AN OPEN-LABEL SINGLE-ARM CLINICAL TRIAL TO EVALUATE THE EFFICACY OF ABATACEPT IN MODERATE TO SEVERE PATCH TYPE ALOPECIA AREATA AND ALOPECIA TOTALIS AND UNIVERSALIS

Investigators:

Julian Mackay-Wiggan, M.D., M.S.
Assistant Professor and Director, Clinical Trials Unit
Department of Dermatology
Columbia University
jc299@columbia.edu

Joan Bathon, M.D.
Professor in Medicine and Chief Division of Rheumatology
Columbia University
jmb2311@columbia.edu

Bibhas Chakraborty
Associate Professor in Biostatistics
Columbia University
bc2425@columbia.edu

Angela Christiano, Ph.D.
Professor in Dermatology and Genetics
Vice-Chair for Research in Dermatology
Columbia University
amc65@columbia.edu

Raphael Clynes, M.D., Ph.D.
Associate Professor in Pathology, Medicine and Dermatology
Director of the Immunogenetics and Cellular Immunology Laboratory
Columbia University
rc645@columbia.edu

Columbia University
Department of Dermatology - Clinical Research Unit
161 Fort Washington Avenue, 12th Fl, Rm 1264
NY, NY 10032
***Tel #:* 212-305-6953**
***Fax #:* 212-305-0286**

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PROTOCOL SYNOPSIS

Protocol Title:	An Open-Label Single-Arm Clinical Trial to Evaluate the Efficacy of Abatacept in Moderate to Severe Patchy Type Alopecia Areata and alopecia totalis and universalis
Site Numbers & Names:	Clinical Research Unit Department of Dermatology Columbia University Medical Center
Research Hypothesis:	Among patients with alopecia areata, patients with higher disease burdens are unlikely to have satisfactory outcomes with current therapies. Our hypothesis is that CTLA4-Ig will be effective therapy in moderate-severe alopecia areata by blocking re-activation of CD8+ memory T cells, thereby aborting the cytotoxic T cell inflammatory response underlying alopecia areata.

Study Rationale	Alopecia areata (AA) is a common autoimmune disease resulting from autoimmune attack on the hair follicles. The histopathology clearly identifies the "swarm of bees", comprised of T cells encircling the human hair follicle. Costimulatory blockade with Abatacept (CTLA4-Ig, a soluble receptor that blocks costimulatory molecules) has recently emerged as an effective therapy in human T cell mediated diseases. Abatacept is FDA-approved for the treatment of Rheumatoid Arthritis and Juvenile Idiopathic Arthritis and is under study for many other autoimmune conditions. There is genetic evidence for the importance of the costimulatory pathway in human AA. Our recent GWAS studies identified several genetic susceptibility alleles that included CTLA4 as well as HLA, IL-2 and its receptor and NKG2D ligands (Petukhova et al, 2010). Many of these AA susceptibility alleles are shared by other common autoimmune diseases including Celiac Disease, Type I Diabetes, and Rheumatoid Arthritis. These autoimmune states may share common pathogenic mechanisms and may respond to common treatments. Our recent studies point to a dominant role for activated NKG2D-bearing CD8 T cells as the likely culprit autoaggressive cellular effector(Petukhova et al, 2010). $CD8^{+}NKG2D^{+}$ effector T cells dominate the peribulbar infiltrate in human AA and are intimately associated with dermal sheath cells aberrantly expressing NKG2D ligands. Our unpublished data in the mouse has confirmed the human pathological findings (Petukhova et al, 2010), identifying activated NKG2D bearing CD8 T cells both adjacent to the hair follicle and in the draining lymph nodes. Thus, the immunopathogenesis of the C3H mouse model faithfully recapitulates human alopecia**.** Consistent with a primary role for autoimmune T cells in the C3H mouse model of alopecia areata, disease can be induced in normal unaffected mice by transfer of T cells from affected mice or humans (Sundberg et al, 1994; Gilhar et al, 2003; McElwee et al, 2005). It is important therefore that proof-of-concept has already been provided for CTLA4-Ig as a treatment in the C3H alopecic mouse model (Carroll et al, 2002). Based on these pre-clinical proof-of-concept studies in the relevant animal model, the genetic evidence for the relevance of the CTLA4 pathway in human alopecia areata, and the

	lack of existing evidence-based data for any treatment in alopecia areata, there is a strong rationale for testing CTLA4-Ig treatment in this disease.
Study Objectives: **Primary:** **Secondary:**	The study's *primary efficacy endpoint* will be the proportion of responders after 6 months of treatment, with response defined as 50% or greater hair re-growth from baseline as assessed by SALT score at week 24. This is a relatively strict definition for defining responders and non-responders and was chosen to minimize the potential for spontaneous remission, in which fewer than 10% are expected to achieve this magnitude of hair regrowth spontaneously. As secondary endpoints, efficacy will be measured by changes in hair re-growth as a continuous variable as determined by physical exam and Canfield photography, as well as patient and physician global evaluation scores. To assess the durability of responses, patients will continue to be followed for an additional 6 months off treatment or until it is determined that relapse has occurred. Additionally, patient reported outcomes, safety measures, incidence and timing of relapse will be important secondary outcomes. We will also explore the efficacy of treating 2 patients with current alopecia totalis or universalis, and in doing so, will compare, on an exploratory basis, the rate of occurrence of hair regrowth in patients with moderate to severe patch type alopecia areata compared to those with current alopecia totalis or universalis. In addition, response to abatacept treatment will be examined on an exploratory basis for correlation with the presence or absence of the AA GWAS risk haplotype.
Study Design:	Open label pilot study of 6 months of abatacept 125mg SC per week in the treatment of moderate to severe AA and current alopecia totalis or universalis, followed by 6 months follow-up off drug to assess the incidence and timing of recurrence of disease. Treatment may be extended by up to 6 additional months beyond the initially planned 6 months of treatment if clinically indicated at the discretion of the investigator.
Study Schema **Drugs / Doses / Length of Treatment)**	A fixed dose of abatacept (125mg) will be self-administered subcutaneously weekly for 24 weeks, with an option to extend treatment for up to an additional 24 weeks at the discretion of the investigator. A loading IV dose will not be employed.

Accrual Goal: (Total number of subjects)	15
Accrual Rate: (Number of subjects expected per month)	1-3
FPFV: **LPFV:** **Follow Up:** **(dd-mm-yy)**	May, 1, 2013 March 31, 2015 12 months
Correlative Studies: (PK/PD, etc.)	Our published work and previous studies in human AA have reported increased NKG2DL expression and augmented expression of IFN response genes in the target hair follicle end organ, and elevated NKG2D expression in circulating CD8 T cells and NK cells (Ito et al, 2008; Petukhova et al, 2010). <u>Clinical Correlative Studies</u> Our study will include longitudinal assessment of AA biomarkers at baseline and during treatment to correlate treatment and disease status with; 1) histological improvement with reduced T cell peribulbar infiltrates. 2) declines in circulating and peribulbar $CD8^{+}NKG2D^{+}$ infiltration and in follicular hair follicle NKG2DL expression. 3) reduced IFN inflammatory biomarkers in the skin and blood. 4) presence or absence of AA GWAS risk haplotype

Inclusion Criteria:	Patients between 18 to 75 years of age. Patients with a diagnosis of moderate-to-severe patch type alopecia areata. **Patients will have ≥30% and <95% total scalp hair loss at baseline as measured using the SALT score.** Patients with alopecia totalis/universalis can be included as long as the current episode of hair loss meets the criteria of 30 to 95% hair loss (i.e. they are not currently AT or AU), and as long as in the opinion of the investigator there appears to be potential for regrowth. Two to five patients with current episodes of alopecia totalis /or universalis (100% scalp hair loss) may be included in this study at the discretion of the investigator. **Duration of hair loss greater than 3 months without an upper limit of duration as long as there is reason to believe that regrowth is possible in the opinion of the investigator.** No evidence of active/ongoing regrowth present at baseline. Patients may be naïve to treatment or unresponsive to intralesional (IL) steroids or other treatments for alopecia areata.

Exclusion Criteria:	Two to five patients with alopecia totalis/universalis at the time of enrollment at the discretion of the investigator. Patients with a history of or active skin disease on the scalp such as psoriasis or seborrheic dermatitis. Patients in whom the diagnosis of alopecia areata is in question. Patients with active medical conditions or malignancies (except adequately treated basal or squamous cell carcinoma) that in the opinion of the investigator would increase the risks associated with study participation, including patients with a history of recurrent infections. Women of childbearing potential who are unable or unwilling to use two forms of birth control for the study duration. Women who are pregnant or nursing. Patients with COPD Patients known to be HIV or hepatitis B or C positive. Patients with history or evidence of hematopoietic abnormality. Patients with history of immunosuppression or history of recurrent serious infections. Patients unwilling or unable to discontinue treatments known to affect hair regrowth in AA.

Criteria for Evaluation: (Efficacy, safety, stopping rules, etc.)	EFFICACY Primary endpoint: SALT (Severity of Alopecia Tool) Scores: The proportion of scalp involvement is determined by dividing the scalp into 4 quadrants and estimating the percentage of the scalp surface that all the alopecic areas would occupy if placed **together.** Secondary endpoint: Changes in hair re-growth as a continuous variable will be determined using physical exams and Canfield photography, as well as patient and physician global evaluation scores. Differences in the incidence of regrowth between patients with patch type AA vs patients with alopecia totalis or universalis will also be analyzed on an exploratory basis. In addition, response to abatacept treatment will be examined on an exploratory basis for correlation with the presence or absence of the AA GWAS risk haplotype. Additionally, patient reported outcomes, safety measures, incidence and timing of relapse will be important secondary outcomes. To assess safety, frequent and close monitoring of clinical and laboratory findings have been implemented. Adverse events will be captured and analyzed as a secondary endpoint. All physical examination findings, vital sign abnormalities, and clinical laboratory abnormalities, will be captured as AEs when deemed medically significant by the investigator. A qualified physician associated with the study will be available to assess clinical signs and symptoms that may be indicative of an adverse event. Safety will be assessed by summarizing the incidence and type of AEs. The proportion of patients who discontinued treatment will be summarized.

Statistics:	This is a small exploratory open label pilot study to identify an efficacy signal in alopecia areata. Based on two recently completed randomized trials (Strober et al, 2008; Price et al, 2009) in similar patient populations (moderate to severe AA) we expect placebo response rates to be between 6% (>50% improvement in SALT score (Olsen et al, 1999)) and 12% (>25% improvement). We have chosen our primary endpoint conservatively (proportion of patients with >50% improvement in SALT index) as a relatively strict criteria that should minimize placebo response rates to 10% or less (0-2 of 15 subjects). This allows a higher degree of confidence that appreciable response rates are attributable to drug rather than spontaneous remission. Power analysis. Assuming a historically known placebo response rate of 10% and the usual 5% level of significance (alpha), the sample size of 15 would provide 80.7% power to detect a difference of 30% in the response rate between the experimental treatment group and the historical placebo group. Since this is a small open label proof of concept study, we recognize that it will likely lack adequate power to conclusively demonstrate small efficacy signals (particularly if the assumed detectable difference of 30% is not met). Yet, descriptive summaries of all the primary and secondary efficacy outcomes (proportions for binary outcomes, means for continuous outcomes) will provide a preliminary indication of the effect size (even if smaller than 30%) that will aid design of subsequent efficacy trials. Differences in the incidence of regrowth between patients with patch type AA vs patients with alopecia totalis or universalis will also be analyzed on an exploratory basis. In addition, response to abatacept treatment will be examined on an exploratory basis for correlation with the presence or absence of the AA GWAS risk haplotype. To assess safety as a secondary endpoint, we will summarize via descriptive statistics, the occurrence of adverse events for the study group. Accrual projections. The Dermatology clinic and private practice at CUMC currently sees 600 AA patients yearly, of which we anticipate 20-30% would be eligible (>40% hair loss). Accrual will be greatly facilitated by targeted recruitment through our existing NAAF registry which includes 400 AA patients in the New York area, the majority of which have patchy type disease. Thus, complete accrual of 15 subjects should be feasible within 1 year from a pool of >100 eligible subjects yearly.

1 INTRODUCTION

1.1 Research Hypothesis

Among patients with alopecia areata, patients with higher disease burdens are unlikely to have satisfactory outcomes with current therapies. Our hypothesis is that CTLA4-Ig will be effective therapy in moderate-severe alopecia areata by blocking re-activation of CD8+NKG2D+ memory T cells, thereby aborting the cytotoxic T cell inflammatory response underlying alopecia areata.

1.2 Product Development Rationale

Abatacept is a recombinant fusion protein consisting of the extracellular domain of human CTLA4 and a fragment (hinge- CH2-CH3 domains) of the Fc domain of human IgG1 that has been modified to prevent complement fixation and antibody-dependent cellular cytotoxicity.

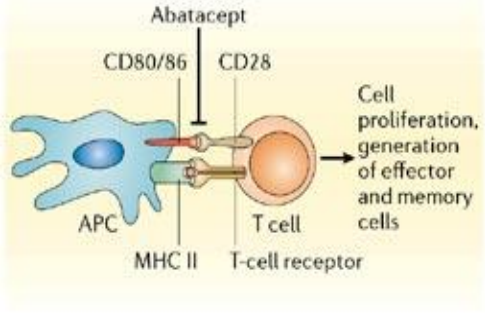


Figure 1. Mechanism of Action. Abatacept disrupts 'signal 2', blocking the costimulatory pathway and preventing autoimmunity.

Abatacept is the first drug in a new class of agents termed "selective costimulation modulators." Abatacept binds specifically to the CD80 and CD86 molecules, proteins prominently displayed on the surface of antigen-presenting cells (APCs) (Figure 1). Activation of naive T cells during an immune response requires two stimuli from APCs. The first signal is antigen-specific; antigens are presented by APCs, with the signal transmitted to the T cell through the T cell's antigen receptor. The second, or costimulatory, signal is not antigen-specific and is delivered following the engagement of a costimulatory ligand on the APC with a cognate receptor on the T cell.

A key costimulatory receptor on T cells is CD28. CD28 is constitutively expressed on resting T cells and binds to both CD80 (B7-1) and CD86 (B7-2) on the APC (Azuma et al, 1993; Freeman et al, 1993; Peach et al, 1994; Linsley et al, 1994) A costimulatory signal is required not only for the full activation of naive T cells, but also may be required for the survival of memory and autoimmune effector cells (Skak et al, 2003; Oliveira dos Santos et al, 1999). At 24 to 48 hours following T cell activation, the T cell expresses CTLA4 on its surface, which engages the CD80 and CD86 molecules on the APC surface interfering with CD28's ability to bind to its ligands on the APC; CD80 and CD86 preferentially bind to CTLA4 with a much higher avidity than with CD28. Although the precise mechanisms are as yet unclear, CTLA4 expression is associated with a decrease in T cell activation.

After the T cell activity has been dampened, the CTLA4 recycles into the T cell's cytoplasm. The CTLA4 section of abatacept binds specifically to CD80 and CD86 (B7-1 and B7-2, respectively) and down-modulates the CD28-mediated costimulation of T cells. Thus, abatacept uses a segment

of a molecule that is part of the normal immune homeostatic mechanism to suppress T cell activity involved in the immunopathogenesis of autoimmune diseases. The Fc region of abatacept was engineered with several point mutations designed to inactivate it. Because of these changes, abatacept does not mediate pathways such as antibody-dependent cell cytotoxicity or complement-dependent cytotoxicity (Davis et al, 2007).

Costimulatory blockade and its rationale as treatment for autoimmunity

Initial studies with CTLA4Ig fusion molecules demonstrated inhibition of naive CD4 T cell activation and proliferation (Linsley et al. 1992; Wells et al. 1997), and *prevention* of autoimmunity and inhibition of graft rejection in animal models (Knoerzer et al. 1995; Pearson et al. 1996). By contrast, it was generally accepted that memory T cells did not require CD28/B7-derived costimulation for recall responses (Salomon and Bluestone 2001). If this were true, then an exclusive activity of CTLA4Ig on naïve T cell activation would limit its use as a *treatment* of ongoing autoimmune diseases, which requires the reversal of injury mediated by effector and memory T cells, previously activated by self-antigens. However, we now know that **memory T cell responses remain costimulation dependent.** This is likely due to effector T cell regeneration from self-reactive memory T cell precursors by B7-expressing APCs in the lymph node and target tissues. Reactivation of antiviral memory T cells is impaired in the absence of B7/CD28 costimulation (Borowski et al. 2007; Fuse et al. 2008; Duttagupta et al. 2009; Garidou et al. 2009; Teijaro et al. 2009; Grujic et al. 2010). In mouse models, CTLA4-Ig limits effector T cell responses from memory cell precursors (Ndejembi et al. 2006) and alleviates ongoing autoimmunity (Finck et al. 1994; Khoury et al. 1995), while anti-CTLA4 enhances CD8 T cell memory responses (Pedicord et al. 2011) potentially a driver in its therapeutic effects in cancer (Wolchok and Saenger 2008; Hodi et al. 2010). **In humans, CTLA4-Ig is effective therapy in diseases known to be driven by memory T cells (Abrams et al. 1999; Kremer et al. 2005), and moreover the therapeutic effect is correlated with a decrease in CD8 T cell effectors ($CD8^+CD28^-$ T cells) (Scarsi et al. 2010), as we would hope to accomplish using Abatacept therapy in alopecia areata.**

1.2.1 Overview of Alopecia Areata

Alopecia areata (AA) is a major medical problem and is the most prevalent autoimmune disease in the US, with a lifetime risk of 1.7%, affecting both males and females across all ethnic groups (Safavi et al. 1995). Additionally, AA represents the second most common form of human hair loss, second only to androgenetic alopecia, and causes significant disfigurement and psychological distress to affected individuals (Figure 2).

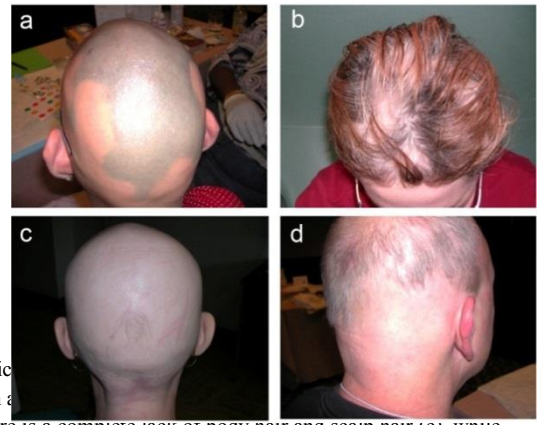


Figure 2. Clinic
the patient is in a
universalis, there is a complete lack of body hair and scalp hair (c), while patients with alopecia totalis lack scalp hair but not body hair. In d, the randomness of hair regrowth is observed, with regrowth in the parietal region but not either the occipital or temporal regions.

Alopecia Areata usually presents with patchy hair loss. Approximately one-third of these patients will experience spontaneous remissions within the first year. However, many patients will develop waxing and waning disease with some progressing to alopecia totalis (total scalp hair loss) or alopecia universalis (loss of all body hair). This population that suffers from a disfiguring disease represents a significant unmet medical need (Alkhalifah et al, 2010a,b).

Alopecia totalis/universalis seldom, if ever, remits spontaneously or with current treatment. In our targeted population of moderate-severe patch-type alopecia placebo response rates in other clinical studies have been in the 6-12% range (Price et al, 2008; Strober et al, 2009).

Clinical development of innovative therapies in AA has lagged far behind other autoimmune conditions. This may be due in part to the perception that AA is merely a cosmetic disorder. In reality, AA carries one of the highest burdens amongst all skin diseases, particularly among children and adolescents whose self-image is so closely linked to their appearance (Bickers et al. 2006).

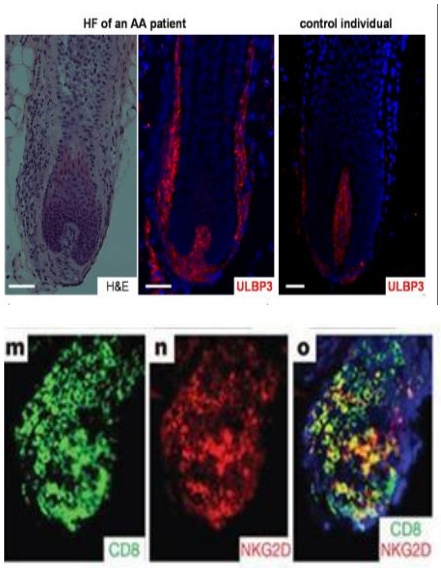
There are ***no*** evidence-based treatments for AA. A comprehensive Cochrane analysis assessment of seventeen randomized clinical trials (RCTs) involving a total of 540 participants found no proven treatment of AA (Delamere et al. 2008). Each trial included from 6 to 85 participants and assessed a range of interventions that included topical and oral corticosteroids, topical cyclosporin, photodynamic therapy and topical minoxidil. Overall, ***none*** of the interventions showed significant treatment benefit in terms of hair growth when compared with placebo. It was concluded that the effectiveness of few (if any) treatments for AA are proven. No RCTs on the use of diphencyprone, dinitrochlorobenzene, intralesional corticosteroids or dithranol were found, although these drugs are commonly used for the treatment of AA. Similarly, although topical corticosteroids and minoxidil are widely prescribed and appear to be safe, there is no convincing evidence that they are beneficial in the long-term. Most trials have been poorly reported and/or are so small that any important clinical benefits are inconclusive.

This study will provide a first efficacy study of Abatacept in alopecia areata. One clear **advantage of immunotherapeutic studies in the skin is the relative ease of access of the target organ.** Thus, our studies here examining the skin could provide important insight into the mechanism(s) of action of Abatacept in related diseases (see "Common Cause" section 1.2.4), which in turn could impact our understanding of autoimmune diseases in which the target organ is not accessible. **Shared genetic and common pathological pathways provide strong rationale for increasing the scope of approved pharmaceuticals (such as Abatacept) for novel indications (such as AA). Studies of abatacept in Type I diabetes are underway (TrialNet T1D, Clinicaltrials.gov).** Indeed, positive studies in any one of these autoimmune diseases that share a common cause could serve as the basis for advancing common treatments.

1.2.2 Pathology and role of T cells in human Alopecia Areata

CD8+ Killer T cells in Human AA

Alopecia areata results from autoimmune attack on the hair follicles. The relevant autoantigens are unknown, but the histopathology clearly identifies the "swarm of bees" encircling the human hair follicle. Infiltrates containing both CD4 and CD8 T cells have been described, but our recent studies pointed to a dominant role for activated NKG2D-bearing CD8 T cells that are the likely culprit autoaggressive cellular effectors1. We recently demonstrated that CD8+NKG2D+ effector T cells dominate the peribulbar infiltrate in human AA that are intimately associated with dermal sheath cells aberrantly expressing NKG2D ligands (Figure 3).



FiFigure 3. NKG2D axis in human AA:

Top panels: The NKG2DL ULBP3 is upregulated in human AA hair follicles but not in control subjects. Bottom panels: Immunostaining of a HF bulb shows dense infiltration with NKG2D staining CD8 T cells.

Interferon driven Th1-response in human AA

Consistent with a pathogenic cellular immune response, AA has been viewed as a Th1-driven disease (Arca et al, 2004; Barahmani et al, 2009; Kuwano et al, 2007); for instance elevated Th1 cytokines/chemokines (Figure 4) are seen in the peripheral blood of AA patients and IFN-inducible gene signatures have been described in the skin of AA patients (Ghoreishi, et al, 2010).

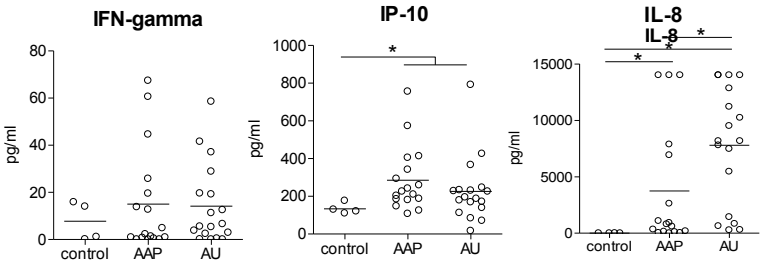


Figure 4. Elevated Serum Chemokines and Cytokines in Human AA. Interferon-γ and IFN-induced chemokines (IP-10/CXCL10) are elevated in the serum of **human** AA, in some cases correlating with disease severity, i.e. patchy disease (AAP) vs. universalis

1.2.3 Preclinical Studies: CTLA4-Ig prevents onset of Alopecia Areata in the C3H-HeJ mouse model

C3H/HeJ mice develop spontaneous alopecia areata and the histopathological changes are identical to human alopecia including the importance of IFN-γ producing CD8+ NKG2D bearing T cells which are present in alopecic skin, and are massively expanded and activated in AA cutaneous lymph nodes (data not shown). As with human alopecia we have demonstrated that IFN-response genes are highly upregulated in C3H/HeJ alopecic skin but in non-lesional skin and is normalized in mice with treated with effective therapy (data not shown).
Consistent with a primary role for autoimmune T cells, in C3H mice disease can be induced in normal unaffected mice by transfer of T cells (either or both CD4 and CD8 T cells) from affected mice or humans (Sundberg et al, 1994; Gilhar et al, 2003; McElwee et al, 2005). Thus the immunopathogenesis of the C3H mouse model faithfully recapitulates human alopecia and provides the rationale for preclinical studies in the C3H/HeJ mouse**. Proof-of-concept has been provided for CTLA4-Ig as a treatment in the C3H alopecic mouse model.** As published by our consultant Carroll et al. (2002), in the AA skin-graft model, CTLA4-Ig treatment prevented alopecia in 13/15 or 14/15 graft recipients (10% overall disease incidence) when given for 1 week or 4 weeks respectively whereas alopecia developed in all 35/35 untreated graft recipients (100% disease incidence). **Our hypothesis is that CTLA4-Ig blocks re-activation of CD8+NKG2D+ memory T cells, aborting the cytotoxic T cell inflammatory response underlying AA.**

1.2.4 Genetics of Alopecia Areata

Common Cause Hypothesis in Autoimmune Diseases
The **'Common Cause' theory of autoimmunity** is well-supported by decades of research using various methodologies and provides strong support for the existence of shared disease mechanisms. Epidemiological studies first demonstrated that some autoimmune diseases cluster within families, suggesting shared pathogenesis. More recently, hypothesis-free research strategies in genetics have shifted away from linkage studies in families, to genome-wide association studies (GWAS) in population-based cohorts. The results of these studies have provided tremendous support to the "common cause hypothesis" (Karopka et al. 2006) and have importantly identified **susceptibility alleles in specific genes that underlie grouped sets of autoimmune diseases, arguing for unifying/general mechanisms that dysregulate tolerance at one of several multiple end organ sites, with autoimmune destruction in the pancreas, joint, or skin, etc., the potential final disease outcome.** In fact, outside of the HLA, at least 23 such genes have been associated with two or more autoimmune diseases in a GWAS (Gregersen and Olsson 2009; Zhernakova et al. 2009). The majority of these shared genes can be mapped onto a discrete set of immunological molecular pathways. **Among these, the costimulatory pathway is one such shared mechanism.**

CTLA4 is a 'Common Cause' Gene within the Costimulatory Locus

Prior to identification of the **'costimulatory locus'** across GWAS studies, a number of **candidate gene studies had provided extensive evidence for the involvement of CTLA4 in numerous autoimmune diseases.** In fact, the CDC-based Human Genome Epidemiology Network (http://www.hugenavigator.net) maintains a database of genetic association studies, and no less than 650 publications report associations of CTLA4 to 198 disease terms. This includes 384 reports for 36 autoimmune conditions, some of which we have summarized in Table 1.

Disease Term (MeSH)	Total	Meta	GWAS	Gene-En
Alopecia Areata	1	0	1	0
Arthritis, Juvenile Rheumatoid	4	0	0	0
Arthritis, Rheumatoid	28	4	2	4
Asthma	11	2	0	2
Diabetes Mellitus, Type 1	73	9	2	2
Graft vs Host Disease	2	0	0	0
Hypersensitivity	1	0	0	0
Hypersensitivity, Immediate	6	1	0	2
Lupus Erythematosus, Systemic	17	0	0	2
Lymphoproliferative Disorders	1	0	0	0
Multiple Sclerosis	25	4	0	0
Psoriasis	3	0	0	0
Graves Disease	44	7	0	3
Thyroiditis, Autoimmune	20	3	0	1
Celiac Disease	13	0	1	0
Colitis, Ulcerative	13	0	0	0

Table 1. Genetic association studies for CTLA4 annotated in a CDC database.

The **costimulatory locus** resides on human chromosome 2q33 and is comprised of a ~300kB region containing three genes, CD28, CTLA4 and ICOS, which likely arose as sequential gene duplication events (Gough et al. 2005)**.** The expression of the three costimulatory genes is differentially regulated insofar as CD28 is constitutively present on naïve T cells, whereas CTLA4 and ICOS become displayed only following T-cell activation, either at the level of transcriptional upregulation and/or endosomal trafficking to the plasma membrane. The engagement of CD28 also influences the expression of CTLA4 and ICOS, suggestive of long-distance and coordinated regulation at multiple levels.

The regulation of immune responses occurs through a balance of activating and inhibitory signals to generate effective immune responses, but prevent autoimmune disease. Despite their colocalization in the genome and evolutionary relationship and 20% sequence homology in their ligand binding domains (Gough et al. 2005), **the functions of CD28 and CTLA4 are almost directly opposite with respect to autoimmunity** (Scalapino and Daikh 2008). CD28 is an activatory/stimulatory signal (an accelerator), and engages as part of 'signal 2' by binding CD80 and CD86 on the surface of antigen presenting cells. CTLA4, on the other hand, is an inhibitor of T-cell costimulation (a brake), and binds to the same receptors with 100x greater avidity than CD28, serving to dampen the immune response, although the mechanism(s) by which this occurs are incompletely understood. In addition to this activity, CTLA4 is also known to play a role in reverse-signaling to the antigen presenting cell once it is engaged, as well as in the generation of regulatory T cells, indicating pleiotropic roles in immune modulation (Scalapino and Daikh 2008).

GWAS Implicates the CTLA4 Region on Chromosome 2q33.2 in AA/AT/AU

In accordance with the common cause hypothesis of autoimmune diseases, our GWAS on AA (Petukhova et al. 2010) revealed a number of risk loci shared with other forms of autoimmunity, such as RA, T1D, CeD, SLE, MS and psoriasis, in particular, **CTLA4,** IL2/IL2RA, IL21, NKG2D ligands and genes critical to Treg function. The genetic commonality with RA, T1D, and CeD is especially noteworthy in light of the pathogenic significance of the expression of an

NK ligand in the end organ (synovial fluid, islets, gut and skin), and the involvement of the NKG2DL/NKG2D pathway in the pathogenesis of each of these three diseases.

Interestingly, according to the NIH database of GWAS (http://www.genome.gov/gwastudies), to date, **six GWAS have identified significant associations with CTLA4 across four diseases:** our own study in AA (Petukhova et al. 2010), RA (Gregersen et al. 2009; Stahl et al. 2010), T1D (Cooper et al. 2008; Barrett et al. 2009) and CeD (Dubois, Trynka et al. 2010). The results of all published SNPs at these loci are shown in Figure 5. Guided by our GWAS findings and immunobiological studies, our goal is to develop treatments to fill the unmet needs of patients with AA. Importantly, since our original publication, **CTLA4 has been replicated as a** bona fide AA locus in an independent cohort (John et al, 2011).

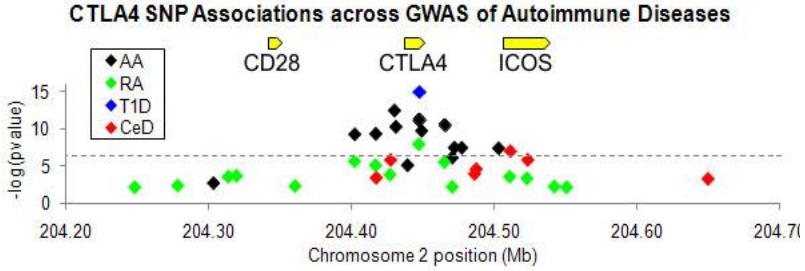


Figure 5. GWAS results for CTLA4. Four diseases have implicated CTLA4 in a GWAS. The dotted line indicates the threshold for genome-wide statistical significance ($p=5x10^{-7}$).

Overall, these results implicate CTLA4 genetically in the pathogenesis of several autoimmune diseases, and suggest that genetic variation at this locus may influence transcriptional and splicing regulation of *CTLA-4* resulting in aberrant control of T cell activation. CTLA4 variants that are associated with AA have been correlated with decreased expression levels, providing further evidence for the involvement of costimulatory pathways in AA pathogenesis.

1.2.5 Haplotype Analysis for CTLA4 Modulation with Abatacept Therapy

Autoimmune diseases that are common in the population, as is alopecia areata, are complex disorders and can arise from a multitude of causes that may not always be aligned within a single pathway. This is thought to, in turn, to contribute to heterogeneity in treatment response. For example, if disease arises in an individual because of perturbations in a particular pathway, drugs that target alternative disease pathways will ultimately not effect molecular corrections and disease will remain unresolved for the patient.

The costimulatory pathway has demonstrated perturbations in a number of autoimmune diseases. We and others have identified haplotypes at the costimulatory locus that confer risk for autoimmunity and alopecia areata in particular (Petukhova et al, Butty et al.). We hypothesize that variants carried on these haplotypes perturb the costimulatory axis and patients carrying

such risk variants in particular will receive benefit from therapies specifically targeted to this pathway.

Long range haplotype analysis using a small set of common SNPs across the costimulatory locus revealed two predominating haplotypes in European populations, termed 15-2-4 and 5-1-4 that are associated with autoimmune protection or risk respectively. Our own targeted deep sequencing across the locus in a cohort of 122 alopecia areata patients revealed significant overlap between 15-1-4 haplotype and the risk haplotypes identified in our alopecia areata GWAS, such that all chromosomes carrying the 15-1-4 haplotype also carried an AA GWAS risk haplotype. Therefore, while the causal variants are not yet completely elucidated, we propose that patients carrying at least one copy of this haplotype will benefit from abatacept therapy. In our dataset of 244 chromosomes, we identified 47 (20%) with this risk haplotype. Furthermore, we identified 166 chromosomes that did not carry either the 15-1-4 haplotype or an AA risk haplotype (67%).

In this study we will analyze the rate of response as correlated with the presence or absence of the risk haplotype. If there appears to be a correlation, future studies of abatacept in AA may be designed to test and enroll subjects a priori based on the presence or absence of the risk haplotype enabling a more direct analysis of response to treatment in relationship to risk haplotype presence or absence.

Table 1.

	Alopecia Areata Haplotype 15-2-4	Protective 15-1-4	Risk- Other	Haplotype- Total
GWAS risk Haplotype	1	47	36	84
No GWAS risk Haplotype	46		114	160
Total	47	47	150	244

Haplotype, Butty et al., 2007

Table 1. The costimilatory locus was targeted for deep sequencing in 122 alopecia areata patients (Chr2: 204544318-204841364), revealing 1209 variants that passed stringent quality control. Variants were phased to reveal sequence for 244 chromosomes, 47 of which carry the 15-1-4 haplotype that increases risk for autoimmunity and 150 of which do not carry this risk haplotype.

1.3 Summary of Results of Investigational Program

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

A full development program conducted in adult RA led to regulatory approval in the United States for this indication in December 2005, in Canada in June 2006, and in Europe in May 2007. In the US, abatacept now has two indications: (1) treatment of moderate to severe active RA in adults, and (2) treatment of moderate to severe juvenile idiopathic arthritis (JIA) in patients who have failed prior therapy with disease-modifying anti-rheumatic drugs (DMARDs).

1.3.1 Core Efficacy Studies of Abatacept in Rheumatoid Arthritis

The RA clinical program consisted of five core studies: IM101-100, IM101-101, IM101-102, IM101-029, and IM101-031 (N=2944) (Kremer et al, 2003a,b; Genovese et al, 2005; Kremer et al, 2006; Weinblatt et al, 2006). Each study had a double-blind placebo-controlled period of 6 months or 1 year. In Study IM101-100, subjects received abatacept 2 mg/kg, 10 mg/kg, or placebo. In the other studies, subjects received abatacept 10 mg/kg or a fixed dose that approximated 10 mg/kg or placebo.

Subjects who completed the double-blind period were offered entry into an uncontrolled, open-label period, in which all subjects received abatacept (in a fixed dose that approximated 10 mg/kg). A total of 2624 subjects in the core RA studies received the approved abatacept dose (10 mg/kg or a fixed dose that approximated 10 mg/kg) in the combined double-blind and open-label periods, representing 4603 person-years of exposure [(i).]

The efficacy of abatacept at a weight-tiered dose approximating 10 mg/kg was demonstrated in placebo-controlled studies in adult subjects with active RA and an inadequate response to methotrexate (IM101-100, IM101-102, and IM101-043), and in one study in adult subjects with active RA and an inadequate response to at least one TNF-blocking agent (etanercept and/or infliximab; IM101-029) (Kremer et al, 2003a,b; Genovese et al, 2005; Kremer et al, 2006; Weinblatt et al, 2006). Other studies have provided additional supportive evidence of efficacy. Abatacept (10 mg/kg or a fixed dose approximating 10 mg/kg) was significantly more effective than placebo in reducing the signs and symptoms of RA, including induction of major clinical response, improving physical function, slowing the progression of structural damage, and improving the quality of life in subjects with moderately to severely active RA.

Disease	No. of Studies
Rheumatoid Arthritis	39
Juvenile Rheumatoid Arthritis	1
Type 1 Diabetes Mellitus	4
Psoriasis Vulgaris	3
Psoriatic Arthritis	1
Systemic Lupus Erythematosus	2
Lupus Nephritis	1
Lupus Nephritis; Systemic Lupus Erythematosus	1
ANCA-associated Vasculitis	1
Ankylosing Spondylitis	1
Atopic Asthma	1
Crohn's Disease	1
Multiple Sclerosis	1
Multiple Sclerosis, Relapsing-Remitting	1
Relapsing Polychondritis	1
Sarcoidosis	1
Scleroderma, Diffuse;	1
Takayasu's Arteritis; Giant Cell Arteritis	1
Ulcerative Colitis	1
Urticaria	1
Uveitis	1
Wegener's Granulomatosis	1

Table 2. Abatacept clinical trials for autoimmune diseases (www.clinicaltrials.gov).

In Studies IM101-102 and IM101-029, improvement in signs and symptoms assessed by the American College of Rheumatology (ACR) 20 response rate versus placebo was observed after administration of the first dose, as measured at Day 15, and it was maintained through the double-blind study phase and for up to 3 years (in IM101-029 and IM101-102) and up to 5 years (in IM101-100) (Westhovens et al, 2007; Kremer et al, 2007). In the open-label extensions of IM101-100, IM101-102, and IM101-029, durable and sustained ACR20, ACR50, and ACR70 responses have been observed through 48, 24, and 18 months, respectively, of abatacept treatment (Westhovens et al, 2007; Genovese et al, 2008; Kremer et al, 2008).

Clinical Trials of Abatacept in other Autoimmune Diseases

Given the established safety and efficacy of abatacept in rheumatoid arthritis, the drug is currently being tested in a variety of autoimmune diseases (Table 2), as well as for organ transplantation. At present there are **79 clinical trials either in progress or completed using abatacept, of which 66 involve an autoimmune disease** (www.clinicaltrials.gov). These include safety, pharmacodynamics and efficacy studies and their primary purpose is mostly treatment, but also prevention in a smaller number of studies.

1.3.2 Pharmacokinetics of Subcutaneous Formulation

Subcutaneous (SC) formulation in adult population

Single SC doses of abatacept (50 to 150 mg) demonstrated approximately dose proportional PK in healthy adult subjects[ii]. Following administration of single doses of 50 to 150 mg of abatacept, the mean Cmax increased from 3.5 to 10.7 μg/mL and the geometric mean AUC(INF) increased from 1490 to 4270 μg·hour/mL. The median time to occurrence of Cmax (Tmax) following SC administration ranged between 48 and 168 hours. Mean $T_{1/2}$ values in healthy subjects ranged from 11.2 to 14.7 days. $T_{1/2}$ values from this study were comparable with the $T_{1/2}$ values obtained with abatacept administered IV to subjects with RA (13 to 14 days)[iii]. The fact that $T_{1/2}$ values following SC dosing were comparable to $T_{1/2}$ values obtained after IV dosing suggests that the elimination characteristics of abatacept were not altered following SC administration.

A double-blind, randomized, placebo-controlled, parallel-group, multiple-dose study (IM101063) assessed the steady-state trough serum concentrations of abatacept following SC administration in subjects with RA[iv]. Subjects were randomized to receive either abatacept or placebo in 1 of 5 parallel groups based on body weight obtained at the screening visit (Table 1.3.2A). The SC dose regimens were selected to target trough levels between 10-30 ug/ml, which was associated with efficacy with the IV formulation.

Table 1.3.2A IM101063 Treatment Groups Based on Body Weight

Treatment Group	Subject weight (kg)	IV dose on Day 1 (mg)	SC dose weekly for 12 weeks (mg)	SC injection volume (mL)
1	< 60	500	75	0.6
2	< 60	500	125	1
3	60 - 100	750	125	1
4	> 100	1000	125	1
5	> 100	1000	200	0.6 + 1.0

Source: IM101063 CSR

On Day 1, subjects received a single IV infusion (loading dose) of abatacept or placebo, based on their weight range. Approximately 1 hour after the completion of the IV infusion, subjects received their assigned SC dose of abatacept or placebo. Abatacept or placebo was administered weekly by the SC route, at the same dose as the SC dose on Day 1, for a total of 12 SC injections. Blood samples for PK analysis were collected on Day 1 prior to and at the end of the IV infusion. In addition, blood samples were collected prior to each weekly SC dose of abatacept.

Steady-state trough serum concentrations were achieved after ~ 4 to 5 weeks following the combined regimen of a single IV loading dose and weekly SC injections. With the exception of Treatment group 4 (abatacept 125 mg SC weekly dose for subjects weighing > 100 kg), the mean steady-state trough concentrations across all other treatment groups appeared to be comparable.

However, to truly represent the steady-state serum levels from SC administration without the contribution of the IV loading dose, Cmin values on Days 71-85 were selected, since contribution from IV was expected to be negligible. Comparison of mean steady-state trough concentrations on Day 71, 78 and 85 indicated that abatacept did not appear to accumulate following weekly dosing (Table 1.3.2B).

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

Treatment Group	Study Day	n	Cmin (μg/mL) Geometric Mean (CV%)	Cmin (μg/mL) Median (Min, Max)
1 (500 mg IV / 75 mg SC)	71	7	22.64 (20.13)	20.92 (17.06, 29.84)
	78	7	21.66 (19.99)	22.40 (16.01, 28.93)
	85	7	23.62 (31.63)	21.91 (18.24, 39.60)
2 (500 mg IV / 125 mg SC)	71	4	28.03 (42.13)	32.57 (13.73, 43.30)
	78	3	34.17 (29.49)	33.10 (25.97, 46.40)
	85	3	36.73 (31.64)	37.50 (26.26, 50.30)
3 (750 mg IV / 125 mg SC)	71	26	24.05 (40.65)	26.53 (7.97, 54.11)
	78	23	24.41 (52.35)	27.54 (5.40, 68.90)
	85	25	24.93 (38.42)	26.01 (9.57, 53.80)
4 (1000 mg IV / 125 mg SC)	71	3	16.22 (24.39)	15.15 (13.37, 21.07)
	78	5	11.57 (32.25)	13.20 (6.89, 16.33)
	85	5	13.01 (41.35)	13.30 (6.66, 22.73)
5 (1000 mg IV / 200 mg SC)	71	5	26.52 (56.53)	26.20 (8.68, 55.20)
	78	5	29.21 (52.96)	40.40 (8.04, 57.10)
	85	5	27.53 (58.87)	29.01 (8.74, 62.00)

Source: IM101063 CSR, Supplemental Table S.8.2.2
n=number of observations

Steady-state pharmacokinetic parameters of abatacept after weekly SC administration were determined between the SC dosing interval from Day 71 to 78. Cmax and AUC(TAU) appear to be comparable in Treatment Groups 1, 3 and 5 (Table 1.3.2C).

Table 1.3.2C Summary Statistics for Abatacept Steady-State Pharmacokinetic Parameters - IM101063

Treatment Group	Pharmacokinetic Parameter	
	Cmax (µg/mL) Geometric Mean (CV%)	**AUC(TAU) (µg*h/mL) Geometric Mean (CV%)**
1 (500mg IV / 75mg SC)	n = 7 26.3 (29.5)	n = 7 4066 (22.2)
2 (500mg IV / 125mg SC)	n = 4 34.9 (46.6)	n = 3 6699 (20.7)
3 (750mg IV / 125mg SC)	n = 26 31.9 (42.8)	n = 24 4607 (38.6)
4 (1000mg IV / 125mg SC)	n = 5 14.7 (44.3)	n = 4 2555 (30.1)
5 (1000mg IV / 200mg SC)	n = 5 41.7 (41.2)	n = 5 5849 (40.5)

Source: IM101063 CSR, Supplemental Table S.8.2.3

n = number of subjects, TAU = 7 days

Cmax and AUC(TAU) were calculated between a SC dosing interval from Day 71 to Day 78 profile. The dose determined by IM101063 was then tested in a large SC program including IM101174, the pivotal efficacy study demonstrating non-inferiority of SC to IV including over 1,400 paitents. SC abatacept was approved based on this and other supportive safety studies in 2011.

1.3.3 Overall Safety of Abatacept

The risks that may be associated with the use of abatacept include infections, some of which may be serious or fatal, infusion related reactions, and an increase in respiratory adverse events and infections in patients with chronic pulmonary obstructive disease (COPD). Other potential risks may include the development of malignancies or autoimmune disorders, but an increased risk of these types of events have not been observed. As with the use of any protein therapeutic, antibodies against abatacept (immunogenicity) may develop. The rate of immunogenicity has generally been low and there has not been an apparent effect on safety, efficacy, or pharmacokinetics (PK). A recent **safety analysis of 5 randomized, placebo-controlled double blind abatacept clinical trials** was performed, which included 1955 patients during the double blind period and 2688 during the cumulative double blind and open label periods. The overall

frequencies of adverse events, serious adverse events, and malignancies were similar between the patients receiving abatacept and those in the placebo arms of the studies. Safety data through cumulative exposure showed no evidence of increased incidence of serious infections or malignancies with increasing exposure to abatacept, suggesting an acceptable safety profile in this population (Sibilia and Westhovens 2007). Similar findings supporting its safety in children 6 years and older with juvenile idiopathic arthritis have been reported. A randomized, double-blind placebo controlled trial reported no difference in the frequency of adverse events between the treatment groups during the double-blind period. Furthermore, there were no reports of serious adverse events in the treatment group (Ruperto et al. 2008).

1.3.4 Safety of SC Formulation of Abatacept

SC formulation in adult population

IM101013

In Study IM101013[(ii)] a double-blind, randomized (within dose), placebo-controlled, parallel-group, single-dose study in healthy subjects weighing ≤ 100 kg, single SC doses of abatacept were well-tolerated by healthy adult subjects. There were no deaths, no discontinuations, and no SAEs reported. All AEs were mild to moderate in intensity. In general, there was no difference between the frequency and types of AEs reported by the abatacept (all abatacept groups combined, n = 40) and placebo (all placebo groups combined, n = 8) groups. The most common type of AEs reported by abatacept and placebo subjects were injection site reactions including erythema, swelling, and tenderness. Infections were commonly reported by both the abatacept and placebo groups and were not more common in abatacept-treated subjects than in placebo-treated subjects. One (1) abatacept-treated subject had laboratory abnormalities (increases in alanine aminotransferase and gamma-glutamyl transferase levels) that were considered by the investigator to be clinically significant and were reported as AEs.

Overall, 11 of the 40 subjects (27.5%) developed antibodies to the CTLA4 region of the abatacept molecule, with endpoint titers in healthy subjects followed for 71 days ranging from Day 33 to Day 872. Only 1 of the 11 subjects developed antibodies that had abatacept neutralization activity. The earliest onset of seroconversion was at Day 43 (seen in 1 subject), after approximately 3 to 4 half-lives of abatacept and accounting for over 94% of the drug being eliminated from the vascular system. The presence of an immune response resulted in increased clearance of abatacept from the vascular system. This resulted in a shorter $T_{1/2}$ (range = 3.2 to 7.5 days) compared with the $T_{1/2}$ for subjects who did not exhibit an immune response to abatacept (range = 11.2 to 14.7 days). The incidence rate of seroconversion in subjects receiving a single SC dose of abatacept (27.5%) was higher compared with subjects who discontinued IV abatacept treatment (7.4%) in the Phase 2/3 development program of IV abatacept for RA. The development of immunogenicity did not appear to be associated with adverse safety outcomes; the safety profile of abatacept in subjects with and without an immune response was comparable.

IM101063

Study IM101063, a double-blind, randomized, placebo-controlled, parallel-group, multiple-dose study in subjects with active RA who are on background DMARDs (MTX or MTX plus no more than 1 additional oral DMARD) was designed to evaluate the safety and immunogenicity of several doses of SC abatacept. No deaths were recorded during the short-term 12-week phase of the study. Safety evaluations from the 51 abatacept-treated subjects and 17 placebo-treated subjects showed that abatacept administered by SC injections weekly was safe and well tolerated. The most common infections observed in both abatacept-treated and placebo-treated subjects were upper respiratory and urinary tract infections. There were 7 SAEs (diastolic dysfunction/chest discomfort/dyspnea/COPD/sleep apnea in 1 subject; wound infection in 1 subject; and drug overdose in 1 subject) reported during the short-term phase of the study. All the SAEs were reported to be unrelated or unlikely related to study drug by the investigator. In addition, injection site reactions from the weekly SC injections were uncommon and predominantly mild in intensity. Overall, the safety profile for SC abatacept was observed to be consistent with that for IV abatacept[(iv)].

IM101173

IM101173[(v)], a multi-center open-label study in adults with active RA requiring a new therapeutic intervention, was designed to evaluate SC abatacept in a monotherapy setting and to assess if the use of background MTX influences the development of immunogenicity. An initial IV abatacept loading dose was not given in this study in order to maximize the potential for immunogenicity following SC administration of abatacept. In addition, this study was designed to assess whether the development of immunogenicity following SC abatacept impacted the PK, safety, or effectiveness of the drug. Safety and exploratory efficacy data for subjects treated for 4 months with SC abatacept in Study IM101173 were available.

A total of 100 subjects with RA and requiring a new therapeutic intervention were stratified based on their current MTX use to 4 months of open-label treatment with SC abatacept monotherapy (N = 49) or to SC abatacept in combination with MTX (N = 51). Subjects in both cohorts received weekly SC injections of abatacept 125 mg (dosing irrespective of body weight).

The safety profile for SC abatacept in adults with RA in this study appeared favorable overall. Treatment with SC abatacept 125 mg/week, with or without background MTX, and in the absence of an IV loading dose, was well tolerated by subjects with RA in this study. During the 4-month short-term treatment period, there were no deaths, SAEs assessed as at least possibly related to study treatment were reported in only 2 subjects, and AEs resulted in treatment discontinuation for 4 (4%) subjects. Local injection site reactions, a common finding for SC-injected drugs, were infrequent (7%); all were mild and did not result in treatment discontinuation. Similarly, systemic injection site reactions occurring within 24 hours following SC injection of abatacept were also infrequent (8%) and mostly mild in intensity. One subject experienced angioedema following the initial SC injection of abatacept, which was moderate in intensity, serious and led to treatment discontinuation. The angioedema resolved the same day. The rate of systemic injection reactions with SC abatacept was consistent with the rates of peri-infusional AEs reported for IV abatacept[(vi)].

Consistent with the experience with IV abatacept, infections and infestations were the most commonly reported AEs in subjects receiving SC abatacept (32% in short-term period). Fewer

than 3% of treated subjects had an infection AE(s) that was serious or required discontinuation of abatacept treatment.

In IM101173, one previously un-labelled SAE was reported: severe grade 4 Pneumocystis jiroveci pneumonia[vii]. The subject had been on study for 3 months, receiving 125 mg of abatacept SC once a week and developed bilateral pneumonia with severe respiratory failure. The subject was hospitalized to receive treatment for the infection and severe respiratory failure; the subject recovered and was discharged 1 month later. Safety data frp, IM101174, the large, pivotal efficacy study is consistent with the overall IV experience and with the other SC studies.

1.4 Overall Risk/Benefit Assessment

The efficacy of abatacept in alopecia areata is uncertain and determination of any activity in this disease is the objective of this pilot study. The long term safety profile of abatacept is reassuring and confirms the potential for a favorable positive benefit/risk of abatacept in the treatment of alopecia areata.

Current therapeutic options for Alopecia Areata

There is no FDA approved drug for alopecia areata. A recent Cochrane report (Delamere et al, 2008) concluded that there was no evidenced based support for any intervention in this disease. Standard of care remains observation for mild disease, and lesional/oral steroids for more advanced cases (Alkhalifah et al, 2010a,b). **In our targeted population of moderate-severe alopecia areata placebo response rates have been in the 6-12% range** (Price et al, 2008; Strober et al, 2009). Spontaneous regrowth is extremely rare in patients with alopecia totalis or universalis. Intralesional steroid responses are unpredictable and occur less frequently in subjects with higher disease burdens. This population that suffers from a disfiguring disease represents a significant unmet medical need (Alkhalifah et al, 2010a,b). Evidence-based and steroid-sparing interventions are needed.

Use of subcutaneous Abatacept carries potential risks, including treatment-associated infection and injection site reactions. **Alopecia areata patients as a whole are young (median age 23-30) and otherwise healthy, which should mitigate risk of adverse effects.** The target population in this proposed study is subjects with greater than 30% hair loss is unusually extensive disease, affecting fewer than 30% of all alopecia subjects, with disfiguring consequences and severe psychosocial morbidity. Although AA does not cause physical pain, several studies have noted that AA seriously impairs quality of life (QoL), mainly by altering self-perception and self-esteem, both of which interfere with social life. **Because AA is chronic, visible to others, and often difficult to treat, its impact on quality of life is underappreciated (Bickers et al, 2006; Hanan et al, 2008; Dubois et al, 2010)** and comparable to psoriasis (Bickers et al, 2006). Patient advocacy groups, including National Alopecia Areata Foundation have developed an active disease registry of over 10,000 subjects to document the impact on quality of life and encourage clinical investigation in this disease.

1.5 Study Rationale

Alopecia areata is a prevalent disease with high unmet need with significant psychosocial morbidity and no current evidence-based treatments. Preclinical studies have set the stage for evaluation of abatacept in alopecia areata. Importantly, CTLA4-Ig prevents disease onset in the C3H-HeJ mouse model. Furthermore based on our GWAS studies (Petukhova et al, 2010) and an independent replication study (John et al, 2011), we know that CTLA4 is relevant in human AA. Based on this clear rationale and the relative safety of abatacept in this young, otherwise-healthy motivated population, we propose an exploratory pilot study to evaluate abatacept as a therapeutic in AA.

To our knowledge, abatacept has never been examined in human AA. Specifically, we propose an exploratory trial using weekly fixed dose of SC abatacept to establish initial efficacy data in 15 subjects with moderate-severe AA. This initial clinical experience with abatacept, if positive, would provide the basis for considering and designing subsequent larger and appropriately powered RCTs.

The study proposed here targets the identical moderate-severe AA patient population as two other preceding RCT studies that also evaluated therapeutic effects of immune biologics (alefacept and efalizumab) (Price et al, 2008; Strober et al, 2009). Moderate-to-severe AA carries significant psychosocial burden and is likely a much more reversible disease process than AA totalis/universalis.

Prior interventional trials in AA have been criticized for inclusion of a heterogeneous participant population with wide disease severity and duration (Delamere et al, 2008). To overcome these sources of patient heterogeneity:

1. Patients who currently have alopecia totalis or universalis (AT/AU) were initially excluded in this pilot study since their response rate was expected to be lower. Patients with alopecia totalis/universalis can be included if the current episode of hair loss meets the criteria of 30 to 95% hair loss (i.e. they may have had a previous episode of AT or AU which demonstrated regrowth of hair, and they are not currently AT or AU), and as long as in the opinion of the investigator there does appear to be potential for regrowth. Based on the early promising results seen to date in our treatment of moderate-severe patch type AA with ruxolitinib, we will enroll at the investigator's discretion 2 to 5 patients with current AT/AU to preliminarily explore the effect of abatacept in these most severe cases of AA.

2. Patients with mild disease are excluded since natural remission is considerably more likely in the early stages of disease or in mild disease (involving less than 25% hair loss) where spontaneous successful regrowth has been reported in up to 50% of individuals[34]. In more extensive disease, remissions are less likely and are usually restricted to incomplete hair regrowth involving a minority of scalp areas. **Thus to minimize placebo response rates this study is specifically**

focused on subjects with moderate to severe alopecia areata with greater than 30% hair loss and disease duration greater than 3 months.

We have adopted the following study plan to identify a treatment "signal" in alopecia areata: The standard dosing schedule of SC abatacept of 125mg per week used in rheumatoid arthritis treatment will also be used here to treat moderate and severe alopecia areata for a period of 6 months. Treatment may be extended by up to an additional 6 months beyond the initial 6 months of treatment if clinically indicated at the discretion of the investigator.

2 STUDY OBJECTIVES

2.1 Primary Objective

The study's *primary efficacy endpoint* will be the proportion of responders after 6 months of treatment, with response defined as 50% or greater hair re-growth from baseline as assessed by SALT score (Olsen et al, 1999) at week 24. This is a relatively strict definition for defining responders and non-responders and was chosen to minimize the potential for spontaneous remission, in which fewer than 10% are expected to achieve this magnitude of hair regrowth spontaneously. To assess the durability of responses, patients who achieve 50% regrowth from baseline during the first 6 months, will continue to be followed for an additional 6 months off treatment or until it is determined that relapse has occurred

2.2 Secondary Objectives

As secondary endpoints, efficacy will be measured by changes in hair re-growth as a continuous variable as determined by physical exam and Canfield photography, as well as patient and physician global evaluation scores. To assess the durability of responses, patients will continue to be followed for an additional 6 months off treatment. The occurrence of adverse events will also be captured as a secondary endpoint.

Secondary efficacy outcomes in detail

1. Percent hair regrowth from baseline determined by SALT measurements following 24 weeks of treatment, up to an optional 48 weeks of treatment at the discretion of the investigator, and during the 6 month period following discontinuation of treatment.
2. Comparison of the proportion of responders in the experimental group with the historically known placebo response rate, with response defined as 50% change in SALT score (50% regrowth) from baseline, at the end of treatment (at week 24, optional treatment up to week 48, as well as any endpoint between the end of treatment and 6 months after end of treatment, as applicable), and the end of the follow up period 6 months after discontinuation of treatment (week 48, optional end of study up to week 72).
3. Comparison of the proportion of subjects in the experimental group and the proportion of subjects in the historical control group attaining global overall improvement SALT score

of A5 (100% coverage) supported by </= SALT 25 at weeks 12, 24, 36 and 48; optional up to weeks 30, 36, 42, 48, 60, 72 for subjects getting optional additional treatment beyond initial 6 months of treatment, at the discretion of the investigator.

4. Change in PGA (Physician Global Assessment) based on evaluation of live evaluations and standardized photographs between baseline, week 12, 24, 36 and 48; up to week 72 for subjects receiving optional additional treatment.
5. Differences in the incidence of regrowth between patients with patch type AA vs patients with alopecia totalis or universalis will also be analyzed on an exploratory basis.
6. Response to abatacept treatment will be examined on an exploratory basis for correlation with the presence or absence of the AA GWAS risk haplotype.
7. Change in patient global assessment between baseline, Week 12, 24, 36 and 48; up to week 72 for subjects receiving optional additional treatment.
8. Change in patient quality of life assessment from baseline to weeks 12, 24, 36 and 48; up to week 72 for subjects receiving optional additional treatment.
9. Frequency of occurrence and timing of relapse (as defined above) in responders followed for 6 months off therapy.
10. Safety will be assessed by summarizing the incidence and type of AEs. The proportion of patients who discontinued treatment will be summarized.

3 ETHICAL CONSIDERATIONS

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

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

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

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

3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g, advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB/IEC with reports, updates, and other information (e.g, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.3 Informed Consent

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

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

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

Screening
A complete medical history will be taken. Patients will be screened for pre-existing renal (basic metabolic and urine analysis), hematologic (CBC with differential and reticulocytes) or hepatic dysfunction or COPD; lipid panel; prior exposure to tuberculosis (PPD and CXR) or hepatitis; pregnancy tests will be done in women of childbearing potential.

Assessments: Baseline assessments of disease severity will be done. This will include SALT score (Severity of Alopecia Tool, Addendum 1), Physician global assessment (PGA), patient global assessment and patient quality of life assessment. In order to minimize or eliminate inter-rater variability, every effort will be made to have the same investigator evaluate an individual subject at each visit. Whenever possible the same investigator (the PI or her designee) will examine the patient's scalp, determine the SALT score, and grade the photographic images.

Visit Schedule and Assessments
Screening assessments and all scheduled study visits are outlined in the Table of Study

Assessments

Baseline to Week 24 (period on study medication)

Patients will be seen at baseline, and at weeks 4, 8, 12, 18 and 24 weeks. Assessments of disease severity will be conducted including SALT (Severity of Alopecia Tool[Addendum2 26])[36], Physician global assessment (PGA) at weeks 4,8,12, 18, 24, 36, and 48, and patient global assessment and patient quality of life assessment at weeks 0, 12, 24, 36, and 48. Patients receiving optional additional treatment, at the discretion of the investigator, will continue to be seen every 6 weeks after week 24 while on treatment.

PGA and patient evaluations will be based on similar 100mm visual analog scales with 0 labeled as no scalp hair loss and 100 labeled as complete scalp hair loss. Patients and physicians will place a vertical mark along the horizontal line depending on their assessment of the degree of hair loss present at the time of assessment.

Patient quality of life assessments will be based on changes in the Dermatology Life Quality Index DLQI (Finlay et al, 2004), which we have previously used for patient evaluation in the AA registry.

Photography will be performed at every scheduled visit; skin biopsies will be performed at baseline and weeks 4, 12 and 24; blood draws for safety parameters and immune studies will be done based on the attached table of study procedures.

Patients will be instructed in study medication administration at baseline (week zero) and will be observed self-administering medication at each visit. Instructions regarding study drug administration will be reinforced as needed. Study medication will be evaluated in order to assess compliance and medication will be dispensed as needed.

Additional biopsies and blood draws may be obtained as clinically indicated. Since the timeline to regrowth may vary from subject to subject, unscheduled biopsies and blood draws will insure that tissue and blood samples are obtained at optimal time points to evaluate the changes occurring at the onset of growth or in the event of any unexpected clinical change. In addition, areas that are resistant to treatment may be biopsied to determine the cellular and immunologic differences of those areas compared to areas that are responding to treatment. The patient will be given the option to agree to, or decline, the additional biopsies and blood draws.

Adverse events will be assessed at every visit.

Week 25 to 48 (follow-up period off study medication)

All patients will be seen at week 36 and 48, after completion of 6 months of study drug, to determine durability of response or evidence for a delayed effect. Importantly patients who achieved >or = 50% regrowth as measured by SALT score (responders) will be seen at week 36,

and 48 after end of study treatment in order to assess the frequency and timing of relapse or to capture the occurrence of further regrowth.

Relapse will be defined as any recurrence of hair loss in responders (subjects achieving greater than 50% decrease in SALT score from baseline during the first 6 months of the study) who had achieved stable regrowth without continued loss for at least 2 months; and loss of >/= 25% of regrowth in patients who had achieved 50% regrowth during treatment but still had chronic low grade hair loss.

Nonresponders will also continue follow-up in order to assess for delayed response.

Efficacy evaluations: SALT, PGA, Patient global assessment and patient quality of life assessment will be performed at Weeks 36, and 48.

Blood draws for safety parameters will be conducted at week 30 if deemed necessary to assess normalization of any previously abnormal values.

Week 25 up to 72 (for subjects receiving optional additional treatment extension)

Patient receiving an optional additional treatment extension of up to 6 months, at the discretion of the investigator, will continue to be seen every 6 weeks after week 24 while on the study medication, then at 12 weeks and 24 weeks after completion of up to 12 months of study drug, to determine durability or response or evidence for a delayed effects.

Efficacy evaluations: SALT, PGA, Patient global assessment and patient quality of life assessment will continued to be performed at every visit during optional additional treatment extension.

Blood draws for safety parameters will be conducted at 12 weeks after completion of study drug if deemed necessary to assess normalization of any previously abnormal values.

Adverse events will be assessed at every visit.

Standardized photographs of the subject's scalp will be done at every scheduled visit and will be used to support determination of percent hair regrowth. Photography will be performed using a high-resolution digital camera with Intellistudio system from Canfield Scientific, Inc. Patients will be positioned using a laser guide, after which photographs of the entire scalp will be taken at standardized locations and at a fixed distance. Close-up photographs may also be taken using an epiluminescent attachment in order to assess for the presence of early regrowth.

Unscheduled Visits

An unscheduled visit can occur at any time during the study for instance as prompted by signs of infection or local injection site reactions. A source document must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on the appropriate CRF. At treatment discontinuation/early termination subjects will undergo end off study evaluations per the Schedule of Assessments.

Telephone contact/retention

Patients will be contacted on a monthly basis, between the planned study visits at weeks 36 and 48, in the observational phase (Weeks 25 to 48, up to Week 72 for subjects receiving treatment extension) of the study to ascertain the occurrence of adverse events as well as to assess the status of hair growth or loss.

Any concerns or questions the patient may have will also be addressed. If deemed necessary, the subject may be asked to come in for an unscheduled visit.

Duration of Treatment

After the screening period, subjects will begin weekly self-administered subcutaneous abatacept and will continue treatment for 6 months. Patients will be instructed in self-administration of study medication at baseline (week zero) and will be observed self-administering medication at each visit. Instructions regarding study drug administration will be reinforced as needed.
The 6-month treatment period is expected to provide adequate time to assess the short-term efficacy and safety of abatacept in patients with moderate to severe AAP. Responders will then be followed for 6 months off drug.

Treatment may be extended by up to an additional 6 months beyond the initial 6 months of treatment if clinically indicated at the discretion of the investigator.

4.2 Study Population

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

4.2.1 Inclusion Criteria

1) **Signed Written Informed Consent**
   Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read.

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

2) Must be between 18 and 75 years of age.
3) Must have a diagnosis of moderate to severe AA - defined as the presence of equal to or more than 30% and equal to or less than 95% total scalp hair loss at baseline as measured using the SALT score. Five patients with current alopecia totalis/universalis may be included in this study at the investigator's discretion.
4) Duration of hair loss greater than 3 months without an upper limit of duration as long as there is reason to believe that regrowth is possible in the opinion of the investigator.
5) No evidence of active, ongoing regrowth present at baseline.
6) Patients with alopecia totalis/universalis can be included as long as the current episode of hair loss meets the criteria of 30 to 95% hair loss (i.e. they may have had a previous episode of AT or AU which demonstrated regrowth of hair, and they are not currently AT or AU), and as long as in the opinion of the investigator there does appear to be potential for regrowth. two to five patients with current episodes of alopecia totalis/universalis may be included in this study at the investigator's discretion.
7) Subjects may be naïve to treatment or unresponsive to intralesional (IL) steroids or other treatments for AA.
8) Must be willing to avoid live vaccines while on the study medication, and within 3 months of its discontinuation.
9) Women of childbearing potential (WOCBP) must use highly effective methods of birth control [for up to 12 weeks after the last dose of investigational product] to minimize the risk of pregnancy]. WOCBP must follow instructions for birth control for the entire duration of the study including a minimum of 90 days after dosing has been completed.
    a. Acceptable methods of highly effective birth control include:
        i. Condom with spermicide
        ii. Diaphragm and spermicide
        iii. Cervical cap and spermicide
    b. The use of intrauterine devices, (IUDs) shall be at the discretion of the investigator.
    c. Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.
    d. Women must not be breastfeeding
10) Sexually active fertile men must use highly effective birth control if their partners are WOCBP. Men that are sexually active with WOCBP must follow instructions for birth control for the entire duration of the study and a minimum of 90 days after dosing has been completed.

4.2.2 Exclusion Criteria

1) **Sex and Reproductive Status**

a. WOCBP who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for up to 10 weeks after the last dose of study drug.
b. WOCBP using a prohibited contraceptive method.
c. Women who are pregnant or breastfeeding.
d. Women with a positive pregnancy test on enrollment or before administration of abatacept.
e. Sexually active fertile men not using effective birth control if their partners are WOCBP.

2) **Target Disease Exceptions**
   a. Two to five patients with current alopecia totalis/universalis at the time of enrollment (i.e. 100% scalp or 100% scalp and body loss, respectively) may be enrolled. The remaining patients most must have 30 to 95% hair loss due to alopecia areata.
   b. Patients with a history of or active skin disease on the scalp such as psoriasis or seborrheic dermatitis.
   c. Patients in whom the diagnosis of alopecia areata is in question.
   d. Patients with active medical conditions or malignancies (except adequately treated basal or squamous cell carcinoma) that in the opinion of the investigator would increase the risks associated with study participation, including patients with a history of recurrent infections.
   e. Patients with COPD
   f. Patients known to be HIV or hepatitis B or C positive.
   g. Patients with history or evidence of hematopoietic abnormality.
   h. Patients with history of immunosuppression or history of recurrent serious infections.
   i. Patients unwilling or unable to discontinue treatments known to affect hair regrowth in AA

3) **Coexisting disease or concurrent medications**
   a. Patients taking TNF antagonists or other biological therapy such as anakinra.
   b. Patients known to be HIV or hepatitis B or C positive.
   c. Patients with evidence of infection or active/untreated skin cancer.
   d. Patients who have been treated with intralesional steroids, systemic steroids, anthralin, squaric acid, DPCP (diphenylcycloprophenone), protopic, minoxidil or other medication which in the opinion of the investigator may affect hair regrowth within one month of the baseline visit.

e. Subjects who are impaired, incapacitated, or incapable of completing study-related assessments.
f. Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease, which, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study.
g. Female subjects who have had a breast cancer screening that is suspicious for malignancy and in whom the possibility of malignancy cannot be reasonably excluded by additional clinical, laboratory, or other diagnostic evaluations.
h. Subjects with a history of cancer in the last 5 years, other than non-melanoma skin cancers cured by local resection or carcinoma in situ. Existing non-melanoma skin cancers should be removed, the lesion site healed, and residual cancer ruled out before administration of the study drug.
i. Subjects who currently abuse drugs or alcohol.
j. Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral infections at the time of potential enrollment, including subjects with evidence of human immunodeficiency virus (HIV) detected during screening.
k. Subjects with herpes zoster or cytomegalovirus (CMV) that resolved less than 2 months before the informed consent document was signed.
l. Subjects who have received any live vaccines within 3 months of the anticipated first dose of study medication.
m. Subjects with any serious bacterial infection within the last 3 months, unless treated and resolved with antibiotics, or any chronic bacterial infection (eg, chronic pyelonephritis, osteomyelitis, or bronchiectasis).
n. Subjects at risk for tuberculosis (TB). Specifically excluded from this study will be subjects with a history of active TB within the last 3 years, even if it was treated; a history of active TB greater than 3 years ago, unless there is documentation that the prior anti-TB treatment was appropriate in duration and type; current clinical, radiographic, or laboratory evidence of active TB; and latent TB that was not successfully treated (≥ 4 weeks).

4) **Physical and Laboratory Test Findings**
   a. Subjects must not be positive for HIV, hepatitis B or C.
   b. Subjects who are positive for hepatitis C antibody if the presence of hepatitis C virus was also shown with polymerase chain reaction or recombinant immunoblot assay.
   c. Subjects with any of the following laboratory values

i. Hemoglobin < 10.0 g/dL
ii. WBC < 3500/mm^3 (< 3 x 109/L)
iii. Platelets < 120,000/mm^3 (< 3 x 109/L)
iv. Serum creatinine > 2 times the ULN
v. Serum ALT or AST > 2 times the ULN
vi. Any other laboratory test results that, in the opinion of the investigator, might place a subject at unacceptable risk for participation in the study.

5) **Prohibited Treatments and/or Therapies**
   a. Subjects who have at any time received treatment with any investigational drug within 28 days (or less than 5 terminal half-lives of elimination) of the Day 1 dose.
   b. Any concomitant biologic DMARD, such as anakinra.
   c. Subjects who have been treated with intralesional steroids, systemic steroids, anthralin, squaric acid, DPCP (diphenylcycloprophenone), protopic, minoxidil or other medication which in the opinion of the investigator may affect hair regrowth within one month of the baseline visit.
6) **Other Exclusion Criteria**
   a. Prisoners or subjects who are involuntarily incarcerated.
   b. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

4.2.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), and who is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or
  NOTE: FSH level testing is not required for women ≥ 62 years old with amenorrhea of ≥ 1 year
- Women on hormone replacement therapy (HRT)

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

Not Applicable.

4.3 Concomitant Treatments

4.3.1 Prohibited and/or Restricted Treatments

Any medication known to affect hair growth in Alopecia areata including but not limited to topical, intralesional or systemic steroids, squaric acid, anthralin, protopic, minoxidil, diphenylcyclopropenone, cyclosporine and any other medications, which in the judgment of the investigator, may affect hair growth in patients with alopecia areata.

4.3.2 Other Restrictions and Precautions

Not applicable.

4.4 Discontinuation of Subjects from Treatment

Subjects MUST discontinue study treatment and withdraw from the study for any of the following reasons:

Withdrawal of informed consent (subject's decision to withdraw for any reason)

Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

Pregnancy

- Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
- The investigator must immediately notify BMS if a study subject becomes pregnant. The mechanism for reporting pregnancy is described in Section 7.6.

Termination of the study by BMS.

Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

5 TREATMENTS

5.1 Study Treatment: Abatacept

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

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care are considered noninvestigational products.

5.1.1 Identification

Abatacept Injection, 125 mg/Syringe (125 mg/mL), is a sterile solution for SC administration, which contains approximately 126 mg abatacept, 171 mg sucrose, 8 mg Poloxamer 188, 0.28 mg monobasic sodium phosphate, monohydrate, and 0.84 mg dibasic sodium phosphate, anhydrous, in Water for Injection. It is packaged in 1 mL long glass syringe barrel staked with a 29 gauge stainless steel needle and stoppered with a 7.1 mm rubber stopper. The composition of this solution has a ratio of monobasic sodium phosphate, monohydrate, and dibasic sodium phosphate, anhydrous, used to achieve the target pH of 7.2.

5.1.2 Storage, Handling, and Dispensing

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

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

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

be inspected visually for particulate matter prior to administration. Refer to the Investigator Brochure for additional information regarding handling, preparation, and storage of abatacept.

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

Abatacept injection, 125 mg/syringe (125 mg/mL) for SC administration are ready to use solutions provided in pre-filled siliconized syringes with a 29 gauge needle. No special drug preparation is required prior to administering to patients. A sufficient amount of abatacept solution is incorporated into each syringe so that 1 ml of solution will be administered upon administration.

Abatacept SC formulations (prefilled syringes) should be stored under refrigeration (approximately 2 to 8°C) and protected from long-term (more than 24 hours) exposure to light. Do not freeze.

Additional information on the use of the abatacept combination product is found in the Appendix.

5.2 Method of Assigning Subjects to a Treatment

This will be an open label study. All subjects will receive active drug for the duration of the 6 month treatment period.

5.3 Selection and Timing of Dose for Each Subject

Patients will be treated with abatacept 125mg SC self-administered each week. Treatment will be continued for 6 months to provide adequate time to assess the short-term efficacy and safety of abatacept in patients with alopecia areata. Patients will then be followed for an additional 6 months to assess the timing and incidence of relapse.

5.3.1 Dose Modifications for Adverse Events

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

5.4 Blinding/Unblinding

Not applicable.

5.5 Concomitant Treatments

5.5.1 Prohibited and/or Restricted Treatments

The following medications are prohibited throughout the complete study period:

Any medications known to affect hair growth in alopecia areata including but not limited to topical, intralesional or systemic steroids, anthralin, squaric acid, diphenylcyclopropenone, protopic, cyclosporine or any other medications which in the opinion of the investigator may affect hair growth in AA.

Live vaccines.

Use of any investigational drug other than study medication.

Corticosteroid use at unstable dose and/or superior to the equivalent of prednisone 10 mg/day is not permitted.

5.5.2 Other Restrictions and Precautions

5.5.2.1 Immunizations

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

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

Committee on Immunization Practices (CDC-ACIP) recommends that subjects should not be administered a live virus vaccination for at least 3 months after discontinuing high-dose corticosteroid therapy (defined as more than 20 mg of prednisone per day for more than 2 weeks). In view of the long half-life of abatacept, study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of abatacept.

5.6 Treatment Compliance

Compliance will be documented via the use of patient diaries to record the date and time of self-administration of medication at home. Study drug reconciliation will be performed at each visit during the treatment period.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Time and Events Schedule

The Time and Events Schedule (Section 6, Table 3) summarizes the frequency and timing of various measurements.

Pre-screening procedures
Written informed consent will be obtained for this study by the principal investigator or his/her designee from all patients prior to any protocol-specific procedures. The study will be conducted in accordance with the Food and Drug Administration (FDA) approved revision of the Declaration of Helsinki, current FDA regulations, and International Conference on Harmonization (ICH) guidelines.

Procedures Performed Prior to Treatment Screening (Day -28 to -1):
The following screening evaluations will be performed within 4 weeks prior to enrollment:

- Informed consent, inclusion/exclusion criteria, prior concomitant medications
- Medical history, physical examination, including a dermatological exam
- Vital signs, body weight
- Assessments of disease severity will be conducted including SALT (Severity of Alopecia Tool)
- Physician's global assessment (PGA)
- Clinical laboratory evaluation (complete blood count, basic metabolic profile, hepatic panel and urinalysis), hepatitis B and C screening panel, HIV test, lipid profile, serum pregnancy test
- Tuberculosis testing (PPD skin test or quantiferon test)
- Chest X ray

A visit will be scheduled 48-72 hours after placement of the PPD for reading of the test results. If possible, this visit will be combined with the baseline visit. The results of all assessments/tests listed above must be reviewed prior to enrollment to ensure that the patient meets entry criteria and that no exclusion criteria are present.

Baseline (Day 0) Procedures Performed Prior to treatment

- Review of inclusion/exclusion criteria
- Vital signs, body weight
- Adverse events reporting, concomitant medication review
- Photography
- Physician evaluation utilizing the PGA and SALT scale
- Patient global assessment and quality of life assessment
- Urine pregnancy testing for WOCBP

- Blood collection for immunological studies including assessment of presence or absence of AA GWAS risk haplotype
- Scalp biopsy (4mm punch biopsy)
- Training of subject in Subcutaneous administration of medication followed by observed patient self-administration of medication

Weeks 4, 8, and 12 (Days 28, 56 and 84)

Visit days will have an acceptable window of ±3 day.

- Vital signs, body weight
- Adverse events reporting, concomitant medication review
- Photography
- Physician evaluation utilizing the PGA and SALT scale
- Patient global assessment and quality of life assessment (week 12 only)
- Urine pregnancy testing for WOCBP
- Physical and dermatological examination (week 12 only)
- Clinical laboratory evaluation (only weeks 4 and 12)
- Scalp biopsy (4mm punch biopsy) (only weeks 4 and 12)
- Blood collection for immunological studies (only weeks 4 and 12)
- Optional Scalp biopsy (4mm punch biopsy) in addition to weeks 4 and 12 – at the discretion of the investigator and with the consent of the subject, based upon perceived utility in context of individual patient response to therapy and durability of that response.
- Optional Blood collection for immunological studies in addition to weeks 4 and 12, at the discretion of the investigator and with the consent of the subject.
- Training/reinforcement of training for self-administered SQ injection
- Patient observed self-administering study medication

Week 18 (Day 126±1)

- Vital signs, body weight
- Adverse events reporting, concomitant medication review
- Photography
- Physician evaluation utilizing the PGA and SALT scale
- Urine pregnancy testing for WOCBP
- Optional Scalp biopsy (4mm punch biopsy) - at the discretion of the principal investigator and with the consent of the subject, based upon perceived utility in context of individual patient response to therapy.
- Optional Blood collection for immunological studies, at the discretion of the principal investigator and with the consent of the subject.
- Training/reinforcement of training for self-administered SQ injection
- Patient observed self-administering study medication

Week 24 (Day 168±7) – End of Treatment

- Vital signs, body weight
- Physical and dermatological examination
- Adverse events reporting, concomitant medication review
- Photography
- Physician evaluation utilizing the PGA and SALT scale
- Patient global assessment and quality of life assessment
- Urine pregnancy testing for WOCBP
- Clinical laboratory evaluation
- Scalp biopsy (4mm punch biopsy)
- Blood collection for immunological studies

Weeks 36 and 48 (Days 252 and 336 ±7 days) – Observational Period

- Vital signs, body weight
- Physical and dermatological examination (only week 48)
- Adverse events reporting, concomitant medication review
- Photography
- Physician evaluation utilizing the PGA and SALT scale
- Patient global assessment and quality of life assessment
- Optional Scalp biopsy (4mm punch biopsy) – at the discretion of the principal investigator and with the consent of the subject, based upon perceived utility in context of individual patient response to therapy and durability of that response.
- Optional Blood collection for immunological studies, at the discretion of the principal investigator and with the consent of the subject.

Weeks 30, 36, 42, 48 (Extension Option)

Visit days will have an acceptable window of ±7 days.

- Vital signs, body weight
- Adverse events reporting, concomitant medication review
- Photography
- Physician evaluation utilizing the PGA and SALT scale
- Patient global assessment and quality of life assessment
- Urine pregnancy testing for WOCBP
- Physical and dermatological examination (week 36)
- Clinical laboratory evaluation, if indicated (at 12 weeks after end of study treatment)
- Optional Scalp biopsy (4mm punch biopsy) – at the discretion of the investigator and with the consent of the subject, based upon perceived utility in context of individual patient response to therapy and durability of that response.
- Optional Blood collection for immunological studies in addition to weeks 4 and 12, at the discretion of the investigator and with the consent of the subject.

Weeks 40 to 72 (Observational Period after Extension Option)

Visit days will have an acceptable window of ±7 days.

- Patient will be observed at 12 and 24 weeks after completing study medication
- Vital signs, body weight
- Physical and dermatological examination (at end of study)
- Adverse events reporting, concomitant medication review
- Photography
- Physician evaluation utilizing the PGA and SALT scale
- Patient global assessment and quality of life assessment
- Optional Scalp biopsy (4mm punch biopsy) – at the discretion of the principal investigator and with the consent of the subject, based upon perceived utility in context of individual patient response to therapy and durability of that response.
- Optional Blood collection for immunological studies, at the discretion of the principal investigator and with the consent of the subject.

Early Termination

- Vital signs, body weight
- Physical and dermatological examination
- Adverse events reporting, concomitant medication review
- Photography
- Physician evaluation utilizing the PGA and SALT scale
- Patient global assessment and quality of life assessment
- Clinical laboratory evaluation
- Optional Scalp biopsy (4mm punch biopsy) - at the discretion of the principal investigator and with the consent of the subject, based upon perceived utility in context of individual patient response to therapy.
- Optional Blood collection for immunological studies, at the discretion of the principal investigator and with the consent of the subject.
- The reason for early withdrawal/study drug discontinuation must be documented

Unscheduled Visits

An unscheduled visit can occur at any time during the study. A source document must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on the appropriate CRF. At treatment discontinuation/early termination subjects will undergo study evaluations per the Schedule of Assessments.

Duration of Treatment

Treatment will be continued for 6 months to provide adequate time to assess the short-term efficacy and safety of abatacept in patients with alopecia areata. Patients will then be followed for an additional 6 months to assess the timing and incidence of relapse of AA.

6.1.1 Study Completion or Early Discontinuation Visit

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

6.1.2 Study Drug Discontinuation

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

Table 3: Schedule of Assessments

Visit	Screening	PPD reading	Base-line	Week 4	Week 8	Week 12	Week 18	Week 24/ET	Week 30, 36, 42, 48 (optional)	12 Weeks after end tx	24 Weeks after end tx
Day	-28 to -1		0	28±1	56±1	84±1	126±1	168±7			
Informed Consent	X										
Inclusion/Exclusion Criteria	X		X								
Medical History	X										
Body Weight	X		X	X	X	X	X	X	X	X	X
Physical/Cutaneous Exam	X					X		X			X
Vital Signs	X		X	X	X	X	X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X
Photography			X	X	X	X	X	X	X	X	X
SALT evaluation	X		X	X	X	X	X	X	X	X	X
Physician global assessment	X		X	X	X	X	X	X	X	X	X
Patient quality of life assessment			X			X		X	X	X	X
Patient global assessment			X			X		X	X	X	X
Clinical laboratory evaluation*	X			X		X		X	X		
Hepatitis screening panel, HIV test	X										
Lipid Profile	X										
PPD test and reading	X	X									
Serum pregnancy test	X										
Urine pregnancy test			X	X	X	X	X	X	X		
Scalp Biopsy			X	X	(X)[c]	X	(X)[c]	X	(X)[c]	(X)[c]	(X)[c]
Phlebotomy for immunological studies			X[d]	X	(X)[c]	X	(X)[c]	X	(X)[c]	(X)[c]	(X)[c]
Training/reinforcement of training for self-administered SQ injection Patient observed self-administering study medication			X[b]	X	X	X	X	X	X		
Chest X ray-1 view	X										

[a]Clinical laboratory evaluation consists of CBC, BMP, hepatic panel, and urinalysis. Additional evaluations will only be performed if needed to verify normalization of previously abnormal lab values.
[b]Baseline dose will be subcutaneous administration of abatacept.
[c] Optional additional Scalp biopsies (4mm punch biopsy) may be performed at the discretion of the investigator and with the consent of the subject, based upon perceived utility in context of individual patient response to therapy and durability of that response. Optional Blood collection for immunological may be performed at the discretion of the investigator and with the consent of the subject.
[d] Includes testing for AA GWAS risk haplotype

6.2 Study Materials

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

6.3 Safety Assessments

Analysis of safety is included as a secondary endpoint. All subjects who receive a dose of abatacept will be evaluated for safety. Safety outcomes include adverse events, clinically significant changes in vital signs, laboratory test abnormalities, and clinical tolerability of the drug. The investigator will determine the severity of each adverse event as mild, moderate, severe, or very severe. Laboratory findings that the investigator feels are clinically relevant should be recorded as adverse events. In addition, the investigator will determine the relationship of the adverse event to the administration of the study drug. Any occurrence of a SAE from time of consent forward, up to and including follow-up visits will be reported. See Section 6.5 for the SAE reporting procedures.

6.3.1 Physical Examinations

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

6.3.2 Tuberculin Skin Testing

A tuberculin skin test (PPD test: purified protein derivative tuberculosis skin test) should be performed and interpreted according to the applicable local Health Authority and/or Medical Society guidelines (those that provide recommendations for tuberculin skin testing for subjects who are to receive biologics, who are immunosuppressed, who have a prior history of BCG

vaccinations[viii,ix],or who have a prior positive test). Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG.

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

6.4 Efficacy Assessments

6.4.1 Primary Efficacy Assessment

The study's *primary efficacy endpoint* will be the proportion of responders after 6 months of treatment, with response defined as 50% or greater hair re-growth from baseline as assessed by SALT score (Figure 6) at week 24. Treatment may be extended by up to an additional 6 months beyond the initial 6 months of treatment if clinically indicated at the discretion of the investigator.

This is a relatively strict definition for defining responders and non-responders and was chosen to minimize the potential for spontaneous remission, in which fewer than 10% are expected to achieve this magnitude of hair regrowth spontaneously.

SALT – Severity of Alopecia Tool

A. The proportion of scalp involvement is determined by dividing the scalp into 4 quadrants and estimating the percentage of the scalp surface that all the alopecic areas would occupy if placed together. The following groups will be used:

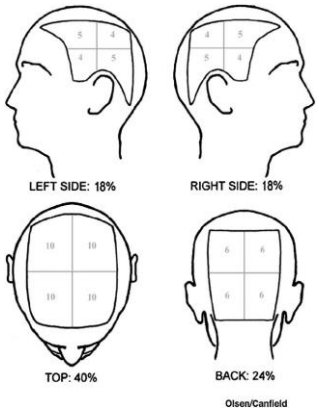
S: Scalp hair loss

_____S0 = No hair loss
_____S1 = ≤25% hair loss
_____S2 = 26%-50% hair loss
_____S3 = 51%-75% hair loss
_____S4 = 76%-99% hair loss
_____a = 76%-95% hair loss
_____b = 96%-99% hair loss
_____S5 = 100% hair loss

Body hair loss
B0 = No body hair loss
B1 = some body hair loss
B2 = total (100%) body hair loss

Nail involvement
N0 = No nail involvement
N1 = some nail dystrophy
N1a = 20 nail dystrophy

Percentage change from baseline (% regrowth) =
[(SALT BL – SALT F/U)/ SALT BL] x 100% = % change from baseline
Absolute regrowth = SALT BL – SALT F/U = absolute change from BL



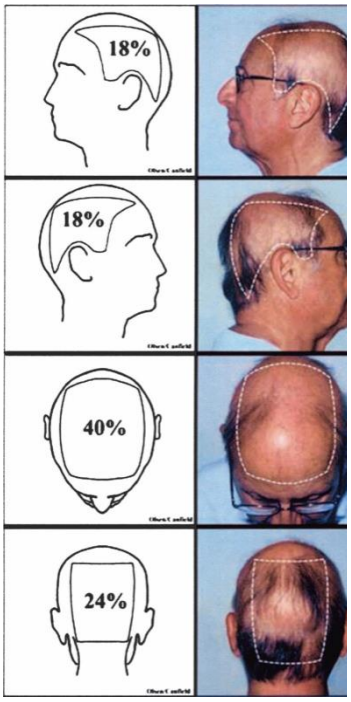


Figure 6. SALT score. The percentage of hair loss in any one of the four views (areas) of the scalp = the percentage hair loss x percent surface area of the scalp in that area. The SALT score then equals the sum of the scalp hair loss in each area.

(a) Top (left side view) = 95% x .18 = 17.1

(b) Second (right side view) = 90% x .18 = 16.2

(c) Third (top of scalp) = 95% x .40 = 38 (realizing that most of hair loss is probably male pattern hair loss)

6.4.2 Secondary Efficacy Assessments

As secondary endpoints, efficacy will be measured by changes in hair re-growth as a continuous variable as determined by physical exam and Canfield photography, as well as patient and physician global evaluation scores. To assess the durability of responses, patients will continue to be followed for an additional 6 months off treatment. To assess the durability of response and the incidence of relapse, patients who achieve 50% regrowth from baseline (50% reduction in baseline SALT score) will continue to be followed for an additional 6 months off treatment or until it is determined that relapse has occurred. Relapse will be defined as any

recurrence of hair loss in responders (subjects achieving greater than 50% decrease in SALT score from baseline during the first 6 mths of the study) who had achieved stable regrowth without continued loss for at least 2 mths; and loss of >/= 25% of regrowth in patients who had achieved 50% regrowth during treatment but still had chronic low grade hair loss. Nonresponders to 6 months study treatment (defined as failure to achieve 50% improvement in SALT score compared to baseline) will not be required to participate in the 6mth follow-up period.. Partial responders will continue to be followed to assess for delayed achievement of complete response. Analysis of safety is included as a secondary endpoint. All subjects who receive a dose of abatacept will be evaluated for safety.

Secondary efficacy outcomes in detail

1. Percent hair regrowth from baseline determined by SALT measurements following 12, 24 weeks of treatment and during the observational phase at weeks 36 and 48.
2. Comparison of the proportion of responders in the experimental group with the historically known placebo response rate (<10%), with response defined as 50% change in SALT score (50% regrowth) from baseline, at weeks 12, 36 and 48.
3. Comparison of the proportion of subjects in the experimental group and the proportion of subjects in the historical control group attaining global overall improvement SALT score of A5 (100% coverage) supported by </= SALT 25 at weeks 12, 24, 36 and 48.
4. Change in PGA (Physician Global Assessment) based on evaluation of live evaluations and standardized photographs between baseline, week 12, 24, 36 and 48.
5. Change in patient global assessment between baseline, Week 12, 24, 36 and 48.
6. Change in patient quality of life assessment from baseline to weeks 12, 24, 36 and 48**.**
7. Frequency of occurrence and timing of relapse (as defined above) in responders followed for 6 months off therapy.
8. Safety will be evaluated as a secondary endpoint using descriptive statistics to summarize the cumulative incidence and types of AEs.
9. The proportion of patients who discontinued treatment will be summarized.

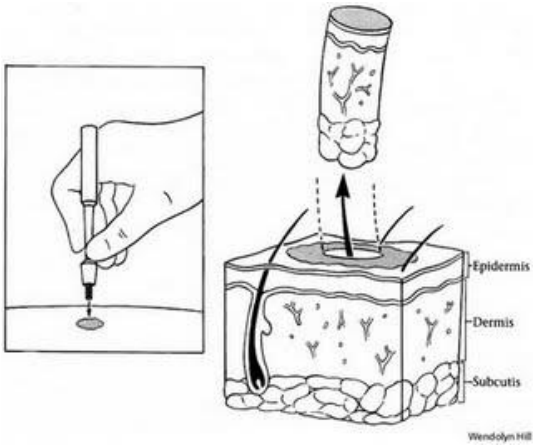
6.4.3 Other Assessments

Photography

Photography will be performed using a high-resolution digital camera with Intelliflash system from Canfield Scientific, Inc., mounted on a stereotactic arm. Patients will be positioned using a fixed guide, after which photographs of the entire scalp will be taken at standardized locations and at a fixed distance. Close-up photographs may also be taken using an epiluminescent attachment in order to assess for the presence of early regrowth.

Biopsy

All punch biopsies will be performed by the study doctor at a specific location and time point according to the schedule of study assessments. The biopsy site will be anesthetized with an injection of 1% lidocaine with epinephrine. After approximately 1 minute, the physician applies pressure to the biopsy site using a 4 mm skin punch (a sterile cylindrical tube with a sharp edge). The punch is twisted until the blade of the skin punch has pierced the epidermis and dermis of the skin and enters the subcutaneous fat. Depending on the thickness of the skin in the area being biopsied, the cylindrical blade may be buried to the hub (approximately 6mm). After the blade has sufficiently cored or carved out a cylinder of skin, the skin punch is removed. Nontraumatic forceps are used to gently grasp the cored skin, pulling upward to remove the core and reveal the subcutaneous fat. Scissors are used to cut the cored tissue free from the underlying subcutaneous fat. The specimen is placed immediately into the appropriate media. Once the specimen has been removed, pressure is applied to the biopsy site with a sterile 2 x 2 gauze. The biopsy site is then closed with several simple interrupted sutures. Either an absorbable or nonabsorbable suture may be used at the investigators discretion. Antibiotic ointment is applied and the area is covered with a standard BandAid or sterile gauze and paper tape. When necessary, a small pressure dressing may be applied. Subjects will be instructed in wound care and will be advised to call the research unit if they have any concerning signs or symptoms during healing.



Biosamples

A recent histological/gene expression study of synovial biopsies from RA patients treated with abatacept noted only mild changes in cellular synovial infiltrates during treatment. However, marked changes in IFN-γ expression was identified, with significant reductions only seen in the clinically responding patients (Buch et al. 2009). The decrease in IFN-γ production in the responders implies that functional inhibition of T cell activity is important for therapeutic outcome. Our proposed studies will include longitudinal biopsies that could provide additional support for interferon-γ modulation and abatacept treatment outcome.

Our procurement of serial biopsies, sera and PBMCs obtained at baseline and during treatment will provide the opportunity to correlate resolution of inflammatory biomarkers with treatment response in AA.

Biosamples will be obtained upon entry and again after 4 weeks, 12 weeks and 24 weeks of treatment and optional blood collection timepoints. Biospecimens at each time point will include: 1) a 4 mm skin biopsy; 2) 5 ml of blood for serum; 3) 60 ml of blood for PBMCs.

Blood volumes for research: 60 ml of blood is required to insure that sufficient viable cells are available after thawing of cryopreserved PBMC aliquots to enable functional T cell studies in triplicate. Our experience is that viable recovery of PBMC in freeze-thawed specimens is highly variable and range from 0.1-1.0 x 106 per ml of blood. Our blood volume obtained for research is 65 ml at one time, a maximum of 130 ml in a 4 week period and 260 ml in total over 6 months.

Biomarker Assessment and Clinical Correlative Studies

Our mechanistic studies are focused on correlating treatment and disease status with;
1) histological improvement of T cell infiltrates;
2) reduced IFN responses in the skin and blood;
3) reduced HF NKG2DL expression; and
4) declines in circulating and peribulbar $CD4^+$ and $CD8^+NKG2D^+$ infiltration.
5) AA GWAS risk haplotype susceptibility

Previous studies in AA have reported elevated NKG2D expression in circulating CD8 T cells and NK cells (Ito et al. 2008), supporting the feasibility of our approach. Here we will be able to correlate the numbers of $CD8^+NKG2D^+$ cells in the blood with those infiltrating the target organ of patients with each other and as a function of disease status. The limited studies proposed here seeking an association of IFN-□cells in$^+NKG2D^+$ positive cells and clinical outcome will not, however, exhaust the "biobank" and all human materials [frozen biopsy tissue & RNA, serum and the remaining (90%) of PBMCs] will remain banked and available for future hypothesis driven questions.

Flow Cytometry Studies. The presence of $CD8^+NKG2D^+$ cells will be tracked in the blood and in the skin during treatment with Abatacept. By assessing $CD8^+NKG2D^+$ involvement in longitudinally obtained skin biopsies at baseline and during treatment we can correlate disease severity and clinical response (progression or regression) with immunopathological evidence of resolution of total cellular infiltration (by H&E) or loss of specific $CD8^+NKG2D^+$ cells in the skin (by IF) or in the blood (flow studies). $CD8^+NKG2D^+$ frequency in the peripheral circulation will be quantified using freshly isolated PBMCs obtained from 30 mls of blood obtained upon scheduled and optional blood collection timepoints. A portion of the PBMCs $2x10^6$ cells will be stained with anti-CD4, anti-CD8, anti-CD25, anti-CD28 and anti-NKG2D antibodies, stimulated with PMA/ionomycin in the presence of brefeldin and stained with anti-FOXP3 and anti-IFN-γ Abs. The remaining PBMCs will be used for RNA analysis (see below) and viably frozen for future ancillary studies. We will seek evidence of a comparable pathogenic T cell subset in the human that we observed in C3H mice, namely an activate $CD25^+$ IFN-γ-producing $CD8^+NKG2D^+$ T cell.

Histology and Immunofluorescence Analysis. As shown in previous studies (Ito et al. 2008; Petukhova et al. 2010) in active AA NKG2D ligands are upregulated on hair follicles in association with peribulbar NKG2D-bearing $CD8^+$ T-cells and natural killer cells. We will seek evidence of resolution of total cellular infiltration (by H & E) and loss of specific $CD8^+NKG2D^+$ cells (by IF) and NKG2D ligands by comparing baseline biopsies with biopsies obtained on treatment after 4,

12, 24 and 36 weeks. Frozen sections will be stained with and anti-CD4, anti-CD8, anti-CD56, anti-NKG2D and anti-IFN-g antibodies to visualize the total number of leukocytes, cytotoxic T-cells and NK cells present in the baseline and drug treated skin, respectively. Immunostaining with anti-ULBP3, anti-MICA antibodies and recombinant NKG2D soluble receptor (NKG2D-Ig, detects all NKG2D ligands, R & D systems) will determine whether NKG2DL "danger/stress" signals are down modulated.

Punch biopsies from patient skin before and after treatment will be embedded in OCT and 7-8 micron frozen sections will be cut. The sections will be fixed in 4% paraformaldehyde and stained overnight with primary antibodies for NKG2D ligands, receptor and immune markers. The following day, sections will be treated for 1 hr with fluorescence labeled antibody, counter-stained and mounted with DAPI containing media. Frozen sections will also be used to for H&E staining. The total number of immune cells, as well as NKG2D bearing cells, will be quantified by counting stained cells per magnification field using the NIH imaging software ImageJ and a student T-test will be carried out to determine significant changes in the number of infiltrating, NKG2D bearing immune cells to quantitatively correlate the simultaneous presence or absence of these cells in lesional skin and in circulation (by flow) during active disease or in remission.

Haplotype Analysis for CTLA4 Modulation with Abatacept Therapy

The costimulatory pathway has demonstrated perturbations in a number of autoimmune diseases. We and others have identified haplotypes at the Costimulatory locus that confer risk for autoimmunity and alopecia areata, in particular 1,2. We hypothesize that variants carried on these haplotypes perturb the costimulatory axis and patients carrying such risk variants in particular will receive benefit from therapies specifically targeted to this pathway. Long range haplotype analysis using a small set of common SNPs across the costimulatory locus revealed two predominating haplotypes in European populations, termed 15-2-4 and 5-1-4 that are associated with autoimmune protection or risk respectively. We will analyze for the presence of haplotype susceptibility for each enrolled subject at baseline. We will utilize these results to explore whether treatment response with abatacept for AA is affected by haplotype susceptibility.

Analysis of Gene Expression by Quantitative RT-PCR

We will analyze the **transcriptional expression signature of costimulatory and IFN-response genes in the skin and PMBC of drug-treated AA patients using qPCR** as an indirect measure of the efficacy of Abatacept. Signature genes were selected based on their differential expression in affected vs. unaffected C3H mice (Carroll et al. 2002), and on published studies on human AA patients vs. controls (Subramanya et al. 2010) The genes in the list represent mediators and effectors of the IFN response, which we found to be instrumental in disease pathology. Briefly, biopsies and peripheral blood from baseline and Abatacept treated patients will be collected at 0, 4, 12 and 24 week time points. RNA will be extracted from the tissues, and Sybr green-based qPCR assays will be performed. Differential gene expression resulting from inhibitor treatment will be normalized to the expression of a housekeeping gene. We expect many of the genes on this list to revert to a basal level of expression, as compared in unaffected skin of an AA patient, or skin from a healthy control.

Serum inflammatory biomarkers
Serum will be obtained at baseline and during treatment and assessed for resolution of elevated levels of IFN-inducible chemokines.

6.5 Adverse Events

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

6.5.1 Serious Adverse Events

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

1) results in death is life-threatening (defined as an event in which the subject was at risk of death at the time of the event;
2) it does not refer to an event which hypothetically might have caused death if it were more severe)
3) requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
4) results in persistent or significant disability/incapacity is a congenital anomaly/birth defect is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.)
   Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

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

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs and should also be reported to BMS in an expedited manner, as described in Section 7.2.

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

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

2) elective surgery planned before signing consent admissions as per protocol for a planned medical/surgical procedure routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

3)medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.

4) admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

6.5.2 Nonserious Adverse Events

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

6.6 Assignment of Adverse Event Intensity and Relationship to Abatacept

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

Mild (Grade 1): awareness of event but easily tolerated

Moderate (Grade 2): discomfort enough to cause some interference with usual activity

Severe (Grade 3): inability to carry out usual activity

Very Severe (Grade 4): debilitating; significantly incapacitates subject despite symptomatic therapy.

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

Related: There is a reasonable causal relationship to investigational product administration and the adverse event.

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

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

6.7 Collection and Reporting

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

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

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

6.7.1 Serious Adverse Events

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

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

All SAEs should be faxed or emailed to BMS at:

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

For studies conducted under an **Investigator IND**, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible **and no later than 7 days** (for a death or life-threatening event) **or 15 days** (for all other SAEs) **after the investigator's or institution's initial receipt of the information.** BMS will be provided with a

simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

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

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

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

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

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

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

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

6.7.2 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union, an event meeting these criteria is termed a

Suspected Unexpected Serious Adverse Reaction (SUSAR). BMS will send investigators an expedited safety report (ESR) to notify them of such an event.

Other important findings that BMS may report as ESRs include increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety findings from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or the decision by BMS to end or temporarily halt a clinical study for safety reasons.

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

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

6.7.3 Nonserious Adverse Events

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

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

6.8 Laboratory Test Abnormalities

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

6.9 Overdose

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

6.10 Pregnancy

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

General Information

Informed Consent Form

Pregnancy Prevention Information Sheet

Drug Interactions with Hormonal Contraceptives

Contraceptives in Current Use

Guidelines for the Follow-up of a Reported Pregnancy.

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

6.10.1 Requirements for Pregnancy Testing

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

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

6.10.2 Reporting of Pregnancy

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

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

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

6.11 Other Safety Considerations

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

7 STATISTICAL CONSIDERATIONS

7.1 Sample Size Determination

Based on two recently completed randomized trials (Price et al, 2008; Strober et al, 2009) in similar patient populations (moderate to severe AA) we expect placebo response rates to be between 6% (>50% improvement in SALT score) and 12% (>25% improvement). We have chosen our primary endpoint conservatively (proportion of patients with >50% improvement in SALT index) as a relatively strict criteria that should minimize spontaneous remission rates to 10% or less (0-2 of 15 subjects). This allows a higher degree of confidence that appreciable response rates are attributable to drug rather than spontaneous remission.

Assuming a historically known placebo response rate of 10% and the usual 5% level of significance (alpha), the sample size of 15 would provide 80.7% power to detect a difference of 30% in the response rate between the experimental treatment group and the historical placebo group.

7.2 Populations for Analyses

The Dermatology clinic and private practice at CUMC currently sees 600 AA patients yearly, of which we anticipate 20-30% would be eligible (>30% hair loss). Accrual will be greatly facilitated by targeted recruitment through our existing NAAF registry, which includes 400 AA patients in the New York area, the majority of which have patchy type disease. Thus, complete accrual of 15 subjects should be feasible within 1 year from a pool of >100 eligible subjects yearly.

7.3 Endpoint Definitions

1. Proportion of patients with >50% improvement in SALT index at 24 weeks

2. Percent hair regrowth from baseline determined by SALT measurements following 12, 24 weeks of treatment and at weeks 36 and 48 following discontinuation of treatment.
3. Comparison of the proportion of responders in the experimental group with the historically known placebo response rate (<10%), with response defined as 50% change in SALT score (50% regrowth) from baseline, at weeks 12, 36 and 48.
4. Comparison of the proportion of subjects in the experimental group and the proportion of subjects in the historical control group attaining global overall improvement SALT score of A5 (100% coverage) supported by </= SALT 25 at weeks 12, 24, 36 and 48.
5. Change in PGA (Physician Global Assessment) based on evaluation of live evaluations and standardized photographs between baseline, week 12, 24, 36 and 48.
6. Change in patient global assessment between baseline, weeks 12, 24, 36, and 48.
7. Change in patient quality of life assessment from baseline to weeks 12, 24, 36, and 48.
8. Frequency of occurrence and timing of relapse (as defined above) in responders followed for 6 months off therapy.
9. To assess safety, we will summarize the incidence of adverse events for the study group.

7.4 Analyses

7.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will summarized via descriptive statistics.

7.4.2 Safety Analyses

To assess safety, we will summarize the incidence of adverse events for the study group. Analysis of safety is included as a secondary endpoint. All subjects who receive a dose of abatacept will be evaluated for safety. Safety outcomes include adverse events, clinically significant changes in vital signs, laboratory test abnormalities, and clinical tolerability of the drug. The investigator will determine the severity of each adverse event as mild, moderate, severe, or very severe. Laboratory findings that the investigator feels are clinically relevant should be recorded as adverse events. In addition, the investigator will determine the relationship of the adverse event to the administration of the study drug. Any occurrence of a SAE from time of consent forward, up to and including follow-up visits will be reported. See Section 6.5 for the SAE reporting procedures.

7.4.3 Efficacy Analyses

Since this is a small open label proof of concept study, we recognize that it will likely lack adequate power to conclusively demonstrate small efficacy signals (particularly if the assumed detectable difference of 30% is not met). Yet, descriptive summaries of all the primary and secondary efficacy outcomes (proportions for binary outcomes, means for continuous outcomes)

will provide a preliminary indication of the effect size (even if smaller than 30%) that will aid design of subsequent efficacy trials.

8 ADMINISTRATIVE SECTION

8.1 Compliance with the Protocol

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

All protocol amendments and revisions to the informed consent will be submitted to the BMS protocol manager and to the IRB/IEC. No protocol amendments will be implemented until written approval has been given by the IRB/IEC, except when necessary to eliminate an immediate hazard to study subjects. Administrative letters should also be sent to the BMS protocol manager and IRB/IEC; however, they do not require approval.

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

8.2 Records Retention

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

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

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number and use date or expiry date
- dates and initials of person responsible for each inventory entry/movement
- amount dispensed to and returned by each subject, including unique subject identifiers

- amount transferred to another area/site for dispensing or storage
- non-study disposition (e.g, lost, wasted, broken), and
- amount destroyed at study site.

8.3 Destruction of Investigational Product

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

9 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor to be related to the investigational product
Expedited Safety Report	Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures.

Term	Definition
SUSAR	Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC).
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g, Investigator Brochure for an unapproved investigational product)

10 LIST OF ABBREVIATIONS

AA AB	Alopecia areata Antibody
ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine Transaminase
APC	Antigen-Presenting Cell
ARA	American Rheumatology Association
AST	Aspartate Transaminase
BCG	Bacillus Calmette-Guérin

BMS	Bristol-Myers Squibb
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC-ACID	Centers for Disease Control and Prevention Advisory Committee on Immunization Practices
CFR	Code of Federal Regulations
CI	Confidence Interval
CMV	Cytomegalovirus
CRF	Case Report Forms
CRP	C-Reactive Protein
CTLA	Cytotoxic T-Lymphocyte Associated
CXR	Chest X-Ray
DMARD	Disease-Modifying Antirheumatic Drug
DNA	Deoxyribonucleic Acid
D5W	Dextrose (5%) in Water
EC	European Commission
ESR	Expedited Safety Report
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HLA	Histocompatibility Leukocyte Antigen
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IND	Investigational New Drug (Application)

IRB	Independent Review Board
IST	Investigator-Sponsored Trial
IU	International Unit
IV	Intravenous
JRA	Juvenile Rheumatoid Arthritis
MHC	Major Histocompatibility Complex
MRI	Magnetic Resonance Imaging
NPV	Negative Predictive Value
NS	Normal Saline
NSAE	Non-Serious Adverse Event
NSAID	Non-Steroidal Anti-inflammatory Drug
OA	Osteoarthritis
PCR	Polymerase Chain Reaction
PPD	Purified Protein Derivative
PPV	Positive Predictive Value
PVC	Polyvinylchloride
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE SALT	Serious Adverse Event Severity of alopecia tool
Se	Sensitivity
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
Sp	Specificity
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWFI	Sterile Water For Injection
TB	Tuberculosis
TNF	Tumor Necrosis Factor
ULN	Upper Level of Normal
VAS	Visual Analog Scale
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

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Footnotes

(i) Abatacept (BMS-188667) Summary of Clinical Safety, 2005: BMS Document Control No. 930013008.

(ii) A study to assess the pharmacokinetics, safety, and immunogenicity of single doses of abatacept (BMS-188667) administered subcutaneously to healthy subjects (Study IM101013). Bristol-Myers Squibb; 2006. Document Control No. 930015830.

(iii) A multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and clinical efficacy of intravenous infusions of abatacept (BMS-188667, 2 mg/kg) given monthly in combination with subcutaneous injections of etanercept (25 mg given twice weekly) to subjects with active rheumatoid arthritis (Study IM101101). Bristol-Myers Squibb; 2004. Document Control No. 930007559.

(iv) Clinical Study report for IM101063: A Study To Assess The Steady-State Trough Serum Concentrations, Safety, And Immunogenicity Of Abatacept (BMS-188667) Administered Subcutaneously In Subjects With Active Rheumatoid Arthritis Who Are Receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs). Bristol-Myers Squibb; 2008. Document Control No. 930025069.

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(vi) Clinical Study Report for IM101102: A Phase III, multi-center, randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of BMS-188667 in combination therapy with methotrexate versus methotrexate alone in subjects with active rheumatoid arthritis and inadequate response to methotrexate. Bristol-Myers Squibb; 2004. Document Control No. 930008345.

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(viii) Preliminary guidelines for diagnosing and treating tuberculosis in subjects with RA in immunosuppressive trials or being treated with biological agents. Ann Rheum Dis. 2002;61(supp):ii62-ii63.

(ix) Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care. 2000;161:221-247.

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