

Protocol Number: 1
EUDRACT Number: 2006-001859-35
Site Number: All
Date: 26.10.2006

Final Version 1.0; 26.10.2006

Use of abatacept in ANCA associated vasculitis (AAV)

Acronym: ABAVAS

Medical Monitor/Study director

Alan Salama, M.D.

Address: Renal Section, Division of Medicine, Imperial College London, Hammersmith Hospital, Du
Cane Road, London W12 0NN

Email: A.salama@imperial.ac.uk

Telephone (office): +44(0)208 383 3980

Fax: +44(0)208 383 2062

Clinical Scientist

Karen Mosley

Telephone (office): 0208 383 3936

Fax: 0208 383 2062

Statistician

Dr Elena Kulinskaya, Director,
Statistical Advisory Service,
Imperial College
Room G06 Sir Alexander Fleming building,
South Kensington Campus
London SW7 2AZ

Telephone (office): +44 (0)207 594 3950

fax : +44(0)207 594 1489

24-hr Emergency Telephone Number

Dr Alan Salama Telephone (office): +44 208 383 3980

Alternate Contact: Dr Karen Mosley +44 208 383 3936

**This protocol contains information that is confidential and proprietary to Imperial College
London, Hammersmith Hospital.**

SYNOPSIS

Title of Study: Use of abatacept in ANCA associated vasculitis (AAV): ABAVAS

Estimated Number of Study Centres and Countries: 15 sites in 7 EU countries

Research Hypothesis: For up to 12 months following the end of 12-months-treatment, a lower relapse rate will be induced with abatacept and methotrexate (+CS) than with placebo and methotrexate (+CS), while there will be a similar safety profile in both arms.

Primary Objective: To assess the relapse rate over 24 months, in patients with Acute AAV, presenting at first diagnosis or relapse, after 12 months of treatment with Abatacept in combination with steroids and methotrexate or placebo in combination with steroids and methotrexate.

Secondary Objectives:

To assess the clinical efficacy of abatacept combined with MTX + steroids vs placebo and MTX + steroids by measuring:

1. Proportion of patients in sustained remission (i.e. remission at 3 months sustained for 6 months and remission at 6 months sustained for a further 12 months);
2. Time to remission;
3. The average steroid dosage at 6 months, 1 year, 18 months and 2 years in abatacept and placebo groups respectively;
4. Time to ANCA negativity by immunofluorescence or negative anti-PR3 or anti-MPO Ab test by ELISA.
5. Proportion of patients defaulting to cyclophosphamide (MMF, azathioprine or other rescue) therapy.
6. Proportion of patients unable to stick with trial protocol.
7. Degree of chronic disease activity
8. Health related quality of life

To assess the safety and tolerability of abatacept in this study population, evaluated by number of adverse events related to drug therapy

Experimental Objectives (Pharmacodynamic measures):

To explore the Mechanism through which abatacept exerts its effects in AAV. Assessed by:

1. Quantifying the autoantigen (MPO and PR3) –specific T cell response using ELISPOT
2. Quantifying the number of regulatory T cells in each patient at different time points using flow cytometry.
3. Validating the use of urinary MCP-1 measurement to assess disease activity
4. Measuring the levels of tryptophan, kynurenine and IDO activity in patient samples at different treatment time points and assessing the correlation to disease activity.
5. Enumerating the proportion of memory T cells in both groups at different time points, and assessing the impact of therapy on these populations.

Examining CTLA4 polymorphisms, which might explain responsiveness, or lack of it, to abatacept.

Study Design:

Phase II (POC) experimental study

Multinational, randomized, double-blind, placebo-controlled, two-arm parallel design study of 24 *months* duration to the primary endpoint. This is an exploratory study.

Subjects will be randomized 1:1 to receive either abatacept or placebo on top of methotrexate +CS for the first 12 months of the study and then will receive MTX only.

Number of Subjects:

Enrolled: 112 patients (56 patients/group)

Randomized: 100 (50/group)

Study Population (Inclusion Criteria):

- Males and females (not nursing and not pregnant) at least 18 years of age. Women of child bearing potential are eligible if they are practicing effective contraceptive measures
- With Acute AAV, presenting at first diagnosis or relapse (not grumblers, to maximize effect seen), defined by clinical presentation, ANCA positivity (anti-MPO or anti-PR3 positive) and a BVAS score of > 8.
- Written informed consent given

Test Product, Dose and Mode of Administration, Duration of Treatment:

Abatacept (active) will be given as a dose based on body weight: 500mg for subjects weighing < 60 kg, 750 mg for subjects weighing 60 to 100 kg and 1 gram for subjects weighing > 100 kg. Study Medication will be administered IV on Day 1, 15, 29 and every 28 days up to and including Day 365

Reference Therapy, Dose and Mode of Administration, Duration of Treatment:

Methotrexate 20-25mg/week, starting at 15 mg/ week from day 1 and increasing to 20-25mg/week after 12 weeks for study duration.

Oral prednisolone (1 mg/kg) started day 1 and reduced according to protocol until end of month 9, then taper so that all steroids stopped by month 12.

In addition all patients receive (unless contraindicated) **prophylaxis** with Septrin 480mg daily

Amphotericin/Nystatin four times a day

Proton pump inhibitor

Calcium / Vitamin D

Statistical Methods:

This is an exploratory study to evaluate the efficacy and safety of abatacept in preventing relapse in patients with acute AAV, after induction of remission.

Sample size :We would need to randomize 100 patients (50 patients/group) to achieve an 80% power with a two-sided 15% significance level (pilot study) to show a 25% difference between groups in relapses rate at 24 months, based on a Log-rank test of survival in two groups followed for fixed time (nQuery Advisor 4.0).

Data Set Descriptions: All subjects who received the study medication will be included in the efficacy data set, but only subjects with pre- and post-treatment data will be tabulated and summarized.

All subjects who receive study medication will be included in the safety data set.

Primary endpoint: The relapse rate over 24 months will be analysed using a survival-type analysis of sustained remission. Comparison of groups will be performed using Log-rank test. Relapse rate (and 95 CI) will be estimated at 24 months, from the survival distribution.

Safety Analyses: All recorded adverse events will be listed and tabulated by primary term and body system. Vital signs and clinical laboratory tests will be listed and summarized by visit. Any physical examination findings, ECG results, chest x-ray results, and clinical laboratory results will be listed.

Pharmacodynamic Analyses: All pharmacodynamic parameters will be listed and summarized along with respective changes from baseline.

TABLE OF CONTENTS

TITLE PAGE	Fehler! Textmarke nicht definiert.
SYNOPSIS.....	2
TABLE OF CONTENTS.....	5
1 INTRODUCTION	7
1.1 Study Rationale.....	7
2. STUDY OBJECTIVES.....	10
2.1 Primary Objective	10
2.2 Secondary Objectives.....	10
3 STUDY DESIGN AND EVALUATIONS.....	11
3.1 Study Design.....	11
3.2 Study Population.....	11
3.2.1 Subject selection criteria	11
3.3 Criteria for evaluation	13
3.3.1 Primary.....	13
3.3.2 Secondary.....	13
3.4. Sample size determination	14
4. STATISTICAL METHODOLOGY	14
4.1 Data Set Descriptions.....	14
4.2 Analyses	14
4.2.1 Demographics and Baseline Characteristics.....	14
4.2.2 Efficacy Analyses	14
4.2.3 Safety Analyses.....	15
4.2.4 Pharmacodynamic Analyses	15
5. STUDY CONDUCT.....	15
5.1 Ethics.....	15
5.2 Study therapy	15
5.2.1 Subject enrollment	15
5.2.2 Treatment administration	16
5.2.3 Discontinuation of Therapy	17
5.2.4 Treatment Compliance.....	17
5.3 Blinding/Unblinding	18
5.4 Prohibited and Restricted Therapies During the Study.....	18
5.4.1 Precautions.....	19
5.5 Non-therapy Precautions and Restrictions.....	19
5.5.1 Precautions.....	19
5.5.1.1 Management of Possible Acute Hypersensitivity Reactions to abatacept	19
5.5.1.2 Infectious Complications	20
5.6 Withdrawal of Subjects from Study.....	20
6. STUDY PROCEDURES AND OBSERVATIONS	20
6.1 Events schedule.....	20
6.2 Procedures by visit.....	21
6.3 Details per procedures.....	22
6.3.1 Safety assessments	22
6.3.1.1 Vital signs	22
6.3.1.2 Physical examination	22

6.3.1.3	Electrocardiograms	22
6.3.1.4	Mammography	22
6.3.1.5	PPD skin testing.....	22
6.3.1.6	Chest X-ray	23
6.3.1.7	Pregnancy.....	23
6.3.1.8	Adverse event monitoring.....	23
6.3.2	Laboratory test assessment	23
6.3.3	Efficacy assessments.....	24
6.3.4	Pharmacodynamic assessments	24
7.	INVESTIGATIONAL PRODUCT.....	25
7.1	Investigational Product Identification.....	25
7.2	Packaging and Labeling.....	25
7.3	Handling and Dispensing of Investigational Product	25
7.3.1	Drug Product Information.....	26
7.3.2	Recommended Storage Conditions.....	27
7.4	Investigational Product Records at Investigational Site(s)	27
7.5	Destruction of Investigational Product	27
8.	ADVERSE EVENT REPORTING IN CLINICAL TRIALS.....	28
8.1	Collection of Safety Information	28
8.1.1	Safety and drug monitoring committee.....	28
8.1.2	Definition and description of an Adverse Event.....	28
8.2	Adverse Events Related to Study Conditions	29
8.3	Overdose	29
8.4	AE Follow-up.....	29
8.5	Reporting of AE Information Following Study Completion	29
8.6	Handling of Serious Adverse Events (SAEs)	30
8.7	Laboratory Test Abnormalities	31
8.8	Other Safety Considerations	31
8.9	Pregnancy.....	31
9.	Administrative section	32
9.1	Informed consent	32
9.1.1	Informed consent procedures	32
10	List of Abbreviations	35
11	References.....	36
	APPENDIX 1. LIST OF COLLABORATING EUVAS CENTRES	38
	APPENDIX 2 DRUG REDUCTION SCHEME	40
	APPENDIX 3. COSTINGS FOR A PAN-EUROPEAN INVESTIGATION	41
	APPENDIX 4. BVAS SCORING SHEET	43
	APPENDIX 5 CONSENT FORM	44

Title: Use of abatacept in ANCA associated vasculitis (ABAVAS)

1 INTRODUCTION

1.1 Study Rationale

The primary systemic vasculitides encompass a number of diverse multi-system disorders. They are characterized by inflammation of small and medium sized blood vessels, and in some cases are associated with anti-neutrophil cytoplasmic antibodies (ANCA). ANCA associated vasculitis (AAV) consists of three clinical conditions, Wegener's granulomatosis(WG), microscopic polyangiitis(MPA) and Churg Strauss syndrome(CSS). They are classified according to the Chapel Hill consensus conference¹, which is now widely accepted. These conditions follow a relapsing–remitting time course and account for considerable morbidity and mortality. They affect numerous organs, and are a major cause of kidney disease, caused by a necrotizing focal segmental glomerulonephritis, often leading to end stage renal failure, despite the best current treatment strategies. Therapeutic protocols for treatment of AAV have been modified over the last twenty years, in an attempt to minimize toxicity, but the main agents have been used in a similar fashion, with high dose induction therapy and lower dose long term maintenance. We have been involved in defining the best treatment strategies for AAV over a number of years²⁻⁴, alone and through a European consortium of investigators. Current gold standard therapy consists of induction with cyclophosphamide, steroids (and plasmapheresis in the case of life-threatening end organ damage), followed by a maintenance phase of steroids and azathioprine. Remission is generally induced in 85 % of patients by three months but relapse rates are approximately 15-20% after 18 months. Adverse effects of this regime are common, and significantly contribute towards the excess morbidity and mortality in such patients, especially in elderly patients who appear to suffer infectious episodes as a result of the leucopaenia^{5,6}. Additionally, and arguably more importantly, disease is frequently not controlled adequately, with many patients reaching end stage renal failure within one year from diagnosis and treatment initiation.

Finally, since a number of patients require repeated treatment courses, this may result in a greater cumulative dose of immunosuppressants, with increased toxicity. The toxicities are well established and include for cyclophosphamide leucopaenias, sepsis, haemorrhagic cystitis, amenorrhea, infertility, transitional cell carcinoma of the bladder and other malignancies. Prolonged steroid use results in a number of metabolic disturbances including diabetes, hypertension, osteoporosis and avascular necrosis. Other therapies have been employed such as methotrexate, recently shown to equivalent at inducing remission to cyclophosphamide for less severe (renal) disease, but with a greater propensity for earlier relapses³ and with a number of potential adverse effects. Newer biologicals have been used off licence, on a compassionate basis, such as anti-TNF therapy with infliximab and etanercept, as well as anti-B cell therapy with rituximab.

In an open label study using infliximab a beneficial effect was observed in newly diagnosed patients and those with grumbling disease. Disease activity and inflammatory markers were normalised by three months². However, in a randomised trial (WGET) using etanercept, in addition to a standard cyclophosphamide regime, in patients with relapsing disease, no benefit was observed in those treated with etanercept compared to placebo⁷. Although there were significant differences in the patients enrolled in these trials, and two different anti-TNF agents used, the lack of efficacy in the WGET study has cast doubt over the role for TNF blockade in systemic vasculitis. Importantly, there was a significantly increased risk of malignancy reported among the etanercept treated patients in the WGET study.

A number of small cohort series have been reported using rituximab, all of which have demonstrated some success in reducing symptoms and disease activity, at least while the B cells remained depleted⁸⁻¹⁰. However, granulomatous lesions appeared to be relatively more resistant than other disease features^{11,12}. Finally, a small number of refractory patients have been treated with anti-thymocyte globulin, with varying degrees of success but with severe adverse reactions in some¹³.

From these trials and cohort studies it can be seen that there is a real need for more effective, less toxic immunotherapy, and this is the rationale for introducing abatacept as therapy for these diseases. Since there is no available data on the efficacy and safety of the combination of abatacept and cyclophosphamide, we have devised an exploratory trial protocol which avoids cyclophosphamide completely. While this will result in recruitment of less severely affected patients, their relapse rates appear to be as high as those with more critical end organ damage³. Moreover, this will enable us to perform a placebo controlled trial, investigating the benefit of abatacept added to a less toxic immunosuppressive agent, methotrexate, in inducing and maintaining remission. Abatacept was already administered in combination with different DMARDs, including MTX in RA trials. Whilst it may be preferable to have a “gold standard” comparator (cyclophosphamide), we believe that investigators will be put off recruiting more severely affected patients as there is a risk of randomising them to not receive cyclophosphamide. Recent data from the NORAM trial³ demonstrate that methotrexate (MTX) and cyclophosphamide induce similar rates of remission at 6 months (89.8% and 93.5% respectively), but the former agent is associated with significantly higher rates of relapse at 18 months (69.5% and 46.5% respectively). In this study, patients received study treatment for a maximum of 12 months and then stopped. Stopping all therapy at 12 months may have contributed to the high relapse rate, and ethically it would not be possible to repeat this MTX protocol as a control arm. We have therefore elected to continue with MTX therapy, but stop steroids at 12 months, which would be in line with recent EUVAS opinion regarding management of such patients.

Although the pathology of AAV remains incompletely understood it is characterized by both humoral and cellular immune disturbances.

i) Humoral responses

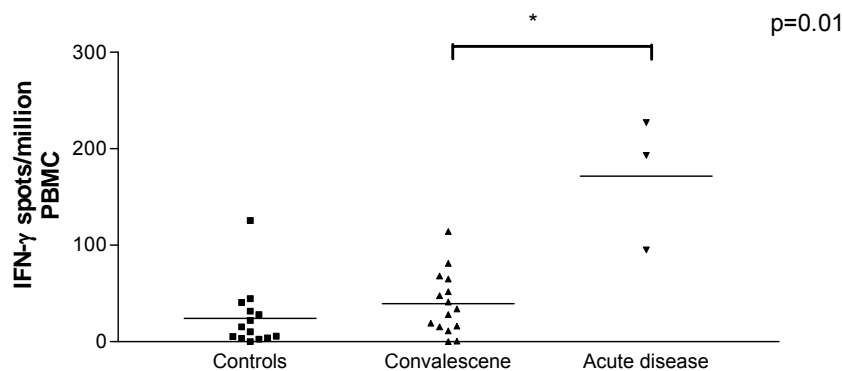
The pathognomonic feature of AAV is the presence of ANCA, reactive with the leukocyte enzymes proteinase-3 (PR3) and myeloperoxidase (MPO). However, it remains unclear whether these antibodies are the sole pathogenic effectors and what controls their generation. In a recently described animal model, transfer of anti-MPO containing sera was sufficient to induce renal injury over a short follow up period¹⁴. In a different model of experimental autoimmune vasculitis, developed in our department, transfer of serum containing anti-MPO ANCA to naïve animals promoted leukocyte adhesion and transmigration, as well as microvascular haemorrhage, as observed by intravital microscopy¹⁵. These data confirm the ability of ANCA to promote vasculitis. More recently, the first case of maternal-fetal transfer of disease by anti-MPO ANCA has been reported¹⁶. Of note, the mother had developed active vasculitis during her pregnancy and the fetus was born with a pulmonary-renal syndrome, while ANCA were detectable in the cord blood. Finally, ANCA are known to be able, in vitro, of activating neutrophils and promoting their respiratory burst, while neutrophils in turn express ANCA antigens on their cell surface¹⁷.

ii) Cellular responses

While antibodies appear necessary they may not be sufficient to generate and sustain disease. Other data, from patients with AAV, have implicated the involvement of T lymphocytes, although their precise role in initiating and regulating disease remains undefined. We and others have observed that levels of ANCA do not always correlate with clinical disease activity, as a significant number of patients may be

in disease remission, but continue to produce ANCA¹⁸. By contrast, T cell frequencies to MPO are elevated in acute disease and diminished in remission (Figure 1, A. Salama unpublished) and levels of MCP-1 chemokine, produced by T cells and monocytes/macrophages are only elevated in acute disease¹⁹. We have recently demonstrated that T cell responses during remission are regulated, not by professional regulatory T cells, but rather through the breakdown of tryptophan into its metabolite kynurenine²⁰. This breakdown is brought about by the enzyme 2,3 indoleamine dioxygenase (IDO), found in monocytes/macrophages as well as renal tubular epithelial cells. An additional clue as to the critical role of cellular effectors is demonstrated by observation of the target organs affected. Immunoglobulins are found within the glomeruli in small quantities and only in half of the patients with AAV²¹, suggesting that other factors are critical in renal disease initiation. By comparison significant numbers of T cells and macrophages are found infiltrating the affected glomeruli, and in certain vasculitides, granulomas are found in affected organs²². Taken together, these data suggest that both B and T cells are intimately involved in disease pathogenesis, although the exact contribution each limb of the immune system plays at different points in the natural history of the disease is undefined.

Figure 1 MPO-specific IFN- γ -producing T cell frequencies in healthy controls and patients with MPO-ANCA associated vasculitis during active disease and remission



New approaches to treatment

Abatacept is an ideal agent for such a purpose, as it induces anergy of activated T cells (expressing CD28). It would therefore be expected to mainly target the activated T cells and none of the memory T cells, critical for infectious defense or tumor surveillance (assuming these were not activated by current infection/malignancy at the time of administration). Thus abatacept should be a more selective agent than those currently utilised, and should allow for preservation of immune responsiveness towards previously vaccinated antigens (such as tetanus and mumps).

Abatacept has been used in our animal model of anti-GBM-induced RPGN, with great success in preventing disease progression²³. Administration of abatacept led to reduced glomerular injury with fewer infiltrating T cells and additionally diminished antibody deposition. Recent data has suggested that abatacept does more than merely prevent B7 engagement of CD28, but positively signals the APC and through the upregulation of IDO, which in turn induces tryptophan degradation and results in subsequent T cell unresponsiveness^{24,25}. Since we have established from our cohort of patients with AAV that levels of tryptophan are decreased in convalescent patients (in clinical and biochemical remission) and that this correlates with T cell unresponsiveness towards the autoantigen²⁰, it is therefore possible that early therapy with abatacept would induce a similar state of T cell unresponsiveness in patients presenting acutely.

Abatacept has proven effective in the treatment of rheumatoid arthritis and has been trialed in autoimmune psoriasis vulgaris^{26,27}, both conditions caused by abnormalities of cellular immune effectors. However, it has never been tested in immune mediated renal disease. Recently, in renal

transplant recipients, belatacept, a modified form of Abatacept, has also been shown to be equally as efficacious as cyclosporin, with less chronic rejection and impairment of renal function²⁸. Acute and chronic rejection are believed to be predominantly T cell mediated processes, confirming that belatacept is an efficacious single agent that can abrogate T cell mediated immune damage. Moreover, these trials demonstrate that the drug is safe and well tolerated.

Both T cells and B cells are implicated in AAV, so the hypothesis is that abatacept will reduce T cell and B cell mediated autoreactivity, and perhaps induce a long lasting remission.

1.2 Research hypothesis

Our hypothesis is that for up to twelve months following the end of 12-months-treatment, a lower relapse rate will be induced with abatacept and methotrexate (+CS) than with methotrexate alone (+CS), while there will be a similar safety profile in both arms.

2. STUDY OBJECTIVES

2.1 Primary Objective

To assess the relapse rate (defined by clinical and biochemical parameters) over 24 months in patients with acute AAV presenting at first diagnosis of relapse after 12 months of treatment with abatacept in combination with steroids and methotrexate or placebo in combination with steroids and methotrexate.

2.2 Secondary Objectives

Clinical objectives

To assess the clinical efficacy of abatacept combined with MTX + steroids versus placebo and MTX + steroids by measuring:

1. The sustained remission rate
2. Time to remission
3. The average steroid dosage at 6, 12, 18 and 24 months in abatacept and placebo groups respectively
4. Time to ANCA negativity by immunofluorescence or negative anti-PR3 or anti-MPO Ab test by ELISA.
5. Proportion of patients defaulting to cyclophosphamide therapy.
6. Proportion of patients unable to stick with trial protocol.
7. Degree of chronic disease activity
8. Health related quality of life

To assess the safety and tolerability of abatacept in this study population, evaluated by number of adverse events related to drug therapy

Experimental Objectives

To explore the mechanism through which abatacept exerts its effects in AAV by:

1. Quantifying the autoantigen (MPO and PR3) –specific T cell response using ELISPOT
2. Quantifying the number of regulatory T cells in each patient at different time points using flow cytometry.
3. Validating the use of urinary MCP-1 measurement to assess disease activity

4. Measuring the levels of tryptophan, kynurenine and IDO activity in patient samples at different treatment time points and assessing the correlation to disease activity.
5. Enumerating the proportion of memory T cells in both groups at different time points, and assessing the impact of therapy on these populations.

Examining CTLA4 polymorphisms, which might explain responsiveness, or lack of it, to abatacept.

3 STUDY DESIGN AND EVALUATIONS

3.1 Study Design

Multinational, randomized, double-blind, placebo-controlled, two-arm parallel design study of 24 months duration to the primary endpoint. This is an exploratory study.

Subjects will be randomized 1:1 to receive either abatacept or placebo on top of MTX+CS for the first 12 months of the study and then be maintained on MTX only.

In order to maximise recruitment in a short time period, (12 months) 15-20 centres would be required. This realistically would require a pan-European approach (with a list of EUVAS collaborating centres attached appendix 1).

3.2 Study Population

3.2.1 Subject selection criteria

Inclusion criteria:

- Males and females (not nursing and not pregnant) at least 18 years of age. Women of child bearing potential are eligible if they are practicing effective contraceptive measures
- With Acute AAV, presenting at first diagnosis or relapse (not grumblers, to maximize effect seen), defined by clinical presentation, ANCA positivity (anti-MPO or anti-PR3 positive) and a BVAS score of > 8.
- Written informed consent given

Exclusion criteria:

- Those with severe life-threatening disease, i.e. lung haemorrhage at the time of presentation, renal impairment with $SCr > 150$ $\mu\text{mol/l}$, or severe CNS dysfunction thought to be due to vasculitis.
- Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, neurological or cerebral disease, or other medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.
- With any other non-vasculitic multisystem autoimmune disease.
- With any serious acute bacterial infection unless treated and completely resolved with antibiotics prior to enrollment
- With any severe chronic or recurrent bacterial infection, e.g. bronchiectasis, osteomyelitis, chronic pyelonephritis

- With Hepatitis B or C or HIV.
- With Herpes zoster infection that resolved less than 2 months prior to enrollment.
- Subjects who have received any live vaccines* within 3 months of the first dose of study medication or who will have need of a live vaccine at any time in the year following enrollment.

**Due to the risk of infection, vaccination of subjects with any live vaccine (including live influenza vaccines such as FluMist) is absolutely contraindicated during the course of the study, as is the administration of live oral polio vaccine to household contacts. The CDC ACIP recommends that subjects should not be administered a live virus vaccination for at least 3 months after discontinuing high dose glucocorticosteroid therapy (defined as more than 20 mg of prednisone or prednisone equivalent 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 study medication, and it is recommended that study subjects not be administered a live virus vaccination for 4 to 5 months following the last dose of study medication.*

- Subjects with current clinical or laboratory evidence of active or latent tuberculosis (TB) and subjects with a history of active TB treated within the last 3 years should be excluded**
- With any previous malignancy, with the exception of non-melanoma skin malignancies, adequately treated previously
- Subjects with a mammogram that is suspicious for malignancy and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations. Mammograms (females only) must be performed within 6 months of study entry or if documentation is not on file. ***
- Pregnancy or breast feeding. Female contraception is necessary; male contraception, only if one of the concomitant medications requires male contraception
- With MTX treatment in prior 3 months
- With allergies to study medications.
- Subjects with prior therapy with rituximab, anti-TNF therapy, or IL-1 receptor antagonists within last year or cyclophosphamide within last six months.
- Subjects with a history of intolerance to methotrexate.
- Subjects who have at any time received treatment with abatacept.
- 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.
- Subject receiving approved or investigational biologics
- Subjects with any of the following laboratory values:
 - Hgb < 8.5 g/dL.
 - WBC < 3,000/mm³ (3 x 10⁹/L)
 - Platelets < 100,000/mm³ (100 x 10⁹/L).
 - Serum ALT or AST > 2 times upper limit of normal.
 - Any other laboratory test results that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.
- Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study.
- Subjects participating concurrently in another clinical trial.

**** TB screening**

Subjects with current clinical or laboratory evidence of active or latent tuberculosis (TB) and subjects with a history of active TB treated within the last 3 years should be excluded.

Subjects who received treatment for active TB greater than 3 years ago may be eligible for inclusion in this study if there is documentation of the prior anti-TB treatment confirming that it was appropriate in duration and type.

All potential subjects will have a screening chest x-ray at baseline. Chest x-rays done within the previous 6 months will be acceptable in lieu of chest x-ray done at screening.

Tuberculin skin test will be used and interpreted according to local country Health Authorities and/or Medical Society guidelines for patients who are to receive biologics or immunosuppressant therapies, e.g. prior RA experience with biologic agents, [i], [ii], [iii] immunocompromised subjects [iv], [v] and subjects with prior BCG vaccination(s)

[i] BTS Recommendation for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. Thorax 2005; 60:800-805

[ii] Preliminary guidelines for diagnosing and treating tuberculosis in patients with rheumatoid arthritis in immunosuppressive trials or being treated with biological agents. Ann Rheum Dis 2002; 61(suppl):ii62-ii63.

[iii] Ex US sites, local guidelines endorsed by medical societies on PPD testing in subjects with RA being treated with biologic may apply.

[iv] Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. Am J Respir Crit Care Med. 2000; Vol 161.pp S221-S247

[v] Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Am J Respir Crit Care Med. 2000; Vol 161.pp 1376-1395

**** During the study, all female subjects will be required to have a breast cancer screening: All female subjects will be required to have a yearly manual breast exam performed by a medical practitioner with results documented. Those female subjects who meet local age and risk factor appropriate screening criteria should continue to have mammography or other imaging modality for breast cancer screening in accordance to local medical guidelines.*

Subjects having a breast cancer screening examination (palpation or imaging) that is suspicious for malignancy will have drug administration withheld until the possibility of malignancy can reasonably be excluded following additional clinical, laboratory or other diagnostic evaluations. Confirmation of malignancy will require the subject to be immediately discontinued from the study.

The requirement for breast cancer screening should be explained in the subject's informed consent.

3.3 Criteria for evaluation

3.3.1 Primary

Response to treatment will be measured by

- the relapse rates in patients who have achieved remission over 24 month study period.

3.3.2 Secondary

Response to treatment will also be measured by:

- The proportion of patients in sustained remission at 6, 12, 18 months and 24 months ;
- The time to remission;
- The average steroid dosage at 6, 12, 18 and 24 months;
- The time to ANCA negativity by immunofluorescence or negative anti-PR3 or anti-MPO Ab test by ELISA; Urinary MCP-1 measurement to assess disease activity.

In both groups, disease will be monitored using the well established and validated BVAS 2003²⁹, in conjunction with biochemical, immunological, radiological and other physiological parameters, which we regularly use to assess disease activity. The definitions of remission (BVAS<1), persistent disease (BVAS>4) and acute disease have been previously established and published³ (see appendix 4: BVAS form)

Pharmacodynamic measures

Mechanism through which abatacept exerts its effects in AAV assessed by:

- Autoantigen (MPO and PR3) specific T cell response (ELISPOT);
- Number of regulatory T cells (flow cytometry);

- Proportion of memory T cells in both groups;
- Levels of tryptophan, kynurenine and IDO activity (and correlation to disease activity).

Safety assessments

Incidence of adverse events. Adverse events will be described as mild, moderate, severe or very severe. Laboratory guidelines outline which laboratory test results should be captured as an adverse event. Severity and relationship of an adverse event to study drug will be determined by the Investigator.

3.4. Sample size determination

Number of subjects/group

This is an exploratory study to evaluate the efficacy and safety of abatacept in preventing the relapse in patients with acute AAV, after induction of remission.

We would need to randomize 100 patients (50 patients/group) to achieve an 80% power with at a two-sided 15% significance level (pilot study) to show a 25% difference between groups in relapses rate at 24 months, based on a Log-rank test of survival in two groups followed for fixed time (nQuery Advisor 4.0).

Thus, the target goal is 100 patients randomized (50 patients/group).

Assuming a 10% drop out rate we would aim to recruit 112 patients (56 patients/group) to achieve adequate power.

4. STATISTICAL METHODOLOGY

4.1 Data Set Descriptions

All subjects who received the study medication will be included in the efficacy data set, but only subjects with pre- and post-treatment data will be tabulated and summarized.

All subjects who receive study medication will be included in the safety data set.

4.2 Analyses

4.2.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, bodyweight and height will be calculated.

4.2.2 Efficacy Analyses

The sustained remission rate and relapse rate over 24 months will be analysed using a survival-type analysis of time-to-first relapse. Comparison of groups will be performed using Log-rank test. Sustained remission and relapse rates (and 95 CI) will be estimated at 24 months, from the survival distribution. For secondary endpoints:

The proportion of patients in sustained remission (i.e. remission at 3 months sustained for 6 months and remission at 6 months sustained for a further 12 months) will be compared between the experimental and control groups using an ANOVA test. Similarly, the time to remission, the average steroid dosage at 6 months, 1 year, 18 months and 2 years, the time to ANCA negativity by immunofluorescence or negative anti-PR3 or anti-MPO Ab test by ELISA, the proportion of patients defaulting to cyclophosphamide (MMF, azathioprine or other rescue) therapy, and the proportion of patients unable to stick with trial protocol will all be tested by an ANOVA test. The Degree of chronic disease activity and health related quality of life will be measured by the VDI and SF36 questionnaires. Results will be analysed using a non-parametric t test.

4.2.3 Safety Analyses

All recorded adverse events will be listed and tabulated by primary term and body system. Vital signs and clinical laboratory tests will be listed and summarized by visit. Any physical examination findings, ECG results, chest x-ray results, and clinical laboratory results will be listed.

4.2.4 Pharmacodynamic Analyses

All pharmacodynamic parameters will be listed and summarized along with respective changes from baseline.

5. STUDY CONDUCT

5.1 Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and will be consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. The study will be conducted in compliance with the protocol. The protocol and any Amendments and the subject informed consent will receive Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favourable opinion prior to initiation of the study. Freely given written informed consent must be obtained from every subject or their legally acceptable representative prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the trial.

5.2 Study therapy

5.2.1 Subject enrollment

Subjects will sign the written informed consent before having any study-related procedures performed including adjustment of any medications for the purpose of the study. On Day 1 (pre-dose), after each subject has qualified for inclusion into the study, the subject will be enrolled and assigned a unique, sequential subject number beginning with 001, 002, 003, etc. for identification throughout the study. This subject number must not be reused for any other participant in the study.

5.2.2 Treatment administration

Test product /reference therapy:

Patients will be randomized on a 1:1 basis to receive Experimental or Control arm therapy. This is a 24 month study. Patients will receive active drug or placebo for 12 months.

Experimental Arm:

Bristol-Myers Squibb Pharmaceutical Research Institute will supply abatacept. The 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.

Abatacept should be administered as a 30-minute intravenous infusion at the dose specified in Table 1. Following the initial administration, abatacept should be given 2 and 4 weeks after the first infusion, then every 4 weeks thereafter. Abatacept will be given at 1, 15, 29 days then every 4 weeks for 12 months.

Body Weight of Patient	Dose	Number of Vials^b
< 60 kg	500 mg	2
≥60 kg to ≤100 kg	750 mg	3
> 100 kg	1 gram	4

^a Approximating 10 mg/kg.

^b Each vial provides 250 mg of abatacept for administration.

Each vial of abatacept (ORENCIA) 250 mg must be reconstituted with 10 ml of sterile water for injection, using a silicone-free syringe. The reconstituted solution must then be diluted to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection, before administration by intravenous infusion. In order to minimize foaming, the stream of SWFI should be directed to the sides of vial.

Care must be taken to assure sterility of the prepared solution, as the drug product does NOT contain any antimicrobial preservatives or bacteriostatic agents.

Infusions should occur at approximately the same time of day throughout the duration of the study. All doses of study medication will be administered at a constant rate over approximately 30 minutes on the pre-specified days. At the end of each infusion, the IV line must be flushed with 25 mL of 5% dextrose in water (D5W) or 0.9% sodium chloride. All intravenous infusions will be administered with the subject in the seated or reclining position.

No adjustments will be made in treatment dose level or schedule.

Subjects will be observed for adverse events and vital signs (blood pressure, heart rate, temperature, respiration rate) will be recorded at the start of the infusion (pre-dose). In addition, vital signs will be recorded 60 minutes after the start of infusion. Blood pressure and pulse will be taken after the subject has been seated quietly for at least 5 minutes. Subjects will be monitored closely in the clinic for a minimum of 90 minutes after the start of the infusion. The observation period should be extended if clinically indicated. In addition, all subjects are to be contacted approximately 24 hours after each study drug infusion for the collection of any peri-infusional adverse events.

Control arm:

Subjects who are randomized to receive placebo will be given Normal Saline (NS). Placebo will be supplied by the investigative site.

Reference therapy

Each investigator will be responsible for supplying methotrexate and steroids found in the protocol.

- Methotrexate will be given to all patients whatever their arm of randomization, starting at 15mg/week from day 1, increasing to 20-25mg/week over 12 weeks and maintained for the duration of trial.
- Steroids will be given to all patients whatever their arm of randomization: Oral prednisolone (1 mg/kg) started at day 1 and progressively reduced according to protocol until steroids stopped at 12 months (see appendix 2).

Prophylaxis

In addition all patients receive (unless contraindicated) **prophylaxis with:**

- Septrin 480mg/daily
- Amphotericin/Nystatin four times a day
- Proton pump inhibitor
- Calcium / Vitamin D

Rescue medication

Treatment of relapse or failure to improve (defined as no reduction in plasma creatinine by week 6, or a BVAS score >6 for more than 4 weeks)

Both Experimental and control Arms:

Major: Pulse methyprednisolone(0.5-1.5g), cyclophosphamide IV until remission(based on age and renal function according to local investigator protocols), and increased oral steroids according to local investigator protocols.

Minor: Increased steroid dose according to local investigator protocols.

5.2.3 Discontinuation of Therapy

Study therapy **MUST** be immediately discontinued for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator or medical monitor, indicates that continued treatment with study therapy is not in the best interest of the subject
- Pregnancy
- Termination of the study by the sponsor
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Disease progression necessitating the introduction of cyclophosphamide, etanercept, adalimumab, infliximab, or plasmapheresis.
- Subjects who miss more than one scheduled dose of study medication will be discontinued from the study

5.2.4 Treatment Compliance

Subjects enrolled into the study failing to receive any infusion of study medication will be deemed pre-treatment dropouts and will not be followed for further evaluation. Subjects receiving at least one dose of study medication will complete an early termination visit for discharge procedures and will be followed for safety requiring two scheduled follow-up visits at 28 (\pm 5) and 56 (\pm 5) days after the last dose of abatacept. Subjects who miss more than one scheduled dose of study medication for any reason will be discontinued from the study.

5.3 Blinding/Unblinding

This is a double-blind study. Subjects will be randomized in a 1:1 ratio to abatacept or placebo.

Blinding

The subjects and clinical assessor(s) will not be aware of which treatment is being administered to the subjects enrolled in the study. The pharmacist (or qualified drug preparation person) will be unblinded to study medication.

The pharmacist (or qualified drug preparation person) will know the schedule assignments and prepare the appropriate dose of active abatacept or placebo accordingly. The prepared drug must be supplied to study personnel in a manner such that neither study personnel nor subjects will be aware of whether they receive active drug or placebo.

Unblinding

Blinding is critical to the integrity of this clinical drug trial. However, in the event of a medical emergency or pregnancy in an individual subject, **in which knowledge of the investigational product is critical to the subject's management**, the blind for that subject may be broken by the treating physician.

Before breaking the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

The need to break the blind must first be discussed with the responsible Medical Monitor and the best method to do this will be determined.

Once the decision to unblind has been made, the Investigator must record the nature of the emergency that required breaking the code along with the date and time of the unblinding and must notify the Medical Monitor/Study Director of the code breakage. However, the Medical Monitor/Study Director and other Investigators must not be informed of the treatment assignment. The treatment assignment must not be noted in the CRF or any other documentation submitted to study director.

In an extreme emergency situation, the pharmacist or qualified drug preparation person will have the treatment information available. By obtaining treatment assignment information the Investigator may render the subject unevaluable for the study.

5.4 Prohibited and Restricted Therapies During the Study

The following medications are prohibited during the study: etanercept, adalimumab, and infliximab. Use of cyclophosphamide, azathioprine, mycophenolate mofetil, leflunomide, ciclosporin, or plasmapheresis as additional or rescue therapy will be counted as treatment failure for that limb of the trial and the patient will be withdrawn from the trial.

5.4.1 Precautions

Immunizations

Due to the risk of infection, vaccination of subjects with any live vaccine is absolutely contraindicated during the course of the study, as is the administration of oral polio vaccine to household contacts. The CDC Advisory Committee on Immunization Practices (ACIP) recommends that patients 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, subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication, and it is recommended that study subjects not be administered a live virus vaccination for 4-5 months following the last dose of study medication.

5.5 Non-therapy Precautions and Restrictions

5.5.1 Precautions

5.5.1.1 Management of Possible Acute Hypersensitivity Reactions to abatacept

Hypersensitivity or acute allergic reactions may occur as a result of the protein nature of abatacept. Should any of these reactions occur during the course of the study, they need to be reported as specified through Adverse Event Reporting. In this study, subjects' vital signs will be monitored before and following study drug administration. Appropriate emergency equipment and qualified personnel should 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. When dosing of abatacept is conducted, equipment such as a portable tank or wall-source of oxygen, endotracheal intubation set, oral airway, mask, ambu-bag, syringes, injectable epinephrine, injectable antihistamine, and injectable corticosteroids should be kept in the vicinity where the subject is treated.

Signs and management of potential acute hypersensitivity reactions include:

- a) Symptomatic Hypotension should be managed by discontinuing the infusion of study medication, placing the subject in the Trendelenburg position and administering intravenous fluid. Additional medical intervention may also include the use of epinephrine, corticosteroids, antihistamines and pressor agents.
- b) Dyspnea should be managed by discontinuing the infusion of study medication and observing the subject for worsening of the event and for the appearance of additional signs and symptoms of anaphylaxis. Antihistamines, epinephrine and corticosteroids may be administered as indicated.
- c) Acute pain in the chest, back or extremities may also be a sign of anaphylaxis and may be treated as described above for dyspnea.
- d) Chills, fever, urticaria or generalized erythema may all be signs of an allergic reaction to protein products. Such signs and symptoms may be treated with acetaminophen and antihistamines.

The decision whether to complete the infusion of study medication if symptoms improve or resolve will be left to the medical judgment of the Investigator.

5.5.1.2 Infectious Complications

Because abatacept has immunosuppressive activity, subjects may be at increased risk of infectious complications.

5.6 Withdrawal of Subjects from Study

Subjects MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator or medical monitor, indicates that continued treatment with study therapy and participation in the trial is not in the best interest of the subject
- Termination of the study by the sponsor.
- Subjects who become prisoners or become involuntarily incarcerated for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Lack of efficacy
- Discretion of the investigator
- Inability or subject's failure to comply with the protocol requirements
- Pregnancy

Treatment with prohibited medication while participating in the study.

- Subjects who miss more than one scheduled dose of study medication will be discontinued from the study

An evaluation, which reflects the status of the subject at premature termination, with a final assessment and reasons for termination, must be provided by the Investigator on the appropriate page of the CRF. No replacements will be allowed for treated subjects who do not complete the study. Subjects who do not complete the study will complete an early termination visit for discharge procedures within 28 days after the last dose of study medication. Follow-up visits will be required 28 (± 5) and 56 (± 5) days after the last dose of abatacept for safety monitoring including serum pregnancy testing (WOCBP only). The early termination visit for discharge procedures may coincide with the first follow-up visit if necessary.

6. STUDY PROCEDURES AND OBSERVATIONS

6.1 Events schedule

Clinical evaluations: Twice monthly for first month; monthly for 12 months; three monthly until the end of the trial. Full clinical assessment each visit, vital signs, adverse events and medication check. Investigations as detailed below

Immunological: ANCA, CRP each visit.
Urinary MCP-1, T cell elispot/proliferation with cytokine assay every 3 months (selected centres).
Serum Tryptophan and RNA from PBMC every three months for Q-PCR for IDO, CD127 and foxp3 expression (selected centres)

Renal : Estimated GFR (MDRD equation), haematuria, proteinuria (by urine dipstick and spot protein:creatinine ratio) each visit-see below

6.2 Procedures by visit

<u>Visits</u>	<u>Data/samples</u>
Entry: time 0	Consent, BVAS 2003, VDI, SF36, blood, urine, serum and urine stored, adverse effects, medication record, blood for cell assay, eGFR
0.5 month	Adverse effects, medication record
1 month	BVAS 2003, blood, urine, serum stored, adverse effects medication record
2 months	BVAS 2003, blood, urine, serum stored, adverse effects medication record
3 months	BVAS 2003, blood, urine, serum and urine stored, adverse effects, medication record
6 months	BVAS 2003, VDI, SF36, blood, urine, serum and urine stored, adverse effects, medication record, eGFR, blood for cell assay
9 months	BVAS 2003, blood, urine, serum stored, adverse effects, medication record
12 months	BVAS 2003, VDI, SF36, blood, urine, serum and urine stored, adverse effects, medication record, blood for cell assay, eGFR
15 months	BVAS 2003, blood, urine, serum stored, adverse effects, medication record
18 months	BVAS 2003, VDI, SF36, blood, urine, serum and urine stored, adverse effects, medication record, blood for cell assay, eGFR
24 months	BVAS 2003, VDI, SF36, blood, urine, serum and urine stored, adverse effects, medication record, blood for cell assay, eGFR
At relapse	BVAS 2003, blood, urine, serum and urine stored, adverse effects, medication record

In summary Evaluations

At entry:

Weight, BP, pulse, temperature

ANCA IF, anti-MPO Ab, anti-PR3 Ab, ANA, dsDNA, C3, C4, anti-GBM, IgM, IgG, IgA

Hep C, HepB sAg, Cryoglobulins,

Hb, WCC (with differential), platelets

Urea, Creat, ALP, Alb, CRP, Blood Glucose, eGFR

Urine dipstick, microscopy, Urine protein:creat ratio

At subsequent visits:

Weight, BP, pulse, temperature

Hb, WCC (with differential), platelets

Urea, Creat, ALP, Alb, CRP, Blood Glucose

ANCA IF, anti-MPO Ab, anti-PR3 Ab(every three months)

Urine dipstick, microscopy, Urine protein:creat ratio

Dose of Prednisolone, MTX

At 6, 12, 18 and 24 months in addition: IgM, IgG, IgA, eGFR

6.3 Details per procedures

6.3.1 Safety assessments

6.3.1.1 Vital signs

A \pm 5 minute window for the collection of vital signs from the scheduled time is allowed

6.3.1.2 Physical examination

The most recent weight collected during the screening visit should be used to determine study drug dosage. All doses administered during the study will be based on this weight.

Complete and/or interim physical examinations may be performed by a Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physician's Assistant (PA), or Nurse Practitioner (NP). While the interim physical exam may not be as comprehensive as the initial full examination, key aspects of the interim examination should evaluate important body systems as clinically indicated. These body systems can include lymph nodes, liver, spleen, and breast, at the discretion of the examiner. An interim physical examination may note any changes in the subject's condition (body systems) since the last assessment and does not preclude examination of any of the body systems as clinically indicated.

6.3.1.3 Electrocardiograms

A 12-lead electrocardiogram (ECG) is required if not already performed within 6 months of obtaining written informed consent or if documentation is not on file.

6.3.1.4 Mammography

After screening informed consent is obtained female subjects are required to have age and/or risk-factor appropriate breast cancer screening. Breast cancer screening should be performed according to published guidelines and/or local standards endorsed by the National Cancer or Medical Society and/or the Ministry of Health. In addition, the breast cancer screening guidelines utilized by the investigational site should be made available to the local IRB/Ethics Committee and explained in the subject's informed consent.

Documented breast cancer screening performed within 6 months of study entry will be accepted as meeting this requirement. However, screening will be required if documentation from the screening facility is not on file or a screening exam was performed more than 6 months prior to entry into study. Based on study entry criteria for breast cancer screening, female subjects are required to have an annual or anniversary repeat breast cancer screening.

6.3.1.5 PPD skin testing

To identify subjects with latent tuberculosis (TB), a PPD test (purified protein derivative tuberculin skin test) is required if not performed within one months of study entry or if documentation of testing within

one month is not on file. All subjects including those with prior BCG vaccination should be evaluated for latent TB.

PPD skin test should be performed in accordance to published guidelines that provide recommendations for PPD testing and interpretation in subjects with rheumatoid arthritis who are being considered for treatment with biologic agents, subjects who are immunosuppressed and subjects with a prior history of BCG vaccinations.

Subjects with a positive PPD at screening will not be eligible for the study unless active TB infection has been ruled out, they have initiated treatment for latent TB for at least 4 weeks prior to dosing of study drug, and they have a negative chest x-ray at enrolment.

A PPD response that is equal to or greater than 10 mm should be considered a positive test, although a lower threshold (5 mm) may be applied as determined by the clinical circumstance and investigator according to published guidelines and/or local standards endorsed by the medical society.

6.3.1.6 Chest X-ray

A chest x-ray at the screening visit is required if not already performed within 1 month of obtaining written informed consent or if documentation is not on file.

Urine or serum pregnancy tests will be performed within 48 hours prior to dosing, for all WOCBP. If any female subject becomes pregnant she will be immediately discharged from the study.

6.3.1.7 Pregnancy

Urine or serum pregnancy tests will be performed within 48 hours prior to dosing, for all WOCBP. If any female subject becomes pregnant she will be immediately discharged from the study.

6.3.1.8 Adverse event monitoring

All safety presentations will include subjects who receive at least one dose of study medication and will group subjects by treatments received. The evaluation of safety is based on clinical AEs, vital signs and laboratory abnormalities reported during the double-blind period of the study. Frequency distribution and individual listings of all adverse events will be generated. Significant physical examination findings and clinical and laboratory tests will be listed. Summary statistics will be tabulated. Changes in clinical laboratory test results from baseline will be listed.

The Data Safety Monitoring board will review adverse events regularly at monthly intervals to monitor for safety signals and assess any safety signals.

Any other SAEs of concern will be notified within 24hrs to the Monitoring Board. If there is any ongoing concern, this will result in a halt to the trial with no further patients recruited until the panel has fully investigated the potential cause/explanations for the AE.

6.3.2 Laboratory test assessment

Blood and/or urine samples will be obtained prior to infusion at all visits from each subject entered in this study. Any laboratory test result that the Investigator considers clinically relevant should be recorded on the appropriate Adverse Event page of the CRF.

The following tests will be performed at each assessment:

Electrolytes, urea and creatinine, liver function tests, calcium, phosphate, Blood Glucose, CRP and a full blood count (Hb, WCC (with differential), platelets).

In addition ANCA immunofluorescence and ELISA (anti-MPO Ab, anti-PR3 Ab) every three months

Urine dipstick and microscopy monthly and urine protein:creat ratio (every three months)

Blood Sample Processing

Detailed instructions on the collection, processing and storage of blood will be provided to the Investigator in a separate manual at or before the time of study initiation.

Specimen Collection and Transport

Detailed instructions on the collection and transport of blood samples will be provided to the Investigator in a separate manual at or before the time of study initiation.

Immunogenicity

The immunogenic potential of the study medication and active comparator will be assessed based on levels of anti-abatacept (BMS-188667) antibodies and Human Anti-Chimeric Antibody (HACA).

6.3.3 Efficacy assessments

The remission and relapse measures will be reviewed and discussed with the investigational staff at the Investigator Meeting or other forum as a method of standardizing the grading between the investigational staff.

Every effort must be made to ensure the same evaluator(s) will complete the assessment for each subject. Visits should be scheduled with the availability of the evaluator(s) taken into account. A +/- three day visit window is allowed to accommodate the evaluator(s) schedule. If the evaluator(s) is unable to complete the evaluation, then a qualified individual, with overlapping experience may perform the evaluation. Documentation of who performed the evaluation is to be recorded in source notes. Clinical assessments of response must be performed by the same assessor(s) and at approximately the same time of day throughout the duration of the study. The clinical assessor(s) should be a different person from the one administering the study medication infusion.

In both groups, disease will be monitored using the well established and validated BVAS 2003²⁹, and VDI, in conjunction with biochemical, immunological, radiological and other physiological parameters, which we regularly use to assess disease activity. The definitions of remission (BVAS<1), persistent disease (BVAS>4) and acute disease have been previously established and published³ (see appendix 4: BVAS form)

6.3.4 Pharmacodynamic assessments

Mechanism through which abatacept exerts its effects in AAV assessed by:

- Autoantigen (MPO and PR3) specific T cell response (ELISPOT);
- Number of regulatory T cells (flow cytometry); foxp3 and CD127 expression by real time PCR
- Proportion of memory T cells in both groups;
- Levels of tryptophan, kynurenine and IDO activity (and correlation to disease activity).
- These assays will be performed in a subgroup of patients from selected centres.

7. INVESTIGATIONAL PRODUCT

7.1 Investigational Product Identification

Bristol-Myers Squibb Pharmaceutical Research Institute will supply the following investigational product(s):

PRODUCT	POTENCY	APPEARANCE
BMS-188667 (CTLA4Ig) for Injection	250 mg/vial	White to off-white, whole or fragmented cake in a vial

Note: Abatacept = BMS-188667 = CTLA4Ig

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 for Injection, 0.9% Sodium Chloride Injection) needed for the reconstitution and dilution of investigational product identified in the protocol.

7.2 Packaging and Labeling

Study medication, abatacept, will be provided as open label supplies packaged in boxes. Each box will contain 18 vials. Each box will be labelled with a 1-panel, open label printed in black with a data entry field for the protocol number. The product identity and strength, batch number, the number of vials, directions for use and storage conditions will also be indicated. **The pharmacist/drug preparer will complete the protocol number on panel 1 of the box label.**

Each vial will be labelled with a 2-panel open label printed in black. There will be data-entry fields for the protocol number, subject number and the date dispensed. In addition, the batch number, product identity and strength, route of administration and storage conditions will be indicated. **The pharmacist/drug preparer will complete the protocol number, subject number and the date dispensed on panels 1 and 2 of the vial label.** Panel 2 is detached and affixed to the appropriate page of the Case Report Form.

7.3 Handling and Dispensing of Investigational Product

Bristol-Myers Squibb will be responsible for assuring that the quality of the investigational product is adequate for the duration of the trial. Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to 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 prescription, and it is the Investigator's responsibility to ensure that an accurate record of drugs issued and returned is maintained.

Care should be taken when handling study medication. Proper aseptic techniques should 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 also to the Investigator Brochure for abatacept for additional information regarding handling, preparation and storage of this drug.

7.3.1 Drug Product Information

A pharmacist or qualified personnel at the site, not otherwise associated with the conduct of the study, will reconstitute the drug for intravenous (IV) administration.

All reconstitution and dilutions must be performed using polypropylene non-siliconized 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.

The continuous infusion solution must be filtered upon administration using an inline, sterile, non-pyrogenic, low protein-binding filter with a pore size of 1.2 μm (to be provided by BMS). This infusion should be administered over a period of approximately 30 minutes. Any unused portion of the infusion solution should not be stored for reuse.

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. When adding, direct SWFI stream to sides of vial. Do not use if vacuum not present in vial. **NOTE: The vial should NOT be vented prior to reconstitution. To avoid foam formation following the addition of SWFI, 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.** 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 Injection (D5W) or 0.9% Sodium Chloride (NS; "Normal" saline). Infusion doses will be based on the subject's weight obtained at the **baseline** visit. Study medication will be administered according to the dosing schedule found in the protocol. All doses of study medication will be administered in a fixed volume of 100 ml, infused intravenously at a constant rate over approximately 30 minutes. The IV line must be flushed with approximately 25 ml of D5W or NS solution at the end of the infusion. Please see the Section "Treatment Administration" for additional details on study medication administration.

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 substance 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.

7.3.2 Recommended Storage Conditions

Vials of Abatacept for Injection, 250 mg/vial, should be stored under refrigeration (2-8°C) and 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 12 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 (59°-77°F) and room light or at refrigeration (2°-8°C) for up to 6 hours in the original vial.
- Dilutions of reconstituted Abatacept for Injection, 10 mg/ml in NS or D5W in polyvinyl chloride (PVC) or non-PVC IV bags may be stored at temperatures from 15°-25°C (59°-77°F) and room light or at refrigeration (2°-8°C) for no more than 12 hours from the time of initial reconstitution.
- Diluted solutions of Abatacept for Injection are compatible with standard PVC-IV infusion sets.

7.4 Investigational Product Records at Investigational Site(s)

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where 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 ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor.
- Amount destroyed at study site, if applicable.
- Retain samples sent to third party for bioavailability/bioequivalence, if applicable.
- Sponsor will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

7.5 Destruction of Investigational Product

If investigational product may be destroyed at the site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal and procedures for proper disposal have been established according to applicable regulations and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

8 ADVERSE EVENT REPORTING IN CLINICAL TRIALS

8.1 Collection of Safety Information

8.1.1 Safety and drug monitoring committee

Since this is a new application for abatacept, we intend to have a 6 week review of disease activity for each patient. If they have failed to demonstrate a significant improvement in renal function and other disease parameters they will be withdrawn from the abatacept treatment and given standard therapy with cyclophosphamide.

The review will be carried out by a drug monitoring committee (DMC) of three people not directly involved in the trial and the treating physician.

Adverse effects for the whole trial cohort will also be assessed by the DMC to decide whether they are in keeping with expected events or may relate to abatacept therapy. This will be carried out at fixed time points such as 3 and 9 months.

Major AE's will result in a halt to the trial with no further patients recruited until the panel have investigated the potential cause/explanations for of the AE

8.1.2 Definition and description of an Adverse Event

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 a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product.

An Investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded.

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

Following the subject's written consent to participate in the study, all serious AEs should be collected. The collection of non-serious AE information should begin at initiation of investigational product. Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the patient.

All identified AEs must be recorded and described on the appropriate Non-serious or Serious AE page of the CRF. 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: date (and time) of onset and resolution, severity of the event (see definitions), investigator's opinion of the relationship to investigational product (see definitions), treatment required for the AE, cause of the event (if known), and information regarding resolution/outcome. The following categories and definitions of severity should be used for all BMS clinical trial AEs:

- Mild (Grade I) - Awareness of event but easily tolerated
- Moderate (Grade II) - Discomfort enough to cause some interference with usual activity

- Severe (Grade III) - Inability to carry out usual activity
- Very Severe (Grade IV) - Debilitating, significantly incapacitates subject despite symptomatic therapy

The following categories and definitions of causal relationship to study drug should be used:

- Certain: There is a reasonable causal relationship between the study drug and the AE. The event responds to withdrawal of study drug (dechallenge), and recurs with rechallenge when clinically feasible.
- Probable: There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge. Rechallenge is not required.
- Possible: There is reasonable causal relationship between the study drug and the AE. Dechallenge information is lacking or unclear.
- Not likely: There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE.
- Unrelated: There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

8.2 Adverse Events Related to Study Conditions

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 complication of a diagnostic procedure), the relationship should be specified in the narrative section of the SAE page of the CRF.

8.3 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event (see Serious Adverse Events). The highest dose of BMS-188667 without dose related toxicity was not determined in Phase I clinical trials. The highest dose level administered was 50 mg/kg at which no dose related toxicity was observed.

8.4 AE Follow-up

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study; such subjects should receive post-treatment follow-up as appropriate. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE entry for the event should be completed.

8.5 Reporting of AE Information Following Study Completion

Collection of safety information following the end of investigational product administration is important in assisting in the identification of possible delayed toxicities or withdrawal effects. All SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In addition, the investigator

should notify the Study Director of any SAE which may occur after this time period which they believe to be certainly, probably or possibly related to investigational product.

8.6 Handling of Serious Adverse Events (SAEs)

A *serious AE* is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (defined as an event in which the subject or patient 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/birth defect,
- results in the development of drug dependency or drug abuse,
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) For reporting purposes, the occurrences of pregnancy or overdose (regardless of adverse outcome) as events which must be reported as important medical events.

Adverse events classified as "serious" must be recorded on the SERIOUS AE (SAE) page of the CRF and require expeditious handling and reporting to Study Director to comply with regulatory requirements. If hospitalization occurs due to protocol specified arthroscopy, it should not be reported as a serious adverse event unless it is for a new or worsening condition for example bleeding, infection, etc. All serious AEs whether related or unrelated to investigational product, must be immediately reported to Study Director (or designee) by confirmed facsimile transmission and mailing of the completed SAE page (top, white, original). A facsimile transmission does not preclude mailing of the SAE page. Overnight express mail may be used in lieu of facsimile. If only limited information is initially available, follow-up reports are required. In selected circumstances, the protocol may specify conditions which require additional telephone reporting.

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

SAE TELEPHONE CONTACT:

Medical Monitor: Dr Alan Salama +44 208 383 3980

Alternate Contact: Dr Karen Mosley +44 208 383 3936

SAE FACSIMILE TRANSMISSION: +44 208 383 2062

SAE MAILING ADDRESS: Dr Salama, Renal Section, Division of Medicine, Imperial College London, Hammersmith Hospital, London W12 0NN

In accordance with local regulations, Study monitor will notify Investigators and BMS of all AEs that are serious, unexpected, and certainly, probably, or possibly related to the investigational product. This notification will be in the form of **an Expedited Safety Report (ESR)**. Upon receiving such notices, the Investigator must review and retain the **ESR** with the Investigator Brochure.

Where required by local regulations or when there is a central Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the study, the sponsor will submit the un-blinded ESR directly to the appropriate IRB/IEC. In this case, the Investigator will receive a blinded copy of the **ESR** which does not need to be forwarded to the 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.

Where required, submission of **ESRs** by the Investigator to Health Authorities, should be handled according to local regulations. Periodically, according to the Investigator Brochure SOP, the Investigator Brochure will be updated to include new and relevant safety information. Until such time that an AE becomes identified in the Investigator Brochure, it should be considered unexpected, regardless of whether the AE has been the subject of a previous **ESR**.

8.7 Laboratory Test Abnormalities

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF, or be submitted electronically from a central lab. In addition, in order for us to collect additional information about clinically important laboratory abnormalities, at a minimum, the following laboratory abnormalities should be captured on the non-serious or serious AE pages of the CRF as appropriate:

- Any laboratory test result that meets the criteria for a Serious Adverse Event
- Any laboratory abnormality that required the patient to have investigational product discontinued or interrupted
- Any laboratory abnormality that required the patient to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anaemia versus low haemoglobin value).

8.8 Other Safety Considerations

Any clinically significant changes 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 on the appropriate AE page of the CRF (i.e., NON-SERIOUS or SERIOUS).

8.9 Pregnancy

All female subjects of childbearing age require a negative pregnancy test at trial entry. If subjects become pregnant during the trial, they will be immediately withdrawn from the trial. All cases of pregnancy must be reported on Pregnancy Surveillance Forms in lieu of SAE pages.

9. ADMINISTRATIVE SECTION

9.1 Informed consent

Investigators must ensure that subjects or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate.

The following sections contain Bristol-Myers Squibb procedures on obtaining informed consent from subjects or their legally acceptable representative prior to participating in a clinical trial. Procedures are described for all subjects, including those who are unable to give informed consent. The relevant procedures must be used whenever they are applicable.

9.1.1 Informed consent procedures

Investigators must ensure that subjects or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Only mentally competent subjects, capable of reading and understanding the consent form will be entered in the trial. Psychiatric patients and prisoners will not be entered. The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. The Investigator must provide the subject or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The Investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial. See also appendix 5

9.2 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by the sponsor. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF.

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

- IRB/IEC for review and approval/favorable opinion;
- the sponsor;
- Regulatory Authority(ies), if required by local regulations.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to the sponsor. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

If an Amendment substantially alters the study design or increases the potential risk to the subject: (

1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion;

(2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are by the Amendment; and

(3) the new form must be used to obtain consent from new subjects prior to enrollment.

9.3 Monitoring for Protocol Compliance

Representatives of the sponsor must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. On site they will review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by internal auditors and government inspectors who must be allowed access to CRFs, source documents and other study files.

THE INVESTIGATOR MUST NOTIFY THE SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

9.4 Records and Reports

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation. Data reported on the CRF, that are derived from source documents, must be consistent with the source documents or the discrepancies must be explained.

The CRF must be completed legibly in ink. Subjects are to be identified by initials, birthdate and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank. The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). The Investigator will maintain a Signature Sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs. A correction must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be dated, initialed and explained (if necessary) by the person making the correction and must not obscure the original entry. The completed CRF must be promptly reviewed, signed, and dated by a qualified physician who is an Investigator or Subinvestigator. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

9.5 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The study will be reviewed by The MHRA and UK COREC ethics committee locally at The Hammersmith Hospitals and will then need to be reviewed locally for participating centres.

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 (e.g., 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 (e.g., Safety Updates, Amendments, Administrative Letters) according to regulatory requirements or Institution procedures.

9.6 Records Retention

The Investigator must retain investigational product disposition records, copies of CRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines,

or Institution procedures, or for the period specified by the Sponsor, whichever is longer. The Investigator must contact the sponsor prior to destroying any records associated with the study. The sponsor will notify the Investigator when the trial records are no longer needed. If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Notice of such transfer will be given in writing to the sponsor.

10 LIST OF ABBREVIATIONS

AAV	ANCA-associated vasculitis
ANCA	Anti-neutrophil cytoplasmic antibodies
AZA	Azathioprine
CS	Corticosteroids
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
ELISA	Enzyme-linked immunosorbent assay
IDO	2, 3 Indoleamine dioxygenase
MCP-1	Monocyte chemoattractant protein-1
MMF	Mycophenolate mofetil
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
MTX	Methotrexate
PR3	Proteinase 3
WG	Wegener's granulomatosis

11 REFERENCES

1. Jennette, J.C. et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* **37**, 187-92 (1994).
2. Jayne, D. et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. in *N Engl J Med* Vol. 349 36-44 (2003).
3. Booth, A. et al. Prospective study of TNF alpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. in *J Am Soc Nephrol* Vol. 15 717-21 (2004).
4. De Groot, K. et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic anti-neutrophil cytoplasmic antibody-associated vasculitis. in *Arthritis Rheum* Vol. 52 2461-9 (2005).
5. Harper, L. & Savage, C.O. ANCA-associated renal vasculitis at the end of the twentieth century--a disease of older patients. *Rheumatology (Oxford)* **44**, 495-501 (2005).
6. Booth, A.D. et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. in *Am J Kidney Dis* Vol. 41 776-84 (2003).
7. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* **352**, 351-61 (2005).
8. Eriksson, P. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. *J Intern Med* **257**, 540-8 (2005).
9. Keogh, K.A., Wylam, M.E., Stone, J.H. & Specks, U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* **52**, 262-8 (2005).
10. Keogh, K.A. et al. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. *Am J Respir Crit Care Med* **173**, 180-7 (2006).
11. Omdal, R., Wildhagen, K., Hansen, T., Gunnarsson, R. & Kristoffersen, G. Anti-CD20 therapy of treatment-resistant Wegener's granulomatosis: favourable but temporary response. *Scand J Rheumatol* **34**, 229-32 (2005).
12. Aries, P.M. et al. Lack of efficacy of Rituximab in Wegener's Granulomatosis with refractory granulomatous manifestations. *Ann Rheum Dis* (2005).
13. Schmitt, W.H. et al. Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. *Kidney Int* **65**, 1440-8 (2004).
14. Xiao, H. et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest* **110**, 955-63 (2002).
15. Little, M.A. et al. Antineutrophil cytoplasm antibodies directed against myeloperoxidase augment leukocyte-microvascular interactions in vivo. *Blood* **106**, 2050-8 (2005).
16. Bansal, P.J. & Tobin, M.C. Neonatal microscopic polyangiitis secondary to transfer of maternal myeloperoxidase-antineutrophil cytoplasmic antibody resulting in neonatal pulmonary hemorrhage and renal involvement. *Ann Allergy Asthma Immunol* **93**, 398-401 (2004).
17. Franssen, C.F. et al. In vitro neutrophil activation by antibodies to proteinase 3 and myeloperoxidase from patients with crescentic glomerulonephritis. *J Am Soc Nephrol* **10**, 1506-15 (1999).
18. Girard, T. et al. Are antineutrophil cytoplasmic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study. *Rheumatology (Oxford)* Vol. 40 147-51 (2001).
19. Tam, F.W. et al. Urinary monocyte chemoattractant protein-1 (MCP-1) is a marker of active renal vasculitis. *Nephrol Dial Transplant* **19**, 2761-8 (2004).
20. Chavele, M. et al. Immune Regulation of MPO-ANCA Disease Is Associated with Activation of the IDO Pathway and Tryptophan Degredation. *JASN* Vol. 16 (2005).

21. Haas, M. & Eustace, J.A. Immune complex deposits in ANCA-associated crescentic glomerulonephritis: a study of 126 cases. *Kidney Int* Vol. 65 2145-52 (2004).
22. Cunningham, M.A., Huang, X.R., Dowling, J.P., Tipping, P.G. & Holdsworth, S.R. Prominence of cell-mediated immunity effectors in "pauci-immune" glomerulonephritis. *J Am Soc Nephrol*, Vol. 10 499-506 (1999).
23. Reynolds, J. et al. CD28-B7 blockade prevents the development of experimental autoimmune glomerulonephritis. *J Clin Invest* Vol. 105 643-51 (2000).
24. Grohmann, U. et al. CTLA-4-Ig regulates tryptophan catabolism in vivo. *Nat Immunol* Vol. 3 1097-101 (2002).
25. Munn, D.H., Sharma, M.D. & Mellor, A.L. Ligation of B7-1/B7-2 by human CD4+ T cells triggers indoleamine 2,3-dioxygenase activity in dendritic cells. *J Immunol* Vol. 172 4100-10 (2004).
26. Genovese, M.C. et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* Vol. 353 1114-23 (2005).
27. Abrams, J.R. et al. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. *J Clin Invest* Vol. 103 1243-52 (1999).
28. Vincenti, F. et al. Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* Vol. 353 770-81 (2005).
29. Luqmani, R.A. et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *Qjm* Vol. 87 671-8 (1994).
30. Tam, F.W. et al. Urinary monocyte chemoattractant protein-1 (MCP-1) is a marker of active renal vasculitis. *Nephrol Dial Transplant* Vol. 19 2761-8 (2004).

APPENDIX 1. LIST OF COLLABORATING EUVAS CENTRES

<u>Name</u>	<u>Affiliation</u>	<u>Contact details</u>
1. Alan Salama/Charles Pusey	Renal Section, Division of Medicine, Imperial College London, Hammersmith Hospital London, UK	A.salama@imperial.ac.uk C.pusey@imperial.ac.uk
2. David Jayne/Rachel Jones	Department of Nephrology, Addenbrooke's Hospital, Cambridge, UK	Dj106@cam.ac.uk rjones@doctors.org.uk
3. Lorraine Harper/Caroline Savage	Division of Medical Sciences, University of Birmingham, UK	c.o.s.savage@bham.ac.uk l.harper@bham.ac.uk
4. Raashid Luqmani/Philip Mason	Rheumatology Department, Nuffield Orthopaedic Centre, Oxford, UK	Raashid.luqmani@noc.anglox.nhs.uk
5. Kirsten de Groot/Marion Haubitz	Division of Nephrology, Hannover Medical School, Germany	Kirsten@de-groot.de Haubitz.marion@mh-hannover.de
6. Wilhelm Schmitt	Fifth Medical Clinic, University Hospital Mannheim, Germany	Wilhem.schmitt@med5.ma.uni-heidelberg.de
7. Ursula Gobel	<u>Franz Volhard Clinic, Humboldt University, Berlin, Germany</u>	ugoebel@berlin.helios-kliniken.de
8. Marten Segelmark/Kerstin Westman	Department of Nephrology, Lund University Hospital, Sweden	Marten.segelmark@njur.lu.se Kerstin.westman@skane.se
9. Vladimir Tesar	Division of Nephrology, Charles University, Prague, Czech Republic	Tesarv@cesnet.cz
10. Jan Willem Cohen Tervaert	Department of Clinical Immunology University Hospital Maastricht, The Netherlands	Jw.cohentervaert@immuno.unimaas.nl
11. Prof Loic Guillevin	Hopital Cochrin, Paris, France	loic.guillevin@cch.aphp.fr
12. Dr Philippe Vanhille	Néphrologie-Médecine Interne Hopital de Valenciennes Av. Désandrouin 59322 Valenciennes France	vanhille-p@ch-valenciennes.fr
13. Prof Peter Mathieson	University of Bristol, Southmead Hospital	P.Mathieson@bristol.ac.uk

14. Dr Peter Andrews	St Hellier Hospital, London	<u>Peter.Andrews@epsom-sthelier.nhs.uk</u>
15. Dr Martin Wissing	Department of Nephrology CUB Hopital Erasme Route de Lennik 808 B-1070 Brussels Belgium	<u>wissing@ulb.ac.be</u>
16. Dr Bernard Hellmich Prof. W.L. Gross	Rheumaklinik Bad Bramstedt & Universitätsklinikum Schleswig Holstein, Campus Lübeck, Poliklinik für Rheumatologie Oskar-Alexander Strasse 26 D-24576 Bad Bramstedt Germany	<u>bernhard.hellmich@rheuma.uni-luebeck.de</u> <u>gross@rheuma-zentrum.de</u>

APPENDIX 2 DRUG REDUCTION SCHEME

time from entry	prednisolone mg/kg/day	methotrexate mg/week MTX
0	1 \pm 12.5% *	15
1 week	0.75 etc.	15
2 weeks	0.5	15
4 weeks	0.4	17.5
6 weeks	0.33	17.5
8 weeks	0.28	20
10 weeks	0.25	20 - 22.5
12 weeks	0.25 = 15 mg/day	20 - 25
3 months	for a 60 kg person	20 - 25
4 months	12.5 mg/day	20 - 25
5 months	10 etc.	20 - 25
6 months	7.5	20 - 25
7 months	7.5	20 - 25
8 months	5	20 - 25
9 months	5	20 - 25
10 months	2.5	20 - 25
11 months	2.5	20-25
12 months	0	20-25
13 months	0	20-25
14 months	0	20-25
15 months	0	17.5-20
16 months	0	17.5-20
17 months	0	17.5-20
18 months	0	15-17.5
19 months	0	15-17.5
20 months	0	15-17.5
21 months	0	12.5-15
22 months	0	12.5-15
23 months	0	12.5-15
24 months	0	12.5-15

APPENDIX 3. COSTINGS FOR A PAN-EUROPEAN INVESTIGATION

Medical Input	25% 3 years	£40 000
Administrator	50% 3 years	£61 000
Regulatory approval	£2 500 per country	£15 000
Drug Abatacept		Provided by BMS
Capitation	£500 per patient	£50,000
HACA analysis	Shipment+ processing	£1000+ processing
T cell assays, cell phenotype analysis, serum tryptophan, RNA processing and analysis (foxp3, IDO)	} Shipment and processing	60 000
Post-doctorate researcher		61 000
DMC (safety)		£2 000
Computer + software		£1 500
Travel expenses		£10 000
Renal histopathology review		£6 000
Office consumables		£2 000
Indirect University costs		£90,000
Estimated CRO costs for:		£93, 000
<ul style="list-style-type: none"> • Study and pre-study activities (project management) • Data Management • Statistical activities • Medical writing (SAE Narrative 		

writing and Final study report & Manuscript preparation & Appendices) <ul style="list-style-type: none"> • Other activities (CRF printing) 		
Packaging and QC support for study supplies; external vendor		£15, 000
TOTAL		£507, 500

ADS 2006

APPENDIX 4. BVAS SCORING SHEET

VASCULITIS ACTIVITY SCORE 2003			
<input type="radio"/> Tick box only if abnormality represents active disease (use the Vasculitis Damage Index, VDI to score items of damage). If there are no abnormalities in a system, please tick the "None" box		<input type="checkbox"/> If all the abnormalities recorded represent smouldering/low grade/ grumbling disease, and there are no new/worse features, please remember to tick the box at the bottom right corner	
	None	Active disease	
1. General	<input type="radio"/>		
Myalgia		<input type="radio"/>	
Arthralgia or arthritis		<input type="radio"/>	
Fever $\geq 38.0^{\circ}\text{C}$		<input type="radio"/>	
Weight Loss ≥ 2 kg		<input type="radio"/>	
2. Cutaneous	<input type="radio"/>		
Infarct		<input type="radio"/>	
Purpura		<input type="radio"/>	
Ulcer		<input type="radio"/>	
Gangrene		<input type="radio"/>	
Other skin vasculitis		<input type="radio"/>	
3. Mucous membranes/eyes	<input type="radio"/>		
Mouth ulcers/granulomata		<input type="radio"/>	
Genital ulcers		<input type="radio"/>	
Adnexal inflammation		<input type="radio"/>	
Significant proptosis		<input type="radio"/>	
Red eye (Epi)scleritis		<input type="radio"/>	
Red eye conjunctivitis/blepharitis/keratitis		<input type="radio"/>	
Blurred vision		<input type="radio"/>	
Sudden visual loss		<input type="radio"/>	
Uveitis		<input type="radio"/>	
Retinal vasculitis/retinal vessel		<input type="radio"/>	
Thrombosis/retinal exudates/Retinal haemorrhages		<input type="radio"/>	
4. ENT	<input type="radio"/>		
Bloody nasal discharge/nasal		<input type="radio"/>	
Crusts/ulcers and/or granulomata		<input type="radio"/>	
Paranasal sinus involvement		<input type="radio"/>	
Subglottic stenosis		<input type="radio"/>	
Conductive hearing loss		<input type="radio"/>	
Sensorineural hearing loss		<input type="radio"/>	
5. Chest	<input type="radio"/>		
Wheeze		<input type="radio"/>	
Nodules or cavities		<input type="radio"/>	
Pleural effusion/pleurisy		<input type="radio"/>	
Infiltrate		<input type="radio"/>	
Endobronchial involvement		<input type="radio"/>	
Massive haemoptysis/Alveolar haemorrhage		<input type="radio"/>	
Respiratory failure		<input type="radio"/>	
6. Cardiovascular	<input type="radio"/>		
Loss of pulses		<input type="radio"/>	
Valvular heart disease		<input type="radio"/>	
Pericarditis		<input type="radio"/>	
Ischaemic cardiac pain		<input type="radio"/>	
Cardiomyopathy		<input type="radio"/>	
Congestive cardiac failure		<input type="radio"/>	
7. Abdominal	<input type="radio"/>		
Peritonitis		<input type="radio"/>	
Bloody diarrhoea		<input type="radio"/>	
Ischaemic abdominal pain		<input type="radio"/>	
8. Renal	<input type="radio"/>		
Hypertension		<input type="radio"/>	
Proteinuria $>1+$		<input type="radio"/>	
Haematuria ≥ 10 rbc/hpf		<input type="radio"/>	
Creatinine 125-249 $\mu\text{mol/l}$		<input type="radio"/>	
Creatinine 250-499 $\mu\text{mol/l}$		<input type="radio"/>	
Creatinine ≥ 500 $\mu\text{mol/l}$		<input type="radio"/>	
Rise in creatinine $> 30\%$ or Creatinine clearance fall $> 25\%$		<input type="radio"/>	
9. Nervous system	<input type="radio"/>		
Headache		<input type="radio"/>	
Meningitis		<input type="radio"/>	
Organic confusion		<input type="radio"/>	
Seizures (not hypertensive)		<input type="radio"/>	
Stroke		<input type="radio"/>	
Cord lesion		<input type="radio"/>	
Cranial nerve palsy		<input type="radio"/>	
Sensory peripheral neuropathy		<input type="radio"/>	
Motor mononeuritis multiplex		<input type="radio"/>	
10. OTHER	<input type="radio"/>		
		<input type="radio"/>	
		<input type="radio"/>	
		<input type="radio"/>	
		<input type="radio"/>	
PERSISTENT DISEASE ONLY:			
Tick here if all the above abnormalities are due to low grade grumbling disease and not due to new/ worse disease			<input type="checkbox"/>

APPENDIX 5 CONSENT FORM

Consent form

Final version 1.0; January 2007

Name of the study: Examining the effect of Abatacept on preventing relapse in ANCA associated vasculitis.

Name of Researcher: Dr Alan Salama

Please complete this section by initialing the boxes and then signing the bottom

Section I - Patient consent to study treatment		
1.	I confirm that I have read and understand the information sheet dated January 2007 for the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation in this study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3.	I understand that relevant sections of any of my medical notes and electronic data collected during the study may be looked at by responsible individuals from Imperial College, from regulatory bodies or from the NHS trust. I give permission for these individuals to access my records.	
4.	I agree to my GP being informed of my participation in this study.	
5.	I agree to take part in the above study.	
Section II – Consent to donate research samples. These next two sections are optional. You do not have to agree to this part of the study		
6.	I agree to give 10ml (about 2 teaspoons) of blood at each visit, an extra 50ml (about 3 tablespoons) of blood at 3 separate visits, and a part of each routinely collected urine sample for research in this project. I understand that giving these samples is voluntary and that I am free to withdraw my approval at any time.	
Section III – Consent to store samples for future use		

7.	I agree that the samples I give can be stored for use in the future	
----	---	--

Name of patient or
Legally Authorized Representative

Date

Signature of Investigator or Designee

Date

