, pulse, systolic and diastolic blood pressure, weight)
- Physical Examination
- 28 Tender and Swollen Joint Count (shoulders, wrists, 1-5 PIP, 1-5 MCP and knees, all bilaterally)
- SLEDAI 2K
- BILAG 2004
- Physician's global assessment. Verify whether the predefined withdrawal criteria or safety stopping rules have been met
- Safety laboratory tests (hematology, biochemistry, urinalysis)
- Urine pregnancy test for women with child-bearing potential
- Immunology assessments (anti-dsDNA, C3, C4, IgG) at weeks 0,8 and 16
- Dispense study drug and review compliance and accountability. Instruct subjects to complete the dosing diary.

Visit 5 (Week _16 from Baseline Visit) (+/-5 days)

- Patient Global Assessment
- SF 36 and fatigue scale questionnaire
- Concomitant medication
- Adverse events
- Vital signs (temperature, pulse, systolic and diastolic blood pressure, weight)
- Physical Examination
- 28 Tender and Swollen Joint Count
- SLEDAI 2k
- BILAG 2004

- Physician's global assessment
- Verify whether the predefined withdrawal criteria or safety stopping rules have been met
- Safety laboratory tests (hematology, biochemistry, urinalysis)
- Urine pregnancy test for women with child-bearing potential
- Immunology assessments (anti-dsDNA, C3, C4, IgG at weeks 0,8 and 16
- Lupus biomarkers (cytokines, T and B cell surface markers) at Week 0 z and 16 (visit 5)
- Ultrasound at Week zero and 16 (visit 5)
- Review compliance and accountability. Instruct subjects to complete the dosing diary.
-

Study follow up phone call, 8 weeks after last study dose (Week 24)

The study coordinator will conduct a follow up phone call 8 weeks after subject's last study visit (week 24) to ask about any Adverse Events. At minimum two attempts should be made to contact the subjects if subject is not available upon first contact.

Early Withdrawal/Termination Visit

Early Withdrawal/Termination Visit will follow procedure as outlined for Visit 7 (week 24).

6.1.1 Study Completion or Early Discontinuation Visit

At the time of study early withdrawal, the reason for early withdrawal and any new or continuing adverse events should be documented.

6.1.2 Study Drug Discontinuation

If study drug administration is discontinued, the reason for discontinuation will be recorded.

Procedure	Screening	Baseline	Visit 2-3-4	Visit 5	Study follow up phone call at Week 24	Early Withdrawal/Termination Visit
Eligibility Assessments						
Phone call					X[i]	
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X[a]				
Verify withdrawal criteria and safety stopping rules			X	X		X
Medical History	X					
Safety Assessments			X	X	X	X
Physical Examination	X	X	X	X		X
Vital Signs Height, weight	X		x	X		X
Assessment of Signs and Symptoms		X[e]	x	X[e]		X[e]
Concomitant Medication review	X	X	X	X	X	X
Adverse Events Assessment		X	X	X	X	X
Review all Laboratory Assessments for safety		X	x	x		
Urine Pregnancy Test		X[b]	X[b]	X[b]		X[b]

Procedure	Screening	Baseline	Visit 2-3-4	Visit 5	Study follow up phone call at Week 24	Early Withdrawal/Termination Visit
Laboratory Assessments						
CBC & Platelets	X	X	X	X		X
Chemistry Panel	X	X	X	X		X
PPD or quantiferon gold	X					
Urinalysis	X	X	X	X		X
Hepatitis B surface antigen, hepatitis C virus antibody	X					
Lupus Biomarkers (cytokines))		X		X[f]		X[f]
Anti-dsDNA, C3, C4, IgG		X	X	X		X
ANA,anti-CCP, rheumatoid factor	X					
HIV testing	X					
ß-HCG serum test	X[b]					
Biomarker Sample Collection		X		X		
Efficacy Assessments						

Procedure	Screening	Baseline	Visit 2-3-4	Visit 5	Study follow up phone call at Week 24	Early Withdrawal/Termination Visit
Physician Global Assessment		X	X	X		X
Patient Global Assessment		X	X	X		X
Joint x-ray		X[c]				
Joint ultrasound		X[d]		X[d]		X[d]
SLEDAI-2K	X	X	X	X		
BILAG 2004	X	X	X	X		
28 Tender/Swollen Joint Count	X	X	X	X		X
Clinical Drug Supplies						
Dispense Study Treatment		X	X[h]			

a. Review all inclusion/exclusion criteria including compliance with allowed concomitant medications and assess subject's final eligibility.

b. Required for women of childbearing potential (Serum pregnancy test must be performed at screening. Urine pregnancy test must be performed at all subsequent visits

c. Bilateral Posterior-Anterior (PA) hand x-rays (including wrists) should be performed for eligible subjects (unless already performed within 4 weeks prior to Baseline visit).

d. Joint ultrasound done at Baseline and Week 16 (visit 5)

e. Study subjects should stay at the study site for 1 hour following the administration of the first dose for assessment of signs and symptoms of adverse reactions

f. Done at Baseline and 16 weeks (Visit 5) only.

h. Dispense study drug and review compliance and accountability. Instruct subjects to complete the dosing diary

i. A follow up phone call at Week 24 (8 weeks after subject's last study visit) should be conducted to ask about any Adverse Events and Concomitant Medication. At minimum, two attempts should be made to contact the subject if the subject is not available upon first contact.

6.2 Study Materials

Bristol-Myers Squibb (BMS) will provide abatacept and placebo at no cost for this study.

6.3 Safety Assessments

All subjects who receive a dose of study drug will be evaluated for safety. Safety outcomes include adverse events, clinically significant changes in vital signs, laboratory test abnormalities, and clinical tolerability of the drug. The investigator will determine the severity of each adverse event as mild, moderate, severe, or very severe. Laboratory findings that the investigator feels are clinically relevant should be recorded as adverse events. In addition, the investigator will determine the relationship of the adverse event to the administration of the study drug. Any occurrence of a SAE from time of consent forward, up to and including follow-up visits will be reported. A data safety monitoring board (one to-be-named Rheumatology faculty member plus one to-be-named statistician) will review the SAEs quarterly and issue a report to the IRB and to the investigators regarding AEs and SAEs, reported according to patient assignments to groups A or B (the double-blind code will not be broken); these reports will also be supplied to the sponsor. See Section 7.3.1 for the SAE reporting procedures.

6.3.1 Physical Examinations

During the treatment period, the physical examination is to be performed before administration of abatacept. While the interim physical examination may not be as comprehensive as the complete physical examination, important body systems should be included as deemed clinically indicated by the investigator. These body systems may include lymph nodes, liver, spleen, and breast. An interim physical examination may note any changes in the subject's condition since the last assessment and does not preclude examination of any of the body systems as clinically indicated.

6.3.2 Manual Breast Examination and Breast Cancer Screening

A manual breast palpation must be performed on all female subjects prior to randomization . A manual breast palpation performed within 1 month of study entry will be accepted as meeting the pre-randomization requirement. Documentation of the prior palpation must be on file at the investigator's site for the screening procedures to be considered complete.

In addition, those female subjects who meet local age and risk factor appropriate screening criteria are required to have a mammography or other imaging modality for breast cancer screening in accordance with local medical guidelines. The breast cancer screening guidelines utilized by the investigational site should be made available to the local IRB/Ethics Committee and explained in the subject's informed consent. Documentation of the most recent breast cancer screening study must be on file at the investigator's site to be considered valid.

Subjects having a manual breast palpation or a breast cancer screening that is suspicious for malignancy will have drug administration withheld until the possibility of malignancy can be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations.

6.3.3 Tuberculin Skin Testing

A tuberculin skin test (PPD test: purified protein derivative tuberculosis skin test) should be performed and interpreted according to the applicable local Health Authority and/or Medical

Society guidelines (those that provide recommendations for tuberculin skin testing for subjects who are to receive biologics, who are immunosuppressed, who have a prior history of BCG vaccinations[44,45], or who have a prior positive test). Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG.

QuantiFERON® testing is an acceptable alternative when tuberculin skin testing is not appropriate. A tuberculin skin test is not required if one was performed within 6 months of screening and documentation of testing is on file. If tuberculin skin testing is performed at screening, then the 72-hour reading must be completed before administration of abatacept.

6.4 Efficacy Assessments

The number of tender and swollen joints will be used to assess Lupus Arthritis activity**.**

Joint tenderness is defined as the presence of tenderness and/or pain in a joint at rest with pressure or on passive movement of the joint/joint manipulation. Joint swelling is soft tissue swelling that is detectable along the joint margins.

Both joint tenderness and swelling are dichotomic measures (swollen versus non swollen and tender versus non tender).

28 joints will be examined for tenderness and 28 joints (same as those examined for tenderness) at all study visits.

Subjects at least 3 tender and swollen joints at Screening will be eligible for the study.

SLE Disease Activity Index 2K (SLEDAI 2K)

The SLE disease activity index (SLEDAI 2K) is a validated tool developed as a global assessment of disease activity in SLE patients. The SLEDAI 2K assesses 24 descriptors (sixteen clinical manifestations and eight laboratory measures) in 9 organ systems. Descriptors are given different weights, based on clinical importance, with dichotomic score (present/not present within the previous 30 days). A descriptor must be attributed to active SLE or otherwise should not be scored. The SLEDAI 2K is intended to evaluate current lupus activity and not chronic damage.

The SLEDAI 2K will be assessed at screening, baseline, and all study visits as well as study follow-up visits at Week 28.

BILAG 2004

The BILAG Index is a validated comprehensive index for measuring clinical disease activity in SLE .BILAG assessment consists of 97 variables based on patient's history, examination findings, and laboratory/imaging results. The questions are grouped under nine systems; Constitutional, Mucocutaneous, Neuropsychiatric, Musculoskeletal, Cardorespiratory, Gastrointestinal, Ophthalmic, Renal and Hematological.

The index capture only SLE related disease activity in the previous 4 weeks prior to each assessment. Each of the clinical variables may be recorded as:

0. Absent.

1. Improved. Sufficient for considering reduction in therapy and improvement present on assessment and for at least 2 weeks or completely resolved within the entire last week.
2. Same. No improvement and no deterioration within the last 4 weeks compared to the previous 4 weeks or improvement dose not meet improvement criteria.
3. Worse. Deteriorated during the last 4 weeks compared to the previous 4 weeks.
4. New or recurrent episode during the last 4 weeks (compared to the previous 4 weeks), which is not improving.

Based upon the scoring of each of these variables, a pre-defined algorithm, specific for each system, provides a disease activity score ranging from A to E for each system:

Grade "A" = severe disease activity requiring treatment with high dose steroids (>20mg/day oral prednisolone or equivalent or IV pulse >500 mg MP), systemic immunomodulators or high dose anticoagulation

Grade "B" = moderate disease activity requiring treatment with low dose oral steroids (<20 mg/day prednisolone or equivalent), IM or IA steroids (equivalent to MP<500 mg), topical steroids or immunomodulators, antimalarials or symptomatic therapy (e.g. NSAIDS).

Grade "C" = mild disease.

Grade "D" = indicate previously affected but currently inactive

Grade "E" = this system has never been involved

The BILAG index will be assessed every visit (except for screening)

Physician Global Assessment

Physician Global Assessment is a Visual Analogue Scale. It measures the disease activity based on the physician subjective assessment from none active to worse disease activity. PGA will be performed at every visit (except for screening)

Patient Global Assessment

Patient Global Assessment is a Visual Analogue Scale. It measures the subject perception of his/hers overall health condition, from very well to very poor. PGA will be performed at every visit (except for Screening). It is important that the Patient Global Assessment be collected before other planned visit activities/evaluations to minimize potential influence on patient's perspective.

SLE Disease Biomarkers

Blood samples for the analysis of disease biomarkers that may correlate with potential clinical effect will be collected from all subjects at Baseline and Visit 5 (16 weeks). The serum and PBMC's from lupus arthritis patients' blood will be analyzed for Panel of SLE relevant cytokines, cell surface markers, T cell helper and suppressor functions and B cell numbers and subsets. Peripheral blood DNA will be obtained for analysis of interferon-induced gene expression and RNA for analysis of differences in transcriptome that may associate with

response compared to no response over the 16 week study period. SLE biomarkers may change upon new research and publication in literature.

Ultrasound

The US will be performed by a rheumatologist with expertise in musculoskeletal ultrasound and images will be digitally saved. US assessments of 18 joints for synovitis and 6 joints for erosions will be obtained.

6.4.1 Primary Efficacy Assessment

1. Proportion of patients who achieve >= 20% Improvement in tender and swollen joint counts at 16 weeks

6.4.2 Secondary Efficacy Assessments

1. Changes in synovitis, tenosynovitis and erosions measured by high-energy ultrasound with Dopper flow at Baseline and 16 weeks.
2. **STEROID SPARING EFFECT OF ABATACEPT, MEASURED AS COMPARISON OF DAILY DOSE AT BASELINE AND 16 WEEKS AND AS CUMULATIVE GLUCOCORTICOID DOSE OVER THE 16 WEEKS PERIOD.**
3. **PROPORTION OF SUBJECTS WITH NO BILAG A IN ANY SYSTEM OTHER THAN MUSCULOSKELETAL AT 16 WEEKS.**
4. Proportion of subjects with no deterioration in physician global assessment at 16 weeks.
5. Comparison of fatigue at baseline and 16 weeks as measured by the FACIT
6. Comparison of quality of life at baseline and 16 weeks as measured by the SF 36
7. Safety, measured in standard methods as AE and SAE, inducing likelihood that the AE/SAE was related to the study biologic.
8. Time to ≥20% response, measured as joint counts (sum of tender and swollen joints) at baseline, 4, 8, 12 and 16 weeks.
9. Change in peripheral blood T cell compartments indicating decline in pro-inflammatory profiles, i.e. we expect decrease in CD4+ effector T cells that make IFNgamma (TH1) and IL-17 (TH17) and increase in ratio of Treg to Teff, as well as increased functions of the Tregs and decreased function of the helper T cells. CD4+CD25+ Foxp3 and CD8+Foxp3+ will be the definition of regulatory T cells. These will be measured at baseline and 16 weeks.
10. Change in anti-DNA and complement levels measured at zero, 8 and 16 weeks.

11. Change in BLyS levels from baseline to 16 weeks. We expect BLyS levels may rise as abatacept interferes with T cell action and thus with T cell help to B cells, with less B cell activation and less progression of B cells to short-lived plasma cells, and therefore a potential drop in B cell numbers and rise in BLyS levels. If this does not occur, then the effects of abatacept on B cells would be considered less dramatic than the effects of B cell depletion by rituximab.

12. Effects of treatment on extra-articular systems involved with SLE, such as skin, mucous membranes, serosal surfaces, systemic symptoms at baseline, 4, 8, 12 and 16 weeks.

7 ADVERSE EVENT REPORTING

7.1 Adverse Events

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

7.1.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- results in persistent or significant disability/incapacity
  - is a congenital anomaly/birth defect
  - is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

All pregnancies, regardless of outcome, must be reported to BMS, **including pregnancies that occur in the female partner of a male study subject. <u>All</u> pregnancies must be followed to outcome.** See Section 7.6 for instructions on reporting pregnancies.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs and should also be reported to BMS in an expedited manner, as described in Section 7.2.

NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event) or administration of intravenous antibiotics
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission or procedures for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

7.1.2 Nonserious Adverse Events

Nonserious adverse events are all adverse events that are not classified as SAEs.

7.2 Assignment of Adverse Event Intensity and Relationship to Abatacept

All adverse events, including those that are serious, will be graded by the investigator as follows:

- Mild (Grade 1): awareness of event but easily tolerated
- Moderate (Grade 2): discomfort enough to cause some interference with usual activity
- Severe (Grade 3): inability to carry out usual activity
- Very Severe (Grade 4): debilitating; significantly incapacitates subject despite symptomatic therapy.

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

- **Related:** There is a reasonable causal relationship to investigational product administration and the adverse event.
- **Not Related:** There is not a reasonable causal relationship to investigational product administration and the adverse event.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

7.3 Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the event was administered, it should be recorded in the medical record. The investigator must supply BMS and the IRB/IEC with any additional information requested, notably for reported deaths of subjects.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

A data safety monitoring board (one to-be-named Rheumatology faculty member plus one to-be-named statistician) will review the SAEs quarterly and issue a report to the IRB and to the investigators regarding AEs and SAEs, reported according to patient assignments to groups A or B (the double-blind code will not be broken); these reports will also be supplied to the sponsor

7.3.1 Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs must continue for 30 days after the last administration of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure. The investigator should notify BMS of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

All SAEs, whether considered related or unrelated to abatacept, must be reported to BMS (by the investigator or designee) within 24 hours of study personnel becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

All SAEs should be faxed or emailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

For studies conducted under an **Investigator IND**, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible **and no later than 7 days** (for a death or life-threatening event) **or 15 days** (for all other SAEs) **after the investigator's or institution's initial receipt of the information.** BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

Serious adverse events, whether related or unrelated to abatacept, must be recorded on the SAE page and reported within 24-hours to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be reported within 24-hours by confirmed facsimile transmission (fax) and mailing of the completed SAE page. In some instances where a facsimile machine is not available, overnight express mail may be used. If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting.

If the investigator believes that an SAE is not related to the investigational product but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the potential relationship should be specified in the narrative section of the SAE report.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent within 24 hours to BMS. As follow-up information becomes available it should be sent within 24 hours using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

7.3.2 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union, an event meeting these criteria is termed a Suspected Unexpected Serious Adverse Reaction (SUSAR). BMS will send investigators an expedited safety report (ESR) to notify them of such an event.

Other important findings that BMS may report as ESRs include increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety findings from a nonclinical (eg, animal) study, important safety recommendations

from a study data monitoring committee, or the decision by BMS to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, BMS will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, BMS will report suspected serious adverse reactions (whether expected or unexpected) to the relevant health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

7.3.3 Nonserious Adverse Events

The investigator will begin collecting nonserious adverse event (NSAE) information once administration of the investigational product is initiated. This NSAE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

All identified NSAEs must be recorded and described in the medical record. If an ongoing NSAE worsens in its intensity, or if its relationship to the investigational product changes, a new NSAE entry for the event should be completed. NSAEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for NSAEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with NSAEs at study completion should receive post-treatment follow-up as appropriate.

7.4 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. When reporting a test result that constitutes an adverse event, the clinical term should be used; for example, the event should be reported as “anemia” not “low hemoglobin.” Test results that constitute SAEs should be documented and reported as such.

7.5 Overdose

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

7.6 Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in such a manner that the risk of failure is minimized. (See Section 4.2.1 for the definition of WOCBP.) Before enrolling WOCBP in this study, investigators must review the BMS-provided information about study participation for WOCBP, which can also be found in the GCP Manual for Investigators. The topics include the following:

- General Information
- Informed Consent Form

- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy.

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and of the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

7.6.1 Requirements for Pregnancy Testing

All WOCBP MUST have a negative pregnancy test within 72 hours before receiving abatacept. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive abatacept and must not continue in the study.

In addition, all WOCBP must be instructed to contact the investigator and/or other study personnel immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.

7.6.2 Reporting of Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify BMS of this event and record the pregnancy on the Pregnancy Surveillance Form (not on an SAE form). Initial information on a pregnancy must be reported immediately to BMS, and information on the outcome provided once it is available. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

Note: Any pregnancy that occurs in a female partner of a male study subject must be reported to BMS using the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed for the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Information regarding the course of the pregnancy, including perinatal and neonatal outcome, must be reported to BMS on the Pregnancy Surveillance Form. Infants should be followed for a minimum of 8 weeks.

7.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the medical record.

7.8 Safety Data Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Frequency of reconciliation will be determined prior to study commencement but will occur no less than once prior to study database lock. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

We based our sample sizes on the preliminary data (unpublished): SLE patients with arthritis at the start of a treatment had a mean score on 66-joint count of 21 ± 8.2. There was a decrease to a mean of 2.0 ± 1.5 after 12 weeks of various interventions in patients who reported they improved. For the study proposed here, if 67% of abatacept pts will achieve 20% improvement in swollen and tender joints vs. 30% of controls by week 16, n=28 per group (with p=0.05, power=0.8). Thus we plan 32 patients for abatacept over 16 weeks and 32 patients for placebo over 16 weeks, a total of 64. The dropout rate in the abatacept non-nephritis lupus trial was 35% (over 12 months). We anticipate one-third that in a 4 month trial, proposed, here – i.e. 12%. If we begin with 64 patients we should have 56 completers, thus approximately 28 in each group.

Thus, we will plan to recruit 32 SLE patients at UCLA and an additional 32 at UCSD (separate contract).

8.2 Populations for Analyses

The study analyses will be performed at the termination of the study; once the last visit of the last patients has been recorded. The analyses will be performed on the 64 SLE patients enrolled in the study based on the inclusion and exclusion criteria as stated above.

8.3 Endpoint Definitions

Starting at baseline and at each visit, the SLEDAI 2K, BILAG, and joint count will be recorded. In addition the patient and physician Global Assessment will be recorded. These are all validated measures to evaluate SLE disease activity and response to therapy. In addition, the US 28-joint synovitis and power Doppler scores will be compared to baseline.

8.3.1 Demographics and Baseline Characteristics

All subjects who receive a dose of study drug will be evaluated for safety. Safety outcomes include adverse events, clinically significant changes in vital signs, laboratory test abnormalities, and clinical tolerability of the drug. The investigator will determine the severity of each adverse event as mild, moderate, severe, or very severe. Descriptive statistics (mean, standard deviation, median, inter-quartile range, and frequency distribution) of safety data will be generated to characterize the study participants by treatment arm. The Chi-square test or Fisher's exact test will be used to compare the percent of subjects presenting with AEs (analyzed separately as SAE, any AE) between the two groups.

8.4.3 Efficacy Analyses

The Fisher's exact test will be used to compare the percent of subjects achieving primary and secondary outcomes between two groups. Wilcoxon rank sum tests will be used to compare ordinal and quantitative outcomes between groups. Logistic regression will also be used to adjust for baseline clinical presentation and demographic factors. A site by treatment interaction effects will be included in the model to account for possible differences in treatment efficacy between our two sites. Bivariate analysis and nonparametric analysis (for example local polynomial regression or generalized additive model analysis) will be carried out to inspect the relationship between outcome and covariates. The goodness-of-fit of logistic models will be evaluated using the Hosmer-Lemeshow test. With the quantitative outcomes such as joint counts, ultrasound measurements, etc we will use Poisson regression to assess the treatment effect or linear regression for continuous outcomes. Poisson regression is a special case of generalized linear model and robust pseudo likelihood inference will be used in the analysis. We also will use multiple imputation technique to accommodate possible missing data at 12 and 24 weeks due to patients lost to follow up. The imputation model will include all baseline 12 week and 24 week outcomes and covariates to impute the missing outcomes [23]. Analyses will be done with and without imputation.

8.4.4Other Analyses

NA

9 ADMINISTRATIVE SECTION

9.1 Compliance with the Protocol

The study must be conducted as described in the final IRB/IEC-approved protocol. Documentation of approval, signed by the IRB/IEC chairperson or designee, will be sent to the BMS protocol manager. The study will be monitored by an individual outside the study team chosen by the PI.

All protocol amendments and revisions to the informed consent will be submitted to the BMS protocol manager and to the IRB/IEC. No protocol amendments will be implemented until written approval has been given by the IRB/IEC, except when necessary to eliminate an immediate hazard to study subjects. Administrative letters should also be sent to the BMS protocol manager and IRB/IEC; however, they do not require approval.

If a protocol amendment mandates a revision to the informed consent, the revised consent must be used to obtain consent from subjects currently enrolled in the study if it affects them (eg, if it contains new information regarding safety), and the revised consent must be used to obtain consent from new subjects before enrollment.

9.2 Records Retention

The investigator will retain, in a confidential manner, all data pertinent to the study for all treated subjects as well as those entered as control subjects. The investigator will retain source documents and accurate case histories that record all observations and other data pertinent to the investigation (eg, the medical record) for the maximum period required by applicable regulations and guidelines or following institutional procedures. If the investigator withdraws from the study (eg, relocation or retirement), the records will be transferred to a mutually agreed upon designee, such as another investigator or an IRB. Written documentation of such transfer will be provided to BMS.

The investigator will ensure that a current record of disposition of investigational product is maintained at each study site where the investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number and use date or expiry date
- dates and initials of person responsible for each inventory entry/movement
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted, broken), and
- amount destroyed at study site.

9.3 Destruction of Investigational Product

If the investigational product is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have

been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor to be related to the investigational product
Expedited Safety Report	Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures.
SUSAR	Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC).
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

AB	Antibody
ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine Transaminase
APC	Antigen-Presenting Cell
ARA	American Rheumatology Association
AST	Aspartate Transaminase
BCG	Bacillus Calmette-Guérin
BMS	Bristol-Myers Squibb
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC-ACID	Centers for Disease Control and Prevention Advisory Committee on Immunization Practices
CFR	Code of Federal Regulations
CI	Confidence Interval
CMV	Cytomegalovirus
CRF	Case Report Forms
CRP	C-Reactive Protein
CTLA	Cytotoxic T-Lymphocyte Associated
CXR	Chest X-Ray
DMARD	Disease-Modifying Antirheumatic Drug
DNA	Deoxyribonucleic Acid
D5W	Dextrose (5%) in Water
EC	European Commission
ESR	Expedited Safety Report
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HLA	Histocompatibility Leukocyte Antigen

HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IND	Investigational New Drug (Application)
IRB	Independent Review Board
IST	Investigator-Sponsored Trial
IU	International Unit
IV	Intravenous
JRA	Juvenile Rheumatoid Arthritis
MHC	Major Histocompatibility Complex
MRI	Magnetic Resonance Imaging
NPV	Negative Predictive Value
NS	Normal Saline
NSAE	Non-Serious Adverse Event
NSAID	Non-Steroidal Anti-inflammatory Drug
OA	Osteoarthritis
PCR	Polymerase Chain Reaction
PPD	Purified Protein Derivative
PPV	Positive Predictive Value
PVC	Polyvinylchloride
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious Adverse Event
Se	Sensitivity
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
Sp	Specificity
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWFI	Sterile Water For Injection
TB	Tuberculosis
TNF	Tumor Necrosis Factor
ULN	Upper Level of Normal
VAS	Visual Analog Scale

WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

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Appendix 1 ACR Criteria

The diagnosis of Systemic Lupus Erythematosus requires the presence of four or more of the following eleven criteria, serially or simultaneously, during any period of observation.

1. Malar rash: fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash: erythematous, raised patches with adherent keratotic scaling and follicular plugging; possibly atrophic scarring in older lesions
3. Photosensitivity: skin rash as a result of unusual reaction to sunlight, as determined by patient history or physician observation
4. Oral ulcers: oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis: nonerosive arthritis involving two or more peripheral joints, characterized by swelling, tenderness, or effusion
6. Serositis: pleuritis, by convincing history of pleuritic pain, rub heard by physician, or evidence of pleural effusion; or pericarditis documented by electrocardiography, rub heard by physician, or evidence of pericardial effusion
7. Renal disorder: persistent proteinuria, > 500 mg per 24 hours (0.5 g per day) or > 3+ if quantitation is not performed; or cellular casts (may be red blood cell, hemoglobin, granular, tubular, or mixed cellular casts)
8. Neurologic disorder: seizures or psychosis occurring in the absence of offending drugs or known metabolic derangement (e.g., uremia, ketoacidosis, electrolyte imbalance)
9. Hematologic disorder: hemolytic anemia with reticulocytosis; or leukopenia, < 4,000 per mm3 (4.0 _ 109 per L) on two or more occasions; or lymphopenia, < 1,500 per mm3 (1.5 _ 109 per L) on two or more occasions; or thrombocytopenia, < 100 _ 103 per mm3 (100 _ 109 per L) in the absence of offending drugs
10. Immunologic disorder: antibody to double-stranded DNA antigen (anti-dsDNA) in abnormal titer; or presence of antibody to Sm nuclear antigen (anti-Sm); or positive finding of antiphospholipid antibody based on an abnormal serum level of IgG or IgM anticardiolipin antibodies, a positive test result for lupus anticoagulant using a standard method, or a false-positive serologic test for syphilis that is known to be positive for at least 6 months and is confirmed by negative *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibodies: an abnormal antinuclear antibody titer by immunofluorescence or equivalent assay at any time and in the absence of drugs known to be associated with drug-induced lupus

Appendix 2 – SLICC

Clinical criteria

1. Acute cutaneous lupus, including:
   - Lupus malar rash (do not count if malar discoid)
   - Bullous lupus
   - Toxic epidermal necrolysis variant of SLE
   - Maculopapular lupus rash
   - Photosensitive lupus rash
   - *in the absence of dermatomyositis*
   - OR subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
2. Chronic cutaneous lupus, including:
   - Classic discoid rash
   - Localized (above the neck)
   - Generalized (above and below the neck)
   - Hypertrophic (verrucous) lupus
   - Lupus panniculitis (profundus)
   - Mucosal lupus
   - Lupus erythematosus tumidus
   - Chilblains lupus
   - Discoid lupus/lichen planus overlap
3. Oral ulcers
   - Palate
   - Buccal
   - Tongue
   - OR nasal ulcers
   - *in the absence of other causes, such as vasculitis, Behçet's disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis, and acidic foods*
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
   - *in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia*
5. Synovitis involving 2 or more joints, characterized by swelling or effusion
   - OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness
6. Serositis
   - Typical pleurisy for more than 1 day
   - OR pleural effusions
   - OR pleural rub
   - Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
   - OR pericardial effusion
   - OR pericardial rub
   - OR pericarditis by electrocardiography
   - *in the absence of other causes, such as infection, uremia, and Dressler's pericarditis*
7. Renal
   - Urine protein–to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours
   - OR red blood cell casts
8. Neurologic
   - Seizures
   - Psychosis
   - Mononeuritis multiplex
   - *in the absence of other known causes such as primary vasculitis*
   - Myelitis
   - Peripheral or cranial neuropathy
   - *in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus*
   - Acute confusional state
   - *in the absence of other causes, including toxic/metabolic, uremia, drugs*
9. Hemolytic anemia
10. Leukopenia (<4,000/mm^3 at least once)
    - *in the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension*
    - OR
    - Lymphopenia (<1,000/mm^3 at least once)
    - *in the absence of other known causes such as corticosteroids, drugs, and infection*
11. Thrombocytopenia (<100,000/mm^3) at least once
    - *in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura*

Immunologic criteria

1. ANA level above laboratory reference range
2. Anti-dsDNA antibody level above laboratory reference range (or >2-fold the reference range if tested by ELISA)
3. Anti-Sm: presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody positivity as determined by any of the following:
   - Positive test result for lupus anticoagulant
   - False-positive test result for rapid plasma reagin
   - Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
   - Positive test result for anti-β_2-glycoprotein I (IgA, IgG, or IgM)
5. Low complement
   - Low C3
   - Low C4
   - Low CH50
6. Direct Coombs' test *in the absence of hemolytic anemia*

* Criteria are cumulative and need not be present concurrently. SLICC = Systemic Lupus International Collaborating Clinics; SLE = systemic lupus erythematosus; ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; ELISA = enzyme-linked immunosorbent assay.

Only record items due to SLE Disease Activity & assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks). ♦♦ TO BE USED WITH THE GLOSSARY ♦♦

Scoring: **ND** Not Done
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
❑ indicate if not due to SLE activity
(default is 0 = not present)

CONSTITUTIONAL
1. Pyrexia - documented > 37.5℃ ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg): **Serum urea (mmol/l):**
African ancestry: Yes/No **Serum albumin (g/l):**

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Acritis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) ❑
79. Diastolic blood pressure (mm Hg) value ( ) ❑
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) ❑
82. Urine albumin-creatinine ratio mg/mmol ( ) ❑
83. Urine protein-creatinine ratio mg/mmol ( ) ❑
84. 24 hour urine protein (g) value ( ) ❑
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) ❑
87. GFR (calculated) ml/min/1.73 m^2 ( ) ❑
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGY
90. Haemoglobin (g/dl) value ( ) ❑
91. Total white cell count (x 10^9/l) value ( ) ❑
92. Neutrophils (x 10^9/l) value ( ) ❑
93. Lymphocytes (x 10^9/l) value ( ) ❑
94. Platelets (x 10^9/l) value ( ) ❑
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

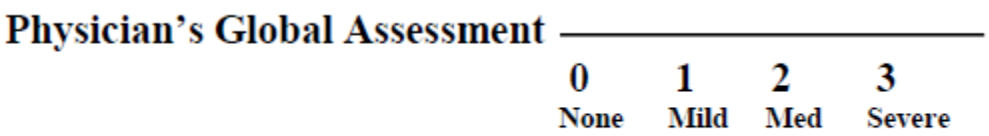
SLEDAI 2 K

SLEDAI-2K: DATA COLLECTION SHEET

Study No.: _____ Patient Name: _____ Visit Date: ____ ____ ____
d m yr

(Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the preceding 10 days.)

SLEDAI 2K Weight	SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes.
1	_____	Leukopenia	<3,000 white blood cells / $x10^9$/L, exclude drug causes.
TOTAL SCORE	_____		


Physician's Global Assessment
0
None
1
Mild
2
Med
3
Severe

Patient Global