Concurrent Pilot Studies in Giant Cell Arteritis and Takayasu’s Arteritis to Examine the Safety, Efficacy, and Immunologic Effects of Abatacept (CTLA4-Ig) in Large Vessel Vasculitis (AGATA)

Vasculitis Clinical Research Consortium (VCRC)
VCRC Protocol No. 5523

This protocol is for research purposes only, and should not be copied, redistributed or used for any other purpose. The procedures in this protocol are intended only for use by Consortium investigators in carefully controlled settings. The Chair of this study should be consulted before using or attempting any procedure in this protocol.

Carol A. Langford, MD, MHS
Cleveland Clinic

Peter A. Merkel, MD, MPH
University of Pennsylvania

Contact Information:
Carol A. Langford, MD MHS
Center for Vasculitis Care and Research
Cleveland Clinic
9500 Euclid Avenue, A50
Cleveland, OH 44195
Tel: (216) 445-6056
Email: langfoc@ccf.org
Table of Contents

1. Synopsis ................................................................................................................... 4
   a. Brief Summary .............................................................................................................. 4

2. Study Endpoints ........................................................................................................ 5
   a. Primary Outcome .......................................................................................................... 5
   b. Secondary Outcome ...................................................................................................... 5

3. Background and Rationale ........................................................................................ 5
   a. Background .................................................................................................................. 5
      i. GCA and TAK: Disease and Current Treatment ......................................................... 5
      ii. Description of Abatacept ......................................................................................... 7
   b. Rationale ..................................................................................................................... 8
      i. Rationale for the Use of Abatacept in GCA and TAK .................................................. 8
      ii. Rationale for Clinical Trial Design and Dosage ......................................................... 9
      iii. Rationale for the Basic Science Research Linked to the Clinical Trial ..................... 11

4. Study Design and Methods ....................................................................................... 11
   a. Overview .................................................................................................................... 11
   b. Identification of Subjects ........................................................................................ 13
      i. Inclusion Criteria ...................................................................................................... 13
      ii. Exclusion Criteria ................................................................................................... 14
   c. Study Medications ....................................................................................................... 15
      i. Initial treatment period: Methods and Doses ............................................................ 15
      ii. Randomized Treatment Period: Methods and Doses ............................................... 16
      iii. Concomitant Medications ..................................................................................... 17
      iv. Prophylactic Medications ...................................................................................... 17
      v. Prohibited Concomitant Medications ................................................................... 17
   d. Study Procedures ........................................................................................................ 18
      i. Recruitment ............................................................................................................... 18
      ii. Screening .................................................................................................................. 18
      iii. Enrollment ............................................................................................................... 18
         1). Inclusion of Pediatric Subjects .............................................................................. 18
         2). Inclusion of Women ............................................................................................ 19
         3). Inclusion of Underrepresented Ethnic/Racial Minorities ....................................... 19
      iv. Visit Frequency/ Visit Schedule ............................................................................ 19
      v. Specimen and Data Collection Schedule ................................................................. 19
         1). Specimen Collection ............................................................................................ 19
         2). Diagnostic Imaging .............................................................................................. 20
         3). Visit and Data Collection Schedule ..................................................................... 22
   e. Common Treatment Closing Date - Study Duration ................................................. 24
   f. Criteria for Withdrawal of Study Medication – Early Termination ......................... 24
   g. Study Endpoints ......................................................................................................... 24
   h. Outcome Definitions ................................................................................................... 25
      i. Disease activity ......................................................................................................... 25
      ii. Remission ................................................................................................................ 26
      iii. Relapse .................................................................................................................... 26
   i. Experimental Design for the Linked Basic Science Studies ....................................... 26

5. Safety Monitoring and Adverse Event Reporting ..................................................... 29
a. Nature of Study -------------------------------------------------------------- 29
b. Study Oversight--------------------------------------------------------------- 29
c. Definitions------------------------------------------------------------------- 29
d. Toxicity Grading of Adverse Events------------------------------------------ 30
e. Relation to Study Therapy---------------------------------------------------- 30
f. Standard Elements------------------------------------------------------------ 31
g. Expected/Known Risks/Discomforts/Adverse Events Associated with Study
   Intervention and Procedures: Definition of Expected Adverse Events--------- 31
   i. Study Drug/Intervention: ----------------------------------------------- 31
   ii. Study Procedures: ------------------------------------------------------- 31
h. Reporting Timeline------------------------------------------------------------ 31
i. Adverse Event Data Management System (AEDAMS)------------------------------- 31
j. Investigational New Drug Application (IND)----------------------------------- 32
k. Criteria to Suspend Enrollment----------------------------------------------- 32
6. Data Analysis and Statistical Considerations........................................... 32
   a. Sample size calculations and statistical methods------------------------ 32
   b. Accrual------------------------------------------------------------------- 34
7. Data Management--------------------------------------------------------------- 34
   a. Registration------------------------------------------------------------- 34
   b. Randomization------------------------------------------------------------ 35
c. Data Entry------------------------------------------------------------------ 35
d. Data Quality Control--------------------------------------------------------- 35
e. Laboratory and Imaging Data Flow------------------------------------------- 35
8. Protection of Human Subjects------------------------------------------------- 36
   a. GCP Statement------------------------------------------------------------- 36
   b. Risks and Benefits-------------------------------------------------------- 36
      i. Overall Risk / Benefit Assessment------------------------------------ 36
      ii. Risks of Abatacept--------------------------------------------------- 36
      iii. Risks of Prednisone----------------------------------------------- 38
      iv. Other Risks--------------------------------------------------------- 39
9. References-------------------------------------------------------------------- 41
1. Synopsis

a. Brief Summary

Giant cell arteritis (GCA) and Takayasu’s arteritis (TAK) are granulomatous vasculitic diseases that share similar clinical, histologic, and immunopathogenic features. Involvement of the aorta and its main branches occurs in both diseases where it causes disability, morbidity, and mortality. Although glucocorticoids (GC) provide symptomatic improvement in GCA and TAK, they are toxic and do not prevent disease recurrence. Studies of arterial tissue support that GCA and TAK are antigen-driven diseases in which activated T cells play a critical role in pathogenesis.

Abatacept (CTLA4-Ig) is a novel agent that modulates the costimulation signal required for antigen-specific T cell activation. The actions of abatacept make this an appealing and innovative therapy to investigate in GCA and TAK, diseases for which there is a great need to identify better treatments.

This protocol to be performed by the Vasculitis Clinical Research Consortium (VCRC) seeks to examine the safety, efficacy, and immunologic effects of abatacept (CTLA4-Ig) in patients with GCA and TAK through the conduct of concurrent randomized withdrawal trials. This study will seek to randomize 66 participants (33 with GCA and 33 with TAK) from the VCRC centers in order to achieve 60 evaluable subjects to be studied over a 4 year period. Subjects will receive abatacept 10mg/kg given intravenously on days 1, 15, 29 and week 8 together with prednisone 60mg/day that will be tapered according to a standardized schedule. At week 12, subjects in remission will undergo a double blinded randomization to continue abatacept or be switched to placebo together with continuing a standardized prednisone taper. All subjects will be followed until the common closing date, defined as 1 year after the randomization of the 33rd subject for each disease. Laboratory based studies that are directly integrated with the conduct of this study were selected on the basis of establishing an immunologic correlation with safety and efficacy observed in this trial and in particular to determine whether abatacept has been dosed effectively.

This project has been funded in whole or in part with Federal funds from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN2682007000036C. The study will be conducted by the VCRC, which is a consortium of vasculitis investigators.
2. Study Endpoints

a. Primary Outcome
- The **primary study endpoint** will be remission duration (relapse-free survival). This will provide preliminary data on the efficacy of the combination of abatacept and GC to prolong relapse-free survival in patients with GCA and TAK.

b. Secondary Outcome
- The **secondary study endpoint** will be toxicity. This will allow us to examine the safety of abatacept in patients with GCA or TAK.

3. Background and Rationale

a. Background

   i. GCA and TAK: Disease and Current Treatment

   GCA and TAK are two forms of vasculitic disease that are both characterized by granulomatous vasculitis affecting large and medium-sized vessels. GCA and TAK share many clinical, histopathologic, and therapeutic similarities. Because of this, it has remained an ongoing question as to whether GCA and TAK represent age-modified expressions of a single disease spectrum. The concurrent investigation of GCA and TAK through a standardized therapeutic and laboratory-based study may shed important insights not only into the safety and efficacy of a promising new treatment but also into the relationship that exists between these diseases.

   GCA, also known as temporal arteritis, is a chronic granulomatous vasculitic disease of unknown cause that preferentially involves medium- and large-sized arteries, such as the carotid arteries, aorta, and their major branches (1, 2). GCA is the most common systemic vasculitis in the Northern Hemisphere with the average annual incidence rate in Olmsted County, Minnesota of 19 per 100,000 persons (3). GCA typically affects patients ≥50 years of age, with women being affected 2-3x more frequently than men. GCA has a predilection to involve branches of the external carotid artery. It commonly manifests as headache, fever, fatigue, myalgias/arthralgias, jaw claudication, and visual impairment. Up to 20% of patients have been reported to develop irreversible visual loss including blindness that occurs as a result of anterior ischemic optic neuropathy from vasculitic involvement of the ocular circulation (4). GCA can also involve the aorta and its main branches. Clinically apparent large-vessel disease affecting the aorta and its major branches has been found in approximately 27% of patients with the risk of potentially fatal thoracic aortic aneurysms being increased more than 17-fold in patients with GCA (5-7). However, in 100% of patients evaluated at post-mortem, the aorta and its branch vessels are histologically abnormal revealing features consistent with GCA (8).

   GC represent the foundation of treatment for GCA. While GC improve symptoms and diminish the risk of blindness (9, 10), up to 91% of patients experience disease relapse requiring an increase in GC dosage (11-14). In one standardized trial, relapses occurred in 77% of newly diagnosed patients within the first 12 months (11). For most patients with GCA, the duration of GC treatment is at least 2 years with many requiring treatment for 4 years or longer (15-19) which can lead to adverse events in up to 80% of patients (20-22). The toxicities of GC are particularly problematic for the older patient population...
who are affected by GCA and includes weight gain, osteoporosis and fractures, osteonecrosis, hypertension, diabetes mellitus, cataracts, accelerated atherosclerosis, myopathy, mood and mental status changes. Because of this, the utility of adjunctive immunosuppressive agents have been explored in GCA. Two randomized trials were performed examining the use of MTX (11, 12). While these studies reached differing conclusions for some outcome parameters, neither study found that MTX was able to reduce GC toxicity. Results from a randomized controlled trial in GCA found that infliximab did not reduce the rate of relapse, the cumulative dose of GC, or GC toxicity (23).

Patients with TAK face similar therapeutic challenges. TAK is characterized by granulomatous vasculitis that preferentially involves the aorta, its major branches, and the pulmonary arteries (24-26). In contrast to GCA, TAK is a disease of young adults with most patients being diagnosed between the ages of 18-40. It is an even more female predominant disease with estimates from Japan and the United States suggesting that TAK affects women 9 times more frequently than men (27). TAK has an estimated incidence rate of 2.6 cases per million per year (25). Patients with TAK typically develop constitutional and/or vascular symptoms (24, 26, 28-31). Vascular symptoms are the direct result of narrowing, occlusion, or aneurysm formation. The most commonly involved sites are stenotic lesions of the subclavian, renal, and carotid arteries where decreased perfusion can result in claudication, hypertension, renal dysfunction, syncope, TIA, or stroke. Aortic aneurysms can also occur resulting in valvular insufficiency, congestive heart failure, and the risk of rupture or dissection.

Similar to GCA, GC are the primary treatment of TAK (24, 32, 33). While this therapy is able to improve symptoms and induce remission, all of our current treatment approaches for TAK are associated with a high rate of disease relapse. The only prospective standardized therapeutic trial conducted to date in TAK examined the use of adjunctive MTX in 16 patients but a sustained remission occurred in only 50% (34). While treatment with MTX is often considered a next step in the treatment of patients with relapsing TAK, no comparative studies have been performed that have clearly proven this regimen to be superior to GC alone. From a Cleveland Clinic series of 30 longitudinally followed patients in which 73% of patients required a second immunosuppressive agent in addition to GC, a sustained remission defined as the absence of clinical, laboratory, and radiographic evidence of new vascular lesions for ≥ 6 months while being treated with less than 10mg/day of prednisone, was seen in only 28% of patients (35, 36). From a National Institutes of Health TAK cohort, although clinically apparent relapses were seen in 45% of patients, relapses occurred in over 80% of all treated patients when this was defined as new lesions in new vascular territories on sequential imaging studies (24).

Because of the young adult population that is affected, TAK carries significant consequences both for individual patients and society as a whole. Progressive arterial disease in TAK can bring about substantial morbidity and potential mortality. In one series, 74% of patients were found to have some compromise in activities of daily living and 47% were permanently disabled (24). Although two North American reports found overall survival to be 94% or greater (24, 25), the 5 year mortality rate of TAK from other series is as high as 35% (37-39).

TAK and GCA are therefore two unique disease entities that share similar features in that they are large to medium-sized vessel granulomatous vasculitides for which there is no
treatment capable of producing sustained remissions. There is a great unmet need in both GCA and TAK to provide safer and more effective therapeutic options beyond GC.

ii. Description of Abatacept

Abatacept (CTLA4-Ig) is comprised of the external domains of CTLA4 linked to a modified Fc of human immunoglobulin 1 (IgG1) engineered to not fix complement (40, 41). In order for T cells to become fully activated in response to antigen stimulation, they require signaling via their antigen-specific T cell receptor (TCR) plus signaling through CD28, a non-antigen-specific costimulatory receptor. CD28 is expressed on T cells and binds to CD80 (B7-1) or CD86 (B7-2) present on activated antigen-presenting cells (APC). CTLA4 is normally expressed on the cell surface of activated T cells and regulatory T cells and binds to CD80 and CD86 with a 20-100-fold higher avidity than CD28, thereby acting as negative regulator of CD28-mediated T cell costimulation (42). By blocking costimulation, CTLA4 is an essential checkpoint for immune function. In the absence of CTLA4, mice develop a fatal lymphoproliferative disease, providing further evidence of the critical role of this surface molecule in T cell regulation (43, 44).

There have been several proposed mechanisms of action of abatacept (Figure 1). As abatacept contains CTLA4, it has been hypothesized to induce protective regulatory immunity by blocking the engagement of CD28 with its ligands CD80 (B7-1) and CD86 (B7-2) thereby inhibiting T cell activation, including progression into cell cycle, effector differentiation, and cell survival. Although original work from in vitro studies suggested that blockade of T cell stimulation resulted in T cell anergy this has not been borne out in vivo. Individual T cells from treated animals have been found to function ex vivo (45). Recent data have suggested that a major effect of costimulation blockade in vivo is to promote passive (growth factor withdrawal) cell death and limit the clonal expansion of antigen-reactive T cells (46, 47).

![Diagram of T-cell activation and costimulation](image)
Another *in vivo* effect of abatacept that has been described in the setting of transplantation is induction of tolerance by triggering APC production of indolamine 2, 3-dioxygenase (IDO), an intracellular enzyme that breaks down tryptophan and suppresses T cell activation (48, 49). One working model is that abatacept induces upregulation of IDO by APCs which in turn increases tryptophan metabolism with more kynurenine, the consequences of which are to turn off pathogenic T cell immunity. The IDO expressing APC may be tolerogenic, helping to induce/expand CD4+ CD25+ Foxp3+ T regulatory cells, which in turn can inhibit disease via contact dependent and or cytokine mechanisms.

Abatacept may also have effects on B cell mediated mechanisms of immunity. There is evidence that costimulation is necessary in autoantibody production through B7 binding. Animal models have found that abatacept may prevent autoantibody formation possibly through interference with T cells mediated help for antibody production.

Abatacept is approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (RA). It is indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA who have had an inadequate response to one or more disease remittive agents, such as MTX or tumor necrosis factor (TNF) antagonists (e.g.:etanercept or infliximab) (50-53). Although caution must be raised with all immunosuppressive agents, to date, abatacept has been well tolerated in patients with RA.

**b. Rationale**

**i. Rationale for the Use of Abatacept in GCA and TAK**

The rationale for the study of abatacept in GCA and TAK is based upon intervening with the pathophysiologic mechanisms that may contribute to the development of granulomatous vasculitis seen in both of these disease processes together with the favorable safety profile of abatacept compared to GC or other immunomodulatory agents.

The etiology of both GCA and TAK remain unclear (54), however, laboratory studies have shed light on the immunological mechanisms involved in the blood vessel inflammation that characterize these diseases (55, 56).

Experimental data support the concept that GCA is an antigen-driven disease in which activated T lymphocytes, macrophages, and dendritic cells (DC) play a critical role in the disease pathogenesis (57). The CD4+ T cell is the critical cellular player in the vasculitic lesion of GCA (58, 59). Although the antigens recognized by CD4+ T cells in GCA are unknown, indirect evidence that stimulation of CD4+ T cells is antigen-driven has come from several sources. Certain allelic variants of class II antigen-presenting HLA molecules constitute a risk factor for GCA (60). In addition, the presence of clonally expanded populations of CD4+ T cells with identical antigen receptors have been found in distinct vascular lesions in GCA patients (61).

Evidence from the laboratory supports that GCA is initiated in the adventitia where CD4+ T cells become activated and orchestrate macrophage differentiation. These
adaptive immune responses in the adventitia are believed to be triggered by a population of indigenous DC located at the adventitia-media junction (62-64). Much has been learned from an animal model that utilizes severe combined immunodeficiency (SCID) mice implanted with an affected human temporal artery from a patient with GCA. In the human GCA artery-SCID mouse chimeras, depletion of CD83(+) DC abrogated vasculitis, suggesting that DC are critical antigen-presenting cells in GCA (62).

In temporal arteries from people with GCA, DC are highly enriched and activated and have matured into fully differentiated cells producing the chemokines, CCL18, CCL19, and CCL21, which have a critical role in trapping DC and attracting T cells and macrophages into the arterial wall (63). In keeping with their advanced maturation, DC in the granulomatous lesions possess the chemokine receptor CCR7 (63). CCR7 binds CCL19 and CCL21, causing the highly activated DC to become trapped in the peripheral tissue site. These activated DC captured in the arterial wall express the co-stimulatory molecule, CD86, which is critical for DC/T-cell interaction and which plays an essential role in T cell activation (63). CCL19 and CCL21 being produced by the trapped activated DC recruits T cells to enter the vessel wall through the vasa vasora in the adventitia where they can become activated and begin secreting cytokines that initiate and maintain granulomatous inflammation. Granulomas in the vessel wall are a characteristic feature of GCA that are formed by IFN-gamma-producing CD4+ T cells and macrophages. These T cells and macrophages infiltrate into all layers of the vessel wall and acquire different effector functions dependent on cues in their immediate microenvironment. The end results are either myofibroblastic proliferation, luminal stenosis and tissue ischemia or attenuation of the media and aneurysm formation (65).

The available data from TAK similarly support the critical role of activated T cells in disease pathogenesis (66). Studies of aortic tissue in TAK have demonstrated that the infiltrating cells consist mainly of activated T cells (67-70) and DC in the adventitia (71, 72). The restricted usage of TCR Vα and Vβ genes by infiltrating cells in TAK suggests that a specific antigen in the aorta is being targeted (73). The nature of this antigen remains unclear but cellular and humoral responses to mycobacterial heat shock protein-65 have been incriminated (67, 74, 75). Increased expression of T cell costimulatory molecules has also been found in vascular cells and infiltrating cells at sites of inflammation in TAK (69).

Based upon these collective observations, blockage of T cell costimulation using abatacept might be a useful therapeutic intervention in GCA and TAK.

ii. Rationale for Clinical Trial Design and Dosage

The primary outcome will be studied utilizing a randomized withdrawal design in which all enrolled subjects will initially receive prednisone and abatacept and then undergo a blinded randomization to continue abatacept or be switched to placebo at week 12 if they are in remission. Prednisone will be tapered on a standardized schedule in all subjects. The major points supporting the rationale for this study design and dosages are:

Study Population
- This trial will enroll newly diagnosed or relapsing subjects as the available data do not support that there are clinical or safety differences to justify limiting enrollment to one specific group. As newly diagnosed patients with GCA (11) and TAK (24, 36) have a high rate of relapse within the first year and experience substantial GC
toxicity, their inclusion in this trial is appropriate and justified. Relapsing patients represent a group for which there is even further concern for GC toxicity and a need to pursue new treatment options. By enrolling subjects with newly diagnosed or relapsing GCA and TAK, this study will make participation available to the widest number of individuals. Inclusion of both groups will additionally provide the greatest applicability of the results to patients in clinical practice.

- The conduct of concurrent clinical trials and mechanistic studies in GCA and TAK has never previously been performed and represents a unique opportunity to augment scientific advancements in both populations.
- GCA and TAK are both diseases for which there are strong unmet needs in which the absence of an effective non-toxic treatment impacts the individual patient as well as society. The older patient population affected by GCA are at potentially greatest risk of prednisone-related toxicity while younger patients with TAK have a high rate of disability due to both disease and treatment side effects.

**Study Design and Dosages**

- As there has been no prior experience with abatacept in GCA or TAK or with the use of abatacept combined with high-dose prednisone, a randomized withdrawal design provides an ideal opportunity to assess safety and to gain preliminary efficacy data. Treating all subjects with abatacept during the initial 12 weeks optimizes the ability to observe safety in combination with high dose prednisone. It also allows all participants the opportunity to receive active study drug, which could potentially provide benefit even if they are randomized to stop treatment.
- Randomization at week 12 was selected based upon a date at which almost all participants can be expected to be in remission from GC treatment and very few would have had the likelihood of relapsing.
- In this trial, all eligible subjects who present with active GCA or TAK will initially be treated with abatacept in combination with GC. It is necessary to include GC as a part of the treatment regimen as active disease in GCA and TAK can be threatening to vascular territories of the eye, CNS, extremities, heart, kidneys, and GI tract. As GC will be included, subjects will not be at risk from withholding therapy that is of known effectiveness.
- GC will be tapered according to a standardized regimen comparable to that used in previous studies based upon which there has been a known rate of relapse. Subjects will be followed for their ability to taper GC without a return of disease activity. In the patient population that will be enrolled in this trial, the use of a tapering schedule that seeks to discontinue prednisone is justifiable on the basis of the randomized withdrawal design in which all patients will initially receive abatacept which may provide an enhanced ability to taper prednisone.
- The abatacept dosages to be used in this study are identical to what has been utilized in RA with which there has been a well described and favorable safety experience (50-53).
- For TAK, although other immunosuppressive agents such as MTX have been used for relapsing disease, their additional efficacy beyond GC is unknown as there have been no comparative trials compared to GC alone. For GCA, there has been no therapy adjunctive to GC that has been of proven benefit in reducing relapse. Based upon this, there is no evidence that treatment with GC alone in combination with the investigational agent abatacept represents withholding of treatment that is necessary for the treatment of relapsing disease for either TAK or GCA.
iii. Rationale for the Basic Science Research Linked to the Clinical Trial

The laboratory based studies that we will be performing as a part of this study were selected on the basis of establishing an immunologic correlation with safety and efficacy observed in this trial and in particular to determine whether abatacept has been dosed effectively. As is outlined in Section 4.i., the methodology that will be used will focus on studies of T cell activation and the effects of abatacept on T cell regulation and the IDO axis in GCA and TAK.

Abatacept is hypothesized to suppress pathogenic, pro-inflammatory immunity and to augment protective, regulatory immunity. If we find that drug treatment is associated with an effect on the T cell response, but there is no clinical difference between groups, the results would suggest that abatacept influences T cell function (and thus had an impact) but this impact was insufficient to alter clinical disease. Further studies would then be warranted to consider alternate approaches which target different aspects of the pathogenic immune response. If we find no clinical effect and no effect on the immune system, this would suggest that the drug was underdosed. In addition, if the drug induces a clinical remission, the remission may or may not be due to effects on the immune system. We can only assess whether the drug is working through these proposed mechanisms by testing the T cell responses and IDO pathway. If we find evidence that proinflammatory T cell immunity is indeed suppressed and regulatory immunity augmented associated with clinical remission, this will confirm our hypothesis. More importantly from a clinical standpoint, it will provide evidence that this drug and other drugs should be targeted to further enhance these protective effects in future studies. In terms of safety, the most concerning side effect would be immunosuppression related infection. If the drug causes infections as a side effect, then we would detect lower T cell immunity in those treated with the drug. Such a finding would support the conclusion that the drug causes enhanced immunosuppression, which would need to be weighing in considering future trials towards possible clinical use in these diseases. Another important aspect is that because the disease phenotypes and the patient populations are heterogeneous, abatacept may have variable effects (with the same dose) from patient to patient. This could be due to baseline immune status, differences in metabolic rates of the drug, genetic or acquired differences in ability to produce regulatory cells, etc. Studying immune responses in each subject will permit us to begin to acquire clues about why the drug is beneficial in some patients and not in others.

4. Study Design and Methods

   a. Overview

This randomized withdrawal study will seek to randomize a total of 66 participants (33 subjects with active GCA and 33 subjects with active TAK) in order to achieve 60 evaluable subjects. All subjects will initially receive abatacept at days 1, 15, 29 and week 8 in combination with prednisone. Prednisone will be tapered according to a standardized schedule. At week 12, subjects in remission will be randomized to placebo or continued abatacept that will be double blinded. Safety and efficacy data will be collected at the time of each abatacept infusion. In the absence of relapse or toxicity, subjects will continue abatacept until the common data closing date, 1 year after the randomization of the final subject for each disease.
At week 12, it is anticipated that nearly all subjects will be in remission and therefore eligible for randomization. Study progress will be closely monitored by the DMCC. After the enrollment of 33 subjects for each disease, in the event that the remission rate is lower than anticipated or if there has been drop-out prior to randomization, additional subjects may be enrolled to a maximum of 40 subjects with each disease, in order to achieve 33 randomized participants.

**Abatacept in Giant Cell Arteritis and Takayasu’s Arteritis – Study Schematic**

- Eligible patients with active Giant cell arteritis or Takayasu’s Arteritis

  - Prednisone 40-60 mg/day with a standardized prednisone taper + Abatacept 10mg/kg IV on days 1, 15, 29 and week 8

  - Is patient in remission at week 12 visit?
    - Yes
      - Randomization With Double Blinded Treatment Assignment
        - Abatacept 10mg/kg IV every 28 days + Continued prednisone taper
        - Placebo IV every 28 days + Continued prednisone taper
        - Continued Remission
          - Common Closing Date: 1 Year after randomization of the Final Participant for each disease
          - Post Treatment visits – 4, 12, and 24 weeks after stopping abatacept or abatacept/placebo
        - Relapse
          - Stop abatacept/placebo
    - No
      - Stop abatacept
b. Identification of Subjects

i. Inclusion Criteria

A total of 33 subjects with GCA and 33 subjects with TAK will be treated in this study. Subjects must meet all of the following criteria to be eligible for enrollment:

1. A diagnosis of GCA or TAK

Diagnostic criteria for GCA
A subject will be said to have GCA by meeting 3 of 5 of the following modified ACR criteria for the classification of GCA in which 1 of the 3 must consist of criteria 4 or 5:

1. Age at disease onset ≥ 50 years.
2. New onset or new type of localized pain in the head.
3. ESR of > 40 mm in the first hour by the Westergren method.
4. Temporal artery abnormality (i.e., temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries).
5. Temporal artery or large vessel biopsy showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cell or characteristic changes of large vessel stenosis or aneurysm by arteriography.

Diagnostic criteria for TAK
A subject will be said to have TAK defined by: Arteriographic abnormalities compatible with TAK (includes conventional dye angiography or MR angiography or CT angiography), plus at least one of the following:

1. Age at disease onset <50 years
2. Claudication of extremities
3. Decreased brachial artery pulse (one or both arteries)
4. Blood pressure difference of >10mm Hg between the arms
5. Bruit over subclavian arteries or aorta

2. GCA or TAK with evidence of active disease (defined below) present within the past 2 months
3. Age of 15 years or older
4. They must be willing and able to comply with treatment and follow-up procedures
5. Both women and men who are of child-bearing potential must be willing to use an effective means of birth control while receiving treatment through this study. Effective contraception methods include abstinence, surgical sterilization of either partner, barrier methods such as diaphragm, condom, cap or sponge, or hormonal contraception.
6. They must be willing and able to provide written informed consent.
ii. Exclusion Criteria

1. Evidence of active infection (includes chronic infection).
2. Subjects who are pregnant or who are nursing infants.
3. Infection with human immunodeficiency virus (HIV), hepatitis C, or a positive hepatitis B surface antigen.
4. Inability to comply with study guidelines.
5. Inability to provide informed consent.
6. Cytopenia: platelet count < 80,000/mm³, absolute neutrophil < 1500/mm³, hematocrit < 20%.
7. Renal insufficiency defined by a serum creatinine of greater than or equal to 3.0 mg/dL or creatinine clearance of less than or equal to 20 ml/min.
8. Other uncontrolled disease (co-morbidity), including drug or alcohol abuse, that, in the investigator’s opinion, that could prevent a subject from fulfilling the study requirements or that would increase the risk of study procedures.
9. History of any malignant neoplasm except adequately treated basal or squamous cell carcinoma of the skin, or solid tumors treated with curative therapy and disease free for at least 5 years.
10. Receipt of an investigational agent or device within 30 days prior to enrollment.
11. A live vaccination fewer than 4 weeks before enrollment.
12. Presence of a positive tuberculin skin test with induration of > 5mm.
14. Poor tolerability of venipuncture or lack of adequate venous access for intravenous abatacept administration and blood sampling during the study period.
15. Past treatment with rituximab within the past 12 months, or past treatment with rituximab more than 12 months ago where the B lymphocyte count has not returned to normal.
16. Patients who have received infliximab within the past 49 days, adalimumab within the past 28 days, or etanercept within the past 21 days.
17. Presence of any of the following disease processes:
   - Microscopic polyangiitis
   - Churg Strauss syndrome
   - Polyarteritis nodosa
   - Cogan’s syndrome
   - Behcet’s disease
   - Sarcoidosis
   - Kawasaki’s disease
   - Tuberculosis or atypical mycobacterial infections
   - Deep fungal infections
   - Lymphoma, lymphomatoid granulomatosis, or other type of malignancy that mimics vasculitis
   - Cryoglobulinemic vasculitis
   - Systemic lupus erythematosus
   - Rheumatoid arthritis
   - Mixed connective tissue disease or any overlap autoimmune syndrome.
c. Study Medications

i. Initial treatment period: Methods and Doses

All participants who are deemed eligible for the study will be initially treated with abatacept and prednisone as outlined below. Treatment will continue until the randomization point at week 12.

**Abatacept**

Subjects will receive a fixed dose of abatacept, approximating 10mg per kilogram of body weight such that subjects weighing:

- < 60kg receive 500mg of abatacept
- 60-100kg receive 750mg of abatacept
- > 100kg receive 1000mg of abatacept

Abatacept will be administered over at least 30-minutes as an intravenous infusion on days 1, 15, 29 and at week 8. Following the infusion, subjects will be monitored for an additional 30 minutes. All subjects will therefore be monitored for a minimum of 1 hour from the start of the abatacept infusion for infusion events. Time windows of one week before or after the scheduled date of administration will be permissible. In the absence of toxicity or relapse, subjects will remain on abatacept at the same dosage until randomization. Abatacept will be discontinued should the subject experience any event listed below in (g) Discontinuation of Study Drug.

**Glucocorticoids**

Prednisone will be tapered according to a standardized schedule as listed in the Table below. Treatment of active GCA or TAK typically involves the use of prednisone 40-60mg/day for approximately 4 weeks followed by a gradual taper. In order to avoid an increased risk of prednisone-related toxicity the reduction schedule to be utilized in this study reflects the potential for participants to have been started on prednisone prior to enrollment in order to protect safety in the setting of active GCA or TAK.

At study initiation (Week 0) subjects will be started on prednisone 40-60 mg/day, which will be maintained at a steady dose for the first 2 weeks. After 2 weeks, they will be treated as indicated in the table based upon their starting dose and whether they had received prednisone 40-60mg/day (defined as given over a 24 hour period) for 2 or more weeks prior to enrollment. Once tapering has been started, prednisone will be reduced in a standardized fashion every 2 weeks in order to reach prednisone 20mg/day by week 12.

At week 12, patients who are in remission and begin their randomized treatment assignment will continue a prednisone taper such that subjects in both the placebo and abatacept arms will be tapered utilizing an identical schedule that will reach a prednisone dose of 0 by week 28.

As some subjects enrolled in this trial may have been on longstanding glucocorticoid therapy, it is possible that they may develop adrenal insufficiency. In instances where the investigator feels that there is compelling clinical evidence to support adrenal insufficiency, they will be permitted to receive prednisone at which the symptoms and/or signs of insufficiency are absent (usually between 5 and 10 mg/day). While such doses will be captured on the data collections sheets, this will be differentiated from prednisone being used in the treatment of GCA or TAK and will not be considered a protocol deviation or an off-study criteria and will not be counted as a treatment failure.
### Schedule of Prednisone Dose-Tapering

<table>
<thead>
<tr>
<th>Week</th>
<th>Received ≥ 2 weeks of prednisone 40-60mg/day prior to enrollment</th>
<th>Received &lt;2 weeks of prednisone 40-60mg/day prior to enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Starting Dose/day</td>
<td>Starting Dose/day</td>
</tr>
<tr>
<td></td>
<td>40mg</td>
<td>50mg</td>
</tr>
<tr>
<td>0</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>27.5</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>27.5</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>22.5</td>
<td>22.5</td>
</tr>
<tr>
<td>11</td>
<td>22.5</td>
<td>22.5</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ii. Randomized Treatment Period: Methods and Doses

At week 12, subjects who are in remission will undergo a double blinded randomization to continue abatacept or stop abatacept and start placebo. Randomization will be performed by the DMCC utilizing methods as are outlined in Section 7.b. If the subject is not in remission at week 12 they will have met a Discontinuation of Study Drug criteria as outlined in section (g) below and will be taken off of abatacept and treated with best medical judgment.

**Abatacept**

Subjects randomized to remain on abatacept will receive the same dosage that they were receiving prior to randomization. Abatacept will be administered over at least 30-minutes as an intravenous infusion every 28 days. The timing of the first abatacept infusion post-randomization at week 12 will be 28 days following the last abatacept infusion prior to
randomization in order to maintain an every 28 day schedule. Time windows of one week before or after the scheduled date of administration will be permissible. In the absence of relapse or meeting another criteria for Discontinuation of Study Drug as outlined in section 4.f., subjects will remain on abatacept at the same dosage until the common treatment closing date.

**Placebo**
Subjects randomized to stop abatacept will begin placebo infusions. Placebo will be administered over at least 30-minutes as an intravenous infusion every 28 days. The timing of the first placebo infusion post-randomization at week 12 will be 28 days following the last abatacept infusion prior to randomization in order to maintain an every 28 day schedule. Time windows of one week before or after the scheduled date of administration will be permissible. In the absence of relapse or meeting other criteria for Discontinuation of Study Drug as outlined in Section 4.f., subjects will remain on placebo until the common treatment closing date.

**Glucocorticoids**
The prednisone taper will be continued in all participants according to the standardized tapering schedule as listed previously. With this regimen, subjects who remain relapse-free will be completely off prednisone by week 28.

**iii. Concomitant Medications**

**Aspirin**
The use of aspirin 81 mg/day should be considered in all subjects with GCA who do not have contraindications as there have been data indicating that low-dose aspirin use is associated with a decreased risk of cranial ischemic complications in GCA (76). The use a proton pump inhibitor will be considered in all aspirin treated subjects. There have as yet been no data on the utility of aspirin in TAK.

**Other medications**
It is expected that many of the subjects in this trial will be on multiple medications including antihypertensives and medications for glycemic control. Subjects will be allowed to continue these medications and make any changes in their dose, as it may be necessary due to the effect of GC therapy or other reasons. In the absence of toxicity, subjects who are on statins at the time of enrollment should continue these medications and be maintained at a consistent dosage throughout the trial.

**iv. Prophylactic Medications**

1. Prophylaxis against prednisone-induced osteoporosis will be recommended in all participants. This cannot be standardized across all subjects as the choice of bone protection regimen must be influenced by individual subject factors that include age, pre-menopausal status for women, pre-existing osteoporosis, and medication contraindications.

**v. Prohibited Concomitant Medications**

1. Etanercept, infliximab, adalimumab, rituximab, alemtuzumab or any other biologic immunomodulatory agent
2. Methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide or any other immunosuppressive medication
3. Any live vaccination
4. Any other investigational medication

d. Study Procedures

i. Recruitment

Recruitment will occur through the clinical practices of each site investigator. Research subjects will also be recruited, as needed, via mailings to appropriate clinicians in the investigators’ catchment areas. All recruitment material will be reviewed by the appropriate oversight bodies (Institutional Review Board (IRB), etc.).

Subject enrollment at the participating center will not begin until the IRB has approved this protocol as well as the consent forms to be used. Details of the goals of the research and the risk and benefits of the protocol will be reviewed with each potential study subject. Recruitment will occur by physicians, study nurses, and research coordinators.

Subjects who decline to participate in any or all parts of the study will still have available the opportunity of evaluation by a vasculitis expert if they or their physician feels this is appropriate.

Strict subject confidentiality will be observed throughout all aspects of the study. While medical records will be reviewed by members of the research team, no individually identifiable subject data will be distributed to non-research or care-giving team members.

ii. Screening

This research study will be explained in lay language to each potential research subject. The subject will sign an informed consent before undergoing any screening procedures. The procedures to be performed in conjunction with screening are outlined in the Visit Table below.

iii. Enrollment

GCA most commonly occurs in women at a ratio of ~2:1. TAK also most commonly affects women although a wide spectrum has been reported going from a female predominance of 9:1 in some Japanese and United States series to nearly equal representation amongst men and women in studies from Israel and India.

The study population will be made up of men and women of all ethnicities and races, in proportion to the prevalence rates of GCA and TAK among these subgroups. There will be no exclusion of any subject secondary to sex, ethnicity, race or socioeconomic status.

1). Inclusion of Pediatric Subjects

Children 15 years and older will be eligible as abatacept has been approved for the treatment of juvenile idiopathic arthritis and thus there has been a safety experience with
this agent in pediatrics (77). While TAK can occur in younger children, it is exceedingly rare and keeping this within an age range that is physiologically close to that of an adult also provides an additional level of safety in this early phase study of abatacept in TAK.

2). Inclusion of Women

Women will be included in all aspects of the proposed study and are expected to be enrolled in greater numbers than men due to the increased prevalence of GCA and TAK among women. Outreach to women will be made through announcements to rheumatologists, the Vasculitis Foundation (vasculitis support group) and through the VCRC Patient Contact Registry.

3). Inclusion of Underrepresented Ethnic/Racial Minorities

Minorities will be included in all aspects of the proposed study and are expected to be enrolled in numbers proportional to their prevalence in GCA and TAK. Outreach to minorities will be made through announcements to local communities and physicians in underserved areas with large minority populations. The study will also be performed in conjunction with the Vasculitis Foundation (vasculitis support group) and through the VCRC Patient Contact Registry that reach a broad range of socioeconomic backgrounds.

iv. Visit Frequency/Visit Schedule

Subjects will be evaluated at the time of each abatacept infusion and within 12 weeks of the determined common treatment closing date with the collection of data as outlined in the following Table.

Subjects who voluntarily choose to withdraw from the trial or who are removed from the trial by the investigator for reasons as stated in the “Criteria for Withdrawal of Study Medication” section will undergo an early termination assessment.

Subjects who return for unscheduled visits for new or worsening symptoms or signs will be assessed as felt to be clinically indicated by the investigator. Data from this assessment will be collected.

v. Specimen and Data Collection Schedule

1). Specimen Collection

Study flowsheets contained on the following pages address the study procedures that will be performed in conjunction with screening, during the treatment period, at early termination, and at the common closing date.

Subject visits, abatacept or placebo infusions, and collection of blood and urine samples will be conducted in the outpatient Clinical Research Unit (CRU).

Subjects will be encouraged to concurrently enroll in the VCRC longitudinal protocols for GCA (VCRC Protocol 5502) or TAK (VCRC Protocol 5503) which contains the collection of blood samples for additional research biomarkers. Even for those subjects concurrently enrolled in the VCRC longitudinal studies, the total volume of collected
blood will be below the limits set forth by Federal guidelines; these volumes include clinical and research blood tests as are outlined in the Visit and Data Collection schedule table. These blood volumes are listed in the Visit and Data Collection Table below.

Care will be taken to prioritize obtaining of blood samples with clinically indicated tests to be performed first followed by mononuclear cells (CPT tubes), RNA (Tempus tubes), serum, and plasma (see Visit and Data Collection Table).

If a subject has anemia and their expected hematocrit is < 27%, 50% of the volume will be drawn and we follow the same prioritizing plans for sample acquisition.

2). Diagnostic Imaging

Diagnostic imaging is an important part of routine clinical care for patients with GCA and TAK. Magnetic resonance imaging (MRI) with angiography (MRA) is an effective and non-invasive means of serially following vessel lumenography in GCA and TAK. For patients who are unable to undergo MRI, computed tomography (CT) is considered an acceptable substitute. Patients who have a serum creatinine of > 2.0 mg/dl will not have clinical or research MRI/MRA performed because of the potential risk of nephrogenic fibrosing dermopathy.

For patients who have GCA with large vessel involvement, and for all patients with TAK, MRI/MRA is considered to part of routine disease monitoring. The frequency of MRI/MRA is outlined in the Visit and Data Collection Schedule below and is based upon standard clinical practice for a patient who is being treated for active TAK or GCA with large vessel involvement. In these subject populations, the MRI/MRAs to be performed in this study would be considered standard clinical care and would not be performed solely for research purposes.

For GCA patients who do not have symptoms or signs of large vessel involvement, MRI/MRA is not considered to be part of standard care. However, as new large vessel disease is part of the definition of disease activity, it is important to know each subjects large vessel anatomy at study entry so as to avoid bias of the trials endpoints. Therefore, in patients with GCA who do not have large vessel disease, we will plan to obtain one MRI/MRA for research purposes prior to the first abatacept infusion. As this would not be considered standard of care for this patient population, the research nature of this MRI/MRA will be carefully explained in the informed consent document. Should this research MRI/MRA reveal evidence of large vessel disease that was not previously suspected, the subject would now be recognized as having GCA with large vessel involvement and would undergo follow-up MRI/MRAs as this would now be clinically indicated. Subjects who have no evidence of large vessel involvement on their research MRI/MRA would have no further MRI/MRAs performed in conjunction with this study unless they were to develop symptoms or signs to suggest large vessel disease.

At study entry, MR or CT imaging may be performed within 2 months prior to entry provided that the imaging was obtained at the time of active disease and that the patient received prednisone for that active disease. The time windows for MRI can be within 2 weeks prior to the week 12 randomization and for the MRIs at weeks 36, 60, and every 24 weeks thereafter, imaging may occur 2 weeks before or after the study visit.
**MRI (or CT) angiographic methodology**

The purpose of the MR or CT angiographic studies is to determine the extent of large-vessel arterial disease in study subjects. MR or CT studies will include evaluation of the status of the arterial lumens of the aorta: from cardiac origin through the take-offs of the renal arteries) and all major arterial branches of the imaged segment of the aorta including the carotid, vertebral, subclavian, renal, and main mesenteric arteries. Data to be captured include stenoses, aneurysms, dissections, or complete absence of flow.

In addition to vascular lumenography, MR technology provides the ability to examine characteristics of the vessel wall. At the current time, it remains unclear whether changes in signal intensity that are sometimes interpreted as edema and/or inflammation, provides any meaningful information with regards to vasculitis disease activity. Given this uncertainty, changes within the vessel wall will not factor into the determination of active disease, remission, or relapse and have not been incorporated into these definitions as described in the Outcome Measures section.
3). Visit and Data Collection Schedule

**Visit schedule and data collection for enrolled study subjects**

Table reflects the potential for subjects to be coenrolled in VCRC Longitudinal studies for GCA (5502) or TAK (5503)

<table>
<thead>
<tr>
<th>STUDY DATE</th>
<th>Screening</th>
<th>D0</th>
<th>D15</th>
<th>D29</th>
<th>W8</th>
<th>W12</th>
<th>W16</th>
<th>W20</th>
<th>W24</th>
<th>W28</th>
<th>W32</th>
<th>W36</th>
<th>W40</th>
<th>W44</th>
<th>W48</th>
<th>Early Termination or Relapse or Common closing</th>
<th>PAV W4</th>
<th>PAV W12</th>
<th>PAV W24</th>
</tr>
</thead>
<tbody>
<tr>
<td>D= Day  W= Week</td>
<td>D0</td>
<td>W0*</td>
<td>D15</td>
<td>D29</td>
<td>W8</td>
<td>W12</td>
<td>W16</td>
<td>W20</td>
<td>W24</td>
<td>W28</td>
<td>W32</td>
<td>W36</td>
<td>W40</td>
<td>W44</td>
<td>W48</td>
<td>Early Termination or Relapse or Common closing</td>
<td>PAV W4</td>
<td>PAV W12</td>
<td>PAV W24</td>
</tr>
<tr>
<td>D0</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Early Termination or Relapse or Common closing</td>
<td>PAV W4</td>
<td>PAV W12</td>
<td>PAV W24</td>
</tr>
</tbody>
</table>

**STUDY DRUG**

- Abatacept infusion: X X X X
- Abatacept or placebo: X X X X X X X X X X

**VCRC LONGITUDINAL VISIT (if coenrolled on 5502 or 5503)**

<table>
<thead>
<tr>
<th>DATA FORMS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal data/sample capture</td>
</tr>
<tr>
<td>Informed Consent: X</td>
</tr>
<tr>
<td>Eligibility Checklist: X</td>
</tr>
<tr>
<td>Demographics: X</td>
</tr>
<tr>
<td>LVV Baseline Medical History: X</td>
</tr>
<tr>
<td>Baseline Vasculitis Medications: X</td>
</tr>
<tr>
<td>Baseline comorbidities: X</td>
</tr>
<tr>
<td>Tobacco, Alcohol &amp; Drug: X</td>
</tr>
<tr>
<td>Angiogram form*: X</td>
</tr>
<tr>
<td>LVV Physical exam: X</td>
</tr>
<tr>
<td>Non-vasculitis Medications: X</td>
</tr>
<tr>
<td>BVAS: X</td>
</tr>
<tr>
<td>SF-36 survey: X</td>
</tr>
<tr>
<td>Damage Index – VDI: X</td>
</tr>
<tr>
<td>Damage Index – LVVID: X</td>
</tr>
<tr>
<td>Lab results: X</td>
</tr>
<tr>
<td>Patient Global Assessment: X</td>
</tr>
<tr>
<td>LVV Follow-up Medical History: X</td>
</tr>
<tr>
<td>Follow-up Co-morbidities: X</td>
</tr>
<tr>
<td>Study visit form: X</td>
</tr>
<tr>
<td>Randomization form: X</td>
</tr>
</tbody>
</table>

**AS NECESSARY:**

- Change of Information: X
- Hospitalization: X
- Adverse event report: X
- Angiogram forms: X
- Death: X
- Sinus and chest imaging: X
- Protocol deviation: X
- Study Therapy Discontinuation: X
- Protocol termination: X

NIH Approved 03/08/2013

HHSN2682007000036C

Version number:7

Date: 24Oct12
Visit schedule for subjects who remain on protocol past week 48 (W48)

Visits for W52 onwards will be conducted as outlined in the W28-W48 schedule. W52 would correspond to the W28 schedule with W28 through 48 corresponding to weeks 52-72, 76-96, 100-120, 124-144, 148-168, 172-192 with the exception of the samples collected for Peter Heeger, MD as outlined by * below. Post abatacept visits (PAV) will be performed at 4,12, and 24 weeks after early termination, relapse, or common closing

* MRI/MRA will be performed at screening, W12, W36, W60, every 24 weeks thereafter and at early termination/relapse/common closing in subjects with TAK, GCA with large vessel disease, or as clinically indicated.

Subjects with GCA who do not have symptoms or signs of large vessel disease will undergo MRI/MRA at screening and will only have subsequent studies performed if large vessel involvement is found.

** Pulmonary function testing (PFT) will be performed on any subject who has clinical evidence of pulmonary disease defined by the presence of significant pulmonary radiographic abnormalities by CXR or chest CT or a known history of chronic obstructive pulmonary disease (COPD). If a subject who meets these criteria has had PFTs performed within 12 months prior to enrollment, these results can be used for the study and PFTs do not need to be repeated unless clinically indicated.

*** Pregnancy testing will only be performed on women who have child bearing potential

† DNA only needs to be drawn if it has not already been drawn for the VCRC Longitudinal studies (5502 or 5503) or if subject co enrolls in the abatacept and longitudinal studies at the same time.

‡ If subjects are coenrolled in the Abatacept and Longitudinal studies, specimens collected for the Longitudinal study will be drawn approximately every 3 or 12 months when a participants visit windows overlap for the 2 studies and should follow a prioritized and decreased draw as will be specified in the Manual of Operations.

* Designates samples to be drawn for studies to be conducted by Peter Heeger, MD. These studies will be collected from screening through W24, at W36, W60, and at termination/relapse/closing

• For subjects who have same day screening and D0 visits, sample collection and forms will be completed as according to the Screening visit.
**e. Common Treatment Closing Date - Study Duration**

The common closing date will be 1 year after the randomization of the final participant for each disease. As it is likely that the GCA and TAK trials will not accrue at an identical rate, it is anticipated that each disease will have a separate closing date. For safety purposes, subjects will remain on study and continue to be seen at 4, 12, and 24 weeks after the common treatment closing date and undergo study assessments and procedures as outlined in the Visit and Data Collection Schedule Table above.

**f. Criteria for Withdrawal of Study Medication – Early Termination**

Participants will be informed that they are free to withdraw from the study without compromising the relationship with their physician or their future medical care. If participants choose to discontinue study medication, they will no longer receive study medication; however, if they agree to remain in the study they will be asked to return for an early termination visit as described in the visit schedule and will be asked to return for post-treatment safety visits at 4, 12, and 24 weeks.

Subjects will be taken off of study medication by the investigator should they meet one or more Discontinuation of Study Drug criteria as outlined below. In this event, the subject will no longer receive study medication; and they will have an early termination visit that includes the procedure described in the visit schedule below. Subjects who are withdrawn from the study for reasons of failure to achieve remission or relapsing disease as defined in Criteria 1 below will be taken off abatacept/placebo and treated with best medical judgment that may consist of reinstitution or increase of GC and use of other immunosuppressive agents as dictated by the manifestations and severity. For safety purposes, subjects who meet one or more Discontinuation of Study Drug criteria will remain on study and continue to be seen at 4, 12, and 24 weeks after the Early Termination visit and undergo study assessments and procedures as outlined in the Visit and Data Collection Schedule Table above.

The randomization assignment will remain blinded until after the common closing date unless unblinding is felt to be necessary to protect the subject’s safety.

The criteria for discontinuation of study drug (early termination) include:
1. Failure to experience remission by the week 12 visit or development or relapsing disease (as defined in the “Outcome Definitions” section).
2. Pregnancy or breast feeding
3. Development of malignancy with the exception of basal or squamous cell carcinoma of the skin that has been completely excised.
4. Grade 4 toxicity
5. Hypersensitivity reactions to abatacept
6. Subject non-compliance with study procedures.
7. Study medications may be discontinued when, in the medical judgment of the physician, discontinuation would be in the best interests of the subject
8. Study medications may be discontinued if the trial is halted by the IRB, DSMB, or FDA.

**g. Study Endpoints**

In Primary Endpoint

The **primary study endpoint** will be remission duration (relapse-free survival, RFS).

**ii. Secondary Endpoint**

The **secondary study endpoint** will be toxicity.
h. Outcome Definitions

i. Disease activity

**GCA**

Active disease will be defined by the presence of clinical features or imaging or both:

**Clinical features**
The new, recurrent, or worsening presence of one or more of the following that cannot be attributed to any cause other than GCA and would usually prompt treatment or additional treatment:

- Sustained fever of >38 °C for > 1 week
- Vascular pain/tenderness producing symptoms such as carotidynia, scalp tenderness, or temporal artery abnormalities (tenderness or nodularity). Such vascular symptoms should be present for more than one day and be non-fleeting.
- Headache that is a) present for more than one day; b) non-fleeting; c) not fully relieved with non-narcotic analgesics; and d) not typical for any pre-existing form of headaches the patient may have experienced (such as migraines or tension headaches).
- Ischemic retinopathy, optic neuropathy, or visual loss
- Tongue/jaw pain and/or claudication
- Transient cerebral ischemia or stroke
- Extremity claudication
- Musculoskeletal symptoms (with inflammatory features including joint swelling or morning stiffness) in combination with an ESR of > 40 mm in the first hour by the Westergren method or a CRP measurement above the laboratory normal limit.
- Malaise and fatigue in combination with an ESR of > 40 mm in the first hour by the Westergren method or a CRP measurement above the laboratory normal limit.
- Other symptoms/signs attributed by the investigator to GCA that necessitate reinstitution or increase in GC for the treatment of GCA

**Imaging features**

Development of new vascular stenosis or aneurysm in new vascular territories as seen by MRI/MRA or arteriogram

**TAK**

Active disease will be defined by the presence of clinical features or imaging or both:

**Clinical features**
The new, recurrent, or worsening presence of one or more of the following that cannot be attributed to any cause other than TAK and would usually prompt treatment or additional treatment:

- Sustained fever of >38 °C for > 1 week
- Vascular pain/tenderness producing symptoms such as carotidynia, scalp tenderness, or temporal artery abnormalities (tenderness or nodularity). Such vascular symptoms should be present for more than one day and be non-fleeting.
- Headache that is a) present for more than one day; b) non-fleeting; c) not fully relieved with non-narcotic analgesics; and d) not typical for any pre-existing form of headaches the patient may have experienced (such as migraines or tension headaches).
- Ischemic retinopathy, optic neuropathy, or visual loss
- Tongue/jaw pain and/or claudication
- Transient cerebral ischemia or stroke
- Extremity claudication
• Musculoskeletal symptoms (with inflammatory features including joint swelling or morning stiffness) in combination with an ESR of > 40 mm in the first hour by the Westergren method or a CRP measurement above the laboratory normal limit.
• Malaise and fatigue in combination with an ESR of > 40 mm in the first hour by the Westergren method or a CRP measurement above the laboratory normal limit.
• Other symptoms/signs attributed by the investigator to TAK that necessitate reinstitution or increase in GC for the treatment of TAK

Imaging features:
Development of new vascular stenosis or aneurysm in new vascular territories as seen by MRI/MRA or arteriogram

ii. Remission

GCA
Remission is defined as: the absence of clinical or imaging features of active disease

TAK
Remission is defined as: the absence of clinical or imaging features of active disease

iii. Relapse

GCA
Relapse is defined as: the presence of clinical or imaging features of active disease occurring after a period of remission

TAK
Relapse is defined as: the presence of clinical or imaging features of active disease occurring after a period of remission

i. Experimental Design for the Linked Basic Science Studies

The laboratory based studies that we will be performing as a part of this study were selected on the basis of establishing an immunologic correlation with safety and efficacy observed in this trial and in particular to determine whether abatacept has been dosed effectively. This will be assessed by testing the T cell responses and IDO pathway.

The below panel of assays will be performed at 1) screening (prior to abatacept), 2) after the third abatacept infusion (day 29), 3) at the time of randomization (week 12) and 4) at week 24 (12 weeks after randomization). These are the most likely times for us to detect the immunological effects of abatacept that could impact safety and to look for significant differences between those subjects on and off abatacept, which will be correlated with the different outcomes.

As outlined in the Visit and Data Collection Table, we will collect and freeze additional samples in the below specified tubes to allow more refined testing of the T cell responses and IDO if needed. Serum and plasma will be also collected and stored at each visit for research purposes. Volumes for all clinical and research blood samples have been calculated and remain well within the NIH guidelines.

The methods discussed below outline the assays that will be used to examine T cell activation, T cell regulation and the indolamine 2, 3-dioxygenase axis to explore the immunologic clinical correlates within this trial.
Testing methodology to examine T cell activation

<table>
<thead>
<tr>
<th>Specifics</th>
<th>Blood volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISPOT autoantigens</td>
<td>HSP65 and HSP60 IFN(\gamma) IL-4 (representative Th1 and Th2 cytokines)</td>
</tr>
<tr>
<td>ELISPOT mitogen</td>
<td>PHA IFN(\gamma), IL-4 (representative Th1 and Th2 cytokines)</td>
</tr>
<tr>
<td>Serum cytokines</td>
<td>Biorad 9-plex panel: IL-2, 4, 6, 8, 10, 12 (p70), GM-CSF, IFN(\gamma), TNF(\alpha)</td>
</tr>
<tr>
<td>PBL Real Time (RT)-PCR</td>
<td>IFN(\gamma), IL-12, IL-2, (Th1 like) IL-4, (Th2) L-10, TGF(\beta), Foxp3, IDO (regulatory)</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>1. CD4/CD8/CD62L/CD44/CD69 (5 color, to assess activation status) 2. CD4/CD25/FoxP3 (3 color alternate to assess Treg) 3. CD19/CD11b/IDO (2 color to assess IDO expression in APCs)</td>
</tr>
</tbody>
</table>

**ELISPOT**

We postulate that markers of T cell activation measurable within the peripheral blood will provide correlative and predictive information regarding disease activity. PBMCs will be isolated at the predefined intervals and frozen as per published protocols (78). This approach will permit us to perform batch analysis, testing samples from the same subjects obtained at different time points within the same assay, thereby permitting direct comparison. Freeze thawing does not significantly impact our ability to detect immune responses in this assay (78). Previous data demonstrated that the overwhelming majority of detected responses derive from T cells (78), and therefore it will be essential to understand the relative numbers of T cells in each sample. In our experience, T cells comprise 50-80% of PBLs.

The PBLs will then be tested against medium alone (negative control), recombinant HSP65 and 60 (0.1-10 micromolar based on published work), and against PHA (positive control), in 2 color IFN\(\gamma\)/IL-4 ELISPOT assays. These 2 cytokines are chosen as prototypic Th1/Th2 cytokines. Results will be quantified by our computer assisted image analyzer and will be entered into the database in two forms. Based on previously published data, we will label each result as either positive or negative to facilitate initial analysis using a dichotomous variable approach. Positive will be considered > 25 ELISPOTs per 300,000 cells (79). We will also report the absolute value of each result such that the findings can be secondarily treated as a continuous variable, that is, to assess whether the frequency of detected responses directly correlates with the presence or absence of disease activity. Our previous publication showed that calculated IFN\(\gamma\)/IL-4 ratios in PHA stimulated samples, a representation of the dominance of Th1 vs Th2 immunity at a given time point, is a strong correlate with subsequent outcome in transplant patients (80). Therefore, we will also calculate this ratio and use the results in the analysis.

**Flow Cytometry**

If disease activity is T cell mediated, it is likely that a higher percentage of T cells will express cell surface phenotypes consistent with activation. Upregulation of CD44, CD69 along with down regulation of CD62L are representations of T cell activation. CD25 and Foxp3 expression in CD4 cells are associated with Tregs that can be induced by the therapy. IDO expression may be upregulated in APCs (B cells and monocytes) by the therapy and thus will be assessed and compared among time points. Results will be entered into the database as percentage of positive cells for each subset within the region of gated live cells.
**mRNA Profiling- Inflammatory Mediators- PBL RNA expression**

If proinflammatory T cell immunity participates in the pathogenesis of GCA and TAK we are likely to detect upregulation of proinflammatory genes in PBMCs during disease activity. We will use real time PCR to quantitatively evaluate gene expression from PBMCs isolated at the above time-points. We will focus on IFNγ, TNFα, IL-2 and IL-12 (as representative Th1/proinflammatory genes), on IL-10, TGFβ, Foxp3 (Treg associated), and IL-4 as a representative Th2/anti-inflammatory gene. All primers are available commercially and we are performing these types of studies presently in our laboratory. We are performing true quantitative PCR as published by Suthanthiran and colleagues, using a standard curve with a control cDNA (81). In this manner we obtain “copy numbers” of the specific RNA expressed rather than relative quantities based on a control gene. The number of molecules detected can then be readily compared between groups or patients. Dr. Suthanthiran is a coinvestigator in Dr. Heeger’s U01 grant and we are active collaborators, thereby providing us with consultative support if need be.

**Serum measurements of proteins by Luminex**

If proinflammatory T cell immunity participates in the pathogenesis of GCA and TAK we are likely to detect upregulation of proinflammatory proteins in subject sera during disease activity. Cross sectional studies performed by others have shown that IL-6 and TNFα expression as detected by ELISA are elevated in sera from patients with active disease versus those without active disease (82), but no prospective analyses have been performed in individual patients. We will therefore assess serum protein levels in subject sera using the Luminex™ platform. This approach allows us to quantitatively test for multiple cytokines in serum samples simultaneously using a bead-based ELISA with a flow cytometry readout using small amounts of serum. We propose to evaluate 9 proteins simultaneously, using the Biorad Human reagents. Each result will be reported as positive or negative and as a continuous variable and compared between groups.

**Measurements of Treg**

If abatacept induces Treg then we will detect significant alterations in the number and/or function of Treg after therapy compared with prior to therapy.

As noted we will stain PBMCs for Foxp3 (intracellular staining) and cell surface markers (CD25/CD4) and determine the percentage of positive cells in each sample. RNA extracted from each sample will also be assessed for Foxp3, and the “regulatory” cytokines TGFβ and IL-10 gene expression by real time PCR.

If abatacept functions via upregulating IDO expression, then we would detect higher levels of IDO and alterations in the kyurenine/tryptophan axis.

We are not initially planning to assess Treg function as we do not anticipate having sufficient numbers of cells for these assays. If we find that sufficient cells are available we will consider the performing the following: To assess Treg function we will test unmanipulated PBMC and PBMC depleted of CD25+ cells using magnetic beads in ELISPOT assays. Antigens will include HSPs (particularly if initial studies show HSP reactivity during disease activity) and alloantigenic stimulator cells. The latter approach, standard in our lab, is useful because essentially all patients respond to allogeneic stimulators in this assay at measurable frequencies (83). If Treg function is enhanced by the therapy, then we would anticipate lower reactivity of unmanipulated PBMC after vs before therapy, but that CD25 cell depletion would recover reactivity. Add back experiments will then be performed to determine whether re-addition of CD25+ T cells inhibits the augmented response.

Kyurenine (Kyn) and tryptophan (Trp) assays will be done by the core lab in Florida (not in the Heeger lab) using HPLC measurements. Two measurements will be made on each sample: Kyn concentration and Trp concentration. The Kyn result will be a continuous variable with no upper limit, and a lower limit of detection in our assay of 1.2 uM. The published normal range of Kyn is approximately 2.0 ± 0.2 uM (84, 85), so some baseline samples may fall in the undetectable (<1.2 uM) range. This does not present a problem, since the only meaningful treatment effect would an elevation in Kyn levels – e.g., into the range seen in chronic inflammatory disorders (3-5 uM) (84, 85). Based on the hypothesis of the current study, a decrease in Kyn would be considered the same as no change (i.e., no biologic effect on IDO).
The Trp result will be a continuous variable with no upper limit, and a lower limit of detection of 1.2 uM. The anticipated range of baseline Trp concentrations is 50-100 uM based on published values (86-88). The biologically-relevant treatment effect would be a decrease in Trp (into the range of 5-50 uM). An increase in Trp would be considered the same as no change for purposes of the study.

5. Safety Monitoring and Adverse Event Reporting

a. Nature of Study

In determining what type of adverse events will be reported, several facts about the drugs being tested and the nature of the underlying disease need to be considered. This trial will enroll subjects with active GCA and TAK which are both known to be diseases that are characterized by frequent relapses. This is a randomized withdrawal design trial in which subjects with GCA or TAK will be treated with prednisone and abatacept. Both prednisone and abatacept will be considered to be study drugs in this trial. The investigators and subjects will have full knowledge of the therapeutic agents that are being administered for the first 12 weeks. At the week 12 visit, the subject will be randomized to continue abatacept or switch to placebo in a manner blinded to both investigator and subject. Abatacept is an FDA approved drug for rheumatoid arthritis since 2006. The side effects with abatacept are described within the drug package insert and investigator brochure. There has been no prior experience with the use of abatacept in GCA or TAK. Prednisone and other GC have been used in GCA and TAK for almost 50 years and its toxicity profile in these and other diseases is well established. The side effects of prednisone are described in the study protocol and drug labeling for prednisone (Deltasone®).

b. Study Oversight

The Study Principal Investigator has primary oversight responsibility of this clinical trial. The NIH appointed DSMB has oversight responsibility of the DSMP for this clinical trial. The DSMB will review accrual, patterns and frequencies of all adverse events, protocol compliance every 6 months. The DSMB makes recommendations to the NIH regarding the continuation status of the protocol.

Each site’s Primary Investigator and their research team (co-Investigators, research nurses, clinical trial coordinators, data managers) are responsible for identifying adverse events. Aggregate reports- detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures- will be available from the DMCC for site review. Adverse events will be reviewed once a month by the research team. A separate report detailing any protocol compliance made will also be available from the DMCC for site review once a month. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

c. Definitions

This section defines the types of adverse events and outlines a process for the appropriate collecting, grading, and reporting procedures. The information in this section complies with ICH Guidelines E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting of the International Conference of Harmonization (ICH) Guideline for Good Clinical Practice and applies the Standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events version 3.0. These definitions will be adhered to in the conduct of this trial.

An adverse event will be defined as: “…an unfavorable and unintended sign, symptom or disease associated with a subject’s participation in this study.”

At the screening visit, preexisting conditions including clinically significant abnormal findings obtained on the physical examination, diagnostic labs or imaging, are considered the participant’s entry values and are not
adverse events. Preexisting conditions that worsen in severity or frequency during the study will be recorded as an adverse event. A preexisting condition identified during screening that does not worsen, however, is not an adverse event. Increase in activity of GCA and TAK are outcomes but will not be considered adverse events.

Serious adverse events include those events that: “result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects.”

Serious adverse events (SAE) will be defined according to 21CFR 312.32. An SAE is any untoward medical occurrence that at any dose:
- Results in death
- Is life-threatening
- Requires hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- An important medical event may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

In addition, the development of malignancy with the exception of basal or squamous cell carcinoma of the skin that has been completely excised, will be reported as an SAE.

An unexpected adverse event is defined as any adverse experience “…the specificity or severity of which is not consistent with the risk information described in the protocol or package inserts”. Therefore, expected adverse events are those that are identified in the research protocol or study drug package inserts as having been previously associated with or having the potential to arise as a consequence of participation in the study.

d. Toxicity Grading of Adverse Events

Toxicity grades will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (http://ctep.cancer.gov/reporting/ctc.html). The purpose of using the CTCAE system is to provide a standard language to describe toxicities, to facilitate tabulation and analysis of the data and to facilitate the assessment of the clinical significance of all adverse events. The CTCAE provides the following grade and descriptions in the CTCAE manual (v3.0). Adverse events should be recorded and graded 1 to 5 according to the CTCAE grade provided below:
- Grade 1 = mild adverse event
- Grade 2 = moderate adverse event
- Grade 3 = severe and undesirable adverse event
- Grade 4 = life-threatening or disabling adverse event
- Grade 5 = Death

e. Relation to Study Therapy

The relation or attribution of an adverse event to an investigational product is determined by the site investigator and then recorded on the appropriate case report form and/or SAE reporting form. The CTCAE provides the following descriptors and definitions for assigning an attribution to each adverse event.

<table>
<thead>
<tr>
<th>Code</th>
<th>Descriptor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unrelated</td>
<td>The adverse event is clearly not related to the investigational product</td>
</tr>
<tr>
<td>2</td>
<td>Unlikely</td>
<td>The adverse event is doubtfully related to the investigational product</td>
</tr>
</tbody>
</table>
f. Standard Elements

A set of standard elements for adverse event data will be collected across this study. These elements include: participant ID, reporter user ID & location, occurrence date for event, date event reported (to the site), whether the event is a primary or secondary event and, if secondary event, the AE ID for the primary event to which it references; information regarding the event itself, including: event category, type of event, site or modifier, severity as per the CTCAE 3.0 classification, and a detailed description of the event; whether the event was expected, location of treatment, causality by reporter, whether the event results in any serious associations (congenital anomaly or birth defect, permanent, disabling or incapacitating condition, death, hospitalization or prolonged hospitalization, life threatening), patient status (at the time of the report), event resolved date and/or date of death; finally, a space for additional comments is provided.

g. Expected/Known Risks/Discomforts/Adverse Events Associated with Study Intervention and Procedures: Definition of Expected Adverse Events

i. Study Drug/Intervention:
Known risks of study intervention, listed below in Heading Number 8.

ii. Study Procedures:
Known risks of venipuncture and IV insertion, listed below in Heading Number 8

h. Reporting Timeline

- Within 24 hours (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that:
  - Is considered life-threatening/disabling or results in death of subject
  - OR-
  - Is Unexpected/Unanticipated

- Investigators must report all other reportable SAEs within 5 working days (of learning of the event). Infections requiring treatment with intravenous (IV) antibiotics or infections commonly understood as opportunistic will fall within this 5-day reporting period.

- Expected or unexpected AEs that are grade 1 will not be collected or reported

- All other expected or unexpected (suspected) reportable AEs must be reported within 20 working days of the notification of the event or of the site becoming aware of the event.

i. Adverse Event Data Management System (AEDAMS)

Upon entry of a serious or unexpected adverse event, the DMCC created Adverse Event Data Management System (AEDAMS) will simultaneously notify the Study Chair, site PIs, the DSMB Safety Officer, NIAMS Project officer, KAI, and Bristol-Myers Squibb of any reported adverse events via email.

**Serious adverse events:** The NIH appointed Medical Review Officer (MRO) determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The MRO may request further information if necessary and possibly request changes to the protocol or consent form as a consequence of the adverse event. A back-up notification system is in place so that any delays in review by the MRO beyond a specified period of time are forwarded to a secondary reviewer. The Adverse Event Data Management System (AEDAMS) maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.
Non-serious expected adverse events: Except those listed above as immediately reportable, non-serious expected adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the DMCC as outlined above. The events will be presented in tabular form and given to the MRO and DSMB on bi-annual basis. Local site investigators are also required to fulfill all reporting requirements of their local institutions including reporting to FDA (Med Watch) and IRB.

The DMCC will prepare aggregate reports of all adverse events (serious/not serious and expected, unexpected) for the DSMB and all site investigators

j. Investigational New Drug Application (IND)

This protocol has been assessed as being IND exempt by the FDA.

k. Criteria to Suspend Enrollment

New subject accrual will be halted in the event of the occurrence of any of the following:

- Any deaths that are possibly, probably, or definitely related to the study drug
- Any grade 4 toxicities that are probably or definitely related to the study drug

6. Data Analysis and Statistical Considerations

a. Sample size calculations and statistical methods

This study will enroll subjects diagnosed with active GCA or TAK and induce remission with combination therapy consisting of abatacept and GC. Subjects who fail to achieve remission by week 12 are off study. Those achieving remission are randomized in a double-blind fashion to continuation therapy with either GC + abatacept or GC + placebo. GC will be tapered in an identical fashion on both arms.

The subject enrollment will be stratified by diagnosis: TAK and GCA. Accrual will be 33 subjects in each stratum, accrued uniformly over a 3 year period. Allowing for a 10% drop out rate, 30 subjects would be evaluable for analysis of the primary outcome. The primary analyses will be based upon intent to treat. Randomization will be balanced by clinical site utilizing randomly permuted blocks. The planned sample size is determined by the minimally clinically meaningful result (i.e., an approximate 30% improvement in relapse-free survival) to be detected such that it the role of abatacept should be studied further in these diseases.

Primary outcome:
The primary study end point will be remission duration (relapse-free survival, RFS). Kaplan-Meier curves of RFS will be constructed along with their 95% confidence intervals using the method of Greenwood.

There are limited data on long term RFS rates. The paper by Hoffman et al estimates the 1-year RFS rate for GCA to be 23% (11). While there are no similarly constructed data for TAK, an estimate of 30% 1-year RFS would be expected based upon clinical impressions (35). Since clinical experience also indicates that relapses continue with longer follow-up, we have used an exponential model to estimate the study power to detect clinically meaningful differences that can be detected with this study design (89). The Kaplan-Meier curves will be compared using the logrank test. With 30 subjects, in each stratum, randomly assigned to each treatment arm over a 3 year period and a minimum of one year follow-up after the last subject is randomized, the study has 80% power to detect a 32% reduction in the one-year event rate comparing RFS of GC + placebo versus GC + abatacept, in each stratum, p=0.1, one-sided, for a relatively wide range of RFS estimates:
Detectable differences as a function of RFS in the Placebo arm

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>.20</th>
<th>.30</th>
<th>.40</th>
<th>.50</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>.52</td>
<td>.62</td>
<td>.71</td>
<td>.79</td>
</tr>
</tbody>
</table>

Because we do not consider this to be a definitive trial, we relax the type 1 error rate in making within stratum comparisons to suggest the need for further study of abatacept. This is a common practice in a number of diseases and clinical trial setting in which the disease is relatively rare. Should we decide at the onset that the Type I error should be 0.05, then the study would have 80% power to detect differences ranging from 38% to 33%, depending upon the RFS rate in the placebo arm.

**Secondary outcome:**
The secondary study endpoint will be toxicity. Rates of adverse events can be estimated across strata for events occurring in the first 12 weeks of treatment. Adverse events occurring after randomization will be tabulated by treatment arm. With 30 evaluable subjects each continuing on combination or single agent therapy, there is a 95% confidence that any adverse event (or serious adverse event) with an incidence of at least 10% will be reported on each treatment arm. As well, the standard error of the estimate of the incidence of reported adverse events will not exceed 9%. For events occurring with a less than 20% incidence, the standard error of the estimate will be no more than 7%.

Because this study is designed as a double blinded comparison of the effect of abatacept on RFS, no differences in toxicity profiles is anticipated. Nonetheless, complete toxicity profiles will be compiled for each treatment arm, and a comparison can be made in the frequency of adverse events of grade 3 or greater. With 30 subjects in each arm, the study would have 80% power to detect a 30% difference (increase) in the proportion of subjects with grade 3 or greater toxicity on the combination therapy arm at p=0.05, one-sided, depending upon the incidence in the GC only arm as shown in the table and graph below:
Table of Study Power to Detect Differences in Observed Adverse Event Rates as a function of adverse event incidence rates.

<table>
<thead>
<tr>
<th>GC alone</th>
<th>.1</th>
<th>.2</th>
<th>.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC+Abatacept</td>
<td>.4</td>
<td>.88</td>
<td>.52</td>
</tr>
<tr>
<td>.5</td>
<td>.98</td>
<td>.79</td>
<td>.46</td>
</tr>
<tr>
<td>.6</td>
<td>.99</td>
<td>.95</td>
<td>.76</td>
</tr>
<tr>
<td>.7</td>
<td>&gt;.99</td>
<td>.99</td>
<td>.94</td>
</tr>
<tr>
<td>.8</td>
<td>&gt;.99</td>
<td>.99</td>
<td></td>
</tr>
<tr>
<td>.9</td>
<td>&gt;.99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**b. Accrual**

It is envisioned that with a sample size of 66 subjects (33 with GCA and 33 with TAK), each site will enroll approximately 4-18 participants (2-9 with GCA and 2-9 with TAK). As the period from first to final participant enrollment is estimated to be about 3 years, it is estimated that each site would accrue 1-3 GCA and 1-3 TAK subjects per year.

**7. Data Management**

All study data will be collected via systems created in collaboration with the DMCC and will comply with all applicable guidelines regarding subject confidentiality and data integrity.

**a. Registration**

Registration of subjects on this protocol will employ an interactive data system in which the clinical site will attest to the subject’s eligibility as per protocol criteria and that an appropriate informed consent has been obtained. IRB approval for the protocol must be on file at the DMCC before accrual can occur from the clinical site.
The DMCC will use a system of coded identifiers to protect subject confidentiality and safety. Each subject enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the subject. When the subject is registered on the study, using the DMCC provided web-based registration system, the system will assign a registration number. Thus each subject will have two codes; the local one that can be used by the registering site to obtain personal identifiers and a second code assigned by the DMCC. For all data transfers to the DMCC both numbers will be required to uniquely identify the subject. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a subject for data entry since the DMCC would require that the numbers match to properly identify the subject. No personal identifiers would be accessible to the DMCC.

b. Randomization

Subjects will be randomly assigned to receive GC + abatacept or GC + placebo in equal allocation at the time that remission is verified at 12 weeks. In order to ensure balance in treatment groups within clinical sites, random number lists with fixed block size are generated. This list is kept internally at the DMCC. A central randomization system is used. This system is implemented as part of the secure study web site which requires entry of a unique user name and password for access. At randomization, the clinical site personnel will confirm eligibility and verify that the subject has signed informed consent (and assent when applicable). At the time of randomization, the study subject will be assigned a treatment number from the list of maintained at the DMCC. An electronic communication is sent to the site’s research pharmacy to direct dispensing of the appropriate treatment and provides the pharmacist with the associated treatment number. The treating physician will match the treatment number with the medication dispensed by the pharmacy. The treatment number will not identify the specific therapy so that the treating physician and the subject are masked as to treatment assignment.

c. Data Entry

Data collection for this study will be accomplished with online electronic case report forms. Using encrypted communication links, on-line forms will be developed that contain the requisite data fields.

d. Data Quality Control

As much as possible data quality is assessed at the data entry point using intelligent on-line data entry via visual basic designed screen forms. Data element constraints, whether independent range and/or format limitations or ‘relative’ referential integrity limitations, can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency. In addition to those described above, we propose to build these checks into the initial tables and cross tabulations that should reveal any remaining data quality issues.

- Data Monitoring: The DMCC identifies missing or unclear data and makes the reports available to the enrolling center.
- Data Delinquency Tracking: The DMCC will monitor data delinquency on an ongoing basis.

e. Laboratory and Imaging Data Flow

The DMCC will provide a distributed data system and direct data transfer using electronic means from clinical sites, reference laboratories and radiology departments. In the laboratory data management system, data is extracted from the clinical laboratory’s information systems, placed in a pre-designed format and electronically transferred (using an FTP protocol) under a secure protocol to the DMCC. Error checking occurs and logs are maintained of all processed data. Minimal errors occur since the entire process is electronically monitored. An
8. Protection of Human Subjects

a. GCP Statement

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements.

b. Risks and Benefits

i. Overall Risk / Benefit Assessment

Benefits
The potential benefits of this study are:
- Abatacept may reduce disease activity and relapse in GCA and TAK
- Abatacept may provide an improved ability to taper GC
- Findings from this study may lead to a better understanding of mechanisms in GCA and TAK
- Benefits of a research MRI in subjects with GCA who do not have large vessel involvement. This MRI offers potential benefit in detecting blood vessel stenoses or aneurysms that were not apparent based on symptoms or signs. As large vessel disease can carry a risk of morbidity or even mortality, knowing that these changes are present can be beneficial in providing opportunities for treatment if this is necessary.

Risks
The potential risks of this study are:
- The risks of the study medication abatacept and prednisone
- While unlikely, it is possible that through unknown and unexpected mechanisms, treatment with abatacept may itself worsen GCA or TAK
- Risks of an intravenous infusion
- Risks of blood drawing
- Risks of a research MRI in subjects with GCA who do not have large vessel involvement

ii. Risks of Abatacept

In studies of RA, abatacept has been well tolerated with a side effect profile similar to placebo. In one study of 220 patients with RA who received abatacept in combination with MTX, no abatacept-related deaths, cancers, opportunistic infections, or atypical presentations of infections were observed during the 12 month study period (51). SAEs were seen in 12.2% of patients who received abatacept 10mg/kg (the dose that will be used in this trial) and were less common than in the abatacept 2mg/kg and placebo groups (18.1% and 16% respectively). These SAEs included chest pain (0.9%), myocardial infarction (0.9%), gastrointestinal disorder (0.9%). No apparent pattern was observed in the types of SAEs reported. In addition there was no apparent relationship between SAEs and the number of infusions. The frequency of drug-related SAEs did not differ between abatacept 10mg/kg and placebo (1.7% for both). For the abatacept 10mg/kg group, the most frequently reported AEs considered related to study drug were nasopharyngitis (6.1% versus 3.4% with placebo), nausea (5.2% versus 5.9% with placebo), and headache (5.2% versus 6.7% with placebo). No patients were shown to seroconvert in regard to forming anti-abatacept antibodies directed at the whole molecule, however 2 patients developed antibodies directed at the CTLA4 portion. In one of these patients,
the antibody response was transient and present at a single measurement and no follow-up data was acquired on the other patient. In these patients, there was no evidence of toxicity due to these antibodies.

In another study, 258 patients were treated with abatacept 10mg/kg in combination with a variety of other immunosuppressive agents (that included MTX 195, AZA 7, penicillamine 1, hydroxychloroquine 23, leflunomide 23, sulfasalazine 18, anakinra 7) (50). The rates of AE and SAEs were similar in the abatacept and placebo groups (79.5% and 71.4%, and 10.5% and 11.3% respectively). The incidence of serious infections was 2.3% in both groups. Infections were more common but not statistically significant in the abatacept group (37.6% vs 32.3% p=0.3) with nasopharyngitis, sinusitis, upper respiratory tract infection, and bronchitis being reported most frequently. Most infections were mild to moderate in intensity. One patient in the abatacept group died of a myocardial infarction that was not felt to be related to study drug. Acute infusion reactions were more frequent in the abatacept group as compared to placebo (5% vs 3% p=0.3) with dizziness and headache being most common. There were no severe acute infusion reactions in either group. Antibodies against abatacept developed in only 3 patients. In one patient, the response was against the immunoglobulin portion of the molecule, and in 2 patients the responses were against the CTLA4 binding portion. All of these responses showed low-level reactivity.

The risks stated in the drug package insert include:

- The most serious adverse events were infection and malignancy.
- Infections: In the placebo-controlled trials, infections were reported in 54% of abatacept treated patients and 48% of placebo treated patients. The most commonly reported infections (reported in 5-14% of patients) were upper respiratory tract infections, nasopharyngitis, sinusitis, urinary tract infection, influenza, and bronchitis. Other infections reported in < 5% of patients at a higher frequency with abatacept compared to placebo were rhinitis, herpes simplex, and pneumonia. Serious infections were reported in 3% of patients treated with abatacept and 1.9% of patient treated with placebo. The most common (0.2-0.5%) serious infections reported with abatacept were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pylonephritis.
- Malignancy: In the placebo-controlled portions of the clinical trials (1955 patients for a median of 12 months) the overall frequency of malignancies were similar in the abatacept and placebo treated patients (1.3% and 1.1% respectively). However, more cases of lung cancer were observed in abatacept treated patients (4, 0.2%) than in placebo treated patients (0%). In the cumulative abatacept clinical trials, a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 34 lymphomas (0.1 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5 fold higher than expected in age and gender matched general population based on the SEER database. Patients with RA, particularly those with highly active disease are at a higher risk for the development of lymphoma. Other reported malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers. The potential role of abatacept in the development of malignancies in humans is unknown.
- Hypersensitivity: Acute infusion related events were more common in the abatacept treated patients than in the placebo treated patients (8% vs 6%). The most frequently reported events (1-2%) were dizziness, headache, and hypertension. Acute infusion related events reported in >0.1% and < 1% of patients included cardiopulmonary symptoms, such as hypotension, increased blood pressure, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritis, rash, and wheezing. Most of these reactions were mild to moderate. Fewer than 1% of abatacept treated patients discontinued due to an acute infusion related event. Of 2688 patients treated with abatacept, there were 2 cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with hypersensitivity such as hypotension, urticaria, and dyspnea each occurred in < 0.9% of abatacept treated patients.
- Adverse reactions in COPD: In one study, there were 37 patients with chronic obstructive pulmonary disease (COPD) who were treated with abatacept and 17 COPD patients treated with placebo. The COPD patients who received abatacept developed adverse events more frequently than those who received placebo (97% vs 88% respectively). Respiratory disorders occurred more frequently in abatacept treated patients compared to placebo treated patients (43% vs 24% respectively) including COPD exacerbation,
cough, rhonchi, and dyspnea. A greater percentage of abatacept-treated patients developed a serious adverse event compared to placebo treated patients (27% vs 6%), including COPD exacerbation (3 of 27 patients (8%)) and pneumonia (1 of 37 patients (3%)).

- In 1965 abatacept treated patients, the most commonly reported adverse events occurring in > 10% of patients were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

- Immunogenicity: antibodies directed against the entire abatacept molecule or the CTLA4 portion of abatacept were assessed by ELISA. 34 of 1993 (1.7%) patients developed antibodies to the entire abatacept molecule or the CTLA4 portion of abatacept. 6 of 9 evaluable patients were shown to possess neutralizing antibodies. No correlation of antibody development to clinical response, pK, and adverse events was observed.

- Parenteral drug products containing maltose can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinoliquinone (GDH-PQQ). The GDH-PQQ based glucose monitoring systems may react with the maltose present in abatacept resulting in falsely elevated blood glucose readings on the day of the infusion. When receiving abatacept, patients that require blood glucose monitoring should be advised to consider methods that do not react with maltose such as those based on glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods.

- Live vaccines should not be given concurrently with abatacept or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving abatacept. The efficacy of vaccination in patients receiving abatacept is not known. Based on its mechanism of action, abtcept may blunt the effectiveness of some immunizations.

iii. Risks of Prednisone

GC have been used therapeutically in humans since 1949 and their side effects are well recognized. The main toxicities of prednisone include infections, hyperglycemia, hypertension, cataracts, osteoporosis, avascular necrosis, gastrointestinal irritation, mood disturbances (including psychosis), bruising, skin changes including acne and striae, increase in appetite and weight, and redistribution of fat. Prednisone is not known to have teratogenic effects on the developing fetus and there has been no evidence to date of an effect on fertility. However, prednisone can cause problems during pregnancy for both the mother (risks of weight gain, gestational diabetes, and infection) and the developing fetus as a result of the maternal problems.

The risks as listed on the package insert for prednisone (Deltasone®) include [http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=3735]:

- Fluid and Electrolyte Disturbances
  - Sodium retention
  - Fluid retention
  - Congestive heart failure in susceptible patients
  - Potassium loss
  - Hypokalemic alkalosis
  - Hypertension

- Musculoskeletal
  - Muscle weakness
  - Steroid myopathy
  - Loss of muscle mass
  - Osteoporosis
  - Tendon rupture, particularly of the Achilles tendon
  - Vertebral compression fractures
- Aseptic necrosis of femoral and humeral heads
- Pathologic fracture of long bones

- Gastrointestinal
  - Peptic ulcer with possible perforation and hemorrhage
  - Pancreatitis
  - Abdominal distention
  - Ulcerative esophagitis
  - Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

- Dermatologic
  - Impaired wound healing
  - Thin fragile skin
  - Petechiae and ecchymoses
  - Facial erythema
  - Increased sweating
  - May suppress reactions to skin tests

- Metabolic
  - Negative nitrogen balance due to protein catabolism

- Neurological
  - Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment
  - Convulsions
  - Vertigo
  - Headache

- Endocrine
  - Menstrual irregularities
  - Development of Cushingoid state
  - Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
  - Suppression of growth in children
  - Decreased carbohydrate tolerance
  - Manifestations of latent diabetes mellitus
  - Increased requirements for insulin or oral hypoglycemic agents in diabetics

- Ophthalmic
  - Posterior subcapsular cataracts
  - Increased intraocular pressure
  - Glaucoma
  - Exophthalmos

- Additional Reactions
  - Urticaria and other allergic, anaphylactic or hypersensitivity reactions

iv. Risks of MRI/MRA
For subjects with TAK or GCA with large vessel involvement, MRIMRA is considered part of the standard of care and therefore MRI/MRA would not be considered to be a research risk.

For subjects with GCA who do not have symptoms or signs of large vessel disease, one research MRI/MRA will be obtained prior to the first abatacept infusion and therefore MRI/MRA in this population would be considered to be a risk of study participation.

Having this research MRI performed could detect large vessel disease that was not apparent. If large vessel disease is found, this will be discussed with the subject. It is also possible that the MRI could reveal other unexpected findings (for example: a mass that was not previously known to be present). Should such an
unexpected finding be discovered, this would be discussed with the subject and recommendations would be
made as to how this should be further evaluated.

The risks of MRI/MRA include:

- Risks of retained metal. MRIs cannot be performed in people who have certain types of metal in their bodies. Prior to having an MRI, patients will be screened for the presence of such metal. Patients who have a piece of metal in their body, such as a metal fragment in their eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, will not be allowed into the MRI room and therefore cannot receive a research MRI.

- Nephrogenic fibrosing dermopathy (previously known as nephrogenic systemic fibrosis) is a rare side effect resulting in skin hardening and thickening that has been observed in people on dialysis or with severe renal insufficiency who have had an MRI. Although this side effect is believed to be related to the contrast agent gadolinium, its exact cause remains unclear. Renal function will be checked routinely as part of protocol screening and participation. Patients will not undergo a research or clinical MRI if their serum creatinine is $>$ 2.0.

- Adverse reactions to the MRI contrast agent gadolinium. As listed by the Institute for Magnetic Resonance Safety, Education, and Research (http://www.MRIsafety.com), the frequency of all adverse events after an injection of 0.1 or 0.2 mmol/kg of gadolinium ranges from 0.07–2.4 percent. The vast majority of these reactions are mild, including coldness at the injection site, nausea with or without vomiting, headache, warmth or pain at the injection site, paresthesias, dizziness, and itching. Reactions resembling an “allergic” response are very unusual and vary in frequency from 0.004–0.7 percent. A rash, hives, or urticaria are the most frequent of this group, and very rarely there may be bronchospasm. Severe, life-threatening anaphylactoid reactions are exceedingly rare (0.001–0.01 percent). In an accumulated series of 687,000 doses there were only 5 severe reactions. In another survey based on 20 million administered doses there were 55 cases of anaphylactoid shock. It would appear that, to date, only one published death has been clearly related to the administration of gadolinium-based contrast. Other deaths in other series have been ascribed to other diseases or to other drugs, or were thought to be coincidental.

- Temporary hearing loss. Patients will be asked to wear hearing protection.

- Claustrophobia from the confined space of the MRI scanner.

- At times during the MRI, patients may be asked not to swallow for a while, which can be uncomfortable.

- Risks of injury from unrestrained metal in the MRI scanner room.

- Unknown risks to the fetus. Pregnant women are excluded from participation in this study and screening will be performed already as part of study participation just prior to when the research MRI would be performed.

- Risks of an intravenous catheter, which include bruising, bleeding, and rarely superficial venous thrombosis or infection.

v. Other Risks

Blood drawing has associated risks, which include bruising, bleeding, and rarely fainting or infection. Blood samples obtained for research purposes will include the collection and storing of DNA, which may be used for future genetic testing to examine CTLA4 polymorphisms.

Abatacept will be administered via intravenous infusion. The risks of an intravenous infusion include bruising, bleeding, and rarely superficial venous thrombosis or infection.

Strict subject confidentiality will be observed throughout all aspects of the study. While medical records will be reviewed by members of the research team, no individually identifiable subject data will be distributed to non-research or care-giving team members.
In the event of adverse effects from the study, the full resources of the hospital will be available to intervene as medically necessary. Licensed physicians expert in the care of subjects with vasculitis are available at all times at each study site.

9. References


