STUDY TITLE:

A phase I/II trial of Abatacept (Orencia) in the treatment of refractory non-infectious uveitis.

Study Drug

Abatacept

Support Provided By

Bristol-Myers Squibb, Co.

Sponsor Investigator/Institution

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PROTOCOL SYNOPSIS

Protocol Title:	**A phase I/II trial of Abatacept (Orencia) in the treatment of refractory non-infectious uveitis.**
Site Numbers & Names:	1 Site
Research Hypothesis:	Among subjects with uveitis that are refractory to conventional immunosuppressive therapy, abatacept is a safe and effective treatment and a decreased dose is effective for maintenance of therapy.
Study Rationale	The majority of non-infectious uveitis cases are thought to be immune-mediated, possibly triggered by environmental stimuli and mediated primarily by T-cells in patients with an immunogenetic predisposition. The implication of cell-mediated immunity in the pathogenesis of uveitis has provided a rationale for treatment with immunosuppressive medications such as corticosteroids, which have been shown to be effective in improving the signs and symptoms of ocular inflammation, as well as the prognosis for preservation of visual acuity. The well-known side effects of chronic corticosteroid therapy, however, have led ophthalmologists to employ corticosteroid-sparing agents to reduce the toxicity of long term corticosteroid use. Continuing effort is underway to identify more effective therapies, which would ideally focus on targeting the action of specific mediators of the immune response, allowing for increased efficacy and decreased side effects of treatment.
Study Objectives: **Primary:** **Secondary:**	To assess the safety of the study drug in patients with refractory, non-infectious uveitis. To assess the efficacy of the study drug in the treatment of subjects with refractory, non-infectious uveitis.
Study Design:	This is a randomized, controlled, dose-modification, phase I/II, prospective clinical trial to examine the safety and efficacy of abatacept in treatment of uveitis.
Study Schema **Drugs / Doses / Length of Treatment)**	Subjects will receive approximately 10 mg/kg abatacept infusions at Day 1, Day 15, Day 30 and then every 4 weeks for 6 months.Subjects will be randomized subsequently to receive either 5 mg/kg or 10 mg/kg doses every four weeks, and will continue receiving infusions for up to 2 years.

Accrual Goal: **(Total number of subjects)**	20 subjects with non-infectious uveitis refractory to standard immunosuppression.
Accrual Rate: **(Number of subjects expected per month)**	Enrollment expected at 1 subject per month.
FPFV: **LPFV:**	**3/2012** **3/2014**
Inclusion Criteria:	**Primary criteria are outlined below. Please see section 4.2 for complete criteria.** 1. Patients with vision-threatening autoimmune uveitis. 2. Failure to respond to prednisone and at least one other systemic immunosuppressive (such as methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, chlorambucil, or a tumor-necrosis factor blocker or other biologic response modifier (BRM)), or intolerance to such medications due to side effects. Washout periods will apply to all patients exposed to BRMs. 3. Patients of both genders ≥ 6 years old. There is no upper age limit as long as there are no other disqualifying health conditions.

Exclusion Criteria:	**Primary criteria are outlined below. Please see section 4.2 for complete criteria.** 1. Women of Childbearing Potential (WOCBP) who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for up to 10 weeks after the last dose of study drug. 2. Uveitis of infectious etiology. 3. Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease. 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 with evidence of active or latent bacterial or viral infection, including subjects with evidence of human immunodeficiency virus (HIV) detected during screening. 6. Subjects with herpes zoster or cytomegalovirus (CMV) that resolved less than 2 months before the informed consent document was signed. 7. Subjects with evidence of current or prior tuberculosis (TB). 8. Serious concomitant illness that could interfere with the subject's participation in the trial. 9. Subjects who are positive for hepatitis B surface antigen. 10. Subjects who are positive for hepatitis C antibody 11. Concomitant use of cyclophosphamide or cyclosporine (unless use is restricted to eye drops). 12. Are taking other biologic medicines to treat RA or JIA such as: Enbrel® (etanercept), Humira® (adalimumab), Remicade® (infliximab), Kineret® (anakinra) or Rituxan® (rituximab). You may have a higher chance of getting a serious infection if you take ORENCIA with other biologic medicines.

Criteria for Evaluation: **(Efficacy, safety, stopping rules, etc.)**	Safety assessments will be done at every visit including inquiring about systemic or ocular adverse events. Blood work and chest x-rays will be done as required for the study drug. The following clinical assessments will provide outcome data at screening, week 12, 24,,52, 76, and at 2 year study closure: Fluorescein Angiography, Ocular Coherence Tomography, graded assessment of anterior and posterior segment ocular inflammation, Best Corrected Visual Acuity, and patient and physician assessments of well-being utilizing Visual Analog Scales.
Statistics:	Safety measures will be assessed at every visit. At weeks 12, 24, 52, 76, and at study closure clinical efficacy will be assessed and compared to baseline values. If the subject is deemed a non-responder at this assessment, the subject will exit the study. For subjects who respond positively to treatment, clinical efficacy data will be collected at week 12, 24, 52, 76 and 104 and will be compared to the baseline values. The primary efficacy endpoint will be at 52 weeks.

1 INTRODUCTION

1.1 Research Hypothesis

Abatacept is a safe and effective treatment for subjects with uveitis refractory to conventional immunosuppressive therapy, and after induction with higher dose therapy (10 mg/kg/dose), will be able to be safely and effectively managedwith maintenance therapy at 5 mg/kg/dose in these subjects.

1.2 Product Development Rationale

Abatacept is a recombinant fusion protein consisting of the extracellular domain of human CTLA (cytotoxic T-lymphocyte antigen) 4 and a hinge fragment of the CH2-CH3 portions of the Fc domain of human IgG1 that has been modified to prevent complement fixation and antibody-dependent cellular cytotoxicity.

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

A key costimulatory receptor on T-cells is CD28. CD28 is constitutively expressed on resting T-cells and binds to both CD80 (B7-1) and CD86 (B7-2) on the APC.[1,2,3,4] A costimulatory signal is required not only for the full activation of naive T-cells, but also may be required for the survival of memory and autoimmune effector cells.[5,6] In the presence of CD28, successful costimulation may occur, leading to T-cell activation. When modulation of the T-cell activation is required, one operative mechanism is to reduce costimulation via expression of CTLA4 on the surface of T-lymphocytes. CTLA-4expression, which may begin 24 to 48 hours following initial T-cell activation, successfully interferes with CD28's ability to bind to its ligands on the APC; CD80 and CD86 preferentially bind to CTLA4 with a much higher avidity than with CD28. Although the precise mechanisms are as yet unclear, CTLA4 expression is associated with a decrease in T-cell activation. After the T-cell activity has been dampened, the CTLA4 recycles into the T cell's cytoplasm.

The CTLA4 section of abatacept binds specifically to CD80 and CD86 (B7-1 and B7-2, respectively) and down-modulates the CD28-mediated costimulation of T-cells. Thus, abatacept uses a segment of a molecule that is part of the normal immune homeostatic mechanism to suppress T-cell activity involved in the immunopathogenesis of autoimmune diseases. The Fc region of abatacept was engineered with several point mutations designed to inactivate it. Because of these changes, abatacept does not mediate pathways such as antibody-dependent cell cytotoxicity or complement-dependent cytotoxicity.[7]

1.2.1 Overview of Uveitis

The term uveitis is used clinically to describe a heterogeneous group of diseases having in common inflammation of intraocular structures. Despite accounting for <1% of ocular disease in most clinical settings, uveitis accounts for 10-15% of legal blindness in some series, and as many as a third of patients affected with the more severe manifestations of uveitis are blinded in series reported from tertiary centers[8]. In addition, uveitis disproportionately affects a younger population compared to more prevalent blinding diseases such as glaucoma and macular degeneration, leading to loss of a disproportionately high number of productive person-years to society. Therefore, despite its relative uncommonness, uveitis is a significant public health problem.

Although frequently associated with systemic inflammatory or autoimmune diseases such as sarcoidosis, multiple sclerosis, Behçet's disease, and the seronegative spondylarthropathies, a significant number of cases defy disease classification and are labeled idiopathic. In many such cases, disease may be limited to the eye. In general, non-infectious cases of uveitis are thought to represent immune-mediated disease, possibly triggered by environmental stimuli and mediated primarily by T-cells in patients with an immunogenetic predisposition.[9,10]

The implication of cell-mediated immunity in the pathogenesis of uveitis has provided a rationale for treatment with immunosuppressive medications such as corticosteroids, which have been shown to be effective in improving the signs and symptoms of ocular inflammation, as well as the prognosis for preservation of visual acuity.[11] The well-known side effects of chronic corticosteroid therapy, however, have led ophthalmologists to employ corticosteroid-sparing agents to reduce the toxicity associated with long term corticosteroid use. Unfortunately, each of these agents may be associated with undesirable toxicity.[12] Continuing effort is underway to identify more effective therapy,

which would ideally focus on targeting the action of specific mediators of the immune response, allowing for increased efficacy and decreased side effects of treatment.

1.3 Summary of Results of Investigational Program

The initial efficacy and safety of abatacept (previously known as CTLA4-Ig and BMS-188667) was established in clinical studies of rheumatoid arthritis (RA), psoriasis, and multiple sclerosis. Currently, there are no active registrational studies for psoriasis or multiple sclerosis. The subsequent registrational program was in juvenile idiopathic arthritis (JIA), with data being collected from the ongoing long-term extension portion. Current active registrational programs for abatacept include studies in systemic lupus erythematosus (SLE) including lupus nephritis, and psoriatic arthritis.

A full development program conducted in adult RA led to regulatory approval in the United States for this indication in December 2005, in Canada in June 2006, and in Europe in May 2007. In the US, abatacept now has two indications: (1) treatment of moderate to severe active RA in adults, and (2) treatment of moderate to severe (JIA in patients who have failed prior therapy with disease-modifying anti-rheumatic drugs (DMARDs). There are no reported or registered studies of abatacept for the treatment of inflammatory eye diseases, although many of the above noted diseases may cause ocular inflammation, providing a rationale for studying this indication.

1.3.1 Immunogenicity Experience with Abatacept

In the RA program, the frequency of development of anti-abatacept antibodies (ie, immunogenicity) was examined in 2337 subjects. Among all subjects, 62 of 2337 (2.8%) developed antibodies to abatacept. Overall, there was no apparent correlation of antibody development to clinical response or adverse events. However, the number of subjects that developed antibodies was too limited to make a definitive assessment. The potential clinical relevance of neutralizing antibody formation is not known.[13,14]

1.4 Overall Risk/Benefit Assessment

Existing data exists on the safety or efficacy of abatacept for patients with inflammatory eye disease is limited to small case reports; however; The published experience in patients with other immune-mediated diseases is instructive, and will be discussed below. In 2010, Zulian and colleagues reported a series of 7 children with juvenile idiopathic arthritis and uveitis, all of whom had failed therapy with multiple standard immunosuppresssives and TNF blockers, and noted six treatment successes using monthly intravenous abatacept. A respondent to this publication in February 2011 added

two other successfully treated patients, along with a single case report of one successful case in 2008.[15, 16] In the past decade, the development of biologic DMARDs such as TNF-α inhibitors, along with other advances and new insights into rheumatoid disease progression, have led to a re-evaluation of management of RA to include earlier use of DMARD and combination DMARD therapy to limit the occurrence of functionally significant complications. Similarly, early aggressive therapy of inflammatory eye disease may limit the occurrence of visually significant complications. The efficacy, tolerability, and safety profile of abatacept was demonstrated in the RA clinical development program. Abatacept, a biologic DMARD with a unique mechanism of action, has demonstrated a good efficacy/safety profile. Abatacept has been on the market in the US since January 2006 and in Europe since May 2007.

The major identified risk of abatacept is an increased incidence of infections. The abatacept RA program identified both non-serious and serious infections, mainly bacterial (upper respiratory tract infections, pneumonias) and viral (herpes simplex), as occurring more frequently in abatacept-treated subjects than in subjects on placebo. Most infections responded appropriately to treatment, and no major differences in outcome were apparent between abatacept and placebo. The risk for serious infections did not increase with increasing exposure in the open-label periods of the clinical studies.

The effect of increasing exposure on the risk of serious infections was assessed by comparing the incidence rate of serious adverse events in the "infections and infestations" classification over the cumulative double-blind and open-label study periods (10,365 person-years) with that observed during the double-blind study periods alone (1688 person-years). This analysis revealed that that the incidence per 100 person-years (double-blind versus cumulative) remained stable for serious infections (3.47 versus 2.98).[17] Opportunistic infections and tuberculosis (TB) were uncommon, although all subjects were screened for latent TB.

The overall risk of malignancy for abatacept-treated subjects was comparable to that of placebo-treated subjects during the double-blind periods. The effect of increasing duration of exposure on the risk of malignancy was assessed by comparing the incidence rates of malignancies (per 100 person-years) in the cumulative double-blind and open-label study periods (10,365 person-years as of December 2007) with that observed during the double-blind study periods alone (1688 person years). This analysis revealed that the incidence per 100 person-years (double-blind versus cumulative) remained stable for malignancies overall, excluding non-melanomatous skin cancer (0.59 versus 0.71). More specifically, the incidence rates for lung cancer (0.24 versus 0.16) and lymphoma (0.06

versus 0.07) remained stable. In addition, in double-blind and cumulative study periods, the incidence rate of malignancy (per 100 person-years) for abatacept-treated subjects was similar to that seen in the double-blind placebo group and RA cohort overall and for major categories (skin, solid, hematologic). Clinical presentation and incidence over time do not suggest increased risk with abatacept.[18]

Treatment with abatacept was associated with an excellent peri-infusional safety profile and a low level of immunogenicity. In the only existing study evaluating the safety and efficacy of abatacept or infliximab versus placebo (IM101-043, the ATTEST study), the safety and tolerability results through 1 year suggest that abatacept may have a superior safety and tolerability profile.[19]

In summary, the potential overall benefit/risk ratio for abatacept-treated patients in this study appears to be favorable. The risks are probably no worse than those of infliximab therapy, which has been extensively studied in inflammatory eye disease, and may be superior. To minimize the overall risk to participating patients, this protocol has inclusion and exclusion criteria appropriate to the population and proposed treatments, exclusionary screening tests, and specific follow up safety assessments. In addition, the adverse events and serious adverse events will be reviewed on an ongoing basis by the medical monitors and pharmacovigilance group to detect trends and any potential safety issues.

1.5 Study Rationale

As noted previously, non-infectious cases of uveitis are thought to represent immune-mediated disease, possibly triggered by environmental stimuli and mediated primarily by T-cells in patients with an immunogenetic predisposition. The implication of cell-mediated immunity in the pathogenesis of uveitis has provided a rationale for treatment with immunosuppressive medications such as corticosteroids, which have been shown to be effective in improving the signs and symptoms of ocular inflammation, as well as the prognosis for preservation of visual acuity. The well-known side effects of chronic corticosteroid therapy, however, have led ophthalmologists to employ corticosteroid-sparing agents to reduce the toxicity associated with long term corticosteroid use. Continuing effort is underway to identify more effective therapy, which would ideally focus on targeting the action of specific mediators of the immune response, allowing for increased efficacy and decreased side effects of treatment.

2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the safety of the study drug in this patient population, ascertained by tracking the type, frequency, severity, and relationship of adverse events during study treatment, and where possible, determining whether or not a causal link exists between the event and study therapy.

2.2 Secondary Objectives

To assess the efficacy of the study drug in the treatment of subjects with refractory, non-infectious uveitis and to assess the efficacy of a reduced dose as maintenance therapy. Refractory disease is defined as that which is unable to be successfully treated by corticosteroids and at least one "standard" immunosuppressive, or when toxicity makes such therapy untenable.

Efficacy of the study drug will be assessed using a composite clinical endpoint comprised of 4 criteria. Treatment will be judged to be successful if there is improvement in at least one of these criteria without significant worsening in any of them. These criteria include:

- Improvement by 2 or more lines of best-corrected ETDRS or Snellen visual acuity in at least one eye
- Reduction in dose of systemic corticosteroid or other immunosuppressive therapy by at least 50%
- Control of ocular inflammation, as judged on clinical criteria, according to standard methods
    - Reduction of anterior chamber cellular activity and/or vitreous haze by 2 grades, and to a level of trace or less (SUN)
    - Reduction of chorioretinal infiltrates or reduction of retinal vasculitis (documented by fundus photography and fluorescein angiography)
- Reduction of cystoid macular edema and/or retinal inflammation, as judged clinically and by fluorescein angiogram and/or optical coherence tomography.

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) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

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

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

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

3.2 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, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.3 Informed Consent

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

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

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study before clinical study participation. The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator. Minors who are judged to be of an age of reason must also give their written assent.

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

This is a single-center, randomized, , dose-ranging, prospective clinical trial to examine the safety and efficacy of abatacept in treatment of refractory uveitis. Subjects will

receive 10 mg/kg intravenous infusions at Day 1, Day 15, Day 30 and every 4 weeks for 6 months, then subjects will be randomized to receive either 5 mg/kg or 10 mg/kg infusions every 4 weeks for up to 1.5 years after to ascertain the effectiveness of the lower dose in maintaining control of inflammation. Subjects will undergo efficacy assessments at weeks 12, 24, 52, 76, and 104 and non-responders will be removed from the study.

The study will be split into 2 segments. The first segment will be Weeks 0 through 24 in which the subjects will receive the standard, validated dose of 10 mg/kg and will undergo graded outcome assessments along with receiving study drug. Upon completion of the first segment, subjects will be randomized to continue receiving study drug masked at either the standard dose of 10 mg/kg or at a reduced dose of 5 mg/kg. Subjects may continue receiving infusions for an additional 1.5 years.After week 52, the subject will be followed as clinically necessary by the physician and will be seen for study grading visits at week 76 and week 104. Concomitant medication exclusion criteria will still need to be followed during this period.

Due to the inherent heterogeneity among this patient group, it is impractical to utilize a single primary end-point to assess effectiveness of the treatment. Different patients are expected to show improvements in different aspects of the clinical assessments, which we would expect to be captured by use of the composite endpoint utilized in this trial. It is because of this heterogeneity that we will enroll 20 subjects who would be expected to have a broad variety of autoimmune uveitides including the following: sarcoidosis, idiopathic intermediate, idiopathic posterior, idiopathic panuveitis, birdshot chorioretinopathy, pars planitis tubulointerstitial nephritis and uveitis (TINU), Vogt-Koyanagi-Harada syndrome (VKH), juvenile idiopathic arthritis (JIA), multifocal choroiditis, retinal vasculitis, and sympathetic ophthalmia.

A detailed description of procedures and timelines can be found in Section 6.

4.2 Study Population

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

4.2.1 Inclusion Criteria

1) Signed Written Informed Consent

1. Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent

document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.

2) Target Population

1. Patients with vision-threatening autoimmune uveitis.
2. Refractory uveitis, defined as failure to effectively and durably respond to prednisone and at least one other systemic immunosuppressive (such as methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, or chlorambucil), or intolerance to such medications due to side effects.
3. Patients with bilateral disease with visual acuity of 20/40 or worse. Vision may be better based on unacceptable doses of systemic immunosuppressive agents. Investigator discretion may apply here.
4. Stable dose of corticosteroids and immunosuppression for at least four weeks. In the case where corticosteroid doses are urgently raised in this time period to treat an inflammatory exacerbation, the "flare dose" of corticosteroid will be used as the baseline level of corticosteroids for the purposes of outcome determination.
5. Screening laboratory test results should be acceptable to the Investigator prior to placing a subject on study drug.
6. Must be willing and able to adhere to the study visit schedule and other protocol requirements.

3) Age and Gender

1. Men and women, ≥ 6 years of age. There is no upper age limit as long as there are no other disqualifying health conditions.
2. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 10 weeks after the last dose of study drug to minimize the risk of pregnancy.

   WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as:

   - Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or
   - For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL.

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

A male subject of fathering potential must use an adequate method of contraception to avoid conception throughout the study and for up to 10 weeks after the last dose of study drug to minimize the risk of pregnancy.

4.2.2 Exclusion Criteria

4) Gender and Reproductive Status

1. WOCBP who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for up to 10 weeks after the last dose of study drug.
2. Women who are pregnant or breastfeeding.
3. Sexually active fertile men not using effective birth control if their partners are WOCBP.

5) Target Disease Exceptions

1. Uveitis of infectious etiology.

6) Medical History and Concurrent Diseases

1. Subjects who are impaired, incapacitated, or incapable of completing study-related assessments.
2. Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease, whether or not related to RA and which, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study.
3. Female subjects who have had a breast cancer screening that is suspicious for malignancy and in whom the possibility of malignancy cannot be reasonably excluded by additional clinical, laboratory, or other diagnostic evaluations.
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. Existing non-melanoma skin cell cancers should be removed, the lesion site healed, and residual cancer ruled out before administration of the study drug.
5. Subjects who currently abuse drugs or alcohol.
6. History of opportunistic infections, including, but not limited to evidence of active cytomeglovirus, active Pneumocystis carinii, aspergillosis, or atypical mycobacterium infection within the previous 6 months.
7. Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral infections at the time of potential enrollment, including subjects with evidence of human immunodeficiency virus (HIV) detected during screening.
8. Subjects with herpes zoster that resolved less than 2 months before the informed consent document was signed.
9. Subjects who have received any live vaccines within 3 months of the anticipated first dose of study medication.

10. 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).
11. Subjects with evidence of current or prior tuberculosis.
12. Serious concomitant illness that could interfere with the subject's participation in the trial.
13. Subjects with Multiple Sclerosis or Behcet's Disease.

7) Physical and Laboratory Test Findings

1. Subjects must not be positive for hepatitis B surface antigen.
2. Subjects who are positive for hepatitis C antibody if the presence of hepatitis C virus was also shown with polymerase chain reaction or recombinant immunoblot assay.
3. Subjects with any of the following laboratory values
   i) Hemoglobin < 9.0 g/dL
   ii) WBC < 2000/mm^3 (< 2 x 109/L)
   iii) Platelets < 150,000/mm^3 (< 150 x 109/L)
   iv) Serum creatinine > 1.5 times the ULN
   v) Serum ALT or AST > 2 times the ULN
4. Any other laboratory test results that, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study.

8) Prohibited Treatments and/or Therapies

1. Subjects who have received treatment with any investigational drug within 28 days (or less than 5 terminal half-lives of elimination) of the Day 1 dose.
2. Concomitant use of cyclophosphamide (unless use is restricted to eye drops).
3. Are concomitantly taking other biologic medicines to treat RA or JIA such as: Enbrel® (etanercept), Humira® (adalimumab), Remicade® (infliximab), Kineret® (anakinra) or Rituxan® (rituximab). You may have a higher chance of getting a serious infection if you take ORENCIA with other biologic medicines. Washout period required for adalimumab and etanercept is eight weeks, and for infliximab is 12 weeks. Washout period for Rituxan is until return of detectable circulating B-cells. Washout period for calcineurin inhibitors, including cyclosporine, tacrolimus, and voclosporine, as well as for alkylating agents, will be four weeks.

9) Other Exclusion Criteria

1. 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 study treatment and withdraw from the study for any of the following reasons:

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

5 TREATMENTS

5.1 Study Treatment: Abatacept

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

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care are considered noninvestigational products. In this protocol, noninvestigational products include prednisone and other systemic immunosuppressives such as methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, and chlorambucil.

5.1.1 Identification

Abatacept (ORENCIA®) is supplied as a 250 mg/vial sterile, white, preservative-free, lyophilized powder for parenteral administration. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the solution is clear, colorless to pale yellow, with a pH range of 7.0 to 8.0.

Product: Abatacept for Injection (Abatacept = BMS-188667 + CTLA4Ig)

Potency: 250 mg/vial

Appearance: White to off-white, whole or fragmented cake in a vial

In addition, Norm-Ject® non-siliconized syringes and in-line filters will be supplied. Each investigator will be responsible for supplying any intravenous admixture solutions (Sterile Water for Injection, 5% Dextrose in Water Injection, 0.9% Sodium chloride Injection) needed for the reconstitution and dilution of investigational product identified in the protocol.

5.1.2 Storage, Handling, and Dispensing

The investigational product should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations.

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

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

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

A pharmacist or qualified personnel at the site will reconstitute the drug for intravenous (IV) administration. All reconstitution and dilutions must be performed using polypropylene nonsiliconized syringes (Norm-Ject®) manufactured by Henke Sass Wolf in Germany (to be provided by BMS).

NOTE: A separate needle and syringe must be used for each vial reconstituted.

Abatacept vials are sealed under vacuum. If any vials are found without this vacuum, they should be segregated and not used. These vials must be retained until reconciliation by your Study Drug Monitor.

NOTE: The vial should NOT be vented prior to reconstitution. To avoid foam formation following the addition of SWFI (Sterile Water for Injection), the vial should be gently swirled until the contents are completely dissolved. Upon complete dissolution of the lyophilized powder, the vial should then be vented with a needle to dissipate any foam that may be present.

Each vial of abatacept for injection, 250 mg/vial, should be reconstituted with 10 mL of Sterile Water for Injection (without bacteriostatic agent) to yield a concentration of 25 mg/mL. In order to minimize foaming, the stream of SWFI should be directed to the sides of the vial.

A sufficient excess of abatacept is incorporated into each vial to account for withdrawal losses so that 10 mL of the reconstituted solution containing 250 mg can be withdrawn for parenteral administration. After reconstitution of the product the solution must be diluted further with 5% Dextrose in Water Injection (D5W) or 0.9% Sodium Chloride (Normal Saline). For all doses the final total volume for infusion is 100 mL.

The continuous infusion solution must be filtered upon administration using an in line, sterile, non-pyrogenic, low protein-binding filter with a pore size of 1.2 μm. This infusion should be administered in a fixed volume of 100 mL over a period of not less than 30 minutes. Any unused portion of the infusion solution should not be stored for reuse.

No data is available on the compatibility of abatacept with other intravenous substances. Abatacept should be administered in a separate intravenous line whenever possible and not mixed with other medications. Assure adequate and appropriate flushing between any other drug substances if other drugs are administered through the same line sequentially. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and

administration sets. Care must be taken to assure sterility of the prepared solution, as the drug product does NOT contain any antimicrobial preservatives or bacteriostatic agents. Vials of abatacept for injection, 250 mg/vial, should be stored under refrigeration (28°C) and should be protected from long-term exposure to light. Intact vials are stable for at least one year under these conditions.

All dilutions of abatacept for injection must be used within the 24 hours after reconstitution of the original vial.

- Specific stability guidelines for each dilution are as follows:
- Reconstituted abatacept for injection, 25 mg/mL, may be stored at temperatures from 15°- 25°C and room light or at refrigeration (2°-8°C) for up to 24 hours in the original vial.
- Dilutions of reconstituted abatacept for injection from 1 to 25 mg/mL in NS or D5W in polyvinyl chloride (PVC) or non-PVC IV bags may be stored at temperatures from 15°-25°C and room light or at refrigeration (2°-8°C) for no more than 24 hours from the time of initial reconstitution.
- Diluted solutions of abatacept for injection are compatible with standard PVC IV infusion sets.

5.2 Drug Accountability

Please refer to Section 9.2 (Records Retention) for details on drug accountability requirements.

5.3 Selection and Timing of Dose for Each Subject

During the first 24 weeks, all subjects will receive approximately 10 mg/kg calculated based on the patient's body weight at each administration, rounded to the nearest 25 mg.

Abatacept will be administered as a 30-minute intravenous infusion. Following the initial administration, abatacept will be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter for up to 2 years. Any unused portions in the vials must be immediately discarded.

After the 24 week infusion, subjects who have responded to treatment will be randomized to receive either the standard 10 mg/kg dose or a reduced dose of 5 mg/kg, rounded to the nearest 25 mg.

5.3.1 Dose Modifications in the Absence of Adverse Events

In the absence of adverse events deemed at least possibly related to abatacept, subjects will complete their scheduled infusions as prescribed per protocol. For visits scheduled

for Day 15 and Day 29, the dose may be administered within 72 hours (± 3 days) before or after the target date to adjust for the subject's or site personnel's convenience. For all subsequent doses, a window of ± 7 days is acceptable.

5.3.2 Dose Modifications for Adverse Events

If there is evidence of toxicity, as determined by laboratory tests or by clinical assessment that could place the subject at increased risk in the judgment of the investigator, administration of abatacept should be interrupted and the investigator should notify BMS. Subjects may be considered eligible to continue with abatacept treatment only if full resolution of the adverse event is documented. If the adverse event completely resolves and the next dose of abatacept cannot be administered within 14 days of the target date, then that scheduled dose should be skipped. The next dose of abatacept should then be administered on the next targeted day for administration.

5.4 Concomitant Treatments

5.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited throughout the complete study period:

- Any biologic DMARD (such as but not limited to: anakinra, infliximab, etanercept, adalimumab, rituximab or any other investigational biologic).
- Cyclophosphamide, Cyclosporine
- Live vaccines.
- Use of any investigational drug other than study medication.

5.4.2 Other Restrictions and Precautions

5.4.2.1 Immunizations

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

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

Committee on Immunization Practices (CDC-ACIP) recommends that subjects should not be administered a live virus vaccination for at least 3 months after discontinuing high-dose corticosteroid therapy (defined as more than 20 mg of prednisone per day for more

than 2 weeks). In view of the long half-life of abatacept, study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of abatacept.

5.5 Management of Possible Acute Hypersensitivity Reactions to Abatacept

Hypersensitivity or acute allergic reactions may occur as a result of the protein nature of abatacept. In this study, subjects' vital signs will be monitored before and following administration of abatacept. Appropriate emergency equipment and qualified personnel must be available where the subjects are treated in the event of a serious anaphylactic reaction.

The following information is provided to assist in the recognition of hypersensitivity reactions and in the management of those reactions should they occur during or after the administration of abatacept. Care should be taken to treat any acute toxicities expeditiously, should they occur. The following equipment and supplies should be readily available when abatacept is administered: a portable tank or wall source of oxygen, endotracheal intubation set, oral airway, mask, manual resuscitation bag, syringes, injectable epinephrine, injectable antihistamine, and injectable glucocorticoids.

Signs and management of potential acute hypersensitivity reactions:

Sign	Management
Symptomatic Hypotension	Discontinue the abatacept infusion. Place the subject in the Trendelenburg position and administering IV fluid. Administer epinephrine, glucocorticoids, antihistamines, and pressor agents as indicated.
Dyspnea	Discontinue the abatacept infusion. Observe the subject for worsening of the event and for the appearance of additional signs and symptoms of anaphylaxis. Administer antihistamines, epinephrine, and glucocorticoids as indicated.
Acute Pain in Chest, Back or Extremities	These are potential signs of anaphylaxis. Follow the same treatment regimen as is used to treat dyspnea.
Chills, Fever, Urticaria, or Generalized Erythema	These may be signs of an allergic reaction to protein products. Treat by administration of acetaminophen and antihistamines.

Because abatacept has immunomodulatory activity, subjects may be at increased risk of infectious complications. Significant infectious complications should be treated

appropriately. Study medication should be withheld, and restarted only when the infection is clinically resolved.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Time and Events Schedule

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

6.1.1 Study Completion or Early Discontinuation Visit

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

6.1.2 Study Drug Discontinuation

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

Table 1: Time and Events Schedule for Protocol

Procedure	Screening	Day 1	Day 15	Weeks 4, 8	Week 12	Week 16, 20	Week 24	Weeks 28, 32, 36, 40, 44, 48	Week 52	Week 76, 104
Eligibility Assessments										
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Medical History	X									
TB Test	X									
Safety Assessments										
Physical Examination	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment			X	X	X	X	X	X	X	
Laboratory Tests	Xa								Xb	
Pregnancy Test	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments										
OCT	X				X		X		X	X
FA/FP	X				X		X		X	X
Inflammation Grading	X			Xc	X	Xc	X	Xc	X	X
Eye Exam/Visual Acuity	X			Xc	X	Xc	X	Xc	X	X
Visual Analogue Scale	X				X		X		X	X
Clinical Drug Supplies										
Infusion (every 4 weeks)		X	X	X	X	X	X	X	X	X
Randomization							X			

a. Lab tests include: HIV, Hep B surface antigen, Hep C antibody, Hemoglobin, WBC, Platelets, Serum Creatinine, ALT/AST, HCG

b. Lab tests include: Hemoglobin, WBC, Platelets, Serum Creatinine, ALT/AST

c. Weeks 8, 16 and Weeks 24, 32, 40.

6.2 Study Materials

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

6.3 Safety Assessments

All subjects who receive a dose of abatacept will be evaluated for safety at every visit. Safety outcomes include adverse events, clinically significant changes in vital signs, laboratory test abnormalities, and clinical tolerability of the drug. The investigator will determine the severity of each adverse event as mild, moderate, severe, or very severe. Laboratory findings that the investigator feels are clinically relevant should be recorded as adverse events. In addition, the investigator will determine the relationship of the adverse event to the administration of the study drug. Any occurrence of a SAE from time of consent forward, up to and including follow-up visits will be reported. See Section 7.3.1 for the SAE reporting procedures.

6.3.1 Physical Examinations

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

6.3.2 Tuberculin Skin Testing

A tuberculin skin test (PPD test: purified protein derivative tuberculosis skin test) should be performed and interpreted according to the applicable local Health Authority and/or Medical Society guidelines (those that provide recommendations for tuberculin skin testing for subjects who are to receive biologics, who are immunosuppressed, who have a prior history of BCG vaccinations,[20,21] or who have a prior positive test). Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG.

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

6.4 Efficacy Assessments

The efficacy assessments during the treatment phase of the study will be done at the intervals specified in the Schedule of Assessments. The following clinical assessments will provide outcome data: visual acuity, graded assessment of ocular inflammation, optical coherence tomography (OCT), fluorescein angiography (FA), and fundus photography.

6.4.1 Visual Acuity

Snellen best corrected visual acuity will be measured at screening/baseline, week 8, 16, 24, 32, 40, 52, 76 and 104. If the subject cannot read or is unfamiliar with the Roman alphabet, then the tumbling E chart will be used.

6.4.2 Graded Assessment of Ocular Inflammation

The grading of ocular inflammation will be performed at screening/baseline, week 8, 16, 24, 32, 40, 52, 76 and 104. The scales for vitreous haze and anterior chamber cells will be based off of the Nussenblatt scoring system and the SUN nomenclature (Appendices A, B).

6.4.3 Measurement of Macular Thickness Using OCT

OCT assessments will be used to document changes in macular thickness. OCT exams will be performed at the baseline visit and weeks 12, 24,52, 76 and 104. This assessment can be performed whenever clinically indicated.

6.4.4 Fluorescein Angiography

Fluorescein angiography will be performed at the baseline visit and weeks 12, 24, 52, 76 and 104. This assessment can be performed whenever clinically indicated. Fluorescein angiography will be used to document inflammatory signs by accepted criteria.

6.4.5 Fundus Photography

Fundus photography will be performed at the baseline visit and weeks 12, 24, 52, 76 and 104. This assessment can be performed whenever clinically indicated. Fundus photography will be used to document chorioretinal infiltrates and/or retinal vasculitis

6.5 Other Assessments

6.5.1 Ocular Examinations

Ocular exams will be performed using slit lamp and dilated fundus exams according to the Table.

6.5.2 Subject and Physician Global Assessments of Disease

The Subject and Physician Global Assessments of Disease Activity will be performed during baseline, week 12, 24, 52, 76 and 104 The assessments will be recorded on the subject's chart as a single vertical mark on a 100-mm VAS. The distance from the mark to the left-hand boundary of the scale will be recorded on the CRF.

6.5.3 Visual Analog Scale for Pain

The VAS for Pain will be completed during baseline, week 12, 24, 52, 76 and 104. The subject will be asked to place a vertical line on a 100-mm scale on which the left-hand boundary represents "no pain," and the right-hand boundary represents "pain as severe as can be imagined." The distance from the mark to the left-hand boundary will be recorded on the CRF.

7 ADVERSE EVENT REPORTING

7.1 Adverse Events

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

7.1.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event 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.

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

Although overdose and cancer are not always serious by regulatory definition, these events should also be reported to BMS in an expedited manner, as described in Section 7.2.

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

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- 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).

7.1.2 Nonserious Adverse Events

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

7.2 Assignment of Adverse Event Intensity and Relationship to Abatacept

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

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

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

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

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

7.3 Collection and Reporting

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

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

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

7.3.1 Serious Adverse Events

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

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

All SAEs should be faxed or emailed to BMS at:

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

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

MedWatch SAE forms should be sent to the FDA at:

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

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

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

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

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

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

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

7.3.2 Handling of Expedited Safety Reports

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

Other important findings that BMS may report as ESRs include increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures

that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety findings from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or the decision by BMS to end or temporarily halt a clinical study for safety reasons.

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

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

7.3.3 Nonserious Adverse Events

The investigator will begin collecting nonserious adverse event (NSAE) information once administration of the investigational product is initiated until completion of the study.

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

7.4 Laboratory Test Abnormalities

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

7.5 Pregnancy

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

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

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

7.5.1 Requirements for Pregnancy Testing

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

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

7.5.2 Reporting of Pregnancy

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

information on the outcome provided once it is available. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

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

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

7.6 Other Safety Considerations

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

8 STATISTICAL CONSIDERATIONS

8.1 Overview

This is a pilot study. The primary safety endpoint will be measured by tracking the type, frequency, severity, and relationship of adverse events to study treatment. The secondary efficacy analysis is to test whether at least 50% of patients show clinical improvement in our composite clinical endpoint, comprised of 1) improvement of visual acuity, 2) reduction of systemic corticosteroid and other immunosuppressive therapy, 3) improved control of inflammation, and/or 4) reduction of cystoid macular edema. Patients will serve as their own controls, and descriptive statistics will be utilized to determine effect of treatment within-patients and in the study cohort as a whole.

8.2 Datasets to be Analyzed

Visual acuity will be used to determine improvement by 2 or more lines of visual acuity. Concomitant medications will be used to monitor systemic corticosteroid and other immunosuppressive therapy. Grading of ocular inflammation using the anterior chamber cellular activity and protein flare, vitreous cellular activity and haze as well as the fundus photography will be used to analyze improved control of ocular inflammation. OCT and

FA will be used to analyze the reduction of cystoid macular edema and signs of retinal inflammation. Corticosteroid reduction from baseline will also be ascertained.

8.3 Endpoint Definitions

8.3.1 Safety Endpoints

This will be measured by tracking the type, frequency, severity, and relationship of adverse events to study treatment.

8.3.2 Efficacy Endpoints

The composite clinical endpoint for success will be comprised of 4 criteria. The primary efficacy endpoint will be at one year. Treatment will be judged to be successful if there is improvement in at least one of these criteria without significant worsening in any of them. These criteria include:

- Improvement by 2 or more lines of best-corrected ETDRS or Snellen visual acuity in at least one eye
- Reduction in dose of systemic corticosteroid or other immunosuppressive therapy by at least 50%
- Control of ocular inflammation, as judged on clinical criteria, according to standard methods
    - Reduction of anterior chamber cellular activity and vitreous haze by at least two grades and to a level of trace or less (SUN)
    - Reduction of chorioretinal infiltrates or reduction of retinal vasculitis (documented by fundus photography and fluorescein angiography)
- Reduction of cystoid macular edema, as judged clinically and by fluorescein angiogram and/or optical coherence tomography.

9 ADMINISTRATIVE SECTION

9.1 Compliance with the Protocol

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

All protocol amendments and revisions to the informed consent will be submitted to the BMS protocol manager and to the IRB/IEC. No protocol amendments will be

implemented until written approval has been given by the IRB/IEC, except when necessary to eliminate an immediate hazard to study subjects. Administrative letters should also be sent to the BMS protocol manager and IRB/IEC; however, they do not require approval.

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

9.2 Records Retention

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

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

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

9.3 Destruction of Investigational Product

If the investigational product is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

10 GLOSSARY OF TERMS

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

11 LIST OF ABBREVIATIONS

AB	Antibody
AE	Adverse event
ALT	Alanine Transaminase
APC	Antigen-Presenting Cell
AST	Aspartate Transaminase
BCG	Bacillus Calmette-Guérin
BMS	Bristol-Myers Squibb
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC-ACID	Centers for Disease Control and Prevention Advisory Committee on Immunization Practices
CFR	Code of Federal Regulations
CI	Confidence Interval
CMV	Cytomegalovirus
CRF	Case Report Forms
CRP	C-Reactive Protein
CTLA	Cytotoxic T-Lymphocyte Associated
CXR	Chest X-Ray
DMARD	Disease-Modifying Antirheumatic Drug
DNA	Deoxyribonucleic Acid
D5W	Dextrose (5%) in Water
EC	European Commission
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
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
MRI	Magnetic Resonance Imaging
NS	Normal Saline
NSAE	Non-Serious Adverse Event
NSAID	Non-Steroidal Anti-inflammatory Drug
OA	Osteoarthritis
PCR	Polymerase Chain Reaction
PPD	Purified Protein Derivative
PVC	Polyvinylchloride
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious Adverse Event
Se	Sensitivity
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
Sp	Specificity
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWFI	Sterile Water For Injection
TB	Tuberculosis
TNF	Tumor Necrosis Factor
ULN	Upper Level of Normal
VAS	Visual Analog Scale
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

12 APPENDICES

Appendix A:

Nussenblatt Scoring System

Nussenblatt RB, et al., Ophthalmology 92:467-471, 1985.

Grade of Vitreous Haze					
0	**0.5+**	**1+**	**2+**	**3+**	**4+**
Clear	Trace	Few opacities, mild blurring of optic nerve and retinal vessels	Significant blurring of optic nerve and retinal vessels but still visible	Optic nerve visible, borders blurred, no retinal vessels seen	Dense opacity obscuring optic nerve head

Standardized photographs illustrating the above may be found in the referenced article.

Appendix B:

Standardization of Uveitis Nomenclature (SUN)

Standardization of Uveitis Nomenclature for Reporting Clinical Data. Results of the First International Workshop. American Journal of Ophthalmology, Volume 140, Issue 3, Pages 509-516

TABLE 1. The SUN Working Group Anatomic Classification of Uveitis

Type	Primary Site of Inflammation	Includes
Anterior uveitis	Anterior chamber	Iritis
		Iridocyclitis
		Anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis
		Posterior cyclitis
		Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse
		Chorioretinitis
		Retinochoroiditis
		Retinitis
		Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or	

TABLE 2. The SUN Working Group Descriptors of Uveitis

Category	Descriptor	Comment
Onset	Sudden	
	Insidious	
Duration	Limited	≤3 months duration
	Persistent	>3 months duration
Course	Acute	Episode characterized by sudden onset and limited duration
	Recurrent	Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration
	Chronic	Persistent uveitis with relapse in <3 months after discontinuing treatment

TABLE 3. The SUN Working Group Grading Scheme for Anterior Chamber Cells

Grade	Cells in Field†
0	<1
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	>50

† Field size is a 1 mm by 1 mm slit beam.

TABLE 4. The SUN Working Group Grading Scheme for Anterior Chamber Flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

TABLE 5. The SUN Working Group Activity of Uveitis Terminology

Term	Definition
Inactive	Grade 0 cells
Worsening activity	Two step increase in level of inflammation (e.g. anterior chamber cells, vitreous haze) or increase from grade 3+ to 4+
Improved activity	Two step decrease in level of inflammation (e.g. anterior chamber cells, vitreous haze) or decrease to grade 0
Remission	Inactive disease for ≥3 months after discontinuing all treatments for eye disease

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