Title

Phase IV Open-Label Study To Evaluate Biomarkers to Predict the Efficacy of Abatacept in Subjects with Rheumatoid Arthritis

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Protocol Synopsis

Study Title	Phase IV Open-Label Study To Evaluate Biomarkers to Predict the Efficacy of Abatacept in Subjects with Rheumatoid Arthritis
Sponsor	Bristol-Myers Squibb (BMS)
Indication	Rheumatoid arthritis (RA)
Objectives	The primary objective of this study is: • To evaluate if baseline levels of T cell-associated biomarkers predict efficacy of abatacept during 24 weeks of treatment in patients with moderate to severe active RA who have had an inadequate response to conventional disease modifying anti-rheumatic drugs (cDMARDs) The secondary objectives of this study are: • To evaluate if baseline levels of B cell-associated or other biomarkers predict efficacy of abatacept in patients with moderate to severe active RA • To evaluate the effects of abatacept on the phenotypic distribution of circulating T cell and B cell subsets and levels of T or B cell-associated or other biomarkers in patients with moderate to severe RA
Study design	This is a phase 4, single-center study in patients with moderate to severe active RA who have had an inadequate response to cDMARDs. Subjects are to be recruited over 16 months. All subjects receive abatacept 125mg subcutaneous injections every week for 24 weeks along with cDMARDs. Visits are scheduled at baseline, 6 weeks, 14 weeks and 24 weeks. Evaluation of primary endpoint occurs at week 14. All

	subjects receive a phone call from study personnel 4 weeks and 15 weeks after the last visit for post-study follow-up.
Number of subjects	25
Target population	Men and women ≥ 18 years of age, with moderate to severe RA who are currently experiencing an inadequate clinical response to cDMARDs therapy
Length of study	24-week treatment with a follow-up 15 weeks after the end of the treatment period
Investigational Medicinal Product	Abatacept 125mg subcutaneous injection every week
Assessment	Primary endpoint • Baseline levels of T cell-associated biomarkers or other biomarkers predict ACR20 response with subcutaneous abatacept at week 14 Secondary endpoints • Baseline levels of T cell-associated biomarkers or other biomarkers predict ACR20 response with subcutaneous abatacept at week 24 • Baseline levels of T cell-associated biomarkers or other biomarkers predict ACR50 & 70 response, EULAR good or moderate response, low disease activity (DAS28 <3.2 or CDAI≤10) or remission (DAS28 < 2.6 or CDAI≤2.8) with subcutaneous abatacept at week 14 and 24 • Change in phenotypic distribution of circulating T cell and B cell subsets, T cell-associated biomarkers and other biomarkers with subcutaneous abatacept at week 14 and 24 • Adverse event monitoring
Statistical analysis	The primary endpoint will be the AUC of the receiver operator characteristic (ROC) curves for the biomarkers predicting AC20 response at week 14. We assume that 60% of the

patients will respond to abatacept therapy based on the data from the AMPLE trial. Thus, a total sample size of 25 patients will yield approximately 15 responders and 10 non-responders. With this sample, the expected margin of error for 95% confidence intervals for the AUC will be 19% or 22% if the AUC is 0.8, or 0.7, respectively.

The area under the ROC curve (AUC) will be the primary measure of the predictive value of the biomarker. Estimates of the AUC's and 95% confidence intervals will be computed for each biomarker. We will also evaluate the predictive value of combinations of any or all baseline biomarker information used in linear risk scores derived using logistic regression models (outcome = response to abatacept therapy). We will evaluate each possible risk-score combination of biomarkers as a predictor by estimating the prediction error using leave-one-out cross-validation (at the 80% specificity cutoff).

Table of Contents

1. Background and rationale

Rheumatoid arthritis (RA) is a heterogeneous disease with multiple cells and cytokines contributing to its pathogenesis. Even if several new advanced therapies targeting a specific pathway in the pathogenesis of RA are available, the response to those treatments is highly variable and unpredictable. Currently, there are no reliable biomarkers to predict therapeutic response to targeted therapies. Many patients with moderate to severe RA have to undergo "trial and error" treatment plans until they find what agent is the most effective for their condition. Therefore, there is an urgent need for effective biomarkers that are predictive of treatment response in RA.

Abatacept is a fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment of the Fc domain IgG1 and works by blocking an interaction between CD80/CD86 on antigen presenting cells and CD28 on T cells. Unlike other targeted therapies for RA such as TNFα or IL-6 inhibitors, abatacept inhibits a pathway which is only involved in T cell activation. Abatacept is reported to be more effective in RA patients who are positive for anti-CCP and patients with the highest baseline anti-CCP concentrations have a better response (1). These results support the notion that abatacept is involved in modulation of adaptive immunity.

CD4 T cells play an important role in RA pathogenesis by stimulating effector cells including macrophages and B cells. In an "alternative" pathway, macrophages are activated and secrete pro-inflammatory cytokines including TNFα and IL-6 likely through Toll-like receptor engagement with lesser involvement of T cells. It has been shown that there are several synovial phenotypes in RA including myeloid, lymphoid, low inflammatory and fibroid with distinct gene expression signature (2). A recent study has demonstrated higher levels of T cells and B cells in synovium from anti-CCP positive RA patients compared to anti-CCP negative patients (3). These findings suggest there may be subsets of RA in which inflammation is primarily driven by T cells, macrophages, or both.

Soluble CD27 (sCD27) is released from activated T cells (4,5) and the levels of sCD27 in cerebrospinal fluid is studied as a diagnostic marker for multiple sclerosis (5). We have shown that serum sCD27 levels are elevated in RA patients compared to healthy controls and significantly higher in seropositive RA patients than in seronegative RA (unpublished data). It's been reported soluble CD28 (sCD28) and soluble CTLA4 (sCTLA4) are elevated in RA (6,7) and baseline numbers of circulating CD28-negative helper T cells (Th) and cytotoxic T cells (Tc) predict the response to abatacept although the number of CD28-negative T cells decreases progressively during therapy (8). The relationship

between the number of CD28-negative T cells and levels of sCD28, sCTLA4 or sCD27 remains to be investigated. Soluble CD40 ligand (sCD40L), a molecule from T cells, is elevated in RA and other autoimmune diseases (9) although it is also released from platelets. Soluble CD137 (sCD137) is released from activated T cells and is elevated in RA (10,11). ICOS plays an important role in development of T follicular helper cells (Tfh) and upregulation of ICOS on T cells is suppressed by abatacept (12). The significance of soluble ICOS (sICOS) in RA is not known although it is shown to be elevated in systemic sclerosis (13). Taken together, these markers could be potentially used to assess T cell activation in RA.

There are markers from other immune cells including macrophages, neutrophils and B cells that could be used to assess inflammation in RA along with T cell markers. Macrophage-associated biomarkers include soluble CD14 (sCD14), soluble CD 163 (sCD163) and calprotectin (S100A8/A9). Both sCD14 and sCD163 are primarily released from macrophages and correlate with disease activity in RA (14, 15). It has been shown sCD14 stimulates pro-inflammatory cytokine production in a manner that is dependent on the TLR4/CD14 membrane complex, NF-κB and inflammasome (16). Although calprotectin is released from macrophages, the main source is neutrophils, whose cytoplasmic content consists of up to 60% calprotectin. Calprotectin is an endogeneous ligand for Toll-like receptor 4 (17) and serum calprotectin levels correlate with synovitis measured by ultrasound (18). It has been reported calprotectin is a predictor of the response to treatments in RA (19). MPO-DNA complexes, a marker of NETosis, a special form of neutrophil death, in which citrullination of RA autoantigens occurs (20), correlate with RA disease activity as demonstrated by us (unpublished data). Other markers are derived from several cell types. Soluble CD25 (sCD25) is a marker for macrophage and T cell activation and the levels of sCD25 decrease in response to abatacept in RA (21). Soluble CD23 (sCD23) is released from activated B cells, monocytes and many other cells and may reflect B cell activity in RA (22,23).

Subsets of CD4 T cells are generated in RA and serum chemokine levels have been used to assess T cell subsets. T helper cell 1 (Th1) pathway is promoted by IL-12 and type I interferon (IFN) and associated with chemokines including CXCL10. It has been shown that type I IFN gene expression signature observed in a subset of RA patients is associated with the response to treatments in RA (24). Therefore, CXCL10, which is shown to correlate with disease activity in early RA (25), could be used as surrogate serum markers for both Th1 cells and type I IFN activities in RA patients.

Recently, PD-1hi CXCR5−T peripheral helper cell (Tph) pathway has been described in synovium of seropositive RA patients (26) as opposed to CXCR5+ T

follicular helper cells (Tfh) which primarily function in lymph nodes. One of the primary functions of Tfh and Tph cells is to stimulate differentiation of B cells into antibody-secreting plasma cells. Both Tfh and Tph pathways are associated with IL-21 and CXCL13, cytokines known to support GC formation and plasma cell differentiation. Serum CXCL13 levels are higher in seropositive RA (27) and may predict the therapeutic response in RA (28).

It has been reported that abatacept is more effective in anti-CCP-positive RA patients (1) and suppresses Tfh cell maturation and proliferation in murine models of RA (12). Abatacept treatment in patients with primary Sjogren's syndrome was recently reported to reduce circulating Tfh cells and lower the expression of the activation marker ICOS on T cells (29). Regarding B cell activation, abatacept has been shown to reduce serum ACPA and RF and lower the frequencies of post-switched memory B cells in RA (30). These results suggest that, inhibition of activated Tfh (and Tph) cells, leading to attenuated T cell-dependent B cell activation may underlie the efficacy of abatacept.

The intent of this study is to demonstrate whether baseline levels of the above biomarkers are helpful in predicting the response to abatacept in RA patients who have an inadequate response to methotrexate and other conventional disease modifying anti-rheumatic drugs (cDMARDs). Further evaluation of the effects of abatacept on the phenotypic distribution of circulating T cell and B cell subsets will provide additional information regarding action mechanisms of abatacept.

2. Objectives

The primary objective of this study is

- To evaluate if baseline levels of T cell-associated biomarkers and other biomarkers predict efficacy of abatacept during 24 weeks of treatment in patients with moderate to severe active RA who have had an inadequate response to cDMARDs

The secondary objectives of this study are

- To evaluate change in phenotypic distribution of circulating T cell and B cell subsets, T cell-associated biomarkers and other biomarkers with subcutaneous abatacept in moderate to severe RA patients

3. Ethical Considerations

3.1. Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH), World Health Organization (WHO) and local directives.

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

3.2 Institutional Review Board

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment material, and any other written information to be provided to subjects. The investigator or designee should provide the IRB with reports, updates, and other information according to regulatory requirements or institutional procedures.

3.3 Informed Consent

Investigators will ensure that subjects are clearly and fully informed about the purpose, potential risk, and other critical issues regarding clinical studies in which they volunteer to participate. The consent form must adhere to the ethical principles that have their origin in the Declaration of Helsinki. The informed consent will include relevant safety information regarding dose and schedule of investigational product, and detailed information regarding other medications and study procedures. The informed consent will include investigator contact information, and information regarding the role of sponsor BMS to provide funding and investigational product for this study.

Study participants will be provided with information regarding the use and access of their personal information and study records by the study team, the institution, the sponsor BMS, and health authorities. The investigator must ensure that a signed and dated informed consent form is obtained prior to any study procedures.

4. Study Design

4.1. Overview of study design

This is a phase 4, single-center study in patients with moderate to severe active RA who have had an inadequate response to DMARDs. A total of 25 patients are to be recruited over a planned recruitment period of 16 months.

All subjects receive abatacept 125mg subcutaneous injections every week for 24 weeks. The following DMARDs are permitted in this study: methotrexate, hydroxychloroquine, sulfasalazine and leflunomide. These DMARDs can be used alone or in combination, except for the combination of methotrexate and leflunomide which is not allowed. Permitted DMARDs are continued at the stable pre-entry dose.

Visits are scheduled at baseline, 6 weeks, 14 weeks and 24 weeks. Evaluation of primary endpoint occurs at week 14. All subjects receive a phone call from study personnel 4 weeks and 15 weeks after the last visit for post-study follow-up.

4.2. Eligibility

Inclusion Criteria

1. Male or non-pregnant, non-nursing female
2. Age ≥18 years
3. Body weight ≤120kg
4. Classification of RA according to the 1987 ACR criteria or 2010 ACR/EULAR criteria
5. Symptoms of RA present for at least 3 months and less than 10 years prior to screening
6. Clinical Disease Activity Index (CDAI) ≥16 corresponding to moderate to severe disease activity
7. Patients taking oral DMARDs must be on stable doses of DMARDs for at least 4 weeks prior to abatacept initiation
8. Treatment within the past year with either methotrexate (MTX), leflunomide (LEF), hydroxychloroquine (HCQ) and/or sulfasalazine (SSZ) for ≥ 8 weeks
9. Patient who have received one prior anti-TNF must have discontinued etanercept, infliximab, adalimumab, certolizumab, or golimumab for at least 6 months prior to screening
10. Patients taking oral corticosteroid, the dose must be ≤ 5 mg/day prednisone or equivalent
11. Females of childbearing potential and males with female partners of childbearing potential may participate in this study only if using a reliable means of contraception

Exclusion Criteria

1. Previous treatment with abatacept
2. Previous treatment with rituximab, tocilizumab, tofacitinib, sarilumab or anakinra
3. Previous treatment with IV immunoglobulin, plasmapheresis, alkylating agents such as cyclophosphamide
4. Intraarticular or parenteral corticosteroids within 4 weeks of screening
5. Rheumatic autoimmune disease other than RA including systemic lupus erythematosus, primary Sjogren syndrome, spondyloarthritis, systemic sclerosis, dermatomyositis, mixed connective tissue disease, vasculitis
6. Non-rheumatic autoimmune disease including inflammatory bowel disease, psoriasis, multiple sclerosis
7. Recurrent or chronic bacterial, viral, fungal, mycobacterial or other infections including HIV, Hepatitis B or C, latent TB (TB not adequately treated according to guidelines)
8. Primary or secondary immunodeficiency
9. Current uncontrolled renal, gastrointestinal, endocrine, pulmonary, cardiac, or neurologic disease
10. History of malignancy within 10 years prior to screening, except for appropriately treated carcinoma in situ of the cervix and non-melanoma skin carcinoma
11. History of alcohol, drug or chemical abuse within 1 year prior to screening
12. Laboratory exclusion criteria at screening including
-eGFR <30 ml/min
-ALT or AST >1.5 times upper limit of normal
13. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery during the study
14. Immunization with a live/attenuated vaccine within 4 weeks prior to screening
15. Pregnant or nursing women, or women of child bearing potential who plan to become pregnant prior to 14 weeks after the last dose of abatacept treatment.
16. Patients of reproductive potential not willing to use an effective method of contraception
17. Prisoners, or subjects who are compulsory detained

4.3. Concomitant medication and treatment

In addition to abatacept, patients receive permitted conventional DMARDs at a stable pre-entry dose. The dose of DMARDs at entry into the study should be continued without change during the study. Oral corticosteroid (5mg/day prednisone or equivalent) and NSAIDs are permitted during the study if the dose has been stable.

4.4. Premature withdrawal

Patients have the right to withdraw from the study at any time for any reason. All patients who withdraw from the study must return to the clinic for a complete final evaluation 1 week following the last dose of study drug.

5. Study Drug/Treatment

5.1. Investigational Product

The investigational medicinal product (IP) for this study is subcutaneous abatacept 125mg once weekly for 24 weeks. All study participants will take abatacept in combination with standard of care anti-rheumatic background therapy, including DMARDs.

5.2. Storage, Administration, and Destruction of Investigational Product

The sponsor, BMS, will provide the IP, abatacept, to the study site for use as specified in this study. Background therapy, including DMARDS, and anti-rheumatic therapies will not be provided by the study. IP will be stored in accordance with the package insert at Investigational Drug Services (IDS), a secure pharmacy. IDS will maintain a record of all IP received, including inventory and dispensation records. Study participants will be instructed to dispose of used IP in accordance with community standards or to return used IP to the site for destruction. If study participants return used IP to the study site, IDS will ensure destruction of used IP in accordance with established institutional policies.

IP will be dispensed only to study subjects who have met all the required eligibility criteria and are enrolled in the study. Participants will take their first and last dose of IP in the clinic. Participants are expected to take their study medication in the clinic at Day 0, Week 6, Week 14, and Week 24. All other study medication may be taken at home.

6. Study procedures

Table 6.1-1 Schedule of Assessments

Procedure	Baseline/Day 0 Visit	Week 6 Visit	Week 14 Visit	Week 24 Visit	Post Treatment 4 Week Follow Up (Telephone)	Post Treatment 15 Week Follow Up (Telephone)
Visit Window		+/- 5 days	+/- 5 days	+/- 5 days	+/- 5 days	+2 weeks
Informed Consent	x					
Eligibility Review	x					
Patient Self-Assessments						
MDHAQ	x	x	x	x		
Patient Global Assessment	x	x	x	x		
FACIT-F	x	x	x	x		
SF-12	x	x	x	x		
Physician Assessments						
Physician Global Assessment	x	x	x	x		
Symptom Targeted Physical Exam	x	x	x	x		
Complete Physical Exam	x					
Joint Exam	x	x	x	x		
Study Procedures						
Biomarker Blood Draw	x	x	x	x		
Laboratory Tests: CBC, CMP, ESR, CRP, Immunoglobulins A, G, M	x	x	x	x		
Vital Signs	x	x	x	x		
Height	x					
Ultrasound Exam	x		x	x		
Adverse Event Review	x	x	x	x	x	x
Medication Review	x	x	x	x	x	
Investigational Product Dispensation	x	x	x			
In clinic IP administration	x	x	x	X (Last Study Dose)		
Urine Pregnancy Test (WOCBP only)	x					

Baseline visit (Day 0)

The following procedures and assessments are to be completed during the baseline visit.

- Informed consent
- Review patient eligibility and ensure that all inclusion and exclusion criteria are met
- Patient self-assessment measures: MDHAQ, patient's global assessment, FACIT-F, SF-12
- Blood samples for laboratory tests: Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), Erythrocyte Sedimentation Rate (ESR), C Reactive Protein (CRP), IgG, IgM and IgA rheumatoid factor, IgG and IgA anti-CCP, Immunoglobulins G, M, A
- Biomarker blood draw (serum, PBMC)
- Joint exam
- Complete physical exam
- Vitals signs: blood pressure, pulse, temperature, weight, height
- Physician's global assessment
- Physician safety assessment
- Ultrasound exam
- Adverse event review
- Medication review
- For women of childbearing potential, a urine pregnancy test should be completed prior to dispensing study medication
- Study drug (abatacept) dispensation and in clinic injection

Treatment visit (Weeks 6, 14, 24)

Patients must return to the clinic for assessments at weeks 6, 14 and 24. The following procedures and assessments are to be completed during the treatment visits.

- Patient self-assessment measures: MDHAQ, PGA, FACIT-F, SF-12
- Blood samples for laboratory tests: Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), Erythrocyte Sedimentation Rate (ESR), C Reactive Protein (CRP), IgG, IgM and IgA rheumatoid factor, IgG and IgA anti-CCP, Immunoglobulins G, M, A
- Biomarker blood draw (serum, PBMC)
- Joint exam

- Symptom targeted physical exam
- Vital signs including blood pressure, pulse, temperature, and weight
- Physician's global assessment
- Physician safety assessment
- Ultrasound exam (weeks 14 and 24)
- Adverse event review
- Medication review
- Study drug (abatacept) dispensation and in clinic injection

Follow-up telephone contact (4 & 15 weeks after the final treatment visit)

Patients receive a follow-up phone call from study personnel 4 weeks and 15 weeks after the week 24 visit. Patients who discontinue from the study early will have telephone visits at 4 weeks and 15 weeks after their end of treatment visit, if continued follow up is acceptable. The following procedures and assessments are to be completed at the follow-up telephone contact.

- Follow-up on transition to standard of care (PT Week 4 only)
- Follow-up on any adverse events

7. Safety and Reporting

7.1. Adverse events

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment.

The causal relationship to study drug will be determined by a physician and will be used to assess all AE's. the causal relationship will be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not Related: there is not a reasonable causal relationship between study drug administration and the AE.

All AE's will be documented from the point the informed consent is signed through 100 days post treatment.

7.2. Serious Adverse Events and Reportable Medical Events

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death

- Is life threatening (defined as an event in which the participant 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
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgement, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.)
- Suspected transmission of an infectious agent via the study drug is an SAE

Following the subject's written consent to participate in the study and through 100 days post study treatment, all SAE's, whether or not related to the IP or study procedures must be collected. All SAE's will be reported to BMS within 24 hours of the study site becoming aware of the event. All SAE's will be reported by fax transmission or reported via email.

SAE Email Address: Worldwide.Safety@bms.com

SAE Fax Number: +1-609-818-3804

7.3. Pregnancy

If it is discovered a patient is pregnancy or may have been pregnant at the time of exposure to IP associated with this study, the pregnancy, AE's associated with maternal exposure and pregnancy will be reported to BMS within 24 hours of the site becoming aware. Every effort should be made to obtain follow up and pregnancy outcomes date for one year following the birth of the offspring.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS within 24 hours of the study site becoming aware.

Study participants who become pregnant during the study will have study treatment discontinued. The treating physician or study investigator will council the study participant on potential risks and treatment options available.

Pregnancy Email Address: Worldwide.Safety@bms.com

Pregnancy Fax Number: +1-609-818-3804

8. Statistical Analysis

8.1. Study end points

8.1.1. Primary end point

- Baseline levels of T cell-associated biomarkers or other biomarkers predict ACR20 response with subcutaneous abatacept at week 14 [Time Frame: 14 weeks]

8.1.2. Secondary end points

- Baseline levels of T cell-associated biomarkers or other biomarkers predict ACR20 response predict ACR20 response with subcutaneous abatacept at week 24 [Time Frame: 24 weeks]
- Baseline levels of T cell-associated biomarkers or other biomarkers predict ACR50/70 response, EULAR good or moderate response, low disease activity (DAS28 <3.2 or CDAI≤10) or remission (DAS28 < 2.6 or CDAI≤2.8) with subcutaneous abatacept at week 14 and 24 [Time Frame: 14 and 24 weeks]
- Change from baseline in T cell-associated biomarkers or other biomarkers with subcutaneous abatacept at week 14 and 24 [Time Frame: 14 and 24 weeks]
- Adverse event monitoring

8.2. Statistical and analytical methods

The primary endpoint will be the AUC of the receiver operator characteristic (ROC) curves for the biomarkers predicting AC20 response at week 14. We assume that 60% of the patients will respond to abatacept therapy based on the data from the AMPLE trial (31). Thus, a total sample size of 25 patients will yield approximately 15 responders and 10 non-responders. With this sample, the expected margin of error for 95% confidence intervals for the AUC will be 19% or 22% if the AUC is 0.8, or 0.7, respectively (32). This is a pilot study and the results from this study would be assessed in other cohorts with bigger subject numbers.

For each candidate biomarker, we will compute receiver operating characteristic (ROC) curves related to response rate to abatacept therapy. We will consider a patient to have responded positively to abatacept if they achieve ACR 20 response at week 14.

The area under the ROC curve (AUC) will be the primary measure of the predictive value of the biomarker. Estimates of the AUC's and 95% confidence intervals will be computed for each biomarker. We will also evaluate the predictive value of combinations of any or all baseline biomarker information used in linear risk scores derived using logistic regression models (outcome = response to abatacept therapy). We will evaluate each possible risk-score combination of biomarkers as a predictor by estimating the prediction error using leave-one-out cross-validation (at the 80% specificity cutoff). Similar analyses will be run evaluating the predictive power of the secondary-objective baseline patient characteristics

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