Clarification of **A**batacept Effects in SLE with Integrated **B**iologic and **C**linical Approaches (The ABC Study)

[BMS PROTOCOL NUMBER: *IM101-345*

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PROTOCOL SYNOPSIS

Protocol Title:	Clarification of **A**batacept Effects in SLE with Integrated **B**iologic and **C**linical Approaches (The ABC Study)The ABC Study:
Site Numbers/ Names:	Site 1: Oklahoma Medical Research Foundation
Research Hypothesis:	Abatacept is effective in lupus arthritis and this will be discernible in a small trial with robust endpoints which incorporates withdrawal of background immune suppressants
Study Schema: Drugs / Doses / Length of Treatment)	1. Abatacept or placebo will be given in a 1:1 randomization subcutaneously q week for six months. Patients may elect to continue six more months on open label Abatacept. 2. Background Immune Suppressants will be withdrawn at any time between screening and the first dosing visit. 3. At or after screening, patients may elect 40-160 mg depomedrol shots prn not to exceed 320 mg total up to and including the Month 2 Visit (two months after the first dosing visit) 4. Additional steroids or immune suppressants, if necessary, will be allowed but the patient will be considered a non-responder on that basis 5. At the 3 month visit patients with significant clinical flare unresponsive to optional per protocol treatments may elect to receive open label Abatacept but will be considered non-responders in the primary endpoint at six months.
Study Objectives: • **Primary:** • **Secondary:**	**Primary Objective:** To compare response rates between Abatacept-Treated and Placebo-Treated Patients with active lupus arthritis in a trial designed with background immune suppressant withdrawal, limited steroid rescue, and a robust, discriminatory endpoint. Statistical powering is based on this primary objective. The trial design and primary endpoint (response by BICLA) have been pre-tested by us for safety and ability to ensure placebo group non-response. This will support a rational decision about further development of abatacept for SLE at minimal cost. **2.) Secondary clinical endpoints will include:** SRI 4/5, changes in joint counts, SLEDAI, BILAG, CLASI, PGA, and LFA simplified instrument measures. PK and immunogenicity studies will be performed to help in interpretation of outcomes. Novel biologic discovery will be integrated into the clinical trial to support both pre-specified and exploratory biomarker discovery. Data will be generated that might be used to help select more appropriate patient subsets for future trials and, along with PK data, help to guide optimal dosing strategies. Optimizing patient selection and dosing are important goals for further increasing demonstrable effect size in trials by increasing the response rates

	in the treatment group.
Study Design:	This study will be a double blind, randomized, placebo-controlled clinical trial with 1:1 randomization of patients to abatacept 125 mg weekly subcutaneous dose or placebo, with the. withdrawal of background immune suppressants. Limited steroid rescue allowed per protocol. Additional meds will define non-response the primary endpoint date of six months. Flaring patients may elect to receive open label abatacept at Month 3 but will also be defined as non-responders in the primary endpoint. All patients may elect to receive open label abatacept for an additional six months after the primary endpoint date, with two follow up visits (2 and 4 months post withdrawal) to assess withdrawal effects and to complete the safety assessment.
Accrual Goal: (Total subjects)	This study will continue to recruit until we achieve the goal of 60 patients who complete study visits through the 6 month endpoint.
Accrual Rate: (Number of subjects expected per month)	We expect to enroll 5 patients/month given entry criteria, recruitment track record, and patient appeal of protocol (in particular the early crossover to open label treatment)
FPFV: **LPFV:** **Follow Up:**	• FPFV: October 30 2013 • LPFV: December 31 2015 • Follow Up: April 31 2016
Correlative Studies: (PK/PD, etc.)	Extensive exploratory protocol-specific and ancillary immune pharmacodynamic studies, focusing first on changes in IFN alpha, BLyS and other B Cell pathways. A major focus will also be on T Cell pathways with a focus on T suppressor/TH17 dichotomy after treatment with abatacept. A responder analysis will be performed in order to generate hypotheses useful for selecting appropriate patients for this treatment and optimizing dosing strategies.
Inclusion Criteria:	**1)** Signed Written Informed Consent **2)** 4 1997 revised ACR Classification Criteria for SLE **3)** Active polyarticular arthritis meeting at minimum BILAG 2004 B definition with a minimum of 3 tender and 3 swollen joints observed at the screening visit **4)** Men and women 18 to 70 years of age. **5)** Women of childbearing potential and men with partners of childbearing potential must use an acceptable method of birth control throughout the study **6)** Women of childbearing potential must have a negative urine pregnancy test at screening and Study Day 1 (baseline visit) and may not be breast feeding
Exclusion Criteria:	**1)** Current severe disease (e.g. acute nephritis appropriate for induction therapy, CNS lupus (excepting chorea, cranial neuropathy, and resolving optic neuritis) or any lupus condition requiring cyclophosphamide, biologic therapy, or IV bolus steroids of >/= 500 mg. **2)** Subjects who are incapable of understanding or

	completing study-related assessments. **3)** Subjects with any condition, whether or not related to SLE, which, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study. **4)** 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. **5)** Subjects who currently abuse drugs or alcohol. **6)** Subjects with acute herpes zoster or cytomegalovirus (CMV) within 2 months of screening. **7)** Subjects who have received any live vaccines within 3 months of first dose. **8)** 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). **9)** Subjects at risk for tuberculosis (TB). **10)** Subjects known to be positive for hepatitis B surface antigen or hepatitis C unless negative by PCR or RIBA **11)** Acute hemolytic anemia with hemoglobin < 7.0 g/dL or known change in Hg by 2.0 g/dL within four months **12)** WBC < 2500/mm^3 (< 3 x 10^9/L) unless due to chronic stable lupus activity **13)** Platelets < 40,000/mm^3 (< 3 x 109/L) (If less than 100,000 must have been stable (within a range of 10,000/mm^3) within two months of screening or in two tests during the screening period. **14)** Serum creatinine > 2 times the ULN **15)** Serum ALT or AST > 2.5 times the ULN **16)** Any other laboratory test results that, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study. **17)** Known allergy/sensitivity to the study agent or carrier. **18)** Treatment with investigational drug within 28 days (or 5 terminal half-lives) of the Day 1 dose. **19)** Cyclophosphamide within 3 months of Day 1 or bolus IV steroids >/=500 mg within 1 month **20)** Prednisone > 20 mg qd after the screening visit
Criteria for Evaluation: (Efficacy, safety, stopping rules, etc.)	**Efficacy:** Primary endpoint will be response rates by "BICLA" (BILAG-based combined Lupus Assessment). Secondary efficacy endoints will be the SRI (SLE Responder Index), changes in SLEDAI, BILAG, PGA, CLASI, DIAL and PRO endpoints. **Safety:** Adverse Events, Serious Adverse Events and Adverse Events of special interest (infusion reactions and infections) will be collected and described. **Stopping Rules:** Patients may be withdrawn by

	the investigator for non-compliance or safety. All patients terminating before six months will be considered non responders in the primary analysis. Use of off protocol immune suppressants will not necessarily dictate withdrawal but will determine non-responder status. A DSMB board will review data on a quarterly basis and may stop the study if needed.
Statistics:	**Primary Clinical Endpoint:** proportion of patients on abatacept vs placebo who meet BICLA criteria at month 6 compared to baseline by Ch sq or Fishers Exact Test. **Powering of the Study Based on the Primary Endpoint:** Powering assumptions assume response rates ranging from 35-50%. based on data from patients with lupus arthritis in the Phase II abatacept study, where physicians rated 40% of the patients treated with abatacept as having "no flare." Using the BICLA, response rates in the epratuzumab EMBLEM trial was also about 40% at optimal dosing, therefore this range seems applicable. Data from the BOLD study confirm that there should be a near zero (2.4%) percent response by BICLA at six months in the placebo group in a study with background IS withdrawal. Therefore our assumption of at least 5% response in the placebo group in an identical trial design is reasonable and with range of 40-50% response in the treatment group power > 0.8 to detect a difference. **Exploratory Analysis of Primary Endpoint:** To address potential confounders in a small study a propensity score will be applied to simplify multiple variables into one variable. **Secondary Clinical Endpoints:** BICLA and SRI at each month. Mean SLEDAI, BILAG, CLASI, PGA, DIAL and PRO by paired T test. Main Biologic Endpoint: Patients who do or do not exhibit proposed relative differences in the ratio of *IL6/IL23/IL17* to *Foxp3/TGFβ* (suggesting T Cell signaling imbalance) or aberrant ErK phosphorylation (indicating abnormal signaling through B Cell receptor) at baseline will be compared for proportion of responders in treatment vs placebo group. Patients identified at baseline with high TH17 signal or ErK phosphorylation with >/= 50% change towards healthy mean (+2SD) after treatment will be compared separately for response rates. These endpoints will be described in terms of confidence intervals based on the primary clinical endpoint. Analysis of Secondary and Exploratory Biologic Endpoints will include mean (or median) change in cytokine, immunoglobulin and gene expression levels explored based on known patterns of overexpression in SLE. Bucketing of baseline profiles might be used to develop propensity scores suitable for a simplified refinement of the primary biologic endpoint by combining variables that might either increase or decrease the likelihood of response. Given the complex array of data we are likely to generate, principal component analysis can be applied to these exploratory studies to identify directions (principal components) along which the variation of the data is maximal.

1 Introduction

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease characterized by sporadic and often unpredictable flares of inflammation which can affect almost any organ in the body (1). The most common manifestations are polyarticular inflammatory arthritis, which can sometimes be disabling, and skin rashes which range from mild photosensitive eruptions to scarring, disfiguring discoid lesions. With current standard of care, many patients go through long periods of less than optimal disease control or be forced to take toxic immune suppressants or steroids, leading to significant morbidity (2). With optimal interventions some patients may be able to lead near normal lives for a long time but still be accruing significant damage to functional and vital organs, leading to long term disability and early mortality. Acutely severe and even life threatening flares can involve the kidneys, brain, heart, GI system, eyes, or lungs. Acquired immune-mediated hematologic disorders (cytopenias and microangiopathy) may also occur (1).

Treatment development for lupus has been hampered by the heterogeneity of both underlying pathology and clinical manifestations (3,4). There is a growing appreciation that there is often a poor correspondence between the organ affected and the specific underlying complex pathology. Thus two people with renal disease may not respond to the same treatment(s) and similarly two given people lupus arthritis may require completely different approaches to therapy. Earlier trials for “general” lupus had limited options between problematic (but validated) endpoints, leading to arcane measurements of response that have caused some confusion between events which do or do not have clinical consequence. This was bound to cloud comparisons between an effective treatment and placebo, especially in a disease which is already clinically and biologically heterogenous. Further confounding this problem has been an understandable community reticence to subject potentially very ill patients to “true” placebo for long periods of time. Most year-long trials of lupus have allowed the use of such effective background and “rescue” treatments that endpoints become virtually uninterpretable (4).

Abatacept has been evaluated for SLE by BMS in moderate sized Phase II clinical trials for nephritis and non nephritis SLE patients (5,6). Neither of these previously completed trials met primary or secondary endpoints, but exploratory analyses suggested that the problematic clinical endpoints (referred to above) and aggressive background treatments might have impaired the interpretation of these studies. Some modifications in clinical trial design for SLE have been recently tested (7-9) suggesting that careful selection of endpoint(s) and minimizing background therapies (with an immediate and effective rescue strategy that itself can define non-response) provides an ethical study with improved discriminatory capacity despite the complexity of the underlying disease. The current application proposes a small trial with an immune suppressant withdrawal strategy coupled to endpoints which have been shown to provide maximal discriminatory capacity by minimizing the “noise” of minor improvements and clinically insignificant disease flares, thus decreasing artifactual response and artifactual non-response. This study will also explore the possibility that biomarkers might be identified to define subsets of patients as appropriate candidates for this targeted treatment and to guide optimal dosing for such definable candidates.

No targeted therapy can be expected to work for all patients in a disease with such heterogenous underlying biology. There is thus an inevitable low ceiling on the percentage of patients likely to respond if they are entered into a trial without biology-based pre-qualification steps. Although the current trial is designed to maximize effect size between treatment and placebo there is little that can be done to increase the inevitable 50% limit on response rates of targeted biologics, regardless of the discriminatory capacity of the endpoints. For this reason, biomarker discovery to provide a more meaningful basis for selecting patients for targeted treatments should be a high priority both for optimizing patient care and for the appropriate dissemination of treatments that are not "first to market." As more biologic treatments enter the field, strategic biomarker-based matching of treatments and individual patients may help to ensure a competitive effect size, gain faster approval at less expense, gain more rapid penetration and retention of the optimal (and medically most appropriate) market, and convince third party payers of the utility of a treatment.

1.1 Pathology of SLE:

SLE is a prototypic complex autoimmune disease which may arise through imbalances in inherited variants throughout the immune system (10,11). The exact pattern of resulting immune imbalance may vary among patients, but there are strong tendencies for hyperstimulation of Toll-Like Receptor, Interferon alpha regulated signals, and aberrant T and B cell mediated pathways which results in a characteristic pattern of autoantibody production and complement activation (10-12). At the same time, regulatory elements of immunity seem to be dampened, including T suppressor activity and immune clearance by myeloid cells (13,14). The net result is sporadic but refractory inflammation in various organs.

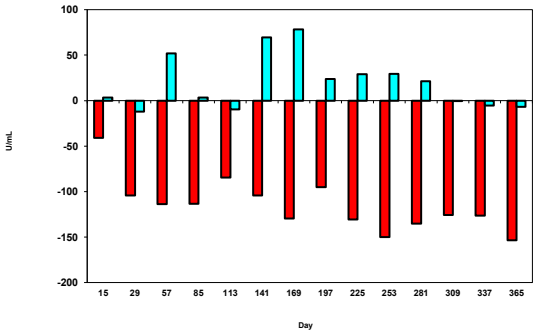
1.2 Relevance of Abatacept Mechanism to Lupus

Genetics studies and studies in twins have demonstrated that Class II major histocompatibility complex (MHC) plays an important role in contributing to the susceptibility and/or severity of rheumatic diseases (15). MHC molecules are prominent on antigen presenting cells, and it is the MHC molecule that binds antigen in its "antigen-binding groove" to "present" the antigen to the T cell's antigen receptor.

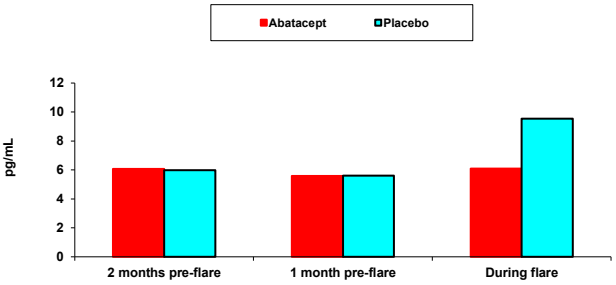
Abatacept was originally developed to finely target T Cell costimulation by blocking the signals between CD 28 and CD80/86. This would be predicted to have effects on both B and T cells as has been borne out in both animal and human studies (16,17). In human RA rheumatoid factor is reduced after 12 months of abatacept therapy suggesting an impact on B Cell activation and autoantibody production (16). Ag-specific T cell proliferation is reduced, and development of an activated T cell phenotype with upregulation of CD69, and ICOS can be suppressed with abatacept (17). Modulation of a number of related inflammatory cytokines by abatacept have been described in patients with RA, some of which might be of critical relevance in SLE. These include reduction of serum interleukin 6 (IL-6) (17), IFN-gamma and IL-17 and a failure of Ag-specific T cells to acquire the CXCR5(+) ICOS(+) T follicular helper cell phenotype (17).

When a targeted agent is applied to the background of SLE immune dysequilibrium, it cannot be assumed to net the same changes in immune balance seen in RA. However preliminary data support some similar patterns in SLE of suppression of B Cell autoantibody production and modulation of T Cell differentiation. In SLE, B cells express increased IL-6 that can autostimulate terminal differentiation of the low density B Cell subsets leading to increased autoantibody production.(17) Data from the Phase II study of abatacept in general SLE

suggests that IL-6 levels are depressed in abatacept treated patients but not placebo patients during flare and abatacept consistently decreases anti-dsDNA antibodies (5) (see figure below). A similar trend was seen in the Phase II nephritis study, with abatacept-treated patients maintaining decreased anti-dsDNA levels after steroid tapering unlike placebo, with expected dampening of complement consumption (6). The exact pathway(s) might connect that apparent connection between IL6 and autoantibodies have yet to be fully sorted out, but IL6 can mediate significant changes in T Cell differentiation patterns, leading to increased IL-17, which accentuate B cell activation and proliferation, antibody production and class switching (18,19).



Change From Baseline in anti dsDNA levels
Red represents Abatacept-treated patients and Blue are Placebo-treated patients. X axis=serial visits in the (Phase II non-nephritis trial, reference 8)



Abatacept May Suppress IL-6 Production These are BMS data showing that even when abatacept study treated SLE patients flare the expected IL-6 increase, seen in the placebo pts (light blue bars), does not occur.

On the basis of these data we speculate that expected biologic effects of abatacept in SLE should include decreases in known volatile autoantibodies such as anti-dsDNA and anticardiolipin, accompanied by signals relevant to terminal B Cell differentiation and the IL6/IL23/TH17 pathway. **The usual relative upregulation of TH17/Tregulatory pathways in SLE might be reversed.** These expected changes will be tested to define the most likely responder group prior to treatment, and explore pharmacodynamic changes in responders after treatment, helping to confirm whether such pharmacodynamic predictors of dose-target efficacy are related to clinical efficacy. **Furthermore we hypothesize that biomarkers of B cell activation such as Erk phosphorylation will be depressed with CTLA4Ig therapy** and that elevation of these markers pre-treatment will predict responders to therapy and a change in the relative balance of these elements in those pre-defined patients will provide an even better predictor of response.

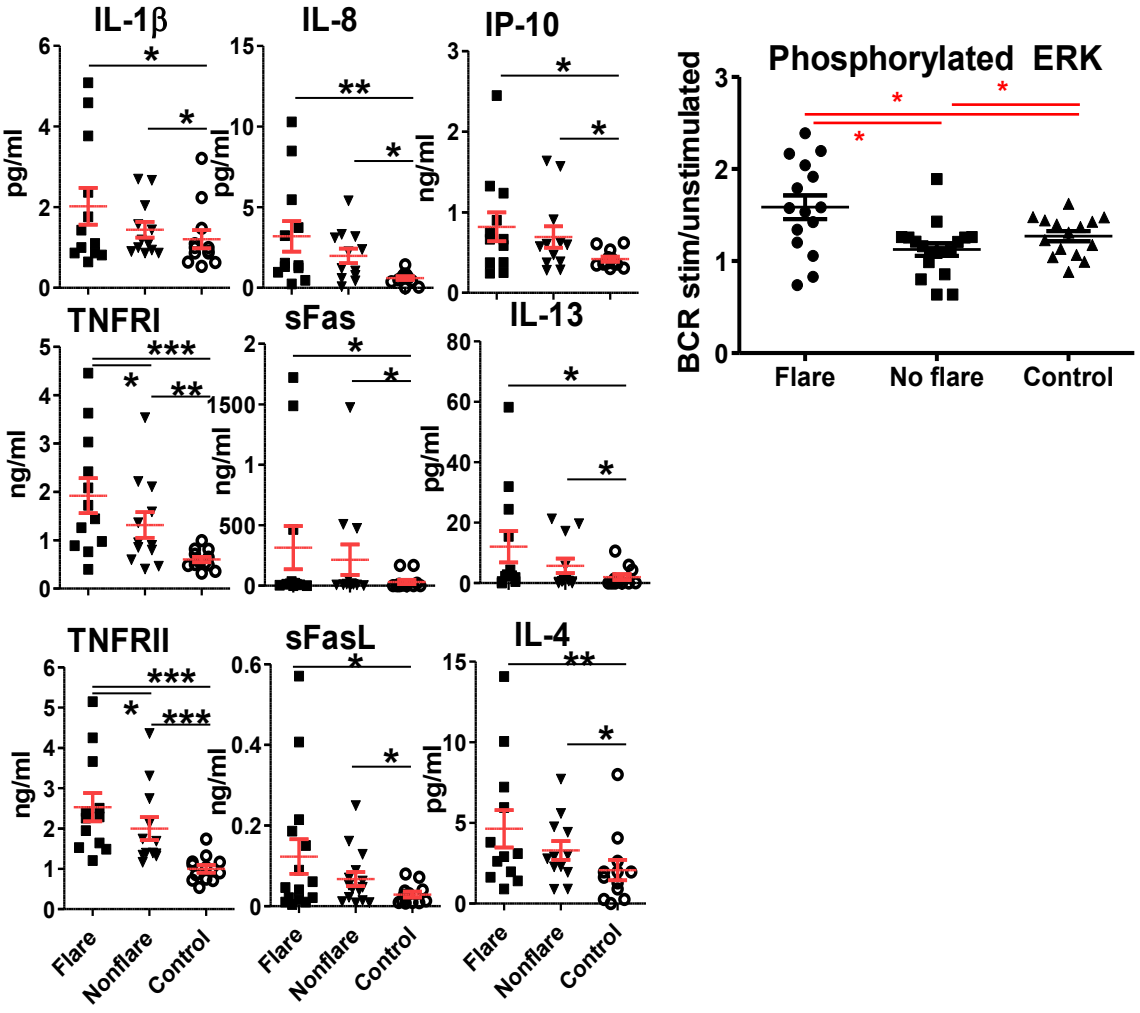
These endpoints will serve as major biologic endpoints (which are secondary endpoints of the study (see below). In exploratory analysis we will also examine unforeseen patterns of gene expression in B Cell and T Cell subsets before and after treatment with abatacept. The biologic endpoints proposed here will employ techniques that have been widely published in human subjects (20-26). Additionally samples of RNA, DNA, and serum and/or plasma will be saved for both pre-specified and exploratory research at OMRF or BMS.

One major hypothesis is that abatacept may affect the elevated ratio of *IL6/IL23/IL17* (and associated TH17 pathway signals) to *Foxp3/TGFβ*. Abatacept would be expected to function

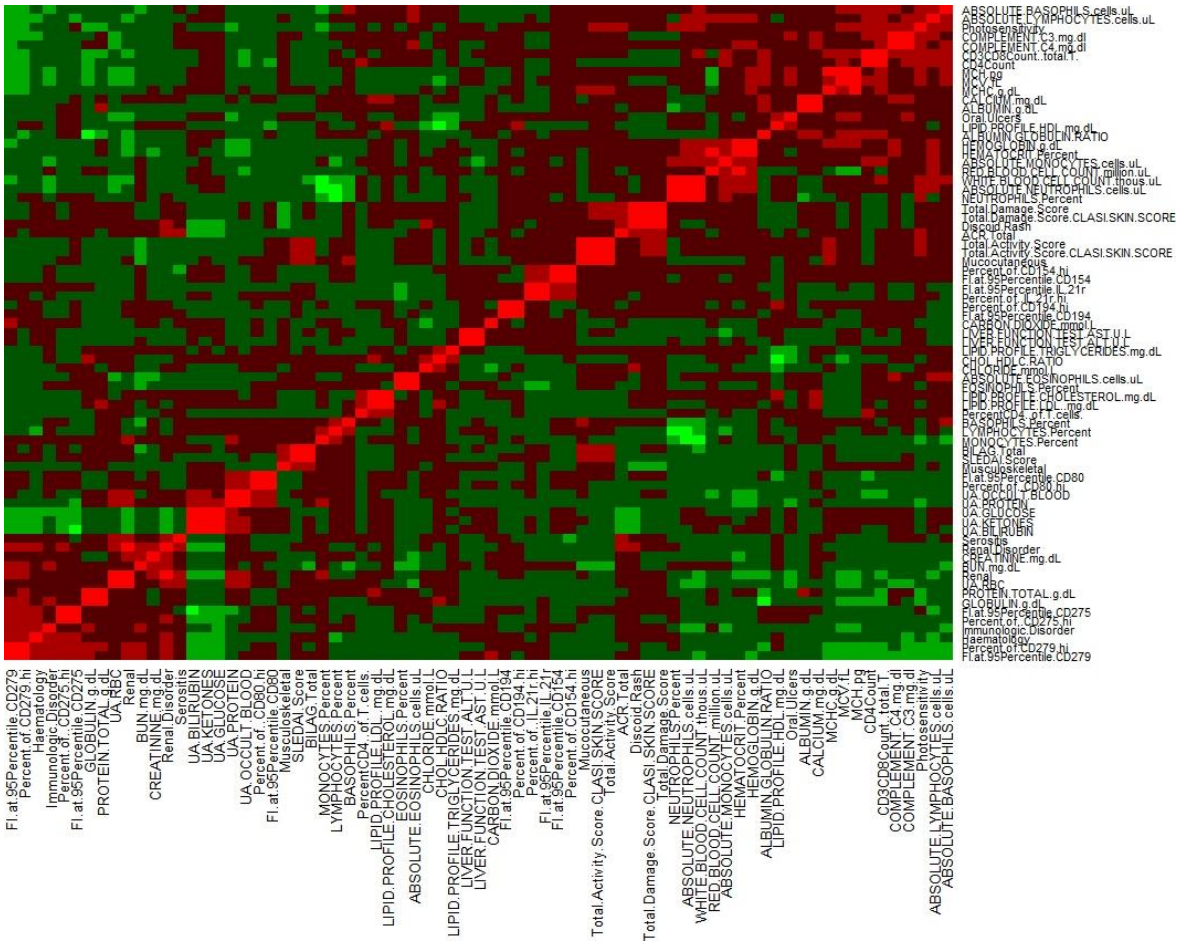
downstream of IL6, this type of signal inconsistency would be a major indicator of abatacept effects as opposed to an effect of rescue steroids that might be given in the study. Based on work by Tsokos et al (a close advisor to our group) (20) we will be performing a gene expression array aimed at detecting the relevant abnormalities in a subset of our patients and tracking abatacept effects on this ratio. As an exploratory biologic analysis, our collaborative groups will also pursue a finding from gene expression profiling in the BOLD study. Ongoing analyses are showing that increased disease activity, cluster with elevated levels of iCOS (CD275) and iCOSL (CD279). iCOS is the third member of the CD28 T cell co-stimulatory pathway (with CD28 and CTLA4) leading to interesting questions in how these expression patterns will be modified with abatacept therapy and whether these patients will be more responsive to abatacept therapy.

We will apply either a parallel approach to explore gene expression profile information from whole blood of SLE patients before and after abatacept therapy, or will expand these studies to use RNAseq approaches which are currently in use in our laboratory to allow assessment of gene expression levels but also of long noncoding, regulatory and viral RNAs in the same experiment.

In ongoing collaborative work, our groups have shown that SLE patients who are experiencing a flare even on background medications have evidence of elevated shed TNF receptors supporting increased B cell activation (e.g. TNFRI, TNFRII, sFASL and sFas), as well as other inflammatory cytokines (see Fig below). These results demonstrate the elevated levels of these shed receptors in the flare visits compared to the same individuals at non-flare timepoints, as well as to other control SLE patients who did not flare in the same study (matched for age, race and gender). These results are interesting; however, every SLE patient does not act the same and the current study will allow us to assess whether shedding (and associated B cell activation) correlates with better SLE abatacept clinical response and whether other background immunomodulatory medications at baseline might influence these plasma cytokine patterns. Evaluation of frozen cells has also showed that SLE patients who were having a clinical flare have increased responses to B cell receptor signaling as is measured by phosphorylated ERK levels in BCR stimulated responses compared to BCR unstimluated. Again, this activation was seen in the same individuals during a flare compared to a nonflare visit, as well as compared to control SLE patients who did not flare. Parallel approaches will assess the role of abatacept on B cell activation, as well as to assess whether patients elevated pERK responses to BCR engagement are more likely to be responders to abatacept therapy.



We conclude that disease activity can be linked to characteristic patterns of plasma biomarkers, cellular responses and gene expression profiles using a principal component analysis from a cell lineage-specific panel based on known pathogenic mechanisms. We will test this hypothesis in the proposed clinical trial with an exploratory analysis of changes in both B Cell and T Cell expression profiles. Pre-specified analyses will include evaluation of B cell activation as measured by ERK phosphorylation after BCR signaling and the fuller gene expression in B and T Cells that is related to the signal impact of IL6, TH17, and iCOS which are expected to be affected by abatacept. Plasma levels of BLyS and TNFRs will also be explored.



1.3 Summary of Results of Investigational Program

1.3.1 Pharmacology of Abatacept

Abatacept is a recombinant fusion protein 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. Consistent with the known biologic activity of CTLA4, Abatacept binds to CD80 (B7-1) and CD86 (B7-2), which are co-stimulatory molecules on the surface of antigen-presenting cells (APCs) which reinforce cognate interactions between B and T Cells. These are commonly bound by CD28, which is constitutively expressed on resting T cells.(15,27-29). A costimulatory signal allows activation of naive T cells in the context of antigen presentation, and promotes the survival of memory and autoimmune effector cells (15, 27). At 24 to 48 hours following T cell activation, the T cell expresses CTLA4 on its surface, which preferentially binds the CD80 and CD86 molecules with high affinity, interfering with the CD28 signal. This is associated with decreased T Cell activation. The CTLA4 section of abatacept binds to CD80 and CD86 and down-modulates the CD28-mediated costimulation of T cells. The FC region of abatacept has several point mutations to inhibit antibody-dependent cell cytotoxicity and complement-dependent cytotoxicity (15).

1.3.2 Human Pharmacokinetics of Abatacept

Support for SC dosing route: Single subcutaneous (SC) dose study of abatacept (50 to 150 mg) where escalating, single, fixed doses were administered demonstrated approximately dose proportional PK in healthy adult subjects based on the geometric means of Cmax and AUC(INF) values (30). The median time to occurrence of Cmax (Tmax) following SC administration ranged between 48-168 hours. Mean $T_{1/2}$ values in healthy subjects ranged 11.2 to 14.7 days, which was 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 SC administration did not alter elimination of abatacept.

Although subcutaneous administration has not been studied previously in SLE, key information about subcutaneous dosing of abatacept in a comparable population can be inferred through data from the IM101063 trial in rheumatoid arthritis. 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 (31). 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 1.3.2A). The SC dose regimens were selected to target trough levels between 10-30 μg/mL, which was associated with efficacy with the IV formulation.

Table 1.3.2A Treatment Groups Based on Body Weight- IM101063

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 Clinical Study report, Table 3.1 (31).

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.

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. 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.

Table 1.3.2B describes the summary statistics of abatacept Cmin values achieved from Day 71 to Day 85.).

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

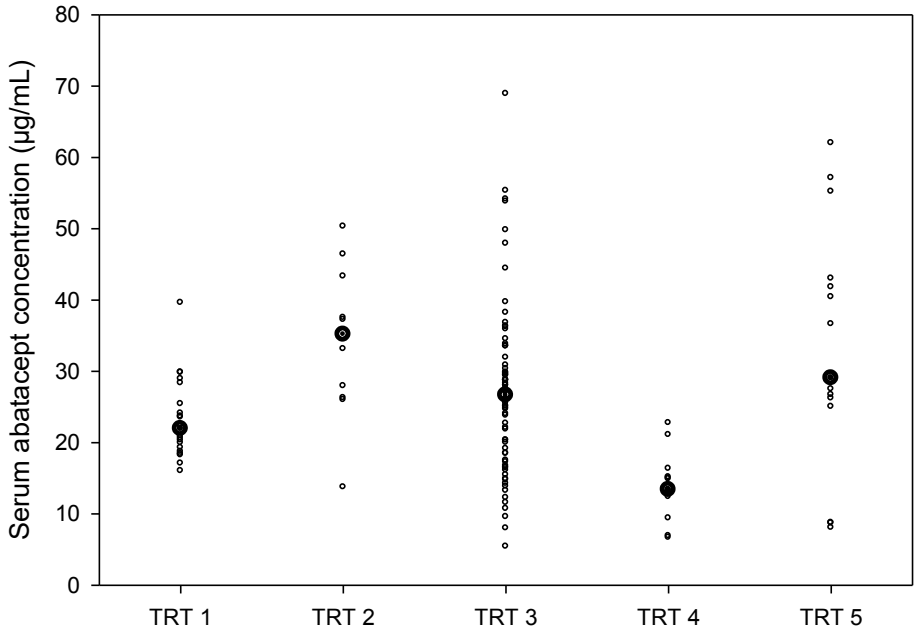
Treatment Group	Study Day	n	Cmin (μg/mL) Geometric Mean (CV%)	Cmin (μg/mL) Median (Min, Max)
1 (500 mg IV / 75 mg SC)	71	7	22.64 (20.13)	20.92 (17.06, 29.84)
	78	7	21.66 (19.99)	22.40 (16.01, 28.93)
	85	7	23.62 (31.63)	21.91 (18.24, 39.60)
2 (500 mg IV / 125 mg SC)	71	4	28.03 (42.13)	32.57 (13.73, 43.30)
	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 Clinical study report, Table 9.2. (31)

Systemic exposure of SC abatacept in terms of the distribution of Cmin was comparable across treatment groups. Geometric mean or median steady-state trough (Cmin) values were comparable for Treatment Groups 1, 3, and 5 and the Cmin values for Treatment Groups 2 and 4 appeared to be higher and lower, respectively, than the observed values associated with the other Treatment Groups.

However, the range of the steady-state trough concentrations in the Treatment Groups 2 and 4 was within the range of trough concentrations achieved in Treatment Group 3 (Please refer to Figure 1.3.2A, shown on the following page).

Figure 1.3.2A: Scatter Plot of Individual Steady-State Cmin Values from Days 71 to 85 by Treatment Group - IM101063



TRT 1 (75 mg/ <60 kg): n=21 data points (from 7 subjects), median = 21.9 µg/mL
TRT 2 (125 mg/ <60 kg): n=10 data points (from 4 subjects), median = 35.2 µg/mL
TRT 3 (125 mg/ 60-100 kg): n=75 data points (from 29 subjects), median = 26.6 µg/mL
TRT 4 (125 mg/ >100 kg): n=13 data points (from 5 subjects), median = 13.4 µg/mL
TRT 5 (200 mg/ >100 kg): n=15 data points (from 5 subjects), median = 29.0 µg/mL

Dark circles (●) represent median values

Source: Clinical study report IM101063, Figure 9.2.2 (31)

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 Clinical study report, Table 9.3. (31)
n = number of subjects, TAU = 7 days

Support for Selection of fixed 125 mg SC dosing in RA

Accumulated data from BMS (32-33) confirming efficacy and safety results of SC abatacept across RA patients of various rates, supports the study of 125 mg SC in lupus patients.

The SC dosing regimen of abatacept was constructed using an integrated assessment of PK, PD, and clinical efficacy and safety data from in vitro, nonclinical and clinical studies. The SC dose was optimized in Phase 2 to target trough concentrations of ≥ 10 μg/mL in > 90% of subjects with RA in order to assure efficacy similar to IV abatacept without any detrimental effects on safety. The E-R relationships and the totality of clinical efficacy and safety data from the Phase 3 Study IM101174 demonstrated that the fixed dose regimen of SC abatacept 125 mg weekly and the monthly regimen of IV abatacept (500, 750, and 1000 mg for subjects weighing < 60 kg, 60 to 100 kg, and > 100 kg, respectively) were therapeutically equivalent for the treatment of RA for the following reasons:

- Despite differences in systemic exposure between SC and IV administration of abatacept, steady-state Cmin concentration of 10 μg/mL or higher, which was associated with near maximal efficacy, was achieved in subjects of all body weights following both IV and SC administration.
  - Abatacept Cmin concentrations were comparable between SC and IV treatments in subjects weighing > 100 kg, and the efficacy response in this weight group was comparable between the SC and IV abatacept treatments, demonstrating that efficacy was not compromised in heavier subjects.
- The clinical efficacy results from the IM101174 study further validated the selection of the fixed-dose SC abatacept regimen, which demonstrated that SC abatacept is non-inferior to IV abatacept.
- In the comparative SC/IV population (IM101174) and the cumulative SC period the frequencies of adverse events, deaths, serious adverse events, adverse events/serious adverse events leading to discontinuation, and adverse events of special interest were consistent with the established safety profile of IV abatacept; no new safety signals were identified for SC abatacept.
  - Additionally, exposure-safety analyses demonstrate that there is no evidence of a relationship between abatacept systemic exposure and probability or time-to-event of infections, or the probability of serious infections.
- Results confirmed that administration of SC abatacept has a similar, low immunogenic profile to that observed with IV abatacept.
- Analysis of clinical response data from the non-inferiority Study IM101174 showed that no clinically relevant differences in the profiles of SC abatacept vs. IV abatacept with respect to efficacy, safety, and immunogenicity could be detected within weight groups defined by baseline body weight (either based on quartiles or on the IV weight-tiered dosing strategy [under 60 kg, 60 to 100 kg, and over 100 kg]).

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Effect of IV loading dose on abatacept trough concentration in RA

The majority of clinical data from the SC abatacept program is associated with the administration of an IV loading dose to initiate therapy with SC abatacept, including the results from the IM101174 noninferiority study. At the time of initiation of this study, the instantaneous achievement of serum concentrations above 10 μg/mL was thought to be needed in order to provide an optimal comparison between the IV and SC regimens.

However, parallel studies were conducted to assess the impact and need of this IV loading dose in the proposed SC regimen. There is limited clinical data from 2 trials, IM101173 (n = 100) and

IM101167 (n=76), where subjects did not receive an IV loading dose prior to initiation or re-initiation of SC abatacept therapy.

In addition to the observed clinical data, simulations were performed using the PPK model to evaluate the distribution of Cmin with respect to time when SC abatacept was administered without an IV loading dose. In the absence of the IV loading dose, steady-state trough serum concentrations were achieved after 6 to 8 weeks of weekly SC abatacept administration and 88% of subjects achieved Cmin concentrations of 10 μg/mL or higher within 2 weeks of SC dosing.

The IV loading dose of abatacept was proposed for clinical evaluation in order to offset the initial low serum concentrations expected immediately following SC dosing alone. While the IV loading dose of abatacept is recommended prior to the initiation of SC abatacept, the PK data from IM101173 and IM101167 and PPK modeling and simulations suggest that target serum trough concentrations of 10 μg/mL, which are associated with near maximal efficacy, could potentially be reached in 88% of subjects within 2 weeks of dosing with SC abatacept alone.

The efficacy, safety, and immunogenicity of SC abatacept were also evaluated across studies when SC abatacept was administered without an IV loading dose. In two open-label studies IM101173 and IM101167 (Period I), albeit slightly different disease severities at baseline, DAS28-CRP decreased comparably over time, up to Day 85, when SC abatacept was administered with (IM101167) or without (IM101173) the initial IV loading dose on Day 1. Treatment with SC abatacept 125 mg weekly in the absence of an IV loading dose was well tolerated by subjects with RA in study IM101173. The safety profile for SC abatacept during the ST and LT periods of IM101173 was consistent with the known safety profile for abatacept. There was no significant increase in immunogenicity rates or antibody titers when SC abatacept was administered in the absence of an IV loading dose (IM101173).

The combined, albeit limited, data from PK, clinical efficacy, safety, and immunogenicity suggest that the loading dose of IV abatacept may not be necessary for initiation or restarting SC abatacept.

1.3.3 Clinical Safety of the Abatacept IV Formulation in SLE and of the SC Formulation in RA

In the year long non nephritis Phase II lupus study (IV formulation) (5), the percentage of patients with any AEs was comparable between the abatacept and placebo groups (90.9 and 91.5% respectively. Ten (8.3%) and three (5.1%) patients in the abatacept and placebo groups discontinued due to AEs. The most frequently reported AEs (>10% patients in either group) were upper respiratory tract infection (25 [20.7%] vs 9 [15.3%]), headache (25 [20.7%] vs 10 [16.9%]), back pain (15 [12.4%] vs 5 [8.5%]), diarrhea (14 [11.6%] vs 4 [6.8%]), nasopharyngitis (3 [2.5%] vs 7 [11.9%]) and urinary tract infection (13 [10.7%] vs 5 [8.5%]) in the abatacept and placebo groups, respectively. This is summarized in the table below

Table 1.3.3a. Safety summary over 1 year

	Abatacept n=121 n (%)	Placebo n=59 n (%)
Adverse events	110 (90.9)	54 (91.5)
Treatment-related adverse events	59 (48.8)	28 (47.5)
Discontinuations due to adverse events*	10 (8.3)	3 (5.1)
Serious adverse events	24 (19.8)	4 (6.8)
Treatment-related serious adverse events	7 (5.8)	2 (3.4)
Discontinuations due to serious adverse events*	7 (5.8)	1 (1.7)
Deaths	1 (0.8)	0

* AE=adverse event;

Serious infections were reported in three abatacept-treated patients and one placebo-treated patient in this study. One abatacept patient was admitted to hospital with bronchitis which resolved allowing the patient to continue the study treatment. One abatacept-treated patient developed nausea, vomiting and abdominal pain, and a presumptive diagnosis of diverticulitis was reported on Day 362. This SAE also resolved and the patient continued in the study. One patient had gastroenteritis on Day 333, which the treating physician considered to be of mild intensity; abatacept was discontinued. Bronchopneumonia was reported in one patient in the placebo group.

Serious AEs of glomerulonephritis, mesangioproliferative glomerulonephritis and lupus nephritis occurred in one patient each in the abatacept group. The glomerulonephritis and mesangio-proliferative glomerulonephritis were deemed unrelated to study drug and occurred in patients with renal medical history. The case of glomerulonephritis was reported after the patient had discontinued due to lack of efficacy on Day 147. The patient was hospitalized on Day 172 with severe alveolitis, and proteinuria of 1.3 g/day was recorded and a renal biopsy showed “mild glomerulonephritis.” Moderate mesangio-proliferative glomerulonephritis was reported in a patient hospitalized with renal flare who discontinued study drug. “Lupus nephritis” was reported in a patient after three doses of abatacept. The patient was hospitalized for increased proteinuria, with biopsy c/w Class II. The investigator considered this unlikely related to study treatment.

In the SLE nephritis study (6), with 298 subjects, abatacept was apparently well tolerated compared to patients receiving background therapy. This was a more ill patient population than the Phase II non nephritis trial and mycophenolate mofetil was used in all patients along with significant steroids. The percentages of patients with adverse events (AEs) and serious AEs (SAEs) were similar among the three treatment groups, with infections being the most

commonly reported. However more gastro-enteritis and herpes zoster occurred in abatacept treated patients compared to placebo.

Fourteen patients died in the double-blind treatment period in the nephritis study; 7 of these were related to an infection (4 placebo; 3 abatacept 30/10 mg/kg; 1 abatacept 10/10 mg/kg). Thus, although Abatacept did not seem to increase risk of infection when added to mycophenolate, that risk appeared higher in this group than in the non-nephritis lupus population studied with abatacept and various background treatments. The current population, should be similar to the latter group, and background immune suppressives, including mycophenolate where it is being used, will be universally withdrawn, with less steroids mandated than in either of the previous abatacept studies.

Table 1.33b. Summary of serious adverse events in the nephritis study

	Abatacept 30/10 (n=99)	**Abatacept 10/10 (n=99)**	**Placebo (n=100)**
Deaths, n (%)	5 (5.1)	2 (2.0)	7 (7.0)
SAEs, n patients (%)	33 (33.3)	28 (28.3)	31 (31.0)
Infections	23 (23.2)	18 (18.2)	17 (17.0)
Pneumonia	4 (4.0)	4 (4.0)	3 (3.0)
Herpes zoster	3 (3.0)	6 (6.1)	0
Gastroenteritis	5 (5.1)	1 (1.0)	2 (2.0)
Urinary tract infection	0	2 (2.0)	2 (2.0)
Renal failure	3 (3.0)	2 (2.0)	3 (3.0)

SAEs seen in the non-nephritis study were predominantly attributed to the underlying disease of SLE and generally reflected single events not localized to a specific organ system. A Data Monitoring Committee (DMC) regularly reviewed emerging efficacy and overall safety data to ensure appropriate benefit-risk. The DMC recommended discontinuation of open label study because of failure to meet the primary outcome measures in face of increased SAEs.

In the non-nephritis study, (most similar to the patient population to be studied here), serious adverse events occurred in (24 [19.8%] of the patients treated with abatacept vs 4 [6.8%] of the placebo patients. . Of these, seven (5.8%) and 1 (1.7%) patients discontinued the study due to SAEs in the abatacept and placebo groups, respectively. SAEs are reviewed in the table below, and generally provide some reassurance that with careful monitoring this medication might be given with reasonable safety to this population.

Table 1.33c. Breakdown of Serious SAE Categories from the non-nephritis lupus trial by Medical Dictionary for Regulatory Activities (MedDRA)

	Abatacept n=121 n (%)	Placebo n=59 n (%)
Total patients with serious adverse events	24 (19.8)	4 (6.8)
Musculoskeletal and connective tissue disorders	6 (5.0)	1 (1.7)
General disorders and administration site conditions	4 (3.3)	0
Infections and infestations	3 (2.5)	1 (1.7)
Renal and urinary disorders	3 (2.5)	0
Gastrointestinal disorders	2 (1.7)	1 (1.7)
Nervous system disorders	2 (1.7)	1 (1.7)
Psychiatric disorders	2 (1.7)	1 (1.7)
Cardiac disorders	2 (1.7)	0
Immune system disorders	2 (1.7)	0
Injury, poisoning and procedural complications	2 (1.7)	0
Respiratory, thoracic and mediastinal disorders	2 (1.7)	0
Blood and lymphatic system disorders	1 (0.8)	0
Metabolism and nutrition disorders	1 (0.8)	0
Skin and subcutaneous tissue disorders	0	1 (1.7)
Vascular disorders	0	1 (1.7)

Table 1.33d Specifics of Serious Adverse Events in Phase II IV Non-nephritisTrial Population Similar to Those to be Recruited into the Current Study

Patient	Event VT/PT	Description
1. 009	Abdominal pain	Mild lower abdominal pain; seen in ER; exam normal; discharged one day later
2. 260	Costal pain/ Musculoskeletal chest pain	Admitted to hospital for bone scan to evaluate abnormalities seen on radiographs. Discharged next day.
3. 6	Systemic lupus flare/SLE	Admitted to hospital for 2 days for lupus flare: facial erythema, vasculitic lesions on finger, and polyarthralgias. Study drug discontinued.
4. 150	Fever due to SLE flare up/SLE	Fever, facial rash; admitted to hospital for treatment via ER.
5. 106	Fever one day/Pyrexia	One day fever, general discomfort, elevated liver enzymes. Admitted for R/O sepsis, lupus flare or hepatitis. Treated with abx and IV steroids. Presumed lupus flare. Study drug discontinued.
6. 196	Facial edema/Face oedema Hand edema/Oedema peripheral Fever/Pyrexia	Admitted with fever, facial, hand and peripheral edema. Treated with high dose prednisone and abx for presumed lupus flare vs. infection. Study drug discontinued.
7. 93	Angio-edema/Angioedema Lupus exacerbation/ SLE Severe lupus activity + vasculitis/ Lupus vasculitis	Facial swelling and myalgias after second study drug infusion. Study discontinued. Diffuse pain thought to be due to lupus activity. Treated with high dose prednisone. No details on the event; close in time to lupus exacerbation SAE.
8. 185	Lupus nephritis	Admitted for evaluation of increasing proteinuria (present at baseline); biopsy performed and Class III nephritis. Study drug discontinued after only month of therapy.
9. 11	Bronchopneumonia Psychosis/Psychotic disorder	Ongoing bronchitis worsened; CXR revealed probable bronchopneumonia. Treated with IV abx and improved. Acute psychosis/mental deterioration thought due to lupus. Study drug discontinued and started on cyclophosphamide IV and azathioprine.
10. 30	Gastroenteritis	Gastroenteritis symptoms; admitted for 3 days for unknown treatment and discharged.
11. 88	Pericarditis	Admitted with lupus flare; CT of chest showed pericardial effusion. Treated with high dose prednisone. Resolved in 3 weeks. Study drug interrupted.
12. 173	Alveolitis	Hospitalized for progressive dyspnea; suspected alveolitis due to lupus. Study drug discontinued. Patient started on high dose prednisone

	Glomerulonephritis	During hospitalization for alveolitis, found to have increased proteinuria. Biopsy revealed non-specific glomerulonephritis. Started on MMF.
13. 103	Worsening of anemia/Anemia Fever/Pyrexia	Admitted for worsening anemia and chronic fever. Fevers not confirmed during hospitalization. Work-up for infection negative. Anemia work-up also non-revealing; thought to be iron deficiency anemia. Study drug interrupted
14. 129	Headache	Unremitting headache with nausea and vomiting. Hospitalized 3 days for unspecified treatment.
15. 116	Polyneuropathy	Patient developed parasthesias in hands and feet. EMG showed symmetric polyneuropathy. Study drug discontinued.
16. 163	Allergy/Hypersensitivity	Itching and erythema on face and throat about 10 hours after study drug infusion. Hospitalized for evaluation and treatment. Found to be due to carbamazepine and not study drug.
17. 69	Gunshot wound to head/Gunshot wound	Patient died from a non-self- inflicted gunshot wound to the head.
18. 238	Diverticulitis	Developed severe abdominal pain, nausea and vomiting. Admitted for 2 days, treated with abx and IV fluids.
19. 132	Acute polyneuropathy Steroid-induced psychosis/ Psychotic disorder	Admitted for acute polyneuropathy. Symptoms began prior to first dose of study drug. Treated with high dose steroids. Study drug discontinued after only one dose. Patient admitted for psychosis thought to be due to high dose steroids used for treatment of polyneuropathy.
20. 230	Bronchitis	Worsening non-productive cough. CXR negative. Admitted for abx treatment and observation. Resolved in 6 days.
21. 47	Lupus peritonitis/ Peritonitis lupus	Patient admitted with pelvic pain; laparascopy normal except for question of hyperemia. Differential PID vs. lupus peritonitis. Final diagnosis of lupus peritonitis. Continued on study drug.
22. 115	Left ankle fracture/ankle fracture	Patient fell and fractured ankle. Admitted for surgery. Study drug interrupted for surgery.
23. 66	Hypersensitivity reaction to study drug infusion/Drug Hypersensitivity	5 minutes into first study drug infusion patient noted itching on face and chest tightness. Wheezing on chest exam. Admitted for observation. Symptoms resolved after cessation of infusion. Study drug discontinued.
24. 158	Superficial gastric ulcer/gastric ulcer Haematemasis	Developed hematemesis. Admitted to hospital for gastroscopy which revealed small ulcer. Treated with proton pump inhibitor.
25. 33	Lupus flare/SLE Anxiety and depression/Depression	Admitted for lupus flare. Treated with pulse prednisolone Admitted for anxiety and depression following the death of patient's brother. No further details provided.

	Dehydration	No details provided (occurred at same time as admission for anxiety and depression). Patient had discontinued study drug just prior to this event.
26. 113	Chest pain Costochondritis	Admitted with chest pain. Treated with pulse Solu-Cortef. As above.
27. 161	Secondary pericarditis/Pericarditis Pleural effusion	Patient admitted with pleuritic chest pain. Found to have pleural effusion and pericarditis. Patient had already been discontinued from study drug prior to this event.
28. 233	Arthritis exacerbation/ Arthritis Mesangioproliferative Glomerulonephritis	Admitted 3 days for treatment of arthritis myalgias. Treated with high dose prednisone. One month after treatment for arthritis, admitted with renal flare activity. Biopsy revealed mesangial glomerulonephritis. Discontinued from study drug and treated with pulse therapy and plasmapheresis.

AEs of Special Interest: *(Note, the data summarized here include the more extensive RA studies given the accumulation of pertinent data from those trials)*

Malignancies: The potential role of abatacept in the development of malignancies in humans is unknown. There was one malignancy reported in the lupus Phase II non-nephritis trial which was a basal cell carcinoma (5). Given the limited accumulation of risk or incidence for malignancy from the lupus program, data from the RA studies will be summarized (32-35).

In RA studies, the incidence rates of malignancy overall, non-melanomatous skin cancers, solid organ, hematologic/lymphatic cancers, as well as each type of malignancy, have remained stable over time at a frequency of 138 of 3256 abatacept-treated patients observed during 9597 patient-years (33) or 1.44 per 100 patient-years. Incidence rates per 100 patient-years were 0.74 for non-melanomatous skin cancer, 0.60 for solid organ malignancies and 0.14 for hematologic malignancies. The most frequently reported solid organ cancer was lung cancer (0.13 per 100 patient-years), and the most common hematologic malignancy was lymphoma (0.08 per 100 patient-years).

The incidence rate did not increase for malignancies overall, by major type (nonmelanomatous skin cancer, solid tumors, and hematologic malignancies), or for individual tumor types in the double-blind and open label period compared to the double blind experience. The type and pattern of malignancies reported during open-label trials were similar to those reported for the double-blind experience. The incidence rate of observed malignancies was consistent with that expected in an age- and gender-matched rheumatoid arthritis population.(36)

Infusion-related and hypersensitivity reactions: In previous clinical studies with abatacept, pre-medication to prevent hypersensitivity was not required. The incidence rate per 100 p-y of acute-infusional event during ST and LT periods was 3.9. The annual incidence rate of acute-infusional events was elevated in the first year of exposure, decreased in the second, and then remained stable with increasing duration of exposure to abatacept. The 4 most common events contributing to this incidence rate per 100 p-y were dizziness (0.67), headache (0.66),hypertension (0.61), and nausea (0.38). The frequencies of these 4 events were 1.9%,1.8%, 1.7%, and 1.1%, respectively. Greater than 95% of all subjects with acute infusional events in the ST, LT, and cumulative ST and LT periods had events that were mild or moderate in intensity.

Two acute-infusional events (chest pain and anaphylactic reaction) during the LT period were considered serious. These 2 events resolved with treatment without clinical sequelae although drug was discontinued for the subject with the anaphylactic reaction (33). The incidence rate of peri-

infusional event during the cumulative ST and LT period was11.21 per 100 p-y. The annual incidence rate of acute-infusional events was elevated in the first year of exposure, decreased in the second, and then remained stable with increasing duration of exposure to abatacept. Limited conclusions should be drawn from the numerical increase in incidence rates for some events at greater years due to the small number of subjects (33).

The occurrence of anaphylaxis remained rare between the double blind and LT open label experience. Hypersensitivity was reported uncommonly. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, which occurred within 24 hours of abatacept infusion, were uncommon (33).

Abatacept and Pregnancy Limited clinical experience with 102 pregnancies in patients using abatacept (37) (as of Dec 2010), included no reports of skeletal abnormalities. The outcomes for these 102pregnancy reports were as follows: outcome unknown (36), normal newborn (31),spontaneous abortion (14), abortion late (1), induced abortion (12), live birth (6),premature baby with medical problems (1), and missed abortion (1). To date, data regarding lactating women with the use of abatacept has not been reported. Five abatacept-exposed pregnancies have been included in the pregnancy registry (1pending outcome); two malformations have been reported (1 woman had a baby diagnosed with pyloric stenosis requiring surgery and 1 woman delivered a baby with cleft lip and palate). Two pregnancies have been reported in IM101045B: 1 miscarriage and 1 live birth.

Safety Experience with SC abatacept (Data From Patients with RA)
The safety experience with SC abatacept was characterized in 2 ways: events during cumulative SC period and events during the comparative SC/IV period. The key safety findings based on these analyses are listed below. (32-35).
The **cumulative SC** period, during which 1879 subjects received SC abatacept for a total exposure of 1945.60 p-y, was based on cumulative (ST/LT) pooled data of the Phase 2 and 3b studies (32). These data include subjects in the SC abatacept treatment group in the ST period of IM101174, subjects in the IV abatacept treatment group in the ST period of IM101174 (including the anti-TNF failure substudy) who were treated with SC abatacept in the LT period, from the start of SC abatacept in the LT period, subjects in ST abatacept treatment groups from IM101063, subjects in the ST placebo group from IM101063 who were treated with SC abatacept in the LT period, from the start of SC abatacept in the LT period, and subjects in IM101167, IM101173, and IM101185. No new safety signal was identified for SC abatacept across the parameters of death, SAEs, AEs/SAEs leading to discontinuation, treatment-related AE/SAEs, and overall AEs.

Table 1.3.3e: Overall Safety for the Cumulative SC Period

	Number (%) of Subjects N = 1879	Incidence Rate (per 100 p-y)	Poisson 95% Confidence Interval
Deaths	9 (0.5%)	0.46	(0.24, 0.89)
SAEs	161 (8.6%)	8.63	(7.39, 10.07)
AEs	1267 (67.4%)	144.36	(136.63, 152.53)
AEs leading to	46 (2.4%)	2.37	(1.78, 3.16)

Table 1.3.3e: Overall Safety for the Cumulative SC Period

	Number (%) of Subjects N = 1879	Incidence Rate (per 100 p-y)	Poisson 95% Confidence Interval
discontinuation			

Source: Subcutaneous abatacept summary of clinical safety. Bristol-Myers Squibb, 2010. Document Control No. 930043734.

Subgroup analyses by body weight did not identify differential safety profile for any of the weight groups, including the 24% of subjects weighing less than 60 kg. No new safety signal was identified for AEs of special interest:

- Infection and infestation AEs were reported in 756 (40.2%) subjects with an incidence rate (per 100 p-y of exposure) of 54.94. The majority of infections were of mild to moderate intensity. The cumulative SC period incidence rate of infections and infestation AEs was consistent with previous IV abatacept experience.
- Malignancies were reported in 20 (1.1%) subjects with an incidence rate (per 100 p-y of exposure) of 1.04. Malignancies excluding non-melanoma skin cancer (NMSC) were reported in 9 (0.5%) subjects with an incidence rate (per 100 p-y of exposure) of 0.46. The cumulative SC period incidence rate of malignancies was consistent with previous IV abatacept experience.
- Pre-specified autoimmune events were reported in 17 (0.9%) subjects with an incidence rate (per 100 p-y of exposure) of 0.88; most were of mild to moderate intensity with the exception of 1 severe event (vasculitis). One pre-specified autoimmune event was reported as serious (sarcoidosis of moderate intensity), which led to premature discontinuation. The cumulative SC period incidence rate of autoimmune events was consistent with underlying disease and previous IV abatacept experience.
- Pre-specified local injection site reactions were reported in 58 (3.1%) subjects with an incidence rate (per 100 p-y of exposure) of 3.09. Most local injection site reactions were of mild to moderate intensity; 1 event (severe injection site reaction) was serious and led to premature discontinuation.
- Systemic injection reaction AEs were reported in 131 (7.0%) subjects with an incidence rate (per 100 p-y of exposure) of 7.21. Most events were of mild to moderate intensity; none were serious; 1 event (moderate angioedema) led to premature discontinuation.
- Pre-specified acute- and peri-infusional AEs were reported in 15 (1.6%) and 35 (3.6%) subjects, respectively; all events were of mild to moderate intensity with the exception of 1 severe event (headache).
- The safety profile of SC abatacept was also assessed under scenarios that might increase immunogenicity and determined the consequences of treating with SC abatacept (e.g., no IV load, monotherapy without MTX, prolonged withdrawal of therapy, switch from IV to SC abatacept).

Overall, consistent safety profiles were observed for the SC abatacept and IV abatacept groups in rheumatoid arthritis across the parameters of death, SAEs, AEs/SAEs leading to discontinuation, treatment-related AE/SAEs, and overall AEs (Table 1.3.3f).

Table 1.3.3f: Overall Safety for the Comparative SC/IV Population - IM101174 (short-term Period)

	Number (%) of Subjects	
	SC Abatacept	IV Abatacept

Table 1.3.3f: Overall Safety for the Comparative SC/IV Population - IM101174 (short-term Period)

	Number (%) of Subjects	
	N = 736	N = 721
Deaths	2 (0.3%)	5 (0.7%)
SAEs	31 (4.2%)	35 (4.9%)
AEs	493 (67.0%)	470 (65.2%)
AEs leading to discontinuation	15 (2.0%)	25 (3.5%)

Source: Subcutaneous Abatacept Summary of Clinical Safety. Bristol-Myers Squibb, 2010. Document Control No. 930043734.

The subgroup analyses by body weight did not identify differential safety profile for any of the weight groups, including the 24% of subjects weighing less than 60 kg indicating that the higher exposures (Cmin) due to the fixed dosing regimen did not result in any additional safety risks.

The safety profiles observed for SC abatacept and IV abatacept were consistent for AEs of special interest:

- Infection and infestation AEs were reported in 234 (31.8%) and 221 (30.7%) subjects in the SC abatacept and IV abatacept groups, respectively. The majority of infections were of mild to moderate intensity.
- Malignancies were reported in 3 (0.4%) and 5 (0.7%) subjects in the SC abatacept and IV abatacept groups, respectively. Of these, 2 malignancies from each group were non-melanoma skin cancers (NMSC).
- Pre-specified autoimmune events were reported in 7 (1.0%) and 6 (0.8%) subjects in the SC abatacept and IV abatacept groups, respectively; all events were of mild to moderate intensity.
- Pre-specified local injection site reactions were reported in 19 (2.6%) and 18 (2.5%) subjects in the SC abatacept and IV abatacept (i.e., SC placebo) groups, respectively. All pre-specified local injection site reactions were of mild to moderate intensity; none led to premature discontinuation.
- Systemic injection reaction AEs were reported in 56 (7.6%) and 56 (7.8%) subjects in the SC abatacept and IV abatacept groups; respectively. No serious systemic injection reactions were reported in the SC abatacept group; 1 subject in the IV abatacept group had serious systemic injection reactions (nausea and headache). In both treatment groups, most pre-specified systemic injection reaction AEs were of mild or moderate intensity; none led to premature discontinuation.
- Pre-specified acute infusional AEs were reported in 20 (2.7%) and 16 (2.2%) subjects in the SC abatacept and IV abatacept groups, respectively. In both treatment groups, most of the pre-specified acute infusional events were of mild to moderate intensity; only 1 event in each treatment group, both reported on Day 1, led to premature discontinuation.

Data from the SC abatacept clinical development program indicates that the SC abatacept formulation did not lead to increased immunogenicity and when present did not affect safety.

1.3.3.1 Drug-Related Adverse Events

As described above, the proportion of patients with SAEs in the Phase II non-nephritis lupus trial (population most similar to the current trial) (5) was higher in the abatacept versus placebo groups (24

[19.8%] vs 4 [6.8%] patients, respectively. 7 patients in the abatacept group and 2 patients in the placebo group had SAEs which were thought to be treatment-related (or possibly treatment-related) by the investigator; for abatacept: facial edema, hand edema and pyrexia in one patient and, in different patients alveolitis, polyneuropathy, diverticulitis, bronchitis, drug hypersensitivity and dehydration. In the placebo group, angioedema and lupus vasculitis occurred in one patient, and lupus peritonitis in one patient. Given the higher proportion of SAEs in the abatacept group, further *post-hoc* analyses were performed, which revealed that 17/24 patients with SAEs in the abatacept group developed the SAEs between the start of the protocol mandated burst and taper of steroids and Month 6 when steroids were to be tapered back to baseline. In the placebo group, 2/4 patients had SAEs that occurred between the start of steroid taper and Month 6 (aba paper mine)

Injection Site Reactions in Adult RA Patients Treated with Subcutaneous Abatacept IM101-174 compared the safety of abatacept including injection site reactions following subcutaneous or intravenous administration to patients with RA. The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous abatacept group and the intravenous abatacept group (subcutaneous placebo), respectively. All these injection site reactions (including

hematoma, pruritus, and erythema) were mild (83%) to moderate (17%) in severity, and none necessitated drug discontinuation.

Immunogenicity in Adult RA Patients Treated with Subcutaneous Abatacept IM101-174 compared the immunogenicity to abatacept following subcutaneous or intravenous administration. The overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous groups, respectively. The rate is consistent with previous experience, and there was no correlation of immunogenicity with effects on pharmacokinetics, safety, or efficacy.

Immunogenicity and Safety of Subcutaneous Abatacept Administration as Monotherapy without an Intravenous Loading Dose IM101-173 was conducted to determine the effect of monotherapy use of abatacept on immunogenicity following subcutaneous administration without an intravenous load in 100 RA patients, who had not previously received abatacept or other CTLA4 Ig, who received either subcutaneous abatacept plus methotrexate (n=51) or subcutaneous abatacept monotherapy (n=49). No patients in either group developed anti-product antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

Immunogenicity and Safety of Subcutaneous Abatacept upon Withdrawal (Three Months) and Restart of Treatment IM101-167 in the subcutaneous program was conducted to investigate the effect of withdrawal (three months) and restart of abatacept subcutaneous treatment on immunogenicity in RA patients treated concomitantly with methotrexate. One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous abatacept or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label abatacept treatment in the final 3-month period of the study (period 3).

At the end of the withdrawal period, 0/38 patients who continued to receive subcutaneous abatacept developed anti-product antibodies compared to 7/73 (9.6%) of patients who had subcutaneous abatacept withdrawn during this period. Half of the patients receiving subcutaneous placebo during the withdrawal period received a single intravenous infusion of abatacept at the start of period 3 and half received intravenous placebo.

At the end of period 3, when all patients again received subcutaneous abatacept, the immunogenicity rates were 1/38 (2.6%) in the group receiving subcutaneous abatacept throughout, and 2/73 (2.7%) in

the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions, and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose. The safety observed in this study was consistent with that observed in the other studies.

1.3.4 Clinical Efficacy of Abatacept Subcutaneous Formulation

The clinical efficacy of abatacept in lupus has not been tested. However, based on data from RA studies, there is no reason to believe that this formulation would not be equivalent to IV dosing in effects. The clinical development program for SC abatacept in RA included 4 Phase 3b efficacy, safety, and immunogenicity studies (IM101167, IM101173, IM101174 and IM101185) plus 2 clinical pharmacology studies (IM101013 and IM101063). Overall, the efficacy data from the SC abatacept development program demonstrated that the efficacy profile of SC abatacept is comparable to IV abatacept in patients with rheumatoid arthritis (31). This justifies the study of the SC formulation in SLE, based on our rationale that exploratory analysis of the IV SLE studies supports the hypothesis that efficacy might be demonstrated in a study in which background treatments are less aggressive and endpoints more discriminatory.

1.4 Overall Risk/Benefit Assessment

Based on the clinical trial experience in adults, the risks that may be associated with the use of abatacept include infections, some 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 have 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).

Recently a subcutaneous form of abatacept has been tested in and approved for rheumatoid arthritis. From substantial data testing the subcutaneous form of Abatacept in rheumatoid arthritis there is little reason to suspect that any novel risks should emerge to make this formulation significantly more problematic than the IV formulation in SLE. Data from the two lupus trials using IV abatacept suggest that safety profile of abatacept in the non-nephritis lupus study IM101042 was generally similar to placebo, with the exception of the incidence of SAEs, which was higher in the abatacept group (19.8%) than that in the placebo group (6.8%), a population that is the most similar to the current one. These SAEs have been reviewed above, and were predominantly short hospitalizations for lupus flares. Of concern (and to be closely monitored in the current study) there were three nephritis flares, albeit none had severe biopsy manifestations (Class II, mesangioproliferative and “mild glomerulonephritis”) and there were three incidences of serious infections (hopefully background medication withdrawal will help ameliorate any combined risks for infection). Allergic/injection reactions will also need to be closely monitored in this study.

Overall, in a population of lupus patients with significant unmet medical need, which develops significant immediate morbidity, long term disability and mortality on current standards of care, the risks as discussed above are reasonable and manageable through careful screening and monitoring and prompt attention to new medical problems. The current study, cognizant that abatacept has potent immune-modulating action, restricts entry to patients with significant and potentially organ-threatening disease who are otherwise not entering the study with seriously damaged renal, liver,

digestive, pulmonary, cardiac or circulatory systems that might increase their risks for infections and other complications, which might cloud the proper assessment of safety in the population.

A further consideration is that alternative treatments available to our patients are known to have high risks for metabolic derangements, organ toxicities and impairment of host defenses against infections and possibly neoplasms (2). Thus the alternative treatments, many of which have broader immune suppressive potential than CTLA4Ig does, are not known or expected to have a better safety profile than that of abatacept. Indeed with a study design that withdraws background immune suppressants, a possible benefit could accrue from diminished toxicity.

1.5 RESEARCH HYPOTHESIS

We hypothesize that use of a novel, simplified trial design which incorporates withdrawal of confounding background immune suppressants with a robust clinical efficacy endpoint, a greater number of patients with SLE who are randomized to abatacept will achieve the primary efficacy endpoint of BICLA than patients randomized to placebo.

1.6 STUDY RATIONALE

This double blind placebo controlled study will randomize lupus patients with active arthritis to abatacept or placebo for a six month trial to determine which group has a greater response rate as measured by the primary endpoint of BICLA (BILAG based Combined Lupus Assessment) (BILAG=British Isles Lupus Assessment Group index). The dose of 125 mg administered subcutaneously weekly has been validated in an RA population and was chosen for this study in SLE on the basis of the assumption that it will be equal in efficacy to intravenous infusion without adversely affecting the safety profile. This current small study is not designed to test that assumption, but on the basis of RA data it seems reasonably likely that any efficacy signal from abatacept will be detectable through this route of administration in SLE. Subcutaneous dosing is a more practical clinical approach in the management of patients overall, is much easier for the patients, and will lessen the costs of an investigator initiated study while being unlikely to negatively affect either patient safety or the information that can be obtained.

The rationale for this study design, which is based on exploratory analysis of previous abatacept and other lupus studies, is to provide a more discriminatory protocol and a more robust endpoint than was available in prior trials for lupus. A further rationale is to provide proof of concept for the general feasibility of smaller pre-Phase III trials in SLE with greater potential effect size than has been possible in the past and ability to make confident go/no go decisions for Phase III development after less investment of time, patient risk, and expense than is usual in Classic Phase II designs.

Indeed this project is specifically powered (based on data about placebo group response rates from our BOLD study, a prior, similar study) to support a rational decision about further development of abatacept for SLE.

2. STUDY OBJECTIVES

2.1 Primary Objective: To compare response rates between Abatacept-Treated and Placebo-Treated Patients with active lupus arthritis in a trial designed with background immune suppressant

withdrawal, limited steroid rescue, and a robust, discriminatory endpoint. Statistical powering is based on this primary objective.

2.2_Secondary Objectives: Secondary clinical endpoints will include: SRI 4/5, changes in joint counts, SLEDAI, BILAG, CLASI, PGA, and DIAL measures. We will also Integrate biologic discovery into the clinical trial to support both pre-specified and exploratory biomarker discovery. Data will be generated that might be used to help select more appropriate patient subsets for future trials and to guide optimal dosing strategies. Optimizing patient selection and dosing are important goals for further increasing demonstrable effect size in trials by increasing the response rates in the treatment group.

Optimizing patient selection and dosing are important goals for further increasing effect size in trials. In fact, the two Aims of this project are co-dependent, since each increases the likelihood of interpretable data and could have high impact on increased effect size for an effective product. Also, Aim 2 would be less feasible without the strategy of Aim 1 to decrease the cacophony of background medications, which have clouded interpretation of many treatments for SLE in the past.

Ethical Considerations:

Integration of biologic discovery into clinical trials will generate data that might be used to help select more appropriate patient subsets for future trials and future treatment in clinic and to guide optimal dosing strategies. This is an ethical consideration since it could decrease the numbers of patients inappropriately exposed to a study medication in trials and in practice, and by allowing a better delineation of efficacy in the right population(s) this could also decrease the likelihood of widespread exposure in Phase III trials prior to acquiring sufficient data supporting potential efficacy.

The ethical basis of the current trial design has been debated widely in the lupus community. There is a realistic concern that withdrawal of background therapy will increase the risk of lupus flares and this trial design would be inappropriate for very ill patients such as those with active nephritis. However by decreasing the continued use of background immune suppressants which were obviously not working at the time of entry, by allowing steroid rescue and even restarting of meds as needed during the trial (defining such patients as non-responders) this design could be argued to be far more ethical than trials which legislate continuance of inadequate and potentially toxic background immune suppressant treatments for an entire year, with probable increase in risk for infections. In such protocols, patients who do not improve have only the choice of minimal rescue steroids or to drop out of the study, leading to unnecessary suffering which will not be required in this trial design. Finally, the concern about increasing flare risk should be somewhat alleviated by the results of the MMF, BOLD and Rontalizumab studies (all three of which have been completed using this trial design, and the latter presented at ACR 2012 (39)

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (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).

3.2 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, the informed 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, as well as descriptions of ancillary pharmacokinetic and pharmaco-dynamics studies.

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.

3.3 Informed Consent

Investigators must ensure that subjects or, in those situations where consent cannot be given by subjects, their 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. Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.

6) Revise the informed consent whenever new information is available relevant to the subject's consent. The investigator, or a designee should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

Minors (subjects under 18) or subjects unable to give informed consent will not be included in this study. The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

Planned Study Design: This will be a randomized, double blind, placebo-controlled trial of patients with active SLE who must have active arthritis (at least BILAG B and at least 3 tender and 3 swollen joints) at the screening visit. Randomization to placebo vs abatacept will be performed on a 1:1 scheme by an unblinded pharmacy technician who will have no contact with study subjects. Patients will give weekly subcutaneous injections of study drug at home except for the first dose which they will give in clinic under the supervision of a nurse/coordinator.

Subjects will be evaluated monthly by an investigator/subinvestigator who are required to have passed LFA testing for Hybrid SLEDAI, BILAG 2004 and CLASI. Additional assays will be PROs (Lupus PRO and SF36) and the DIAL endpoint (endpoints are defined below and case report forms for each endpoint can be found in Appendices). The primary endpoint will be measured at 6 months. This will be a comparison of response rates by the BICLA (BILAG-based Combined Lupus Assessment) which is a scoring system incorporating several measures. Improvement must be documented using the BILAG (British Isles Lupus Assessment Group) index, with no worsening in any organ by BILAG or SLEDAI (SLE Disease Activity Index) and less than 10% worsening in PGA (Physicians Global Assessment) as well as no initiation of off protocol immune suppressants or steroids.

Secondary endpoints will include changes in each of the above mentioned single outcome measures, CLASI, and assessment of patient reported outcomes (secondary endpoints are further described below). Biomarker evaluations with a specific focus on T Cell subset pathways and B Cell pathways will also be explored in a responder analysis.

Screening procedures: At the screening visit, patients who are known to have 4 ACR classification criteria (1997 revised) for SLE who present with active arthritis (a minimum of 3 swollen and 3 tender joints) will be invited to undertake screening procedures unless an exclusionary criteria is already known. Screening procedures will begin with the informed consent process during which patients will review the complete informed consent information as approved by the IRB, which will include a full description of the study and the procedures involved, patients' rights and responsibilities, and alternative treatments that are available if the patient does not decide to participate in the study.

Subjects will have a chance to have their questions answered prior to making a decision. Once the informed consent procedures are completed, the following will be completed: medical history, physical examination, review of inclusion and exclusion criteria (some of which will require awaiting blood test results), EKG, PRO measures filled out by the participant (Lupus PRO and SF-36), and clinician measures (SLEDAI, BILAG 2004, CLASI, DIAL, PGA).

To the extent that a history and physical examination was already performed by one of the investigators that day in the course of routine medical care they will not need to be repeated. Screening blood tests will be drawn (maximum 160 cc) including baseline PK and PD samples, and arrangements will be made to contact the patient for the first dosing visit or (if is determined the subject is ineligible) a visit to discuss alternative care. Patients who donate blood at screening for PK and PD and who are later deemed ineligible for the trial will be told, as part of the informed consent process, that these samples may be used for various analyses. Patients retain the right to withdraw

permission for the use of their blood samples at any time. Screening procedures can be performed on the same day the informed consent is signed or any other time up to and including the baseline visit (the screening period) as long as full eligibility is established at the time of randomization.

The study population will include patients between the ages of 18 and 70 who meet a minimum of 4 1997 revised ACR criteria for SLE and who present with a minimum of 3 tender and 3 swollen joints attributable to lupus arthritis. Patients may have other active manifest
ations of SLE, and, in the opinion of the investigator, they must be sick enough for intention to treat with a biologic and stable enough for this trial design, which includes withdrawal of any background immune suppressants, to be appropriate.

This study will enroll patients until 60 have completed the protocol through at least the six month point. Randomization will be 1:1 to abatacept or placebo. Approximately 30 patients are expected to complete each arm. At each visit history, physical, and blood tests appropriate to complete the outcome measures will be performed, and adverse event reporting and medication updates will be performed.

Subjects may continue to take nonsteroidal anti-inflammatory medications (including *prn* NSAIDS) and up to 20 mg prednisone (or oral steroid equivalent) daily during the study although steroids will be tapered as tolerated. If the patient is taking an immune suppressant (e.g. antimalarials, mycophenolate mofetil, azathioprine, leflunomide, methotrexate, a calcineurin inhibitor or belimumab) at screening, this must be stopped prior to or on the day of the baseline visit. Patients can elect to receive one or more depomedrol injection(s) up to a total of 320 mg total at the time of the screening visit and/or up to and including the Month 2 visit. Daily oral steroids will be tapered as tolerated if and when the patient begins to improve.

Subjects will be encouraged to avoid off protocol medications if possible, but if off protocol medications are given, the patient may, at the discretion of the investigator continue in the protocol as a designated “non-responder”, and continue to be followed at monthly visits until the subjects reaches Month 6. Furthermore, patients may elect to receive open label abatacept as early as Month 3 (three Months after the first Dosing Visit) if their disease activity is not improved at that visit compared to baseline. Such subjects will also be designated as non-responders for the primary endpoint at Month 6. For those patients taking daily oral steroids at screening, they will be encouraged to taper these as tolerated if and when they begin to improve. Patients who withdraw from the protocol for any reason will be encouraged to come for safety follow up visits 2 and 4 months after the last study visit.

The primary endpoint will be determined at six months, but all patients can then choose to receive open label abatacept for an additional six months. Maximal duration of treatment will be 12 months. There will be two follow up visits two and four months after the end of study. However, patients who withdraw after six months will be considered completers of the primary study in the amassing of 60 completers. The criteria for evaluation will be improvement (without worsening) in signs, symptoms and diagnostic results as defined by the BICLA (primary endpoint). Additionally joint counts, the SRI 4/5, hybrid SLEDAI, BILAG 2004, CLASI, DIAL, Lupus PRO and SF-36 will be evaluated.

After receiving the first injection in clinic, patients will administer the study medication at home. Subjects will return to the clinic monthly for six months, and those who continue will be evaluated every 4weeks for the second six months. There will be two follow up visits at two month intervals after the end of study for each patient. Visits at which maximal blood samples are taken due to PD scheduling are Screening, and Months 3, 6, 9 and 12 (up to 160 cc). At all other visits no more than 80 cc maximally can be drawn.

Please refer to the Time and Events Schedule for a grid of procedures.

4.2 Study Population: For entry into the study, the following criteria MUST be met.

4.2.1 Inclusion Criteria

1) Signed Written Informed Consent 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. Their questions will be answered. 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.

2) Target Population:

Patients with at least 4 1997 revised ACR classification criteria for SLE

Active polyarticular arthritis with a minimum of 3 tender and 3 swollen joints observed at the screening visit and a history consistent with BILAG 2004 “B” arthritis

3) Age and Reproductive Status

Age: Men and women 18 to 70 years of age.

Reproductive Status: *Definition of Women of Child-Bearing Potential (WOCBP).* WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who are not post-menopausal (see definition below)

Post-menopause is defined as:

i. Women who have had amenorrhea for $\geq$ 12 consecutive months (without another cause)
ii. Women who have irregular menstrual periods and a documented serum FSH level > 35 mIU/mL.
iii. Women who are taking hormone replacement therapy (HRT).

The following women are WOCBP:

iv. Women using the following methods to prevent pregnancy: Oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as intrauterine devices or barrier methods (diaphragm, condoms, spermicides).
v. Women who are practicing abstinence.
vi. Women who have a partner who is sterile (eg, due to vasectomy).

WOCBP and sexually active men with WOCBP partners must use contraception throughout the study and for up to 10 weeks after the last dose of study drug. This will be discussed with each subject individually and the plan documented. WOCBP must have a negative urine pregnancy test result (minimum sensitivity 25 IU/L) within 0 to 48 hours before the first dose of study drug and at all subsequent visits. Women must not be breast-feeding.

4.2.2 Exclusion Criteria

Target Disease Exceptions Patients with acute nephritis requiring induction therapy, CNS lupus (except chorea, cranial neuropathy, and resolving optic neuritis) or any lupus condition requiring cyclophosphamide, biologics, or IV bolus steroids of >/= 500 mg.

1) Medical History and Concurrent Diseases

a. Subjects who are incapable of understanding or completing study-related assessments.

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

c. 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.

d. Subjects who currently abuse drugs or alcohol.

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

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

g. 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).

h. Subjects at risk for tuberculosis (TB). Subjects with active TB within 3 years, even if treated; history of active TB > 3 years ago, unless documented prior anti-TB treatment appropriate in duration and type; current known or suspected active TB; and latent TB not successfully treated (≥ 4 weeks at baseline).

2) Physical and Laboratory Test Findings

a) Subjects must not be known to be positive for hepatitis B surface antigen.

b) Subjects who are known to be positive for hepatitis C antibody may participate if the presence of hepatitis C virus can be excluded by polymerase chain reaction or recombinant immunoblot assay at screening.

c) Subjects with any of the following laboratory values

i) Acute hemolytic anemia with hemoglobin < 7.0 g/dL or known change in Hg by 2.0 g/dL within the last four months unless due to SLE and stable for the past month

ii) WBC < 2500/mm^3 (< 2.5 x 10^9/L) unless due to chronic lupus activity and stable for the past month

iii) Platelets < 40,000/mm^3 (< 3 x 109/L) (If less than 100,000 must have been stable (within a range of 10,000/mm^3) either by historical testing of known chronic thrombocytopenic patients within two months of screening or in two tests during the screening period at least one week apart.

iv) Serum creatinine > 2 times the ULN

v) Serum ALT or AST > 2.5 times the ULN

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

4) Allergies and Adverse Drug Reactions: Known allergy or adverse sensitivity to any components of the study agent or carrier.

5) Sex and Reproductive Status: *See Section on WOCBP (Section 4.2.1, item # 3.)*

6) Prohibited Treatments and/or Therapies

a) 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.

b) Subjects who have received cyclophosphamide within 3 months of the Day 1 dose or bolus parenteral steroids >/= 500 mg within 1 month of screening.

c) Ongoing treatment (after the baseline visit) with immune suppressants (such as antimalarials, methotrexate, azathioprine, mycophenolate mofetil, leflunomide, calcineurin inhibitors or belimumab) after the baseline visit. These may be stopped or tapered as soon as informed consent procedures have been completed at the screening visit.

d) Prednisone > 20 mg po qd at the time of the screening visit (steroids will additionally be tapered during the study if possible at the discretion of the investigator). The exception to this are the protocol-allowed Depomedrol shots which will be used for rescue if needed. A total of 320 mg of intramuscular depomedrol can be given in increments of 40-160 mg at any time from the Screening Visit (after informed consent is signed and blood drawn) until the end of the Month 2 Visit (after blood drawn) If subjects remain on prednisone, no dose increases will be allowed during the study.

Other Exclusion Criteria

- Prisoners or subjects who are involuntarily incarcerated.
- 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.

4.2.3 Discontinuation of Subjects from Treatment: Subjects MUST discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, 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: WOCBP will be instructed to contact the investigator or study staff if they suspect they might be pregnant (eg, missed/late menstrual period) at any time during study. Urine pregnancy tests will be performed at each monthly visit as well. The investigator will immediately notify BMS if a study subject becomes pregnant.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness.

All subjects who discontinue should comply with protocol-specified follow-up procedures outlined in Section 6. This will entail monthly visits if subjects discontinue treatment prior to month 6, and then a visit 2 months after withdrawal and an additional visit four months after withdrawal at which safety and efficacy evaluations will be performed the same as the Month 6 visit. The only exception to this is when a subject withdraws consent or loses the ability to consent freely

(ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject withdraws before completing the study, the reason for withdrawal must be

documented appropriately. The second six months of open label therapy are optional. Patients will be determined to complete the protocol if they complete Month 6 and two follow up visits. Patients will be considered evaluable for the primary endpoint if they complete Month 6. Patients lost to follow up before Month 6 will be considered non-responders.

5. Treatments

5.1 Study Treatment: Abatacept:

Definition of Investigational Product: 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.

Definition of Non-Investigational Product: 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. In this protocol, the non-investigational products are optional depomedrol 40-160 mg intramuscular shots given prn (only if needed) at screening, baseline, or at Months 1 and/or 2. No more than 320 mg total may be given before/at Visit 2.

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. It appears clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection.

5.1.2 Packaging and Labeling

Abatacept SC is known to be supplied in a box of 4 syringes with an open-label. We will require abatacept SC and placebo suitable for the unblinded pharmacist to prepare and dispense in syringes appropriate to maintain the blind.

5.1.3 Handling and Dispensing

The investigational product should be stored in a secure area according to local regulations. At the OMRF we have a locked pharmacy, an experienced clinical trials pharmacy technician who is on site full time, and appropriate storage conditions for a range of investigational products. An inventory will be kept by the unblended pharmacy technician to ensure that the blinded study medication is dispensed only to authorized study personnel (the coordinator) to ensure that it is given only to the appropriate study subjects.

The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity), as described below. This task will be delegated to our well trained pharmacy technician who will be monitored by an outside

pharmacist from the University of Oklahoma to ensure ongoing completeness of inventory, temperature logs, assignment logs, chain of custody documentation, and regulatory records. Abatacept SC formulations (prefilled syringes) and corresponding placebo will be stored under refrigeration (approximately 2 to 8°C) and protected from long-term (more than 24 hours) exposure to light. Temperature logs will ensure stability of temperature and prevention of freezing. Abatacept injection, 125 mg/syringe (125 mg/mL) and placebo for SC administration are ready to use solutions provided in pre-filled siliconized syringes with a 29 gauge needle. Care will 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. If concerns regarding the quality or appearance of the investigational product arise, it will not be dispensed and BMS will be contacted immediately.

5.2 Drug Ordering and Accountability

5.2.1 Initial Orders

The site will request initial shipment with a Drug Request Form. The unblinded pharmacy technician will provide at least weekly reports of inventory use or more frequently if needed to maintain inventory.

5.2.2 Re-Supply

All resupply requests will be initiated by the site by completion of the Drug Request Form.

5.3 Method of Assigning Subjects to a Treatment

There will be no stratification in this protocol. Patients will be randomized 1:1 to treatment or placebo from Month 1-4. At month 3 patients who are flaring or have not improved despite availability of steroid rescue protocols will be allowed to choose open label Abatacept from Month 4 onwards, however they will be considered non responders at Month 6. From Month 6 onwards, all patients will receive the option to continue in the study and open label Abatacept until Month 12. Patients will continue to be followed Monthly until Month 12 with follow up visits at Months 14 and 16.

5.4 Selection and Timing of Dose for Each Subject

Patients will be randomized in a 1:1 scheme to receive abatacept at recommended dosing or placebo. The recommended dosage is 125 mg/mL single-dose prefilled glass syringe for subcutaneous injection. Patients will give themselves the first injection in clinic under the supervision of the study nurse and will self-inject at home thereafter on a weekly basis. If desired a family member can give the injection but must come to the clinic to be supervised by the nurse at the first dose.

5.4.1 Dose Modifications

Immune suppressants will be stopped on or before baseline. Patients will be encouraged to taper any daily oral steroids as tolerated, if and when they begin to improve. Dose increases of oral steroids will not be allowed. No specific changes in dosing of abatacept are part of the protocol, however study medication may be held for one visit once (maximum) during the first 6 months in the protocol due to medical decision or extenuating circumstances, however open label study medication can be withheld at any time at the discretion of the investigator.

5.5 Blinding/Unblinding

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in a subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken. Before breaking the blind of an individual subject's treatment, the investigator should have determined that the information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is not investigational product-related, the problem may be properly managed by assuming that the

subject is receiving active product without the need for unblinding. The BMS Bioanalytical Science representatives and contract resource organizations performing the testing will be unblinded to the randomized treatment assignments in order to minimize unnecessary analysis of PK and immunogenicity samples from the placebo group of subjects.

5.6 Concomitant Treatments

5.6.1 Prohibited and/or Restricted Treatments

See Exclusion Criteria for limitations to treatments that may have been taken prior to entry into the protocol. During the protocol, immune suppressants will be withdrawn at or before the baseline visit (with optional steroid rescue therapy as described in the main body of the protocol) and will not be restarted unless the patient flares at or after Month 3 or earlier to a degree that the protocol-allowed steroid injection is not considered appropriate. Initiation of immune suppressant medication at that point would not be considered a protocol violation, but may dictate non-responder status during the rest of the trial. However, should a patient develop a degree of flare which, in the opinion of the investigator is inappropriate for continuing the protocol, this will be counted as non-response and the patient must be withdrawn from the protocol and study treatment stopped.

5.6.2 Other Restrictions and Precautions

SLE is a complicated disease and it is sometimes difficult to determine if acute illness is caused by infection, lupus disease, or medication side effects. For this reason, supervision of the study clinic by a physician experienced in the care of lupus patients is imperative. Five such physicians will be available to follow the patients in this study, Drs. Merrill, Chakravarty, James, , Arriens and Thanou, as well as Joe Rawdon, DNP, APRN. Adverse events will be reported to the IRB and reviewed by the DSMB as described elsewhere in this protocol.

5.7 Treatment Compliance

After the first injection, patients will self-administer injections at home and will keep a diary to record date and time of each injection. They will be asked to return the used syringes to the clinic at each

visit. They will be questioned at each visit about problems with administration and/or degree of compliance that has been possible. These records will be kept as part of the study records so that overall compliance in the treatment vs placebo group can be estimated.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Time and Events Schedule

Qualified subjects who meet screening criteria will return to the clinic within one month for randomization (Treatment Visit 1). Because study treatments are weekly, window for dosing shall be ±3 days.

All visits include sufficient history, physical examination, and diagnostic testing to meet the requirements for scoring the SLEDAI and BILAG. Because of this they are all adequate for performing a complete safety and well-being assessment. Therefore no specific new procedures will be specified for either end of study or safety follow up visits. Interim visits for adverse events will be performed as clinically warranted. The reason for any early withdrawal/study drug discontinuation will be documented. Patients are referred to our research cohort from throughout Oklahoma and surrounding states.

TIME AND EVENTS SCHEDULE: PROTOCOL *IM101-345*

Procedure	Screening Visit	Treatment Visit 1 1st Dosing	Treatment Visit 2-7 Month 1-6	Follow up Visits post-Rx	Visits 8-13 Month 7-12
Eligibility Assessments					
Informed Consent	X*				
Inclusion/Exclusion Criteria	X	X			
Medical History	X	X	X	X	X
Safety Assessments					
Medication List	X	X	X	X	X
History, Vital Signs, Physical Examination	X	X	X	X	X
Adverse Events Assessment		X	X	X	X
Clinical Laboratory Tests	X	X	X	X	X
PK sampling	X**	X**	X**		X**
Immunogenicity	X***	X***	X***		X***
PD sampling	X****	X****	X****		X****
Pregnancy Test	X	X	X	X	X
Efficacy Assessments					
SLEDAI/SSFI/PGA	X	X	X	X	X
BILAG 2004	X	X	X	X	X
CLASI	X	X	X	X	X
DIAL	X	X	X	X	X
Patient Questionnaires (SF-36, LupusPRO)	X	X	X	X	X
Clinical Drug Supplies					
Randomize		X			
Dispense Study Treatment baseline and q month		X	X		X

*Repeated for protocol amendments or new safety data
** Screening, Months 1,2, 3,4, 6, 7,8, and 12 and/or EOS (if patients withdraw early)
***Screening, Months 1,2, 6, 7, 8, 12 and/or EOS
**** At Screening Visit, first dosing, visits 3, 6, 9 and 12 and/or EOS (</= 160 cc blood, up to 30cc urine, up to 10cc saliva)

Non PD visits are restricted to </= 80 cc blood, up to 30 cc urine, up to 10 cc saliva)
Note that PK/PI/PD labs at screening should be drawn at the screening visit if possible, otherwise may be drawn anytime up to and including the First Dosing Visit, but must be draw prior to receiving any steroid injection(s) in the protocol.

6.2 Study Materials Bristol-Myers Squibb (BMS) will provide abatacept subcutaneous formulation at no cost for this study.

6.3 Safety Assessments All subjects who receive a dose of abatacept will be evaluated for safety. Safety outcomes include adverse events, clinically significant changes in vital signs, laboratory test abnormalities, and tolerability of the drug. The investigator will determine the severity of each adverse event as mild, moderate, severe, or very severe. Reference will be made to the National Cancer Institute Common Terminology Criteria for Adverse Events. Laboratory findings that the investigator rates as clinically significant will be recorded as adverse events. The investigator will determine the relationship of the adverse event to the study drug. Any occurrence of a SAE from time of consent forward, up to and including follow-up visits will be reported. See Section 7.3.1 for the SAE reporting procedures.

6.3.1 Physical Examinations

Physical examinations will be performed at every visit, suitable to assess patient safety and to perform the efficacy evaluations which are multisystem indices (see below)

6.3.2 Breast and Hematologic Cancer Screening

Patients with SLE have a slightly decreased risk for breast cancer compared to healthy controls and a slightly increased risk for lymphoma. Appropriate general cancer screening procedures will be discussed with each patient entering the study. Female subjects who are greater than 50 years of age will have a manual breast examination performed at the screening visit and all subjects will be examined for lymphadenopathy. Subjects having a 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. The screening period may be extended under such circumstances at the discretion of the investigator.

6.4 Efficacy Assessments

The efficacy assessments that have been documented in the Time and Events Schedule are described below. Case report forms are included in the Appendices.

6.4.1 Primary Efficacy Assessment: BICLA Response

BICLA stands for BILAG-based Combined Lupus Assessment. The BILAG refers to the British Islese Lupus Assessment Group Index. We will be using the version known as BILAG 2004 (37).This consists of 97 descriptors for signs and symptoms of lupus divided into 9 organ systems (see appendices for case report forms). Each organ system receives a rating of A (severe disease activity), B (moderate disease activity) C (mild disease activity) D (no disease activity in an organ previously affected) or E (organ inactive and never previously active). These ratings are derived from assessments made on each descriptor within each organ and the determination of whether activity is not present, improving, same, worsening or new/recurrent when comparing the degree of disease activity during the past month to the previous month.

The BICLA (8) includes scores from the BILAG, the SLEDAI and the PGA. The SLEDAI which will be used is the hybrid SLEDAI which incorporates components of two SLEDAI versions, the SLEDAI 2K and the SELENA SLEDAI which was devised for the Safety of Estrogens in Lupus Erythematosus

National Assessment (SELENA) trial. The PGA refers to Physician's Global Assessment which is performed on a weighted 100 mm scale devised specifically for lupus designed as part of the SSFI (SELENA SLEDAI flare index). Based on the BILAG scores at entry (A-E in each organ) the BICLA response is defined by at least one letter grade improvement in each organ without an increase in the SLEDAI score or an increase of 10% in the PGA. There must also be no off-protocol treatment in order to meet this response criteria. The primary endpoint is BICLA response rates at month 6 in the abatacept treatment group vs the placebo group. BICLA response at each month will also be assessed as a secondary endpoint.

6.4.2 Secondary Efficacy Assessments

All of the individual components of the BICLA will be assessed in different ways as secondary endpoints. These will include:

1. BICLA response at each month
2. SRI 4 and 5: Response is defined at an endpoint date (EOS and each month vs baseline) The SRI endpoint (7) is defined as a 4 (or 5) point drop in SLEDAI compared to baseline without and increase in BILAG or 10% worsening by PGA.
3. Tender and swollen joint counts (to be analyzed separately and as composite score)
4. Change in SLEDAI scores (EOS and each month vs baseline)
5. Change in PGA scores (EOS and each month vs baseline)
6. Change in BILAG numerical scores (Addition of organ scores where each A=12, B=8, C=1 and D or E=0).
7. Musculoskeletal BILAG response (% with one grade drop and % who reach C or lower)
8. Responder Analysis using the primary endpoint and assessing baseline evidence of (and changes in) a panel of markers selected to identify high levels of IL6/TH17 signalling, and/or B Cell signaling (Erk/Blys). All methods proposed have been previously standardized and are currently available in our laboratory as reviewed above. These will be re-standardized for the current study.

Primary Biologic Endpoint (Which is a secondary endpoint for the trial):

To test the applicability of baseline imbalance in a.) relative differences in the ratio of *IL6/IL23/IL17* to *Foxp3/TGFβ* (suggesting T Cell signaling imbalance) OR an elevated B cell activation profile to predict clinical response to abatacept either through pre-dose elevation or post-dose reversal of this profile. Based on considerations reviewed in the preliminary data section, the primary biomarker for T

Cell signaling impbalances will be gene expression levels of *IL6/IL23/IL17* and *Foxp3/TGFβ.* The primary biomarker for T Cell signaling-induced B Cell signaling imbalance will be ERK

phosphorylation after cognate interactions between T Cells and the B cell receptor as has been described above.

This will require 8 ml of blood for several cellular response/ stimulation experiments. Follow up samples will be drawn at Month 3 prior to "non-responders" starting new immune suppressant medications, which could confound later biologic assays. This will be repeated at Month 9 to include changes in placebo-treated patients after 3 months on abatacept **respecified Secondary Biologic Analyses**

1. Circulating cytokines of interest (Baseline Month 3 and Month 9) The cytokines to be measured are more easily detected in plasma than in serum. Our Serum Analyte and Biomarker Core has expanded extensive effort in optimizing a 51-plex cytokine assay which is based upon the

BioRad200 platform. Preliminary data from this approach is presented above. This will allow direct testing of select hypotheses, such as abtacept effects on IL-6, IFN alpha, BLyS and TNFRI/II pathways, but also in providing a more exploratory analysis of additional cytokines and chemokines important in T and B cell activation. This method uses a two laser immunobead multiplex technology allowing the levels of 51 cytokines to be monitored with a only 5-8 ml of blood. Serum levels of BLyS and APRIL will also be tested but are unable to be multiplexed based upon features of those analytes.

2. Abatacept Effects Relevant to Other Known B and T Cell Abnormalities of SLE (Baseline Month 3 and Month 9) We hypothesize that efficacy of abatacept will be related to the correction of one or more additional known B or T Cell abnormalities in SLE. We propose to assess response of immune cell subsets to cytokine stimulation or receptor signaling, as well as through basic immunophenotyping, to assess the influence of abatacept on the cells of responders (and potentially non-responders).

3. Effects of Abatacept on B Cell/T Cell gene expression (Baseline Month 3 and Month 9) Prespecified Analysis to determine whether select aspects of gene expression profiling by either microarray analyses or RNAseq (and changes after dosing) can be fit to abatacept pharmacodynamics and efficacy. BLyS, interferon alpha pathway expression, ICOS signaling panel will be primary candidates for further analysis.

4. Ig production by B cells (All Visits). These will be monitored throughout the study

Other Assessments: Optional Exploratory Analyses

1. Cytokine induction assay (Baseline, Month 3 and Month 9): Induced production of cytokines will be measured in the supernatants of cultured (stimulated T or B cells) using multiplex technology.

2. Functional studies (Baseline, Month 3 and Month 9) will be performed as sample size allows including:a. Calcium concentration in cells stimulated with anti-CD3, b. Protein tyrosine phosphorylation, c. Intracellular IL-2, IL17, STAT3, d. Levels of kinases (Syk and CaMKIV) e. Levels of pERM and ROCK

Expected results: Abatacept should affect function of both T and B cells and several abnormalities –outlined above and routinely studied in our labs- will be corrected. The

correction sequence will illuminate mechanism of action of abatacept (beyond the known blockade of costimulation) and focus future efforts at developing pharmacodynamic markers.

Exploratory Clinical Correlative Studies: We propose to test the sensitivity and specificity of several lupus quality of life outcome measures and a physician-friendly treat to target system for clinical improvement and biologic changes. The primary clinical and biologic endpoints will be used as the standard comparators. The patient reported outcomes included will be the SF-36, (widely used in SLE trials) and the Lupus PRO (27-29 from original application), none of which have been directly compared against efficacy endpoints.

Exploratory Biologic Studies: Serum, plasma, urine, RNA, DNA and buffy coats will be saved and stored. Correlative studies will be performed using samples stored for use by BMS

scientists. Appendix 3, Appendix 4 and Appendix 5 describe ancillary studies to be performed by Dr. Thierry Dervieux of Exagen Inc, Dr. Joseph Craft of Yale University and Drs Vasileo Kyttaris and George Tsokos of Harvard Medical School. Appendix 6 will update any additional studies to be performed at BMS, and will be submitted to the IRB as an addendum.

ANCILLARY STUDY BY OMRF TEAM;

This Summarizes an overlapping project Submitted as Hyperaccelerated R01 (April 15, 2013): Joel Guthridge PI, Judith James, Joan Merrill, Mikhail Dozmorov. The entire application is also included along with this protocol and the Investigator's Brochure as part of the IRB approval package.

2. SPECIFIC AIMS: Systemic lupus erythematosus (SLE) is a diverse, systemic autoimmune disease which causes significant morbidity and early mortality, especially in minority populations and in women of child-bearing age. By the time patients receive the devastating SLE diagnosis, the majority have ongoing aggressive inflammatory processes and oftentimes damage that cannot be reversed (1). Clinical trials for lupus for many potential therapies have been hampered by problematic trial designs including 1) endpoints clouded by confusion over events which do or do not have clinical consequences and 2) high placebo response rates which are driven by background use of corticosteroids and "standard of care" medication use in the placebo arms (2, 3).

Abatacept (CTLA-Ig) has been evaluated for SLE by Bristol-Myers Squibb (BMS) in moderate sized Phase II clinical trials for nephritis and non-nephritis SLE patients (4, 5). These previously completed trials failed to meet primary or secondary endpoints, but exploratory analyses suggested that the problematic clinical endpoints (referred to above) and aggressive background treatments might have impaired the interpretation of these studies. The current clinical trial "Clarification of **A**batacept Effects in SLE with Integrated **B**iologic and **C**linical Approaches (ABC) funded by Bristol-Myers Squibb (BMS) utilizes an immune suppressant withdrawal strategy coupled to endpoints which have been shown to provide maximal discriminatory capacity by minimizing the "noise" of minor improvements and clinically insignificant disease flares. This trial uses the trial design introduced in the recently completed Biomarkers of Lupus Disease (BOLD) study (6).

Abatacept was originally developed to finely target T cell costimulation by binding CD80/CD86 on antigen presenting cells (APCs), thus blocking the signals delivered to T cells through CD28 (7-9). However, abatacept likely has effects on both APCs and T cells. The

exact biologic mechanism(s) that result in improved clinical outcomes is still unclear. By partnering ancillary NIAMS funding to assess the immune activating and regulatory pathways in subjects from

the ABC Study, we create an ideal study which needs to be considered for the hyperaccelerated award mechanism. The trial design of the parent study makes these particular samples invaluable for

answering not only important questions about abatacept function, but also critical questions about mechanisms of SLE disease flare in patients off immunomodulatory drugs. Results from these studies will also provide information about additional biologic endpoints that allow for more appropriate SLE therapeutic trial designs.

This application takes advantage of the novel clinical trial design of the parent ABC study to directly address questions about how abatacept affects 1) naïve or memory T cell activation, 2) plasma cell survival, 3) regulatory T cell development and 4) regulatory B cell development and function. The CD28:CD80/CD86 interaction is crucial in regulating these immune processes, however understanding whether any or all of these mechanisms function to limit clinical disease activity and/or

systemic autoimmunity in human SLE (10), especially in patients where background immunosuppressants are not used, has not been investigated. We will address these critical issues through the following specific aims.

Specific Aim 1: Determine if abatacept reduces the number of activated T cells in the peripheral blood in lupus patients. *Hypothesis: Since activation of naïve T cells requires CD80/CD86 engagement with CD28 on the T cell, blockade of this interaction by abatacept should reduce activated T cells in peripheral blood in patients responding to treatment with abatacept.*

Specific Aim 2: Evaluate if abatacept alters plasmablast survival in patients treated with abatacept. *Hypothesis: Interactions between plasmablasts expressing counter receptors for CD28 or CTLA4 are important for signaling survival of plasmablasts. Treatment with abatacept may reduce autoantibody producing plasmablasts in peripheral blood by blocking those signals.*

Specific Aim 3: Characterize regulatory T cell frequencies in lupus patients in abatacept treatment group compared to placebo group. *Hypothesis: T regulatory cell frequencies will be influenced by abatacept treatment of SLE patients and will help define which of the outcomes a) promote Treg development/ expansion or b) block Treg development leading to increased autoimmunity are observed clinically.*

Specific Aim 4: Determine whether abatacept treatment alters the development of IL-10 producing B regulatory cells. *Hypothesis: Abatacept interruption of CD28:CD80/CD86 interactions, which in lupus patients might be reducing Breg development or survival. This treatment may increase Breg frequencies and ability to better regulate autoimmune responses.*

Note: Experimental approaches are summarized in the tables below and are more fully detailed in the full protocol submitted to NIH which is included with this protocol, along with the abatacept investigator brochure in the IRB submission package.

Table 1: *Lyoplate Immunophenotyping PBMCs.*

Table X: Staining Profiles (Lyoplates)					
Fluorochrome	T cell	Treg	B cell/Breg	DC/mono/NK	Th1/2/17
FITC	PD-1	CD39	CD10	CD86	CXCR5
PE	CD197 (CCR7)	CD25	CD24	CD56	CXCR3
PE-Texas Red	Live/dead	Live/dead	Live/dead	Live/dead	Live/dead
PerCP-Cy5.5	CD4	CD4	CD19	CD123	CD4
PE-Cy7	CD45RA	CCR4	CD27	CD11c	CCR6
APC	CD38	CD127	CD38	CD16	CD38
Alexa 700	CD27		IgD	CD80	
APC-H7	CD8	CD45RO	CD20	CD3+19+20	CD8
V450	CD3	CD3	CD3	CD3	CD3

Table 2: *Single-cell proteomics: Intracellular cytokine*

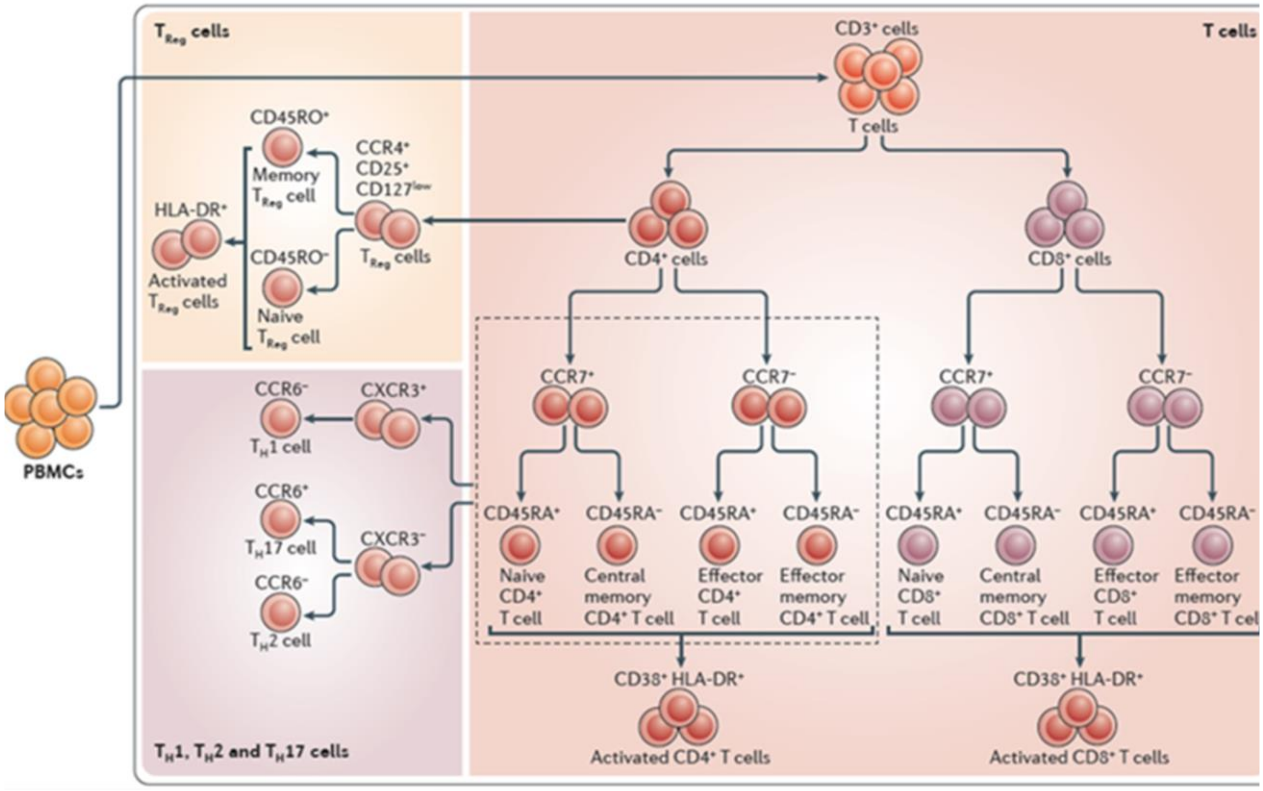
Intracellular Staining Panels		
Fluorochrome	T cell	B cell/Breg
Pacific Orange	barcode	barcode
Alexa 750	barcode	barcode
FITC	IFN-γ	CD10
PE	IL-17	CD24
PE-Texas Red		IL-10
PerCP-Cy5.5	CD4	CD19
PE-Cy7	IL-2	CD27
APC	IL-4	CD38
Alexa 700	TNFα	IgD
APC-H7	CD8	TGFβ

Table 3: *Single-cell proteomics: Phosphoflow*

B & T Cell Activation Phosphoflow Panel	
Fluorochrome	**Biomarker**
Pacific Orange	barcode
Alexa 750	barcode
Pacific Blue	CD3
PerCP-Cy5.5	CD4/CD20
Qdot 605	CD45RA
PE-Cy7	CD33
APC-H7	CD14/CD16 (dump)
FITC	p38 MAPK
PE	pPLCγ2

Table 4:

Functional Categories of 51-plex Bioplex200 Cytokine/Chemokine Panels		
Th1-like	**Chemokine-Adhesion**	**Homeostasis**
IL-12(p70)	IL-8/CXCL8	IL-7
IFN-γ	IP-10/CXCL10	IL-15
IL-2	RANTES/CCL5	
IL-2RA	MIP-1a/CCL3	**Other**
	MIP-1b/CCL4	LIF
Th17-like	MCP-1/CCL2	PAI-1
IL-17A	MCP-3/CCL7	PDGF-BB
IL-21	GROα/CXCL1	Resistin
IL-23	SDF-1/CXCL12	Leptin
IL-6	MIG/CXCL9	SCF
	Eotaxin/CCL11	
Th2-like	ICAM-1	
IL-4	VCAM-1	
IL-5	sE-selectin	
IL-13	VEGF-A	
Regulatory	**NGF/TNFR Superfamily**	
IL-10	BLyS**	
TGF-β	APRIL**	
	sCD40L	
Innate	sFas	
IL-1α	sFasL	
IL-1β	TNF-α	
IL-1RA	TNFR1 (p55)	
IFN-α	TNFRII (p75)	
IFN-β	TRAIL	
G-CSF	NGFβ	



from Maecker, et.al. *Nat. Immunol*. 2012

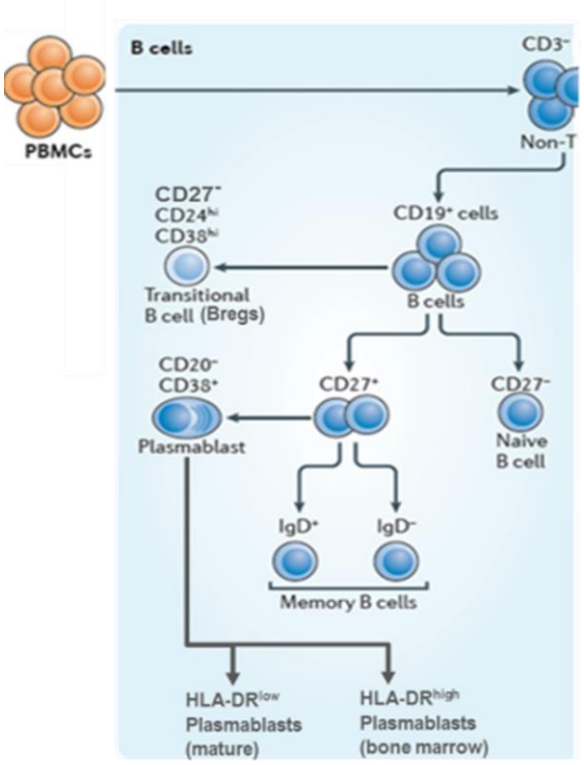


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Figure 9: *B cell subset identification using*

References for OMRF Biologic Study

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Exploratory Clinical Assessments

Exploratory clinical endpoints will include:

Changes in CLASI, (cutaneous lupus endpoint)
LFA REAL (Rapid, Evaluation of Activity in Lupus)
Patient-reported outcomes: (LUPUS PRO and SF-36 domains)

These analyses will be performed according to the training on the LFA POINT website (Lupus Foundation of America Professional Online Instrument Training) which all investigators will be required to use for certification.

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.

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

7.11 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 that may not be immediately life-threatening or result in death or hospitalization but, based on 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 above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. Potential drug induced liver injury (DILI) us also considered an important medical event (see Section 7.6 for the definition of potential DILI).

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.
Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs (See Section 7.5 for reporting pregnancies).

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)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission 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).

7.12 Nonserious Adverse Events:

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

7.13 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.

7.2 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.

7.2.1 Serious Adverse Event Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur within 30 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

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

All SAEs, whether related or unrelated to abatacept, and all pregnancies must be reported to BMS (by the investigator or designee) within 24 hours.
All SAEs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com
SAE Fax Number: <<609-818-3804>>

MEDWATCH SAE forms will 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

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

7.2.2 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. 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. 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 study drug, or those that are present at the end of study treatment as appropriate. All identified NSAEs must be documented appropriately.

Monitoring of Blood Draws: No more than 120 cc will be drawn at major PD visits (baseline, Month 3, Month 6) and no more than 60 cc will be drawn at interim visits (all others).

7.3 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy

7.4 Overdose

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

7.5 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 product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 7.2.1

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant will be reported to BMS. Information on this pregnancy will be collected on a Pregnancy Surveillance Form.

7.6 Potential Drug-Induced Liver Injury (DILI): Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 7.2.1 for reporting details).

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

   AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

   AND

3. No other immediately apparent and/or possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

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 as a nonserious or serious AE, as appropriate, and reported accordingly.

8 Data Monitoring Committee

A data monitoring committee will be formed with four members and a minimum of two rheumatologists who are expert lupus physicians. SAE reports will be sent to the DSMB members along with IRB/BMS submission. Routine AEs will be reported on a quarterly basis. A full set of laboratory reports will also be sent to the DSMB. Flare data will also be reported, whether or not any given flare was attributed to adverse event or study medication. Safety reports will be reviewed quarterly or as deemed appropriate, based on SAE reports. The DSMB can be unblinded at request but will not be routinely unblinded to data, nor will efficacy data be reported during the trial, since the small number of patients does not justify a specific risk/benefit assessment during the course of the trial. The DSMB will be

provided with the safety and flare data from the previous abatacept lupus trials to use as a comparison to what they are reviewing. Unexpected flare or AE reports could then trigger unblinding

of the DSMB. The DSMB may request consultation by an infectious disease or other specialist to help with their assessment of the data.

9. Statistical Considerations

Enrollment is expected to include at least 70 screened and 60 randomized subjects subjects have either reached a six month endpoint and/or been defined as a permanent non-responder for off protocol treatment or by dropping out of the protocol.

The primary endpoint is the proportion of placebo vs treatment subjects who meet the primary endpoint of BICLA response using Chi Square analysis at month 6 as determined by an intent to treat analysis

Subjects who drop out prematurely for any reason or are treated with off protocol medications or cross over to open label for lack of response at Month 3-6 are considered non responders at month 6.

9.1 Sample Size Determination

Sample Size Based on data from the BOLD study confirming the low response rates in a placebo group at 6 months in a study design identical to the structure of this protocol (1/41 patients or 2.4% met the BICLA response at 6 months in that study) and based on the assumption that the response rate to abatacept using this design and these endpoints would be at least equivalent to what was found in the Phase II Epratuzumab or Phase III BLISS studies (roughly 40-50% response). The sample size was optimized at 60 patients in a 1:1 randomization scheme with alpha = 0.5 and desired power 0.8.

9.2 Populations for Analyses

The subject population As further detailed in the inclusion and exclusion criteria will consist of consecutive consenting lupus patients between ages 18 and 70 who have active polyarticular arthritis characterized by 3 or more tender and 3 or more swollen joints at the screening visit meeting the BILAG 2004 criteria for >/= B disease (+/- additional evidence of disease activity in other organs).

The clinical justification is based on the combination of unmet need in treating a significant, potentially disabling illness, while ensuring a healthy enough population to justify the risks of studying a biologic treatment vs placebo.

Power Analysis: Chi Sq or the Fisher's exact test will be used for analysis. The table below has been powered on the assumption that the placebo group will have a result similar to (or even a bit more responsive than) that found in the BOLD study (which was the test prototype for this protocol to determine the safety and feasibility of the statistical assumptions for the placebo study). Data from the BOLD study confirm that there should be a near zero (2.4%) percent response by BICLA at six months in the placebo group in a study with background IS withdrawal. Therefore our assumption of at least 5% response in the placebo group in an identical trial design is reasonable. The second assumption is that the treatment group will have a response rate somewhere between those found in the epratuzumab (by BICLA) and BLISS phase II/III (by SRI) biologic studies e.g. a predicted response rate between 35 and 50%. The most important basis for this assumption, however are the data from patients with lupus arthritis in the Phase II abatacept study, where physicians rated 40% of

the patients treated with abatacept as having “no flare” after baseline. Therefore this expected range by BICLA seems reasonable. (please see power analysis table below which is based on powering the primary endpoint at a range of expected response rates in treatment and placebo groups with a sample size of 60 patients, alpha=0.05).

Power of 60 patient study if alpha=0.05 with response rates:

	Rate 1	Rate 2	Rate 3	Rate 4	Rate 5	Rate 6	Rate 7
abatacept	60%	55%	50%	45%	40%	35%	35%
placebo	20%	15%	10%	10%	5%	5%	3%
power	0.84	0.86	0.89	0.80	0.86	0.77	0.84

9.3 Endpoint Definitions:

9.3.1 Primary endpoint (and how it tests the study hypothesis)

The primary endpoint is to compare the response rates of abatacept treated to placebo treated patients which addresses the main study hypothesis by specifically testing the efficacy of abatacept in lupus patients with active arthritis at baseline who complete a protocol designed with withdrawal of confounding background medications using a robust endpoint that has shown the ability to discriminate between effective treatment and placebo.

9.3.2 Secondary and Exploratory Endpoint Definitions (see specific descriptions of endpoints in 6.41 and 6.42, below some further discussion of the analysis plan

9.4 Analyses To Be Performed

9.4.1 Demographics and Baseline Characteristics

The demographics of the patients who are likely to participate in this study should be reflective of the Oklahoma Lupus Cohort which will be the source for most of our recruitment activity. The age range of participants in this study will be between 18 and 70, and based on our experience with interventional trials requiring significant disease activity, we expect the majority of subjects to be within the ages of 25 and 55. There is no stratification scheme to be imposed based on demographics and baseline characteristics, but variables of age, race, gender, steroid use, autoantibody positivity, complement consumption, and BILAG score at baseline will be described in order to identify any glaring imbalances in group assignments..

9.4.2 Safety Analyses

In a study this size, and based on data from earlier trials of abatacept in RA and SLE it is unlikely that statistically significant differences will be found in overall AEs, SAEs or AEs of special interest. Safety Analyses will be descriptive in nature and complete in their presentation, following the examples of the earlier lupus and RA safety reports.

9.4.3 Efficacy Analysis

Primary Endpoint: The primary analysis upon which this study is powered will be a two by two analysis of response rates to BICLA endpoint in treatment vs placebo group.

Exploratory Analysis of Primary Endpoint: To address potential confounders in a small study a propensity score will be applied to simplify multiple variables into one variable.

Analysis of Secondary Clinical Endpoints: include the BICLA and SRI response performed at each month using a Chi Square approach as well as mean SLEDAI, BILAG, CLASI, PGA, DIAL and PRO by paired T test comparing baseline to endpoint (EOS or each month) in placebo patients and separately in abatacept treated patients.

9.4.4 Other Analyses

Analysis of the Primary Biologic Endpoint (which is a secondary endpoint of the trial): Patients who do or do not exhibit proposed relative differences in the ratio of *IL6/IL23/IL17* to *Foxp3/TGFβ* at baseline (suggesting a classic lupus T Cell signaling imbalance that might be reversed by Abatacept) will be compared for proportion of responders in treatment vs placebo group. Patients identified at baseline with TH17 hi with >/= 50% change towards normal after treatment will be compared separately for response rates. These endpoints will be described in terms of confidence intervals based on the primary clinical endpoint. Similar analysis will be done for patients with high vs low BlyS or high vs low interferon alpha inducible gene expression.

Analysis of Secondary and Exploratory Biologic Endpoints: Mean or median change in cytokine, immunoglobulin and gene expression levels will be explored. Bucketing of baseline profiles might be used to develop propensity scores suitable for a simplified refinement of the primary biologic endpoint by combining variables that might either increase or decrease the likelihood of response. Given the complex array of data we are likely to generate, principal component analysis can be applied to identify directions (principal components) along which the variation of the data is maximal.

It should, however be pointed out that even if statistical significance is not met, a large enough effect size in the primary endpoint of a small pilot study this size might still be encouraging enough to continue development of this drug, particularly if biologic subanalyses provide insight into the responder profile.

10. Study Management

10.1 Compliance with the Protocol: All protocol deviations or violations will be collected and reported to the IRB and DSMB. Compliance with the protocol is a high priority and we will hire a professional study monitor to ensure compliance and accuracy in data collection.

10.1.1 Compliance with the Protocol and Protocol Revisions*: The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.*

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

10.2 Records Retention

10.2.1 Records Retention: The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. This includes a minimum of fifteen years after the end of the study as per usual practice in industry supported trials. If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

10.2.2 Study Drug Records: It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the BMS) is maintained at each study site where study drug and noninvestigational product(s) is/are inventoried and dispensed. In this case there will be one site at the Oklahoma Medical Research Foundation. Records and logs will be kept by our unblended pharmacy administrator within the locked pharmacy space and must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- 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)
- amount destroyed at study site, if applicable
- amount returned to the BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

10.3 Destruction of Investigational Product: If the study drugs are 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. Records of the disposal must be maintained.

11 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)

12 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
BICLA	BILAG-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
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
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CMV	Cytomegalovirus
CRF	Case Report Forms
CRP	C-Reactive Protein
CTLA	Cytotoxic T-Lymphocyte Associated
CXR	Chest X-Ray
DIAL	Directed Integrated Assessment of Lupus
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
SLEDAI	SLE Disease Activity Index
SRI	SLE Responder Index
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: Hybrid SLEDAI with SSFI and PGA

(Circle in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 4 weeks) (The same instrument can also be used going back only ten days)

Item no.	SLEDAI SCORE	Descriptor	Definition
1	**8**	**Seizure**	Recent onset, exclude metabolic, infectious or drug causes
2	**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, disorganised, or catatonic behaviour. Exclude uraemia and drug causes
3	**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
4	**8**	**Visual disturbance**	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, or optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes
5	**8**	**Cranial nerve disorder**	New onset of sensory or motor neuropathy involving cranial nerves
6	**8**	**Lupus headache**	Severe, persistent headache; may be migrainous, but must be non-responsive to narcotic analgesia THIS WOULD RARELY BE ATTRIBUTED TO SLE...ALMOST NEVER SCORED
7	**8**	**CVA**	New onset Cerebrovascular accident(s). Exclude arteriosclerosis
8	**8**	**Vasculitis**	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy or angiogram proof of vasculitis
9	**4**	**Arthritis**	> 2 joints with pain and signs of inflammation (i.e. tenderness with swelling or effusion)
10	**4**	**Myositis**	Proximal muscle aching/weakness, associated with elevated creatinine phosphokinase (CK)/aldolase, or EMG changes or a biopsy showing myositis
11	**4**	**Urinary casts**	Heme-granular or RBC casts
12	**4**	**Hematuria**	> 5 RBC/high power field. Exclude stone, infection or other cause
13	**4**	**Proteinuria**	> 0.5 gram/24 hours
14	**4**	**Pyuria**	> 5 WBC/high power field. Exclude infection
15	**2**	**Rash**	Inflammatory type rash
16	**2**	**Alopecia**	Abnormal, patchy or diffuse loss of hair
17	**2**	**Mucosal ulcers**	Oral or nasal ulcerations
18	**2**	**Pleurisy**	Pleuritic chest pain or pleural rub or effusion, or pleural thickening (does not require an objective component if medically convincing)
19	**2**	**Pericarditis**	Classic pericardial pain and/or rub, effusion or ECG or echocardiogram confirmation (does not require an objective component if medically convincing)
20	**2**	**Low complement**	Decrease in CH50, C3 or C4 below lower limit of normal for testing laboratory
21	**2**	**Increased DNA**	Increased DNA binding above normal range for testing laboratory

		binding	
22	**1**	**Fever**	> 38ºC. Exclude infectious cause
23	**1**	**Thrombocytopenia**	< 100 x 10^9 platelets/L, exclude drug causes
24	**1**	**Leukopenia**	< 3 x 10^9 WBC/L, exclude drug causes

SCORE:

SELENA SLEDAI FLARE INDEX (Can be used with any version of the SLEDAI)

Note as an experimental endpoint the revised SELENA SLEDAI FLARE INDEX will also be tested

Physician's Global Assessment (PGA)
Visual Analog Scale with anchors

0 1 2 3 (this is a three inch or 10 cm scale)
None Mild Moderate Severe

Mild or Moderate Flare □

□ Change in SELENA-SLEDAI instrument score of 3 points or more (but not to more than 12)
□ New/worse: Discoid, photosensitive, profundus, bullous lupus,
Nasopharyngeal ulcers
Pleuritis
Pericarditis
Arthritis
Fever (SLE)
□ Increase in prednisone, but not to >0.5 mg/kg/day
□ Added NSAID or hydroxychloroquine for SLE activity
□ ≥1.0 increase in PGA score, but not to more than 2.5

Severe Flare □

□ Change in SELENA-SLEDAI instrument score to greater than 12
□ New/worse: CNS-SLE
cutaneous vasculitis,
Vasculitis
Nephritis
Myositis
Plt <60,000
Hemolytic anemia: Hb <70 g/L or decrease in Hb >30 g/L
Requiring: double prednisone, or prednisone increase to
>0.5 mg/kg/day, or hospitalization
□ Increase in prednisone to >0.5 mg/kg/day
□ New cyclophosphamide, azathioprine, methotrexate for SLE activity
□ Hospitalization for SLE activity
□ Increase in Physician's Global Assessment score to >2.5

GUIDELINES FOR USE OF HYBRID SLEDAI MODIFIED FOR ASSESSMENT OVER 28 DAYS: TO ASSESS DISEASE ACTIVITY

General guidelines for filling out the HYBRID SLEDAI:

The HYBRID SLEDAI includes the definitions of proteinuria used in the SLEDAI 2K and is otherwise identical to the SELENA SLEDAI.

- The main principle to keep in mind is that this instrument is intended to evaluate current lupus activity and not chronic damage, severity is accounted for in part by the "weightedness" of the scale.
- Points are given exactly as defined.
- A descriptor is either scored the exact points allotted or not scored, i.e. given a zero. Descriptors are scored only if they are present at the time of the physician encounter or in the preceding 28 days. Windows acceptable in a clinical trial are acceptable in scoring the SLEDAI. However, it is never acceptable to fill in gaps which cover activity over 2-3 months or more. The reason for this is that disease activity at the visit might have changed several times in such intervals and the recording of distant activity becomes meaningless.

  Please note that in the original SLEDAI the disease activity being scored was meant to cover only a ten day period, the modification to 28 days is a more useful assessment for use in clinical trials, in order to capture disease activity between monthly visits.
- The descriptor must be documented by the notes written in the physician encounter form and generally applies to the clinical data and not to the laboratory data. The laboratory data is strictly defined as per cutoffs and documentation is provided by the reports from the commercial laboratory.
- Descriptors do not have to be new but can be. They can be ongoing, recurrent, or initial events. Each would be scored the same way. An example would be a malar rash or mucosal ulcer. In these situations a malar rash observed at the initial visit but which remains unchanged for the next six months, irrespective of any treatment, is scored 2 points each time the SLEDAI is completed. Since the nature of lupus is that manifestations are not usually fleeting it would be rare for descriptors to be present 10 days before and not at the time of the encounter. This is discussed in more detail for each descriptor but is especially relevant for the neurologic, pulmonary, and cutaneous manifestations.
- In some descriptors the exclusions written may not be exhaustive. The intent of the SLEDAI is that the descriptor be attributed to SLE. If the physician does not attribute the descriptor to SLE it should not be scored, but full documentation must be provided.

Written in italics is the definition for each descriptor precisely provided in the SLEDAI SCORE

SEIZURE

Definition: Recent onset (last 28 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.

This descriptor is scored if the patient has had a witnessed seizure or convincing description (such as tongue biting or incontinence) within 30 days of the current encounter. The patient need not have a positive EEG, CT scan, PET scan, QEEG, or MRI. The CSF may be totally normal.

A seizure is also not counted:

1. If a metabolic cause is determined.
2. In the presence of a proven infectious meningitis, brain abscess, or fungal foci.
3. If there is a history of recent head trauma.
4. In the presence of an offending drug.
5. In the presence of severe hyperthermia or hypothermia.
6. If the patient has stopped taking anticonvulsant medication.
7. If the patient has a documented sub-therapeutic anticonvulsant drug level.

PSYCHOSIS

Definition: 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.

This descriptor is scored if any of the criteria above are met.

With regard to drug causes the most problematic situation is glucocorticoids. If the treating physician attributes the psychosis to glucocorticoids this descriptor should not be counted.

ORGANIC BRAIN SYNDROME

Definition: Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.

a. reduced capacity to focus as exemplified by new inability to perform everyday mathematical computations or disorientation to person, place, time, or purpose

   OR

b. inability to carry on a conversation

   OR

c. reduction in short term memory

PLUS: Documented abnormality on neuropsychiatric testing

Neuropsychiatric testing may take the form of a "mini-mental-status exam" or a formal neuropsychiatric examination. The important aspect for scoring OBS is that it be reversible. Consideration should be given to the improvement of OBS after institution of glucocorticoids.

This descriptor is not scored in the presence of a metabolic, infectious, or drug cause. If the problem is chronic this descriptor is not scored in SLEDAI but is scored on the damage index.

VISUAL DISTURBANCE

Definition: Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection or drug causes.

This is scored exactly as defined with the understanding that it must be supported by objective evidence.

CRANIAL NERVE DISORDER

Definition: New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.

This is scored exactly as defined with the understanding that it must be supported by objective evidence. However, it should be noted that hydroxychloroquine can affect the eighth cranial nerve.

LUPUS HEADACHE

Definition: Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.

For this descriptor to be counted, the headache must be present for greater than 24 hours and must not be responsive to narcotic analgesia. Objective documentation need not be present although it is expected that such a complaint, given the severity, would prompt formal testing such as MRI, CT, LP, etc. Furthermore, the headache should be of sufficient severity to warrant the initiation of glucocorticoids or additional immunosuppressive agents. Scoring of this descriptor means attribution of the headache to CNS lupus.

Most headaches, including most severe and/or migrainous headaches are not attributable to lupus and this descriptor should only be scored very rarely.

CVA

Definition: New onset of cerebrovascular accident (s). Exclude arteriosclerosis or hypertensive causes.

This descriptor is scored if the patient has had a CVA within 28 days of the current encounter. A patient recovering from a CVA that was documented more than 28 days prior to the current encounter is not given points for this descriptor. A patient may have had a previous CVA but to be scored the current CVA must be new.

This descriptor is scored in the presence or absence of anti-phospholipid antibodies, i.e., the precise pathophysiologic mechanism need not be known.

The CVA is scored even in the presence of a normal CT or MRI. A TIA is also scored if the patient gives a convincing history. To exclude atherosclerosis the patient has to have a normal carotid and/or vertebral Doppler and cannot have uncontrolled hypertension.

VASCULITIS:

Definition: Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.

To score this descriptor the above definitions must be present. For example, erythematous lesions on the hands or feet which may be characteristically considered "leukocytoclastic vasculitis" but do not fulfill at least one of the above definitions and if not biopsied, are not counted. Similarly livedo reticularis is not counted. Healed ulcers with residual scar are not to be counted, but be sure to count these in the damage index. A lesion consistent with erythema nodosum should be counted regardless of whether it is biopsied or not. Purpura in the presence of a normal platelet count should be counted regardless of whether it has been biopsied or not.

ARTHRITIS

Definition: More than two joints with pain and signs of inflammation, i.e., tenderness, swelling, or effusion.

Arthritis is scored if it is ongoing; it need not be new or recurrent.

Arthritis is scored only if *more than two* joints manifest signs of inflammation. For example if only the right second and left third PIPs are involved or only both wrists, points for this descriptor are not given.

Inflammation is strictly defined in this activity index as the **presence of tenderness** (the patient complains of pain on palpating the joint or upon going through range of motion) **PLUS** any one of the following:

1. swelling
2. effusion
3. warmth
4. erythema, but must exclude overlying cellulitis

The presence of tenderness alone is not sufficient. A patient's complaints of pain in specific joints without objective findings is not sufficient. An exception would be arthritis of the hip in which case pain in the groin on range of motion accompanied by decreased range of motion in the absence of swelling, warmth, or erythema would be counted.

Inflammation of the tendons, ligaments, bursae, and other periarticular structures are not scored. For example subacromial bursitis and trochanteric bursitis are not scored. If further evaluation reveals osteonecrosis or osteoarthritis, this descriptor is not counted.

MYOSITIS

Definition: Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.

The patient complains of muscle aching and/or weakness in the proximal muscles PLUS one of the following must be present:

1. elevated serum creatine phosphokinase and/or aldolase
2. abnormalities on electromyogram consistent with myositis
3. biopsy-proven myositis

URINARY CASTS

Definition: Heme-granular or red blood cell casts.

This is scored if red blood cell casts are seen, even if it is only one. Pigmented casts are counted but non-pigmented granular casts, hyaline or waxy casts are not counted.

HEMATURIA

Definition: >5 red blood cells/high power field. Exclude stone, infection or other cause.

With regard to this descriptor, every attempt should be made to see patients when they are not menstruating. If this is not possible the urinalysis should be deferred until the next visit.

This descriptor is not scored if there is documented renal calculi or infection. The latter must be confirmed by a positive urinary culture. However it is acknowledged that associated conditions such as chlamydia or urethral

irritation may result in mild hematuria and the physician's best judgment is warranted. **The important point is attribution: there must be other evidence of nephritis and other causes of hematuria must be excluded.** In the complete absence of proteinuria, attribution of hematuria to active nephritis would be very unlikely unless pathology is limited to the mesangium.

PROTEINURIA

Definition: proteinuria of more than 0.5 g/24 hours.

Must be attributed to active lupus nephritis.

PYURIA

Definition: >5 white blood cells/high power field. Exclude infection.

This descriptor is not scored if there is evidence of vaginal contamination (presence of any squamous epithelial cells) or a documented infection. The latter must be confirmed by a positive urinary culture. However, it is acknowledged that associated conditions such as chlamydia, trichomonas or urethral irritation may result in mild pyuria and the physician's best judgment is warranted. **The important point is attribution; there must be other evidence of nephritis, and other causes of pyuria should be excluded.** In the complete absence of proteinuria, attribution of hematuria to active nephritis would be very unlikely unless pathology is limited to the interstitium.

RASH

Definition: Ongoing inflammatory lupus rash.

A rash is scored if it is ongoing, new or recurrent. Even if it is identical in terms of distribution and character to that observed on the last visit and the intensity is improved, it is counted. Therefore, despite improvement in a rash, if it is still ongoing it represents disease activity. The rash must be attributable to SLE. A description of the rash must appear in the physical exam and should include distribution, characteristics such as macular or papular, and size.

The following should not be scored:

1. Chronic scarred discoid plaques in any location.
2. Transient malar flush, i.e., it is not raised and is evanescent

A common problem one may encounter is the differentiation between scoring a lesion as "rash" and/or "vasculitis". If a lesion meets the descriptive criteria of the latter it should not also be counted as rash, i.e., the score would be 8 points not 10 points. If a separate rash characteristic of SLE is present only then would "rash" also be scored.

ALOPECIA:

Definition: Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.

This should be scored if any of the following conditions are present:

1. There is temporal thinning which is newly present for less than six months (if temporal alopecia is present for more than six months with no change it should not be counted)

2. Areas of scalp with total bald spots if present for less than six months (does not need to have accompanying discoid lesion or follicular plugging)
3. The presence of "lupus frizz" i.e., short of strands of unruly hair in the frontal or temporal area

If a patient complains of hair loss and there is nothing apparent on exam this descriptor is not scored.

MUCOSAL ULCERS:

Definition: Ongoing oral or nasal ulcerations due to active lupus.

An ulcer is scored if it is ongoing, it need not be new or recurrent. Ulcers can be present in either the nose or oral cavity. Erythema alone without frank ulceration is not sufficient to be scored, even if the erythema is present on the upper palate. Ulcers on the buccal mucosa and tongue are counted.

Mucosal ulcers are not counted as vasculitis.

PLEURISY

Definition: Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.

This descriptor is scored if the patient complains of pleuritic chest pain lasting greater than 12 hours. The pain should be classic, i.e., exacerbated by inspiration, to help distinguish it from musculoskeletal conditions such as costochondritis, which could be confused with pleurisy. The symptom does not have to be accompanied by any objective findings. The presence of objective findings such as pleural rub or pleural effusions (in the absence of infection, congestive heart failure, malignancy, or nephrosis) is counted, even if not accompanied by symptoms. New pleural thickening should be counted only if other causes as described above are absent.

PERICARDITIS:

Definition: Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.

The symptom does not have to be accompanied by objective findings.

LOW COMPLEMENT:

*Definition: Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.*Exclude a low C4 or CH50 in patients with known inherited deficiency of C4.

INCREASED DNA BINDING

Definition: >25% binding by Farr assay or above normal range for testing laboratory.

FEVER:

Definition: >38°C. Exclude infectious cause.

This would be scored if one of the following conditions are present:

1. A documented temperature elevation >100.4°F or >38°C at the time of the visit.
2. A convincing history from the patient that she/he has been febrile within the preceding 10 days prior to the visit without any signs or symptoms suggestive of infection. Febrile is defined as above and not simply that the patient felt feverish. In this case the patient need not be febrile at the time of the visit for a score of 2 to be given.

As stated in the SLEDAI, fever secondary to infection is not to be scored although it is acknowledged that concomitant lupus activity and infection can occur. Fever in the presence of infection should only be scored on the SLEDAI if other evidence of lupus activity is present.

THROMBOCYTOPENIA:

Definition: <100,000 platelets/mm^3.

LEUKOPENIA:

Definition: <3,000 white blood cells/mm^3. Exclude drug causes.

This is exactly as described, WBC <3,000/mm^3. The presence of an absolute lymphopenia does not count in the SLEDAI. A note of caution, do not confuse this WBC with that used to satisfy the ACR criteria for SLE which is WBC <3,500/mm^3.

With regard to current use of possible offending drugs, the following guidelines are to be considered:

1. The nadir after cyclophosphamide, i.e., low WBC at 10 days after receiving cyclophosphamide in a patient known to have a WBC ≥ 3,000 at the time of receiving cyclophosphamide should not be counted.
2. Do not score leukopenia appearing after initiation of a new medication known to be associated with leukopenia, such as azathioprine or sulfa drugs. If the patient develops a WBC <3000 while taking drugs which may cause leukopenia, score this only if the dosage of medication is unchanged since the last WBC determination.

Revised SELENA SLEDAI FLARE INDEX

This instrument, shown on the next pages, can be scored (experimentally either with only the clinical components, when clinical OR treatment components are met, or with the rule that "treatment trumps." This instrument is still under evaluation and this study will compare these different scoring options.

SELENA Flare Index-Revised

The 2009 revision of the SELENA Flare Index evaluates increases in SLE disease activity within eight organ systems: mucocutaneous, musculoskeletal, cardiopulmonary, hematological, constitutional, renal, neurological, and gastrointestinal.

Within each organ system the Investigator assesses clinical manifestations and treatment recommendations to arrive at a flare categorization as no flare, mild flare, moderate flare, or severe flare.

In the event that the assessment of a clinical manifestation and the recommendation for a treatment change are discrepant the treatment choice takes precedence (in the direction of a higher flare definition). Treatment changes recommended because of intolerance, toxicity or safety do not count towards a flare definition.

SLE manifestations within each organ system are given on the following pages.

1. MUCOCUTANEOUS SYSTEM

None	Mild D	Moderate D	Severe D
D	Clinical: New/worse/recurrent malar rash New/worse mild oral/nasal ulcers New/worse discoid in a small existing lesion or a very localized area such as ear New mild photosensitive or maculopapular rash New mild alopecia New mild bullous lupus AND/OR Treatment: any of No treatment or analgesic Topical treatment New/increased hydroxychloroquine or other antimalarial New/increased prednisone ≤ 7.5 mg/day	Clinical: New/worse extensive oral/nasal ulcers New/worse discoid beyond a very localized area, such as new areas, enlargement, or deepening lesions New/worse moderate photosensitive or maculopapular rash New/worse marked alopecia New/worse small cutaneous ulcers, very limited periungual infarcts New/worse mild to moderate angioedema New/worse moderate bullous lupus New/worse mild to moderate panniculitis AND/OR Treatment: any of New/increased prednisone to > 7.5 mg/day but < 0.5 mg/kg/day for > 3 days Intramuscular corticosteroid New or increased dose of immunosuppressive (not cyclophosphamide) Two antimalarials Thalidomide Dapsone New/increased retinoids	Clinical: New/worse extensive and/or severe vasculitis, panniculitis, bullous lesions, large cutaneous ulcers, desquamating, necrosis, gangrene, angioedema AND/OR Treatment: any of New/increased prednisone > 0.5 mg/kg/day (including IV methylprednisolone) Cyclophosphamide Rituximab or other biologic Hospitalization

2. Musculoskeletal System

None	Mild D	Moderate D	Severe D
D	Clinical: New/worse/recurrent polyarthralgias New/mild arthritis of 1 or 2 joints AND/OR Treatment: any of No treatment or analgesia New/increased hydroxychloroquine or other antimalarial New/increased prednisone ≤ 7.5 mg/day New or increased NSAID New/increased dehydroepiandrosterone (DHEA)	Clinical: New/worse/recurrent polyarthritis (3 or more joints) AND/OR Treatment: any of New/increased prednisone to > 7.5 mg/day but < 0.5 mg/kg/day for > 3 days Intramuscular corticosteroid Methotrexate < 15 mg/wk New or increased dose of immunosuppressive (not cyclophosphamide) Intraarticular corticosteroid	Clinical: New/worse/ polyarthritis (3 or more joints) with marked reduction in range of motion or mobility AND/OR Treatment: any of New/increased prednisone > 0.5 mg/kg/day (including IV methylprednisolone) Methotrexate > 15 mg/wk Cyclophosphamide Rituximab or other biologic Hospitalization for severe activity

3. Cardiopulmonary System

None	Mild D	Moderate D	Severe D
D	Clinical: New/worse mild pleurisy or pericarditis (symptoms sufficient) AND/OR Treatment: any of No treatment or analgesic New/increased hydroxychloroquine or other antimalarial New/increased prednisone ≤ 7.5 mg/day New or increased NSAID	Clinical: New/worse moderate pleurisy, pericarditis, small pleural effusion (with physical examination findings, radiographs or echo) AND/OR Treatment: any of New/increased prednisone to > 7.5 mg/day but < 0.5 mg/kg/day for > 3 days Intramuscular corticosteroid New or increased dose of immunosuppressive (not cyclophosphamide) IV methylprednisolone if one dose	Clinical: New/worse pleural or pericardial effusion requiring tap or window, tamponade New/worse pulmonary hemorrhage, shrinking lung New/worse myocarditis, coronary arteritis AND/OR Treatment: any of New/increased prednisone > 0.5 mg/kg/day (including IV methylprednisolone) Cyclophosphamide Rituximab or other biologic Hospitalization for severe activity

4. Hematological System

None	Mild D	Moderate D	Severe D
D	Clinical: Leukopenia - new/worse/recurrent < 3,000 Thrombocytopenia - New/worse/recurrent 50 to 100,000 Hemolytic anemia or anemia of active SLE - HCT > 30 AND/OR Treatment: any of No treatment or analgesic New/increased hydroxychloroquine or other antimalarial New/increased prednisone ≤ 7.5 mg/day	Clinical: Leukopenia - < 1500 but > 1000 Thrombocytopenia - 30 to 50,000 Hemolytic anemia or anemia of active SLE - HCT < 30, but > 25 AND/OR Treatment: any of New/increased prednisone to > 7.5 mg/day but < 0.5 mg/kg/day for > 3 days Intramuscular corticosteroid New or increased dose of immunosuppressive (not cyclophosphamide)	Clinical: Leukopenia - < 1000 Thrombocytopenia - < 30,000 or thrombotic microangiopathy Hemolytic anemia or anemia of active SLE - HCT < 25 AND/OR Treatment: any of New/increased prednisone > 0.5 mg/kg/day (including IV methylprednisolone) Cyclophosphamide Rituximab or other biologic Hospitalization for severe activity Intravenous immunoglobulin Plasmapheresis

5. Constitutional

None	Mild D	Moderate D	Severe D
D	Clinical: Fever New/worse/recurrent up to 101°F (38.3°C) Lymphadenopathy New/worse up to a few small cervical/axillary nodes (< 1cm) Weight loss New weight loss < 5% AND/OR Treatment: any of No treatment or analgesic New/increased hydroxychloroquine or other antimalarial New/increased prednisone ≤ 7.5 mg/day New/increased NSAID	Clinical: Fever New/worse > 101°F (38.3°C) but < 103°F (39.4°C) Lymphadenopathy New/worse lymph nodes outside cervical chain Weight loss 5% to 10% weight loss AND/OR Treatment: any of New/increased prednisone to > 7.5 mg/day but < 0.5 mg/kg/day for > 3 days Intramuscular steroid New or increased dose of immunosuppressive (not cyclophosphamide)	Clinical: Fever New/worse > 103°F (39.4°C) Weight loss > 10% weight loss AND/OR Treatment: any of New/increased prednisone > 0.5 mg/kg/day (including IV methylprednisolone) Cyclophosphamide Rituximab or other biologic Hospitalization for severe activity

6. Renal System

None	Mild D	Moderate D	Severe D
D	Clinical: New/worse protein/cr > 0.2 but < 0.5 AND/OR Treatment: any of No treatment New/increased hydroxychloroquine or other antimalarial New/increased prednisone ≤ 7.5 mg/day Angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), spironolactone, low protein diet, low sodium diet Statins	Clinical: New/worse urine pr/cr > 0.5 but < 1.0 Increase in RBC/hpf from < 5 to > 15 with > 2 acanthocytes/hpf AND/OR Treatment: any of New/increased prednisone to > 7.5 mg/day but < 0.5 mg/kg/day for > 3 days Intramuscular corticosteroid New or increased dose of immunosuppressive (not cyclophosphamide)	Clinical: Urine pr/cr > 1.0 if baseline < 0.3 Urine pr/cr doubled if baseline is > 1 Urine pr/cr > 5.0 New RBC casts or mixed RBC casts Biopsy with new/worse aggressive lesions (necrosis, crescents) Biopsy with Class IV Rapidly progressive glomerulonephritis Decreased GFR in last 3 months If baseline Cr < 2, increase of > 0.2 mg/dl If baseline Cr > 2, increase of > 0.4 mg/dl AND/OR Treatment: any of New/increased prednisone > 0.5 mg/kg/day (including IV methylprednisolone) Mycophenolate mofetil or azathioprine for severe nephritis Cyclophosphamide Rituximab or other biologic Hospitalization for severe activity

7. Neurological System

None	Mild D	Moderate D	Severe D
D	Clinical: Minimal/intermittent ACR neuropsychiatric SLE syndrome AND/OR Treatment: any of No treatment or analgesic New/increased hydroxychloroquine or other antimalarial New/increased prednisone ≤ 7.5 mg/day	Clinical: New/worsening persistent ACR neuropsychiatric SLE syndrome AND/OR Treatment: any of New/increased prednisone to > 7.5 mg/day but < 0.5 mg/kg/day for > 3 days Intramuscular corticosteroid New or increased dose of immunosuppressive (not cyclophosphamide)	Clinical: Acute delirium or confusional state (organic brain syndrome) Coma Status epilepticus Cranial nerve palsy (including optic) Stroke due to CNS vasculitis Aseptic meningitis Mononeuritis multiplex Longitudinal myelitis Chorea Cerebellar ataxia Myositis with weakness AND/OR Treatment: any of New/increased prednisone > 0.5 mg/kg/day (including IV methylprednisolone) Cyclophosphamide Rituximab or other biologic Hospitalization for severe activity Plasmapheresis Intravenous immunoglobulin

8. Gastrointestinal System

None	Mild D	Moderate D	Severe D
D	Clinical: New/worse LFTs > 2x normal but < 4x normal AND/OR Treatment: any of No treatment or analgesic New/increased hydroxychloroquine or other antimalarial New/increased prednisone ≤ 7.5 mg/day	Clinical: New/worse LFT's > 4x normal New/worse pancreatitis with increased amylase, but no IV therapy New/worse clinical peritonitis with no ascites AND/OR Treatment: any of New/increased prednisone to > 7.5 mg/day but < 0.5 mg/kg/day for > 3 days Intramuscular corticosteroid New or increased dose of immunosuppressive (not cyclophosphamide)	Clinical: New/worse lupus peritonitis with ascites New/worse enteritis, colitis or protein-losing enteropathy New/worse intestinal pseudo-obstruction with hypomotility New/worse pancreatitis requiring IV therapy New/worse GI vasculitis (mesenteric or other GI organ) AND/OR Treatment: any of New/increased prednisone > 0.5 mg/kg/day (including IV methylprednisolone) Cyclophosphamide Rituximab or other biologic Hospitalization for severe activity

APPENDIX 2 BILAG 2004 CASE FORM

Only record items due to SLE Disease Activity & assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks).

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)

1 CONSTITUTIONAL

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

2 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	( )

3 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 ( )

4 MUSCULOSKELETAL

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

5 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. Aortitis ( )
55. Coronary vasculitis ( )

6 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 ( )

7 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 ( )

8 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	( )	

9 HAEMATOLOGICAL

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	( )	

BILAG-2004 INDEX GLOSSARY

INSTRUCTIONS

- only record features that are **attributable to SLE disease activity and not due to damage, infection, thrombosis (in absence of inflammatory process) or other conditions**

- assessment refers to manifestations occurring in the **last 4 weeks compared with the previous 4 weeks**

- activity refers to disease process which is reversible while damage refers to permanent process/scarring (irreversible)

- damage due to SLE should be considered as a cause of features that are fixed/persistent (SLICC/ACR damage index uses persistence ≥ 6 months to define damage)

- in some manifestations, it may be difficult to differentiate SLE from other conditions as there may not be any specific test and the decision would then lies with the **physician's judgement on the balance of probabilities**

- ophthalmic manifestations usually need to be assessed by an ophthalmologist and these items would need to be recorded after receiving the response from the ophthalmologist

- guidance for scoring:

(4) NEW

- manifestations are recorded as new when it is a new episode occurring in the last 4 weeks (compared to the previous 4 weeks) that has not improved and this includes new episodes (recurrence) of old manifestations

- new episode occurring in the last 4 weeks but also satisfying the criteria for improvement (below) would be classified as improving instead of new

(3) WORSE

- this refers to manifestations that have deteriorated in the last 4 weeks compared to the previous 4 weeks

(2) SAME

- this refers to manifestations that have been present for the last 4 weeks and the previous 4 weeks without significant improvement or deterioration (from the previous 4 weeks)

- this also applies to manifestations that have improved over the last 4 weeks compared to the previous 4 weeks but do not meet the criteria for improvement

(1) IMPROVING

- definition of **improvement**: (a) the amount of improvement is sufficient for **consideration of reduction in therapy** and would not justify escalation in therapy

AND

(b) improvement must be **present currently and for at least 2 weeks** out of the last 4 weeks

OR

manifestation that has **completely resolved and remained absent** over the **whole of last 1 week**

(0) NOT PRESENT

(ND) NOT DONE

- it is important to indicate if a test has not been performed (particularly laboratory investigations) so that this will be recorded as such in the database & not as normal or absent (which is the default)

❑ INDICATE (TICK) IF NOT DUE TO SLE ACTIVITY

- for descriptors that are based on measurements (in renal and haematology systems), it is important to indicate if these are not due to lupus disease activity (for consideration of scoring) as they are usually recorded routinely into a database

CHANGE IN SEVERITY CATEGORY

- there are several items in the index which have been divided into categories of mild and severe (depending on definition). It is essential to record mild and severe items appropriately if the manifestations fulfil both criteria during the last 4 weeks

- if a mild item deteriorated to the extent that it fulfilled the definition of severe category (ie changed into severe category) within the last 4 weeks:
  severe item scored as new (4)
  AND mild item scored as worsening (3)

- if a severe item improved (fulfilling the improvement criteria) to the extent that it no longer fulfilled the definition of severe category (ie changed into mild category) within the last 4 weeks:
  severe item scored as not present (0) if criteria for severe category has not been met over last 4 weeks
  or as improving (1) if criteria for severe category has been met at some point over last 4 weeks

AND

mild item scored as improving (1) if it is improving over last 4 weeks
or as the same (2) if it has remained stable over last 4 weeks

<u>CONSTITUTIONAL</u>

1. Pyrexia	temperature > 37.5˚C documented
2. Unintentional weight loss > 5%	
3. Lymphadenopathy	lymph node more than 1 cm diameter
	exclude infection

4. Anorexia

MUCOCUTANEOUS

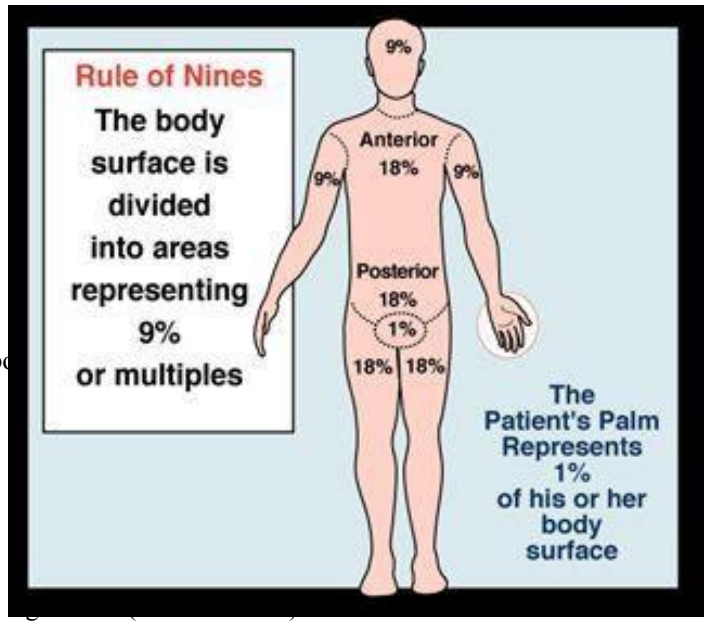
5. Severe eruption

> 18% body surface area

any lupus rash except panniculitis, bullous lesion & angio-oedema

body surface area (BSA) is estimated using the rules of nines (used to assess extent of burns) as follows:

palm(excluding fingers) = 1% BSA
each lower limb = 18% BSA
each upper limb = 9% BSA
torso (front) = 18% BSA
torso (back) = 18% BSA
head = 9% BSA
genital (male) = 1% BSA



6. Mild eruption

≤ 18% bo

7. Severe angio-oedema

potentially life-threatening eg: stridor

angio-oedema is a variant form of urticaria which affects the subcutaneous, submucosal and deep dermal tissues

8. Mild angio-oedema

not life threatening

9. Severe mucosal ulceration

disabling (significantly interfering with oral intake), extensive & deep ulceration

	must have been observed by a physician
10. Mild mucosal ulceration	localised &/or non-disabling ulceration
11. Severe panniculitis or bullous lupus	any one: > 9% body surface area
	facial panniculitis
	panniculitis that is beginning to ulcerate
	panniculitis that threatens integrity of subcutaneous tissue (beginning to cause surface depression) on > 9% body surface area, panniculitis presents as a palpable and tender subcutaneous induration/nodule note that established surface depression and atrophy alone is likely to be damage
12. Mild panniculitis or bullous lupus	≤ 9% body surface area does not fulfil any criteria for severe panniculitis
13. Major cutaneous vasculitis/thrombosis	resulting in extensive gangrene or ulceration or skin infarction
14. Digital infarct or nodular vasculitis	localised single or multiple infarct(s) over digit(s) or tender erythematous nodule(s)
15. Severe alopecia	clinically detectable (diffuse or patchy) hair loss with scalp inflammation (redness over scalp)
16. Mild alopecia	diffuse or patchy hair loss without scalp inflammation (clinically detectable or by history)
17. Peri-ungual erythema or chilblains	chilblains are localised inflammatory lesions (may ulcerate) which are precipitated by exposure to cold
18. Splinter haemorrhages	

NEUROPSYCHIATRIC

19. Aseptic meningitis	criteria (all): acute/subacute onset headache fever abnormal CSF (raised protein &/or lymphocyte predominance) but negative cultures
	preferably photophobia, neck stiffness and meningeal irritation should be present as well but are not essential for diagnosis, exclude CNS/meningeal infection, intracranial haemorrhage

20. Cerebral vasculitis	should be present with features of vasculitis in another system supportive imaging &/or biopsy findings
21. Demyelinating syndrome	discrete white matter lesion with associated neurological deficit not recorded elsewhere ideally there should have been at least one previously recorded event supportive imaging required exclude multiple sclerosis
22. Myelopathy	acute onset of rapidly evolving paraparesis or quadriparesis and/or sensory level exclude intramedullary and extramedullary space occupying lesion
23. Acute confusional state	acute disturbance of consciousness or level of arousal with reduced ability to focus, maintain or shift attention includes hypo- and hyperaroused states and encompasses the spectrum from delirium to coma
24. Psychosis	delusion or hallucinations does not occur exclusively during course of a delirium exclude drugs, substance abuse, primary psychotic disorder
25. Acute inflammatory demyelinating polyradiculoneuropathy	criteria: progressive polyradiculoneuropathy loss of reflexes symmetrical involvement increased CSF protein without pleocytosis supportive electrophysiology study
26. Mononeuropathy (single/multiplex)	supportive electrophysiology study required
27. Cranial neuropathy	except optic neuropathy which is classified under ophthalmic system
28. Plexopathy	disorder of brachial or lumbosacral plexus resulting in neurological deficit not corresponding to territory of single root or nerve supportive electrophysiology study required
29. Polyneuropathy	acute symmetrical distal sensory and/or motor deficit

	supportive electrophysiology study required
30. Seizure disorder	independent description of seizure by reliable witness
31. Status epilepticus	a seizure or series of seizures lasting ≥ 30 minutes without full recovery to baseline
32. Cerebrovascular disease (not due to vasculitis)	any one with supporting imaging: stroke syndrome transient ischaemic attack intracranial haemorrhage exclude hypoglycaemia, cerebral sinus thrombosis, vascular malformation, tumour, abscess cerebral sinus thrombosis not included as definite thrombosis not considered part of lupus activity
33. Cognitive dysfunction	significant deficits in any cognitive functions: simple attention (ability to register & maintain information) complex attention memory (ability to register, recall & recognise information eg learning, recall) visual-spatial processing (ability to analyse, synthesise & manipulate visual-spatial information) language (ability to comprehend, repeat & produce oral/written material eg verbal fluency, naming) reasoning/problem solving (ability to reason & abstract) psychomotor speed executive functions (eg planning, organising, sequencing) in absence of disturbance of consciousness or level of arousal sufficiently severe to interfere with daily activities neuropsychological testing should be done or corroborating history from third party if possible exclude substance abuse
34. Movement disorder	exclude drugs
35. Autonomic disorder	any one: fall in blood pressure to standing > 30/15 mm Hg (systolic/diastolic) increase in heart rate to standing ≥ 30 bpm

	loss of heart rate variation with respiration (max – min < 15 bpm, expiration:inspiration ratio < 1.2, Valsalva ratio < 1.4)
	loss of sweating over body and limbs (anhidrosis) by sweat test
	exclude drugs and diabetes mellitus
36. Cerebellar ataxia	cerebellar ataxia in isolation of other CNS features
	usually subacute presentation
37. Severe lupus headache (unremitting)	disabling headache unresponsive to narcotic analgesia & lasting ≥ 3 days
	exclude intracranial space occupying lesion and CNS infection
38. Headache from IC hypertension	exclude cerebral sinus thrombosis

MUSCULOSKELETAL

39. Severe myositis	significantly elevated serum muscle enzymes with significant muscle weakness
	exclude endocrine causes and drug-induced myopathy
	electromyography and muscle biopsy are used for diagnostic purpose and are not required to determine level of activity
40. Mild myositis	significantly elevated serum muscle enzymes with myalgia but without significant muscle weakness
	asymptomatic elevated serum muscle enzymes not included
	exclude endocrine causes and drug-induced myopathy
	electromyography and muscle biopsy are used for diagnostic purpose and are not required to determine level of activity
41. Severe arthritis	observed active synovitis ≥ 2 joints with marked loss of functional range of movements and significant impairment of activities of daily living, that has been present on several days (cumulatively) over the last 4 weeks
42. Moderate arthritis or Tendonitis	tendonitis/tenosynovitis or active synovitis ≥ 1

or Tenosynovitis	joint (observed or through history) with some loss of functional range of movements, that has been present on several days over the last 4 weeks
43. Mild arthritis or Arthralgia or Myalgia	inflammatory type of pain (worse in the morning with stiffness, usually improves with activity & not brought on by activity) over joints/muscle inflammatory arthritis which does not fulfil the above criteria for moderate or severe arthritis

CARDIORESPIRATORY

44. Mild myocarditis	inflammation of myocardium with raised cardiac enzymes &/or ECG changes and without resulting cardiac failure, arrhythmia or valvular dysfunction
45. Cardiac failure	cardiac failure due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis) cardiac failure due to myocarditis is defined by left ventricular ejection fraction ≤ 40% & pulmonary oedema or peripheral oedema cardiac failure due to acute valvular regurgitation (from endocarditis) can be associated with normal left ventricular ejection fraction diastolic heart failure is not included
46. Arrhythmia	arrhythmia (except sinus tachycardia) due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis) confirmation by electrocardiogram required (history of palpitations alone inadequate)
47. New valvular dysfunction	new cardiac valvular dysfunction due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis) supportive imaging required
48. Pleurisy/Pericarditis	convincing history &/or physical findings that you would consider treating in absence of cardiac tamponade or pleural effusion with dyspnoea do not score if you are unsure whether or not it is pleurisy/pericarditis
49. Cardiac tamponade	supportive imaging required
50. Pleural effusion with dyspnoea	supportive imaging required

51. Pulmonary haemorrhage/vasculitis	inflammation of pulmonary vasculature with haemoptysis &/or dyspnoea &/or pulmonary hypertension supportive imaging &/or histological diagnosis required
52. Interstitial alveolitis/pneumonitis	radiological features of alveolar infiltration not due to infection or haemorrhage required for diagnosis corrected gas transfer Kco reduced to < 70% normal or fall of > 20% if previously abnormal on-going activity would be determined by clinical findings and lung function tests, and repeated imaging may be required in those with deterioration (clinically or lung function tests) or failure to respond to therapy
53. Shrinking lung syndrome	acute reduction (> 20% if previous measurement available) in lung volumes (to < 70% predicted) in the presence of normal corrected gas transfer (Kco) & dysfunctional diaphragmatic movements
54. Aortitis	inflammation of aorta (with or without dissection) with supportive imaging abnormalities accompanied by > 10 mm Hg difference in BP between arms &/or claudication of extremities &/or vascular bruits repeated imaging would be required to determine on-going activity in those with clinical deterioration or failure to respond to therapy
55. Coronary vasculitis	inflammation of coronary vessels with radiographic evidence of non-atheromatous narrowing, obstruction or aneurysmal changes

GASTROINTESTINAL

56. Lupus peritonitis	serositis presenting as acute abdomen with rebound/guarding
57. Serositis	not presenting as acute abdomen
58. Lupus enteritis or colitis	vasculitis or inflammation of small or large bowel with supportive imaging &/or biopsy findings
59. Malabsorption	diarrhoea with abnormal D- xylose absorption test or increased faecal fat excretion after exclusion of coeliac's disease (poor response to gluten-free diet) and gut vasculitis
60. Protein-losing enteropathy	diarrhoea with hypoalbuminaemia or increased faecal excretion of iv radiolabeled albumin after exclusion of gut vasculitis and malabsorption

61. Intestinal pseudo-obstruction	subacute intestinal obstruction due to intestinal hypomotility
62. Lupus hepatitis	raised transaminases
	absence of autoantibodies specific to autoimmune hepatitis (eg: anti-smooth muscle, anti-liver cytosol 1) &/or biopsy appearance of chronic active hepatitis
	hepatitis typically lobular with no piecemeal necrosis
	exclude drug-induced and viral hepatitis
63. Acute lupus cholecystitis	after exclusion of gallstones and infection
64. Acute lupus pancreatitis	usually associated multisystem involvement

OPHTHALMIC

65. Orbital inflammation	orbital inflammation with myositis &/or extra-ocular muscle swelling &/or proptosis
	supportive imaging required
66. Severe keratitis	sight threatening includes: corneal melt peripheral ulcerative keratitis
67. Mild keratitis	not sight threatening
68. Anterior uveitis	
69. Severe posterior uveitis &/or retinal vasculitis	sight-threatening &/or retinal vasculitis not due to vaso-occlusive disease
70. Mild posterior uveitis &/or retinal vasculitis	not sight-threatening
	not due to vaso-occlusive disease
71. Episcleritis	
72. Severe scleritis	necrotising anterior scleritis, anterior &/or posterior scleritis requiring systemic steroids/immunosuppression &/or not responding to NSAIDs
73. Mild scleritis	anterior &/or posterior scleritis not requiring systemic steroids
	excludes necrotising anterior scleritis
74. Retinal/choroidal vaso-occlusive disease	includes: retinal arterial & venous occlusion serous retinal &/or retinal pigment epithelial detachments secondary to choroidal vasculopathy

75. Isolated cotton-wool spots	also known as cytoid bodies
76. Optic neuritis	excludes anterior ischaemic optic neuropathy
77. Anterior ischaemic optic neuropathy	visual loss with pale swollen optic disc due to occlusion of posterior ciliary arteries

RENAL

78. Systolic blood pressure 79. Diastolic blood pressure 80. Accelerated hypertension	blood pressure rising to > 170/110 mm Hg within 1 month with grade 3 or 4 Keith-Wagener-Barker retinal changes (flame-shaped haemorrhages or cotton-wool spots or papilloedema)
81. Urine dipstick 82. Urine albumin-creatinine ratio	on freshly voided urine sample conversion: 1 mg/mg = 113 mg/mmol it is important to exclude other causes (especially infection) when proteinuria is present
83. Urine protein-creatinine ratio	on freshly voided urine sample conversion: 1 mg/mg = 113 mg/mmol it is important to exclude other causes (especially infection) when proteinuria is present
84. 24 hour urine protein	it is important to exclude other causes (especially infection) when proteinuria is present
85. Nephrotic syndrome	criteria: heavy proteinuria (≥ 3.5 g/day or protein-creatinine ratio ≥ 350 mg/mmol or albumin-creatinine ratio ≥ 350 mg/mmol) hypoalbuminaemia oedema
86. Plasma/Serum creatinine	exclude other causes for increase in creatinine (especially drugs)
87. GFR	MDRD formula: GFR = 170 x [serum creatinine (mg/dl)]$^{-0.999}$ x [age]$^{-0.176}$ x [serum urea (mg/dl]$^{-0.17}$ x [serum albumin (g/dl)]$^{0.318}$ x [0.762 if female] x [1.180 if African ancestry] units = ml/min per 1.73 m^2 normal: male = 130 ± 40 female = 120 ± 40

conversion:
serum creatinine - mg/dl = (μmol/l)/88.5
serum urea - mg/dl = (mmol/l) x 2.8
serum albumin - g/dl = (g/l)/10

creatinine clearance not recommended as it is not reliable

exclude other causes for decrease in GFR (especially drugs)

88. Active urinary sediment

pyuria (> 5 WCC/hpf or > 10 WCC/mm^3 (μl))

OR

haematuria (> 5 RBC/hpf or > 10 RBC/mm^3 (μl))

OR

red cell casts

OR

white cell casts

exclude other causes (especially infection, vaginal bleed, calculi)

89. Histology of active nephritis

WHO Classification (1995): (any one)
Class III – (a) or (b) subtypes
Class IV – (a), (b) or (c) subtypes
Class V – (a), (b), (c) or (d) subtypes
Vasculitis

OR

ISN/RPS Classification (2003): (any one)
Class III – (A) or (A/C) subtypes
Class IV – (A) or (A/C) subtypes
Class V
Vasculitis

within last 3 months

glomerular sclerosis without inflammation not included

HAEMATOLOGICAL

90. Haemoglobin — exclude dietary deficiency & GI blood loss
91. White cell count — exclude drug-induced cause
92. Neutrophil count — exclude drug-induced cause
93. Lymphocyte count
94. Platelet count — exclude thrombocytopenia of antiphospholipid syndrome & drug-induced cause

95. TTP	thrombotic thrombocytopaenic purpura clinical syndrome of micro-angiopathic haemolytic anaemia and thrombocytopenia in absence of any other identifiable cause
96. Evidence of active haemolysis	positive Coomb's test & evidence of haemolysis (raised bilirubin or raised reticulocyte count or reduced haptoglobulins)
97. Isolated positive Coomb's test	

10 ADDITIONAL ITEMS

These items are required mainly for calculation of GFR

i. Weight
ii. African ancestry
iii. Serum urea
iv. Serum albumin

BILAG-2004 INDEX SCORING

- scoring based on the principle of physician's intention to treat

Category	Definition
A	**Severe disease activity requiring any of the following treatment:** **1. systemic high dose oral glucocorticoids (equivalent to prednisolone > 20 mg/day)** **2. intravenous pulse glucocorticoids (equivalent to pulse methylprednisolone ≥ 500 mg)** **3. systemic immunomodulators (include biologicals, immunoglobulins and plasmapheresis)** **4. therapeutic high dose anticoagulation in the presence of high dose steroids or immunomodulators** **eg: warfarin with target INR 3 - 4**
B	**Moderate disease activity requiring any of the following treatment:** **1. systemic low dose oral glucocorticoids (equivalent to prednisolone ≤ 20 mg/day)** **2. intramuscular or intra-articular or soft tissue glucocorticoids injection (equivalent to methylprednisolone < 500mg)**

	3. topical glucocorticoids **4. topical immunomodulators** **5. antimalarials or thalidomide or prasterone or acitretin** **6. symptomatic therapy** **eg: NSAIDs for inflammatory arthritis**
C	**Mild disease**
D	**Inactive disease but previously affected**
E	**System never involved**

CONSTITUTIONAL

Category A:
Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **AND**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss
Lymphadenopathy/splenomegaly
Anorexia

Category B:
Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **OR**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss
Lymphadenopathy/splenomegaly
Anorexia

BUT do not fulfil criteria for Category A

Category C
Pyrexia recorded as 1 (improving) **OR**

One or more of the following recorded as > 0:

Weight loss
Lymphadenopathy/Splenomegaly
Anorexia

BUT does not fulfil criteria for category A or B

Category D
Previous involvement

Category E
No previous involvement

MUCOCUTANEOUS

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - severe
Angio-oedema - severe
Mucosal ulceration - severe
Panniculitis/Bullous lupus - severe
Major cutaneous vasculitis/thrombosis

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - mild
Panniculitis/Bullous lupus - mild
Digital infarcts or nodular vasculitis
Alopecia - severe

Category C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Angio-oedema - mild
Mucosal ulceration - mild
Alopecia - mild
Periungual erythema/chilblains
Splinter haemorrhages

Category D
Previous involvement

Category E
No previous involvement

NEUROPSYCHIATRIC

CATEGORY A Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Aseptic meningitis
Cerebral vasculitis
Demyelinating syndrome
Myelopathy
Acute confusional state
Psychosis

Acute inflammatory demyelinating polyradiculoneuropathy
Mononeuropathy (single/multiplex)
Cranial neuropathy
Plexopathy
Polyneuropathy
Status epilepticus
Cerebellar ataxia

CATEGORY B Any Category A features recorded as 1 (improving) OR Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Seizure disorder
Cerebrovascular disease (not due to vasculitis)
Cognitive dysfunction
Movement disorder
Autonomic disorder
Lupus headache - severe unremitting
Headache due to raised intracranial hypertension

Category C
Any Category B features recorded as 1 (improving)

Category D
Previous involvement

Category E
No previous involvement

MUSCULOSKELETAL

CATEGORY A Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Severe Myositis
Severe Arthritis

Category B Any Category A features recorded as 1 (improving) **OR** Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Mild Myositis
Moderate Arthritis/Tendonitis/Tenosynovitis

CATEGORY C Any Category B features recorded as 1 (improving) OR Any of the following recorded as > 0:

Mild Arthritis/Arthralgia/Myalgia

CATEGORY D

Previous involvement

Category E

No previous involvement

CARDIORESPIRATORY

Category A Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Myocarditis/Endocarditis + Cardiac failure
Arrhythmia
New valvular dysfunction
Cardiac tamponade
Pleural effusion with dyspnoea

Pulmonary haemorrhage/vasculitis
Interstitial alveolitis/pneumonitis
Shrinking lung syndrome
Aortitis
Coronary vasculitis

Category B

Any Category A features recorded as 1 (improving) **OR** Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Pleurisy/Pericarditis
Myocarditis - mild

Category C

Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

GASTROINTESTINAL

CATEGORY A Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Peritonitis
Lupus enteritis/colitis
Intestinal pseudo-obstruction
Acute lupus cholecystitis
Acute lupus pancreatitis

CATEGORY B Any Category A feature recorded as 1 (improving) OR Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Abdominal serositis and/or ascites
Malabsorption
Protein losing enteropathy
Lupus hepatitis

CATEGORY C Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

OPHTHALMIC

CATEGORY A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Orbital inflammation/myositis/proptosis
Keratitis - severe
Posterior uveitis/retinal vasculitis - severe
Scleritis - severe
Retinal/choroidal vaso-occlusive disease
Optic neuritis
Anterior ischaemic optic neuropathy

CATEGORY B

Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):
Keratitis - mild
Anterior uveitis
Posterior uveitis/retinal vasculitis - mild
Scleritis - mild

CATEGORY C

Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Episcleritis
Isolated cotton-wool spots (cytoid bodies)

CATEGORY D

Previous involvement

CATEGORY E

No previous involvement

RENAL

CATEGORY A Two or more of the following providing 1, 4 or 5 is included:

1. Deteriorating proteinuria (severe) defined as
   (a) urine dipstick increased by ≥ 2 levels (used only if other methods of urine protein estimation not available); **or**
   (b) 24 hour urine protein > 1 g that has not decreased (improved) by ≥ 25%; **or**
   (c) urine protein-creatinine ratio > 100 mg/mmol not decreased (improved) by ≥ 25%; **or**
   (d) urine albumin-creatinine ratio > 100 mg/mmol not decreased (improved) by ≥ 25%
2. Accelerated hypertension
3. Deteriorating renal function (severe) defined as
   (a) plasma creatinine > 130 μmol/l and having risen to > 130% of previous value; **or**
   (b) GFR < 80 ml/min per 1.73 m^2 and having fallen to < 67% of previous value; **or**
   (c) GFR < 50 ml/min per 1.73 m^2, and last time was > 50 ml/min per 1.73 m^2 or not done
4. Active urinary sediment
5. Histological evidence of active nephritis within last 3 months
6. Nephrotic syndrome

CATEGORY B

One of the following:
1. One of the Category A features
2. Proteinuria (that has not fulfilled Category A criteria)
   (a) urine dipstick which has risen by 1 level to at least 2+ (used only if other methods of urine protein estimation not available); **or**
   (b) 24 hour urine protein ≥ 0.5 g that has not decreased (improved) by ≥ 25%; **or**
   (c) urine protein-creatinine ratio ≥ 50 mg/mmol not decreased (improved) by ≥ 25%; **or**
   (d) urine albumin-creatinine ratio ≥ 50 mg/mmol that has not decreased (improved) by ≥ 25%
3. Plasma creatinine > 130 μmol/l and having risen to ≥ 115% but ≤ 130% of previous value

CATEGORY C

One of the following:
1. Mild/Stable proteinuria defined as
   (a) urine dipstick ≥ 1+ but has not fulfilled criteria for Category A & B (used only if other methods of urine protein estimation not available); **or**
   (b) 24 hour urine protein > 0.25 g but has not fulfilled criteria for Category A&B ; **or**
   (c) urine protein-creat ratio > 25 mg/mmol but has not fulfilled criteria for Category A&B; **or**

(d) urine albumin-creatinine ratio > 25 mg/mmol not fulfilled criteria for Category A & B

2. Rising blood pressure (providing the recorded values are > 140/90 mm Hg) which has not fulfilled criteria for Category A & B, defined as

(a) systolic rise of ≥ 30 mm Hg; **and**

(b) diastolic rise of ≥ 15mm Hg

CATEGORY D

Previous involvement

CATEGORY E

No previous involvement

Note: although albumin-creatinine ratio and protein-creatinine ratio are different, we use the same cut-off values for this index

HAEMATOLOGICAL

CATEGORY A

TTP recorded as 2 (same), 3 (worse) or 4 (new) **OR** Any of the following:

Haemoglobin	< 8 g/dl
White cell count	< 1.0 x 10^9/l
Neutrophil count	< 0.5 x 10^9/l
Platelet count	< 25 x 10^9/l

CATEGORY B

TTP recorded as 1 (improving) **OR**

Any of the following:

Haemoglobin	8 - 8.9 g/dl
White cell count	1 - 1.9 x 10^9/l
Neutrophil count	0.5 - 0.9 x 10^9/l
Platelet count	25 - 49 x 10^9/l
Evidence of active haemolysis	

CATEGORY C

Any of the following:

Haemoglobin	9 - 10.9 g/dl
White cell count	2 - 3.9 x 10^9/l
Neutrophil count	1 - 1.9 x 10^9/l
Lymphocyte count	< 1.0 x 10^9/L
Platelet count	50 - 149 x 10^9/l
Isolated Coombs' test positive	

CATEGORY D OR E

Previous involvement or no Previous involvement respectively

APPENDIX 3: ANCILLARY STUDY WITH EXAGEN DIAGNOSTICS

Exagen proposes to collaborate on this study under a Materials Transfer Agreement with OMRF which includes protocol-specific disclosures between OMRF, OMRF IRB, BMS and Exagen, Exagen will provide sample shipping and diagnostic testing (the FDA approved Lupus Avise) which includes cell bound complement testing known as CBCAPS at no charge. Exagen is engaged in the development and validation of biomarkers associated with the diagnosis and treatment optimization of patients affected by autoimmune diseases. The scope of this collaboration with an Investigator Initiated research study will include validation of the CBCAPS technology in predicting and/or tracking improvement after treatment as well as testing of other diagnostics in development at Exagen. Specific plans are below:

CBCAPS have been offered as a diagnostic test though Exagen's clinical laboratory accredited by the College of American Pathologists in 2012. Anticoagulated blood (10ml in EDTA) will be collected and shipped overnight to Exagen Diagnostics in transportation kits provided. The primary objective of the research study will be to establish the relationship between the change in disease activity and CBCAPS levels. A total of 3-4 study visits are expected in the time period of the trial to include baseline, 3 month and 6 month and/or EOS for up to 200 total CBCAPS determinations. In addition, the Lupus AVISE testing includes measures for antibodies to extractable nuclear antigens. There will be no protocol intervention into the study other than the transport of deidentified blood samples (which will be included in the informed consent procedures) and the physician will be blinded to CBCAPS results. Clinical information will also be withheld from Exagen until end of study.

CBCAPS consisting of C4d deposited on erythrocytes (EC4d), B lymphocytes (BC4d), platelets (PC4d) and CR1 expressed on erythrocytes (ECR1) will be measured using a validated FACS assay.

Methods: For EC4d and ECR1: whole blood (50µl) is washed with Dulbecco's phosphate buffered saline, centrifuged for 5 minutes (800g) and erythrocytes pellets are resuspended with 500µl of 1% normal goat serum solution (Jackson Immunoresearch Laboratories, West Grove, PA). A 10µl erythrocyte suspension is subsequently stained with purified mouse monoclonal antibodies against human C4d (mouse anti human C4d, Quidel inc, San Diego), human CR1 (mouse anti-human antibody produced by Taconic Biotechnology, Hudson, NY), or alternatively using non-specific mouse anti-human IgG1 kappa antibody (MOPC-21, BD Biosciences, San Jose, CA) for 45 minutes at 4°C. Samples are then washed as described above. Erythrocyte pellets are re-suspended in a solution (25 µl) containing goat anti-mouse antibody conjugated to fluorescein isothiocyanate (FITC, Jackson ImmunoResearch Laboratories, West Grove, PA) for 45 minutes at 4°C (in the dark). Following staining, washing and resuspension with 250µL of cold 1% normal goat serum solution the erythrocytes are subjected to FACS analysis for detection of C4d or CR1 deposited on cell surface.

BC4d levels: following lysis of erythrocytes from whole blood (700µl) using ammonium chloride-based reagent (BD Pharm Lyse, BD Bioscience, San Jose, CA) and centrifugation (5 minutes at 800g), cell pellets are resuspended in 500µl of a 1% normal goat serum solution and stained using monoclonal C4d antibody (45 minutes at 2-8°C) as described above. A 25 µl cell suspension is subsequently stained using purified mouse monoclonal antibodies against human C4d or non-specific mouse anti-human IgG1 kappa antibody as above for 45 minutes at 4°C. Cell surface C4d staining is detected using goat anti-mouse fluorescein isothiocyanate (FITC) antibody (45 minutes at 2-8°C, dark). A monoclonal antibody against human CD-19 (CD-19 reacts with the 95 kDa type I transmembrane glycoprotein expressed during all stages of B-cell differentiation and maturation) conjugated to R-phycoerythrin (R-PE) is used to detect the C4d complement activation derived fragment specific to the B-lymphocytes.

PC4d levels: platelet cells obtained from patient whole blood samples are tested using the C4d monoclonal antibody to measure cell surface levels of C4d by FACS as above. Whole blood samples (50µl) are diluted and stained with the monoclonal antibody against human C4d (45 minutes at 2-8ºC), followed by staining with goat anti-mouse conjugated to FITC (45 minutes at 2-8°C, dark). A monoclonal antibody against human CD-42b conjugated to R-PE is used to identify the C4d complement activation derived fragment specific to the platelets.

All FACS analyses use a Beckman Coulter FC500 cytometer and CXP software (Beckman coulter, Brea CA). The mean fluorescence intensity (MFI) for the isotype background control and each complement protein (C4d, CR1) is obtained, and the net MFI is then determined by subtracting the non-specific MFI from the specific MFI results.

A secondary objective will consist of support studies for other diagnostic test development to help select and guide dosage of standard of care treatments. The Principal Applicant for these materials at Exagen has previously applied information on azathioprine and methotrexate metabolism to focused pharmacologic studies and the current plan is to use the CBCAPS study to explore some additional questions that could lead to improved pharmacologic monitoring of immune suppressants that are currently being selected and dosed largely empirically in the lupus population. The proposed exploratory studies will be to study (without interfering with) the standard of care changes that will be applied in the protocol over serial visits) and explore the relationship of drug levels of immunosuppressants and their metabolites with outcomes. Biological materials including plasma, red cells and genetic materials from consenting patients will be stored for future correlation studies of pathway metabolites with relevant treatment-induced pharmacodynamic changes. Plasma, red cells and genetic materials will be extracted from the same small whole blood sample received for CBCAPS analysis. For example this might include correlation of adenosine pathway-induced inflammatory signals vs. lymphocyte subset markers to clinical efficacy and pharmacokinetic markers (e.g. metabolites of 6 mercaptopurine in the case of azathioprine or methotrexate polyglutamates in the case of methotrexate). The goal is to improve the diagnostic capabilities of tests supportive of improved pharmacologic

application of standard of care interventions in SLE by specific identification of relevant proteomic and genomic markers associated with treatment efficacy and outcome of SLE. In collaborative work, these findings may be integrated with the results of other biomarkers being studied by other teams working on the ABC study.

For Methotrexate polyglutamate and azathioprine levels determination the method will used liquid chromatography (Dervieux et al Clin Chem 2003; Dervieux et al Clin Chem 1998), a portion of whole blood received for CBCAPS analysis will be centrifuged and red cells pellets will be washed with saline. Following red cell lysis packed RBC hemolysate will be homogenized with water and perchloric acid will be added to the mixture, vortexed and centrifuged. The acidic supernatant will be directly injected onto the HPLC system for MTXPG analysis while a portion will be heated for one hour to hydrolyze azathioprine nucleotides to their respective base. The HLPC separation will be achieved with linear gradient of acetonitrile on reversed phase colums. MTXPG photolytic product will be measured using flurometric detection while azathioprine metabolites will be measured using UV. Results will be reported as nmol/L packed red blood cells.

Materials Transfer Agreement Exagen will be restricted to the studies described in a Materials Transfer Agreement between Exagen and OMRF prior to the shipment of samples.

Study of Abatacept Levels is Not Approved For This Protocol. Exagen requested from BMS the possibility of studying Abatacept levels in the samples. This has not been approved and it is agreed that Exagen will be prohibited from doing so at this time.

APPENDIX 4: Ancillary Project to be Performed by Dr. Joseph Craft, Yale University

This project will track phenotypic changes in T follicular helper cells before and after treatment with abatacept. These findings will be correlated with clinical results and might later be compared to other biomarker studies being performed by members of the ABC team at the discretion of Dr. Craft. A Materials Transfer Agreement will be developed between OMRF and Yale University to govern this project and the use of blood samples. A summary of this project, written by Dr. Craft is below:

Significance. Systemic lupus erythematosus (SLE) is characterized by the generation of pathogenic autoantibodies. In both humans and mice with lupus, such autoantibodies undergo affinity maturation, indicative of a breakdown in germinal center (GC) B cell tolerance[1]. In GCs, T follicular helper (Tfh) cells provide B cells with survival and differentiation signals, including CD40 ligand (CD40L), programmed death receptor-1 (PD-1), and IL-21, essential for B cell selection with maturation into memory B cells and long-lived antibody-secreting (plasma) cells, as we have recently reviewed[2,3]). Dysfunctional Tfh cells are likely to be a main contributor to the development of systemic autoimmunity[4-6], a notion supported by the finding that abrogation of Tfh cell development or function in murine lupus is therapeutically beneficial, as we and others have shown[5-9]. Yet, the exact role of these cells in the genesis of immune, and in particular, autoimmune responses, remains incompletely understood, as does their post-GC fate and their contribution, if any, to the pool of memory T cells that provides B cell help for recall responses in mice and in humans[10-13], and that are presumably important in recall of pathogenic autoreactive memory B cells in patients with SLE. The goal of our proposal is to seek and identify these cells in the blood of humans with SLE, during and after remittitive therapy. Our specific aim is to:

Aim: Seek and characterize circulating follicular helper T cells in patients with SLE, during and after therapy that potentially alters their development and ability to promote autoreactive, and pathogenic, B cell activation.

Methods

We will analyze PBMCs from patients (1-2 green [heparinized] top tubes, shipped overnight), asking if they have circulating Tfh (cTfh) cells, and assessing their phenotype and their relationship to disease activity and therapeutic intervention. We plan to enumerate cTfh and CD4 T central memory (Tcm) cells, respectively; as Tcm cells home to follicles of SLOs, and perhaps contribute to reactivation of atuoreactive memory B cells therein, the residence of Tfh cells, it is critical to distinguish these populations. Markers to be used for cTfh cells include CXCR5, ICOS, IL-21, and PD-1, with CCR7 and CD62L added to distinguish Tcm cells. We will also determine the frequency of plasmablasts, correlating them with disease activity. We anticipate that $CXCR5^{hi}ICOS^{hi}PD\text{-}1^{hi}$ CD4 T (cTfh) cells will be expanded in SLE patients, with decreases following appropriate therapeutic intervention, and corresponding increases upon tapering of therapeutic agents. cTfh cells should be IL-21 competent with lower expression of CCR7, the latter compared to Tcm cells, enabling the distinction between these subsets. PD-1, but not ICOS or CXCR5, expression should be elevated in cTfh

cells from SLE patients compared to controls, with its MFI correlated with the SLE activity (SLEDAI), circulating plasmablasts, and anti-dsDNA antibody titers.

We anticipate that these results will demonstrate that cTfh cells will be associated with disease activity in SLE, and suggest their presence indicates aberrant homeostasis of T-B cell collaboration and a causal relationship central to disease pathogenesis. We also expect to underscore the idea that Tfh cells are a valid therapeutic target in SLE.

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APPENDIX 5 ANCILLARY STUDY TO BE PERFORMED BY DR VASILEO KYTTARIS AND DR GEORGE TSOKOS OF HARVARD UNIVERSITY

Rationale: T cells from patients with systemic lupus (SLE) have a strong calcium response (1) to T Cell Receptor engagement. This causes egress of the transcription factor NF-ATc2 into the nucleus at higher rates than is found in healthy volunteers (2,3). The enhanced T Cell response may be due to aggregation of lipid rafts (4), substitution of CD3-chain/ZAP-70 signaling by Fc receptor (FcR)/Syk (5,6), and/or mitochondrial hyperpolarization (7) SLE T cells have been found to provide aberrant help to B cells leading to increased expression of costimulatory molecules, such as CD154, (or CD40L) (8) with infiltration into diseased tissue by specialized T cells which produce the proinflammatory cytokine interleukin-17 (IL-17) (9). In a recent study, we demonstrated that MRL/*lpr* mouse T cells provide aberrant help to normal mouse B cells in a calcineurin dependent manner, linking SLE T cell hyperactivity to T cell helper function. Moreover, we showed that the enhanced calcium/calcineurin/NF-AT pathway in human and murine SLE T cells can be suppressed in the presence of dipyridamole, a recently recognized specific inhibitor of calcineurin–NF-AT interactions (10). Finally, administration of dipyridamole to MRL/*lpr* mice improved disease pathology.

Since abatacept interferes with cognate B and T cell interactions and may influence the phenotype and/or prevalence of IL-17 producing T cells, we propose to study SLE samples before, during and after treatment with abatacept or placebo in order to determine the impact of this treatment on T Cell stimulated cytokine production.

Methods: Isolation and Stimulation of T Cells for Assessment: T cells will be isolated from peripheral blood samples (20 cc) at OMRF by negative selection using a magnetic bead process that is in frequent use at OMRF. Cells will be incubated in RPMI 1640 medium with 10% (volume/volume) heatinactivated fetal calf serum (FCS; Sigma-Aldrich) supplemented with L-glutamine and 100 units of penicillin and 100 _g of streptomycin per ml. These incubations will take place in a culture incubator at a temperature of 37°C in a humidified atmosphere containing 5% CO2. Cells will be stimulated with plate-bound anti-CD3 antibody and anti-CD28 antibody for 48 hours. To achieve this 24 well plates will be coated with anti-CD3 and anti-CD28 antibodies in 1 mL of PBS in each well and the well plate incubated for 2 hr in 37C prior to emptying the wells and adding the cell suspension. Supernatant will be isolated from 0, 24, 48 hour cultures and frozen until batched shipments to Boston are possible. The cells will then be lysed in RLT buffer for retrieval of mRNA.

After transfer of these pre-processed samples to Boston, immunoglobulin and cytokines will be measured by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions using a kit from Immunology Laboratories. Human CD154 and murine CD154 were measured using an ELISA kit from R&D Systems and an ELISA kit from PromoCell, respectively, according to the manufacturers' instructions. Human cytokines will be measured using flow cytometry–based cytokine bead array systems (BD Biosciences).

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APPENDIX 6: STUDIES BY BMS TRANSLATIONAL R&D, PK TEAM, GENETICS and EPIGENETICS TEAMS

Rationale:

1. Patient Subset and PD Analyses: To expand on the proposed biomarker endpoints incorporated into the study, and further support the goal of identifying phenotypes and or signatures that may stratify patients with regard to clinical response to abatacept, BMS proposes to interrogate additional mechanism based and exploratory biomarkers as well as perform additional data analyses using clinical samples from this study.

2. PK and immunogenicity studies: To better understand dose/effects and to illuminate PD analysis.

EXPERIMENTAL PLAN

Correlation of target and pathway-specific receptor levels with clinical response. Aberrant receptor expression and numerous dysregulated signaling pathways in peripheral T/B lymphocytes and other antigen presenting cells (APCs; monocytes, dendritic cells), leading to auto-antibody production, are associated with SLE disease pathogenesis, and support the development of co-stimulation blockade inhibitors, i.e. abatacept, for therapeutic intervention2,[3]. This proposed analysis would measure baseline levels of constitutively expressed receptors in the co-stimulation cascade, including CD28, CD40 and CD86 on T cell subsets, B cell subsets, monocytes and dendritic cells using flow cytometric methods, for correlation with clinical response measures. .A similar analysis was performed measuring CD28 levels in rheumatoid arthritis patients treated with abatacept. In this study, decreases in CD4+ and CD8+ / CD28 negative T cells were observed over 48 weeks of abatacept treatment, and correlated with improvements in the DAS28-CRP score [1]. For the ABC study, baseline receptor levels will be tracked in a similar manner and evaluated for changes from baseline as well as correlations with changes in disease indices.

Evaluation of soluble and cell surface activation markers for correlation with clinical response. Inducible co-stimulatory molecules are often expressed constitutively on peripheral leukocytes in SLE patients, indicating a chronically activated phenotype[2,3,4]. Moreover, soluble receptors associated with B7/TNFR family members have been observed at elevated levels in SLE patients and are associated with increased disease severity. [5] Using flow cytometric and multiplex serum methods, we will measure a panel of co-stimulation-related molecules on peripheral leukocytes as well as in serum samples that may both correlate with clinical response and show pharmacodynamic changes over the course of abatacept treatment. These will include, but are not limited to cell surface CD25, CD69 and CD40L, ICOS, PD-1, CD244, CD80, HLA-DR and others on leukocyte immunophenotypes. Pro-inflammatory serum analytes will include but are not limited to sCD30, sIL-1RI and II, sIL-2Rα, sIL-4R, sIL-6R,

sTNFRI and II, FLT3L[6], solCD62L, pentraxin 3, APRIL, TWEAK, ST-2, and a-defensin 3. Exploratory analyses of urine analytes will also be performed and will include but are not limited to uMCP-1, uTWEAK, uNGAL,and IL-18.

Evaluation of gene expression profiled related to T cell / APC mRNA pathway signatures, Unpublished studies from BMS laboratories have identified genes that are up- or down-regulated during activation of specific co-stimulatory pathways, e.g., anti-CD3/CD28 stimulation of T cells, and soluble CD40L stimulation of B cells and dendritic cells. It is therefore of interest to interrogate mRNA profiles from patients for mRNA signatures indicating an activated T cell / APC phenotype, for correlation with clinical response. Additionally, we propose to track changes in these pathway-specific profiles to evaluate the impact of abatacept treatment on mRNA levels.

Measurement of complement C3d deposition on T cells as a measure of T cell responsiveness. A recent publication identified complement C3d deposition on T cells at increased levels in SLE patients versus healthy controls. C3d deposition was associated with decreased calcium responsiveness and increased cytokine production, and appeared to localize at lipid rafts[7]. Given that T cell:APC co-stimulation also co-localizes to lipid raft regions, it will be informative to ascertain the effects, if any, of abatacept treatment on C3d+ T cell levels over time for correlation with cytokine responsiveness. C3d+ T cells may represent a hyperactive subpopulation that contributes to the pathogenesis of SLE.

Methods and analysis. CD4+ and CD8+ T cell subtypes, including naive, central and effector memory T cells, double negative (DN), Tfh[8], and CD3+ γδ T cells, naive and memory Bs cells, plasmablasts, monocytes, plasmacytoid and myeloid dendritic cells for cell surface or intracellular expression of pathway-related markers. Frequency of the above cell subtypes will also be tracked as a percentage of total T cells, B cells, or leukocytes. Samples will be analyzed by multicolor flow cytometry using established phenotypic markers. Soluble receptor panels in serum or plasma will be analyzed by Luminex, other multiplex technologies, or ELISA.

While this study is not statistically powered for detailed SNP analysis, samples will be assessed to determine the frequency of both disease-associated (e.g. PDCD1, RUNX1, PTPN2, IRF5) and pathway-associated (e.g. CTLA4, CD28, ICOS) SNPs that have demonstrated associations with SLE disease susceptibility. Additionally, gene-specific DNA methylation changes have been demonstrated to occur in SLE and also may have associations with SLE disease severity and flare. DNA samples will collected for whole genome DNA methylation analysis. More extensive mRNA profiling may be performed using Affymetrix for whole genome profiling, or targeted mRNA panels may be analyzed by TLDA,OpenArray or other technologies.

PBMCs will be isolated, frozen and banked, then batch analyzed for C3d levels on resting T cells, cytokine levels (e.g., IL-2, IL-4, γIFN and IL-17) and C3d levels following anti-CD3/anti-CD28 stimulation. In addition to C3d deposition, other functional studies may be performed, including but not limited to mitogen and antigen response assays.

Additional Genomic DNA analysis and epigenetic evaluation. While this study is not statistically powered for detailed SNP analysis, we propose to collect samples to determine the frequency of both disease associated (e.g. PDCD1, RUNX1, PTPN2, IRF5) and pathway-associated (e.g. CTLA4, CD28, ICOS) SNPS that have demonstrated associations with SLE disease susceptibility.

Additionally, gene-specific DNA methylation changes have been demonstrated to occur in SLE and also may have associations with SLE disease severity and flare. DNA samples will be collected for whole genome DNA methylation analysis.

PK Studies:

1. PK samples at baseline (Day 1) and at pre-dose of Months 1 (Day 28), 2 (Day 57), 3 (Day 85), 4 (Day 113), and with matching immunogenicity at month 6 (Day 169) in the DB period, as well as at follow-up visits at Months 7, 8 and 12 will be analyzed for Abatacept treated patients. These data can provide information of immunogenicity rate and trough drug levels following 125 mg SC Orencia in SLE. The results are also useful for comparison with IV Orenca as well as to gain some understanding of how to interpret PD variables.

2. PK parameters such as trough concentrations can be derived from the concentration-time data.

Sample Required:.

Maximum 30 ml blood and 10 ml urine at baseline, 3, 6, 9 and 12 months or early termination visit. Saliva is also being requested. Blood samples requested include 1 x 2 ml ACD-A blood tube, 2 x-1ml serum samples 1 x 8.5ml CPT tube for PBMC collection Two (2) PAXgene RNA tubes, 5 ml EDTA tube.

However, please note that we are minimizing the total amount of blood donation required for these studies by consolidating use of materials between BMS and Oklahoma scientific groups for different analyses, making more efficient use of available materials.

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APPENDIX 7: Repository

In addition a small repository will be set aside to provide backup materials and to be able to make some materials available to other investigators in the future. Given the scope of studies already included in this protocol this repository will be quite modest. The informed consent will describe the currently planned ancillary studies and explain the purpose of the repository and patients will have the opportunity to give or withhold advance permission for use of their samples in future IRB-approved studies. One Paxgene tube, sera, and EDTA for a total of 20cc blood as well as up to 20 cc urine and up to 5 cc saliva will be set aside in this repository.