Abatacept for the Treatment of Refractory Juvenile Dermatomyositis (JDM)

AID (Abatacept in dermatomyositis) Trial

BMS PROTOCOL NUMBER: Abatacept BMS study ID IM101-479

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ABBREVIATIONS

AE	adverse event
ACR	American College of Rheumatology
AIHA	autoimmune hemolytic anemia
ANA	antinuclear antibody
BSA	Body Surface Area
CHAQ	child health assessment questionnaire
CTD	connective tissue disease
DOI	definition of improvement
DM	dermatomyositis
FDA	Food and Drug Administration
FVC	forced vital capacity
HACA	human anti-chimeric antibody
HAQ	health assessment questionnaire
HIV	human immunodeficiency virus
IBM	inclusion body myositis
ICF	informed consent form
ID	identification
IIM	idiopathic inflammatory myopathy
IMACS Group	International Myositis Assessment & Clinical Studies Group
IND	Investigational New Drug
IRB	Institutional Review Board
IS	immunosuppressive
JDM	juvenile dermatomyositis
JRA	juvenile rheumatoid arthritis
MDI	Myositis Damage Index
MDAAT	Myositis Disease Activity Assessment Tool
MMT	manual muscle testing
MOOP	Manual of Operations
MSAs	myositis specific autoantibodies
PCP	primary care physician
PK	pharmacokinetics
PM	polymyositis
PRINTO	Pediatric Rheumatology International Trials Organization
RA	rheumatoid arthritis
SAE	serious adverse event
SLE	systemic lupus erythematosus
SQ	Subcutaneous
TNF	tumor necrosis factor
VAS	visual analog scale

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PROTOCOL SYNOPSIS

Complete the Protocol Synopsis <u>after</u> you have finalized all content in the protocol. Make sure the information in the Synopsis matches the corresponding information in the body of the protocol.

Protocol Title:	**Abatacept for the Treatment of Refractory Juvenile Dermatomyositis (JDM)**
Site Numbers & Names:	The George Washington University (GWU), Medical Faculty Associates, GWU Myositis Center, The George Washing University Hospital.
Research Hypothesis:	To assess the safety and efficacy of subcutaneous abatacept in 10 patients seven years of age and older with refractory JDM. Our hypothesis is that abatacept will be well-tolerated and safe, and clinically efficacious with improvement in myositis disease activity following 6 months of subcutaneous abatacept weekly
Study Schema: **Drugs / Doses / Length of Treatment)**	Study participation will consist of a screening visit and 5 protocol visits over six months (week 0, week 6, week 12, week 18, and week 24) for each subject, and phone follow-up (week 2, week 4, week 8, week 10, week 14, week 16, week 20, and week 22). At Visit 1, which will be treatment initiation, eligible subjects will be instructed on the use and side effects of subcutaneous abatacept and will be started on the study drug (abatacept 125 mg SQ weekly for subjects with body weight ≥ 50 KG or abatacept 87.5mg SQ for subjects with body weight < 50 KG). For patients not improving with therapy by at least 5% on at least 3 of 6 core set measures at week 12 and who are clinically unchanged or worse by physician assessment, they would be offered the opportunity to increase their dose of treatment to abatacept 212.5 mg (87.5 + 125 mg) for subjects with body weight ≥ 50 kg or to abatacept 137.5 mg (87.5 mg + 50 mg) once a week subcutaneously for subjects with body weight < 50 kg, or to continue on their present dose. An open label extension of 6 months will be offered to subjects who met improvement criteria and are rated as at least minimally improved by physician assessment.

Study Objectives: • **Primary:** • **Secondary:**	**Primary:** a) To evaluate tolerance and safety of abatacept in treatment –refractory JDM patients. b) To assess the improvement in myositis disease activity: the myositis definition of improvement will be achieved in at least 6 of 10 patients at the end of the trial. **Secondary:** a) Steroid-sparing benefit will be obtained. We hypothesize that we can reduce daily corticosteroid therapy by at least 20% in at least 6 of 10 treatment-refractory JDM patients in this trial b) To examine response to treatment in individual core set measures of disease activity as developed by IMACS and PRINTO c) To examine improvement in patient reported outcomes d) To examine improvement in cutaneous dermatomyositis disease activity e) To examine improvement in muscle inflammation by examining a thigh/pelvis STIR MRI f) To examine that disease damage does not increase while under treatment with abatacept g) To examine improvement of biomarkers that may relate to disease pathogenesis and the mechanism of action of abatacept in JDM h) To estimate the PK and immunogenicity of SC abatacept weekly in JDM
Study Design:	Open label, non-randomized trial
Accrual Goal: **(Total number of subjects)**	10 receiving abatacept therapy
Accrual Rate: **(Number of subjects expected per month)**	0-1

FPFV: **LPFV:** **Follow Up:** **(dd-mm-yy)**	6 months
Correlative Studies: **(PK/PD, etc.)**	Biomarkers (please see below) Pharmacokinetics per BMS
Inclusion Criteria:	Adults or pediatric patients seven years of age and older with definite or probable JDM Body weight of at least 25 kg Refractory myositis At least moderately active disease
Exclusion Criteria	Drug –induced myositis Juvenile myositis, cancer-induced myositis, inclusion body myositis Myositis in overlap with another CTD Concomitant illness Pregnant or nursing mothers Life threatening non-myositis illness Any history or evidence of severe illness

Criteria for Evaluation: **(Efficacy, safety, stopping rules, etc.)**	**SAFETY**: To assess safety the NCI Common Terminology criteria version 4.0 June 2010 will be applied. Particular attention to serious adverse events and infections will be given. Patient evaluations will include: vital sign measurement, physical examination, and laboratory parameters for hematology and routine chemistries. **EFFICACY**: To assess efficacy, the primary endpoint will be the Definition of Improvement (DOI): 3 of any of the 6 core set measures improved by ≥ 20%, with no more than 2 of the core set measures worsening by ≥25% (worsening measure cannot include the muscle strength). **STOPPING RULES**: Subjects in this study may be discontinued for any of the following reasons: • Severe allergic reaction to the study medication • Participation in another investigational drug study • Any medical condition which, in the opinion of the investigator, warrants discontinuation from the study for the safety of the patient, either as a cause of the study drug or protocol violations, including non-compliance or inability to perform protocol-required procedures • Voluntary withdrawal (withdrawal of consent) • Pregnancy • If 3 or more patients develop a serious adverse event thought to be related to study drug, no new patients will be enrolled into the study until the adverse events have been reviewed by the Medical Safety Officer and/or Data Safety Monitoring Board.

Statistics:	n-randomized trial to assess the safety and efficacy of subcutaneous abatacept in 10 patients (children and adults) with juvenile-onset refractory dermatomyositis (JDM). Summary statistics will be generated to describe the study data. Descriptive statistics, including measures of central tendency (e.g. means, medians) and estimates of spread (e.g. standard deviations) will be used for continuous variables, including reporting of adverse event frequencies, core set measure assessments, and demographic and clinical variables. Non-parametric Wilcoxon signed rank tests will be used to investigate changes in continuous variables. 95% confidence intervals will be calculated for all point estimates.

APPENDICES

PROTOCOL TITLE: Abatacept the Treatment of Refractory Juvenile Dermatomyositis

PRODUCT: Abatacept

BMS Protocol Number: ID IM 101-479

1.0 INTRODUCTION

This is an open label interventional study to test the safety and efficacy of Abatacept for treatment of refractory juvenile dermatomyositis (JDM). JDM is a rare autoimmune disease affecting 1 to 3 per million children per year at ages less than 18 years [1]
The clinical manifestations include inflammatory changes in the muscle and skin tissue. The disease often presents with progressive muscle weakness, which can lead to severe disability.(2) In addition there are characteristic skin rashes (Gottron's papules and heliotrope rash), but also a number of photosensitive rashes and other systemic features, including arthritis, joint contractures, calcinosis, dysphagia and other gastrointestinal manifestations, and involvement of other systems (2,3). The diagnosis of JDM requires the presence of proximal muscle weakness, characteristic rashes, and often elevation of serum muscle enzymes. The diagnosis is often confirmed with muscle biopsy, which shows several pathognomonic changes, including perivascular inflammatory cells, immune complex deposition in the walls of the intramuscular arteries and veins, and perifascicular muscle fiber atrophy (4-6). JDM is a serious and potentially life threatening illness unless there is adequate treatment. With the advances in medicine, the current mortality is 3-6% in published series (4). There is significant morbidity associated with JDM, as 30-50% of patients demonstrate a chronic illness course, 15-30% have used wheelchairs, and 20-35% develop dystrophic calcification (4,7). In addition, understanding of disease pathophysiology is incomplete, but clearly involves specific immunity by T and B cells. The most striking histopathologic feature of affected muscle in JDM is vasculopathy that is believed to be secondary to endothelial changes due in part immune complex mediated inflammation.(8) This vasculopathy is critical in the pathogenesis of JDM and extent of occlusive vasculopathy is predictive of prognosis (8,9). High dose corticosteroids have traditionally been and are still to date is the first line therapy, but are associated with significant drug-related toxicity. Over 30% of JDM patients fail to respond adequately to corticosteroids and require additional immunosuppressive medications, none of which have been tested in controlled trials (10,11). These include DMARDs such as methotrexate, cyclosporine and azathioprine, and intravenous gamma globulin (IVIG) (10, 11). There are efforts toward standardizing treatment for JDM (11), but the outcomes are variable for the existing treatment modalities. The response to treatment can be partial and children often need prolonged treatment with combination drugs. The treatment of a child with steroids and DMARDs can cause adverse effects, including growth arrest and other sequelae as a result of long-term steroid usage.(7,12,13) Intolerance to other immunosuppressive medications also occurs, including frequent aseptic meningitis after IVIG, nausea and abdominal discomfort with certain DMARDs such as methotrexate, infusion reactions with biologics,

and increased risk of infections.(14) Poorly treated JDM can lead to calcinosis and vasculitic damage in the mucosa of the gastrointestinal tract as well as other organs and may be fatal. Agents for treatment-refractory patients have been studied primarily in small, retrospective case series. Etanercept was studied in treatment-refractory JDM patients and appeared to have little effect (15,16) Rituximab has been studied in a large multi-center therapeutic trial and had a positive effect in treatment-refractory dermatomyositis (DM), polymyositis (PM) and JDM patients, but failed to meet the trial endpoint of a difference in time to response between the treatment arms (17). Documentation of benefit of additional agents, particularly biologic therapies, is important for treatment refractory patients, as there is a dearth of studied agents in this population. The rationale for use of abatacept in the therapy of JDM includes the expression of CTLA4, CD28, CD86, and CD40 on inflammatory cells of muscle biopsies of patients with DM, as well as CTLA4 and CD28 on muscle cells (18,19) Abatacept also completely inhibits antigen presentation by cytokine-induced myoblasts to HLA-DR-matched antigen-specific CD4+ T cell lines (19). Co-stimulatory molecules and their receptors are also seen on CD4+ T cells and BB-1-positive muscle fibers in cell-to-cell contact in patients with scleroderma-myositis overlap syndrome (20,21).

The goal of this study is to examine the safety and efficacy of Abatacept for the treatment of refractory JDM as a novel biologic agent that is being increasingly utilized in adult and pediatric autoimmune diseases to modulate and down regulate lymphocytes(18)

1.2 ABATACEPT BACKGROUND

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. Abatacept is the first drug in a new class of agents termed “selective co-stimulation modulators.” Abatacept binds specifically to the CD80 (B7-1) and CD86 (B7-2) molecules, those expressed on antigen-presenting cells (APCs). Activation of naive T cells during an immune response requires two stimuli from APCs. The first signal is antigen-specific upon binding of MHC restricted antigen on APC to T cell receptor; the second signal is antigen-nonspecific and is delivered through engagement of CD80 or CD86 co-stimulatory ligand on APC with CD28, a cognate receptor on the T cell. CD28 is constitutively expressed on resting T cells (22-25). A co-stimulatory 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 (22,23). At 24 to 48 hours following T cell activation, the T cell expresses CTLA4 on its surface that has higher affinity for CD80 and CD86, thus limiting cell activation by interfering with CD28’s ability to bind CD80 and CD86. Upon engagement of CTLA4 to CD80 or CD86, the resultant inhibition of signal transduction inhibits T cell activation. Abatacept binds specifically to CD80 and CD86 and blocks binding of CD28, and the co-stimulation of T cells. The Fc region of abatacept was engineered with several point mutations preventing antibody-dependent cell cytotoxicity or activation of complement-cascade (22).

Pathogenesis and significance: Role of CTLA-4 in idiopathic inflammatory myopathies

It is widely accepted that DM and JDM are autoimmune conditions derived from chronic activation of immune system following specific environmental exposures in genetically susceptible individuals (26,27). The initial trigger and molecular pathogenesis is not fully understood. Histologically these illnesses are characterized by early changes in the intramuscular capillaries, leading to vasculopathy and perivascular inflammation. Thus, the cumulative insults from the vascular damage lead to development of perifascicular atrophy or typical skin rashes. (8, 26,27)

There has been convincing evidence that JDM immunopathogenesis predominantly involves heightened activation status of both the innate (macrophages and dendritic cells) as well as specific (B cells, CD4+ T cells) immune systems and is associated with chronic endothelial changes (26, 27). In fact, pro-inflammatory cytokines and cell adhesion molecules, including interleukin IL1-α, IL-β, ICAM-1, and TGF-β, are present in the inflamed muscle tissues of adult and juvenile myositis patients. Several studies have noted a strong expression of TNF-alpha in macrophages, myofibers, regenerating myoblasts, and endothelial cells (28,29). Furthermore, immune complex-mediated complement activation is likely to have central importance as the terminal C5b-9 membrane attack complex is often found deposited on muscular capillaries resulting in endothelial damage, capillary loss, and ischemic injury (26). The degree of such vasculopathy in the muscle correlates with the clinical disease course of JDM. It has been suggested that the vasculopathy may result from the decreased ability to repair vascular damage observed at early stages of the disease secondary to impaired angiogenic mechanisms (8). . Also, both mature and immature dendritic cells can be found in the perivascular infiltrates, along with implicated chemotactic chemokines, such as CCL19/21 and CCL20 (18), which can perpetuate the tissue damage.

The pathogenesis also involves alterations in immune regulation; in this regard, CTLA-4, the negative modulator of T cell activation, has been found important for following reasons: CTLA-4 is expressed by antigen presenting cells (dendritic cells and B cells) as well as by the muscle fibers. There is increased expression of CTLA-4 in the biopsy samples from inflammatory myopathies (18) and this is believed to be a natural mechanism of disease control. CTLA-4 gene knockout mice develop a massive lymphoproliferative disorder along with profound and spontaneous autoimmunity affecting skeletal and cardiac muscle (30,31) It was suggested muscle CTLA-4 and CD28 may play a role in protecting muscle cells from apoptosis. Alternatively, or perhaps in addition, they may contribute to the repair of damaged muscle by influencing muscle cell cytokine production (18-20) or by acting on myoblast proliferation, differentiation, and fusion. Unlike T cells, unstimulated muscle cells express neither CTLA-4 nor CD28. In vitro experiments showed that CTLA-4 and CD28 are differentially expressed under the influence of different cytokines: IL-1-α and IFN-γ induce both, IL-1-β and TNF-α induce only CTLA-4, and IL-6 had no effect on the expression. These cytokines are present in varying amounts in myositis biopsies (32). Of note, the expression of CTLA-4 has also been observed in the muscle biopsy of patients with scleroderma-PM syndrome. (21)

Thus, abatacept-based treatment is likely to deliver immune modulation that naturally blends in the physiologic pathways of down regulation of inflammation. Furthermore, because activated T cells undergo capping of CTLA-4 to reduce its surface expression, it is conceivable that disease control by abatacept in JDM is through the targeting of activated and autoreactive T cells in perivascular and perimysial regions through down regulation of dendritic cells and B cells.

1.3 PREVIOUS CLINICAL STUDIES OVERVIEW

Current knowledge about the safety profile of abatacept is derived from clinical trials and post marketing experience. Detailed information can be found in the Investigator's brochure.

1.3.1 Clinical Experience with Abatacept in Adult & Pediatric Patients

Abatacept is approved for the treatment of **adult rheumatoid arthritis (RA)** and **juvenile idiopathic arthritis (JIA)**.

The efficacy and safety of intravenous abatacept were assessed in randomized, double-blind, placebo-controlled clinical trials in adult patients with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Studies I, II, III, V, and VI required patients to have at least 12 tender and 10 swollen joints at randomization. Study IV did not require any specific number of tender or swollen joints. The accumulated long-term experience with abatacept shows that efficacy is maintained in subjects treated for up to 8 years with abatacept. Hence, these data confirm that the consistent efficacy profile of abatacept observed in the pivotal studies is maintained over an extended duration of exposure.
The key efficacy results are the following:

- Abatacept provided a clinically meaningful long-term efficacy benefit in a highly consistent manner for subjects with moderate to severe RA across 3 populations, (methotrexate (MTX) -naïve, MTX-inadequate responder [IR], and TNF-IR, in multiple measures of disease (Signs and Symptoms, Physical Function, and Health-related Outcomes).
- MTX-naive and MTX-IR subjects maintained inhibition of structural damage for up to 2 years and 5 years of long-term treatment with abatacept, respectively (radiographic assessments were not performed in the TNF-IR population).

Clinical Efficacy - IV Formulation in Pediatric JIA Population
The IM101033 study evaluated response using the ACR Pediatric 30 definition of improvement. Subjects who met the criteria for improvement at the end of Period A were randomized 1:1 to either abatacept or placebo into the double-blind phase (Period B). The primary efficacy endpoint evaluated in the double-blind phase (Period B) was the

time to polyarticular JIA disease flare and was compared between the treatment groups using a log-rank test.

The efficacy of abatacept was assessed by additional prospectively defined measures as secondary objectives, including comparison of the rate of disease flare and an assessment of the changes from baseline during Periods B and C for each of the 6 individual ACR Pediatric core response variables. Additionally, subjects were assessed for ACR Pediatric 30, 50, 70, and 90 definitions of improvement and inactive disease during Periods A and C.

- The time to disease flare was statistically significantly shorter for the placebo-treated group than the abatacept-treated group based on the log-rank test (p = 0.0002). The risk of disease flare among subjects continuing on abatacept was less than one-third that for the subjects who had been randomly withdrawn from the abatacept treatment (hazard ratio = 0.31, 95%CI [0.16, 0.59]).

- A higher proportion of subjects in the placebo group (53.2%, 33/62) than in the abatacept group (20.0%, 12/60) experienced a flare of polyarticular JIA (p < 0.001).

Clinical Efficacy - Subcutaneous abatacept

The subcutaneous and intravenous formulations of abatacept demonstrate comparable efficacy, safety and immunogenicity in adult rheumatoid arthritis. (33)

1.3.2 **Risk/Benefit Ratio:**

Study Medications
Abatacept is FDA-approved since 2005 in the United States for the treatment of adult RA and JIA patients with an inadequate response to anti-TNF agents. Current knowledge about the safety profile of abatacept is derived from clinical trials and post marketing experience. Detailed information can be found in the Investigator's brochure.

Clinical Studies Experience in Adult RA Patients Treated with Intravenous Abatacept
Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The data described herein reflect exposure to abatacept administered intravenously in patients with active RA in placebo-controlled studies (1955 patients with abatacept, 989 with placebo). The studies had either a double-blind, placebo-controlled period of 6 months (258 patients with abatacept, 133 with placebo) or 1 year (1697 patients with abatacept , 856 with placebo). A subset of these patients received concomitant biologic DMARD therapy, such as a TNF blocking agent (204 patients with abatacept , 134 with placebo).

The majority of patients in RA clinical studies received one or more of the following concomitant medications with abatacept: methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, TNF blocking agents, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide, sulfasalazine, and anakinra.
The most serious adverse reactions were serious infections and malignancies.
The most commonly reported adverse events (occurring in ≥10% of patients treated with abatacept) were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

The adverse events most frequently resulting in clinical intervention (interruption or discontinuation of abatacept) were due to infection. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1.0%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).

Infections
In the placebo-controlled trials, infections were reported in 54% of abatacept -treated patients and 48% of placebo-treated patients. The most commonly reported infections (reported in 5%-13% of patients) were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, influenza, and bronchitis. Other infections reported in fewer than 5% of patients at a higher frequency (>0.5%) with ABATACEPT compared to placebo, were rhinitis, herpes simplex, and pneumonia.
Serious infections were reported in 3.0% of patients treated with abatacept and 1.9% of patients treated with placebo. The most common (0.2%-0.5%) serious infections reported with abatacept were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis.

Malignancies
In the placebo-controlled portions of the clinical trials (1955 patients treated with Abatacept for a median of 12 months), the overall frequencies of malignancies were similar in the abatacept - and placebo-treated patients (1.3% and 1.1%, respectively). However, more cases of lung cancer were observed in abatacept -treated patients (4, 0.2%) than placebo-treated patients (0). In the cumulative abatacept clinical trials (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid and uterine cancers. The potential role of abatacept in the development of malignancies in humans is unknown.

Infusion-Related Reactions and Hypersensitivity Reactions

Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion) in were more common in the abatacept -treated patients than the placebo patients (9% for abatacept , 6% for placebo). The most frequently reported events (1%-2%) were dizziness, headache, and hypertension.

Acute infusion-related events that were reported in >0.1% and ≤1% of patients treated with abatacept included cardiopulmonary symptoms, such as hypotension, increased blood pressure, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild (68%) to moderate (28%). Fewer than 1% of abatacept -treated patients discontinued due to an acute infusion-related event. In controlled trials, 6 abatacept -treated patients compared to 2 placebo-treated patients discontinued study treatment due to acute infusion-related events. Anaphylaxis was observed in patients dosed with abatacept administered intravenously in controlled and open-label clinical trials, and the occurrence was rare (<0.1%). Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea that occurred within 24 hours of abatacept infusion, were uncommon (<1%). Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction.

Other Adverse Reactions

Adverse events occurring in 3% or more of patients and at least 1% more frequently in abatacept -treated patients during placebo-controlled RA studies are summarized in Table

Adverse Events Occurring in 3% or More of Patients and at Least 1% more Frequently in abatacept -Treated Patients During Placebo- Controlled RA Studies

Adverse Event (Preferred Term)	ORENCIA (n=1955)[a] Percentage	Placebo (n=989)[b] Percentage
Headache	18	13
Nasopharyngitis	12	9
Dizziness	9	7
Cough	8	7
Back pain	7	6
Hypertension	7	4
Dyspepsia	6	4
Urinary tract infection	6	5
Rash	4	3
Pain in extremity	3	2

[a] Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).
[b] Includes 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in RA patients for up to 2 years following repeated treatment with Abatacept. Thirty-four of 1993 (1.7%) patients developed binding antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept. Because trough levels of abatacept can interfere with assay results, a subset analysis was performed. In this analysis it was observed that 9 of 154 (5.8%) patients that had discontinued treatment with abatacept for over 56 days developed antibodies. Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies in a cell-based luciferase reporter assay. Six of 9 (67%) evaluable patients were shown to possess neutralizing antibodies. However, the development of neutralizing antibodies may be underreported due to lack of assay sensitivity. No correlation of antibody development to clinical response or adverse events was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to abatacept in specific assays. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to abatacept with the incidence of antibodies to other products may be misleading.

Clinical Experience in Adult RA Patients Treated with Subcutaneous Abatacept

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Study SC-1 was a randomized, double-blind, double-dummy, non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (SC) and intravenously (IV) in 1457 subjects with RA, receiving background methotrexate, and experiencing an inadequate response to methotrexate (MTX-IR). The safety experience and immunogenicity for abatacept administered subcutaneously was consistent with intravenous Studies I-VI. Due to the route of administration, injection site reactions and immunogenicity were evaluated in Study SC-1 and two other smaller studies discussed in the sections below. The highest dose tested in adults is 200 mg weekly.

Injection Site Reactions in Adult RA Patients Treated with Subcutaneous ABATACEPT

Study SC-1 compared the safety of abatacept including injection site reactions following subcutaneous or intravenous administration. The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous abatacept group and the intravenous abatacept group (subcutaneous placebo), respectively. All these injection site reactions (including hematoma, pruritus, and erythema) were mild (83%) to moderate (17%) in severity, and none necessitated drug discontinuation.

Immunogenicity in Adult RA Patients Treated with Subcutaneous abatacept : Study SC-1 compared the immunogenicity to abatacept following subcutaneous or intravenous administration. The overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous groups, respectively. The rate is consistent with previous experience, and there was no correlation of immunogenicity with effects on pharmacokinetics, safety, or efficacy.

Immunogenicity and Safety of Subcutaneous abatacept Administration as Monotherapy without an Intravenous Loading Dose:
Study SC-2 was conducted to determine the effect of monotherapy use of abatacept on immunogenicity following subcutaneous administration without an intravenous load in 100 RA patients, who had not previously received abatacept or other CTLA4Ig, who received either subcutaneous abatacept plus methotrexate (n=51) or subcutaneous abatacept monotherapy (n=49). No patients in either group developed anti-product antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

Immunogenicity and Safety of Subcutaneous abatacept upon Withdrawal (Three Months) and Restart of Treatment:
Study SC-3 in the subcutaneous program was conducted to investigate the effect of withdrawal (three months) and restart of abatacept subcutaneous treatment on immunogenicity in RA patients treated concomitantly with methotrexate. One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous abatacept or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label abatacept treatment in the final 3-month period of the study (period 3). At the end of the withdrawal period, 0/38 patients who continued to receive subcutaneous Abatacept developed anti-product antibodies compared to 7/73 (9.6%) of patients who had subcutaneous abatacept withdrawn during this period. Half of the patients receiving subcutaneous placebo during the withdrawal period received a single intravenous infusion of abatacept at the start of period 3 and half received intravenous placebo. At the end of period 3, when all patients again received subcutaneous Abatacept, the immunogenicity rates were 1/38 (2.6%) in the group receiving subcutaneous Abatacept throughout, and 2/73 (2.7%) in the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose. The safety observed in this study was consistent with that observed in the other studies.

Clinical Studies Experience in Juvenile Idiopathic Arthritis: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In general, the adverse events in pediatric patients were similar in frequency and type to those seen in adult

patients. Abatacept has been studied in 190 pediatric patients, 6 to 17 years of age, with polyarticular juvenile idiopathic arthritis. Overall frequency of adverse events in the 4-month, lead-in, open-label period of the study was 70%; infections occurred at a frequency of 36%. The most common infections were upper respiratory tract infection and nasopharyngitis. The infections resolved without sequelae, and the types of infections were consistent with those commonly seen in outpatient pediatric populations. Other events that occurred at a prevalence of at least 5% were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain. A total of 6 serious adverse events (acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare [2], and joint wear) were reported during the initial 4 months of treatment with Abatacept. Of the 190 patients with juvenile idiopathic arthritis treated with abatacept in clinical trials, there was one case of a hypersensitivity reaction (0.5%). During Periods A, B, and C, acute infusion-related reactions occurred at a frequency of 4%, 2%, and 3% respectively, and were consistent with the types of events reported in adults. Upon continued treatment in the open-label extension period, the types of adverse events were similar in frequency and type to those seen in adult patients, except for a single patient diagnosed with multiple sclerosis while on open-label treatment.

Immunogenicity
Antibodies directed against the entire Abatacept molecule or to the CTLA-4 portion of Abatacept were assessed by ELISA assays in patients with juvenile idiopathic arthritis following repeated treatment with Abatacept throughout the open-label period. For patients who were withdrawn from therapy for up to 6 months during the double-blind period, the rate of antibody formation to the CTLA-4 portion of the molecule was 41% (22/54), while for those who remained on therapy the rate was 13% (7/54). Twenty of these patients had samples that could be tested for antibodies with neutralizing activity; of these, 8 (40%) patients were shown to possess neutralizing antibodies. The presence of antibodies was generally transient and titers were low. The presence of antibodies was not associated with adverse events, changes in efficacy, or an effect on serum concentrations of Abatacept. For patients who were withdrawn from Abatacept during the double-blind period for up to 6 months, no serious acute infusion-related events were observed upon re-initiation of Abatacept therapy.

Laboratory monitoring: Complete blood counts (CBC) and platelet counts will be obtained at regular intervals during the study Blood Drawing: Subjects may experience pain, bruising and/or bleeding at the site of the needle insertion for blood drawing. Very rarely an infection may occur at the site. Subjects may also experience dizziness and/or fainting.

Hepatitis B and C and HIV blood testing: The hepatitis testing requires the drawing of blood. Being tested for hepatitis may cause anxiety regardless of the test results. If a subject has a positive test results, they may have trouble obtaining insurance or employment. There is always the possibility the test result is wrong and therefore a repeat test would be done.

Magnetic resonance imaging (MRI): MRI involves no x-rays and there are no known risks from the test, although some people may feel claustrophobic about being in a small space. No contrast agent will be administered for the MRI examination.

Photography: Photographs of skin rashes and the periungual capillaries (Optional) are taken throughout the study. The possibility exists that patients may be identifiable in some of the photographs when unique birthmarks or other identifiable skin changes are present.

Loss of privacy: Every effort will be made to protect the subject's privacy and information will be handled in a confidential manner. The only information that will be provided with the subject's stored blood and urine samples is a study code. Files that link the subjects name to the code number will be kept in a locked cabinet and only the study staff will have access to them. The samples will be provided to the researchers in such a manner whereby it will not be possible for them to connect the subject's identity with the sample or medical information. Information about race, ethnicity, sex and medical history may be made available to the investigators studying the blood, muscle tissue and urine samples. Such information might be important for research. Although no one can absolutely guarantee confidentiality, using a code number greatly reduces the chance that someone will ever be able to link the subjects name to their sample or to their results.

Confidentiality: All records pertaining to the subject's involvement in this research study will be stored in locked file cabinets. Only a subject number in these records will identify him or her. Any information about the subject or his or her treatment will be handled in a confidential manner consistent with other identifiable health information. The subject will not be specifically identified in any publication of research results.

Potential benefits: There may be no direct benefit to participate in this study. There is no guarantee that participants will receive any personal benefit from participating. It is hoped that the information gained from the study will be beneficial to patients in the future.

Alternative Treatments: Other treatments available to patients include other immunosuppressive medications known to be considered as possibly effective in patients with immunological diseases. These drugs may be effective in managing the symptoms associated with JDM. The Principal Investigator or Associate Investigators will discuss all of the treatment options with potential participants.

Evaluation of Risk/Benefit Ratio: If abatacept proves to be effective, many such patients with JDM may ultimately benefit from this therapy. Such benefits may include improved symptoms and health. Practitioners may gain increased knowledge and treatment of myositis in clinical practice. Subjects participating in this study may experience some benefit during the period of study medication therapy. Evaluation is performed as per the statistical information provided in the protocol. The risks for those subjects involved in this study are reasonable when compared to the potential

disease damage and catastrophic sequelae that occurs in adult and pediatric patients with inflammatory myopathy.

Reproductive Risks: Animal studies to determine the effects of the study drug on the fetus have not been done. To avoid risk to the fetus, it is important that female participants or female partners of male participants take care to avoid becoming pregnant during this study. Avoiding sexual activity is the only certain method to prevent pregnancy. However, females of child-bearing potential must be willing to use an appropriate method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed “birth control” pills, injections, or implants throughout the study. Even with use of these birth control measures, pregnancy could still result. The risks of receiving the study drug while pregnant include potential loss of pregnancy or possible birth defects. Females of child-bearing potential will undergo a urine pregnancy test prior to exposure to the study drug. In the pediatric group the parent signing the consent will be informed of the result of the pregnancy test.

1.3.3 Abatacept in IIM: Pilot Data

The efficacy of Abatacept has been established in adult RA and JIA. However, there have been only a few reports on the use of abatacept to treat inflammatory myopathies. These few case reports suggest a beneficial effect. We have had direct experience at the George Washington University (GWU) Myositis Center in the treatment of two patients with severe treatment-refractory JDM who responded very well to Abatacept SC therapy and tolerated this with no side effects. From our published report (34), our first patient at GWU responded with a significant improvement in muscle strength and function, skin rashes and ulceration, ability to reduce daily prednisone therapy over a 6 month period and also in the extent of calcinosis, after initiation of Abatacept and failure so suppress disease activity with a number of other agents, including prednisone, IVIG, methotrexate, tacrolimus and cyclophosphamide (34). A second patient under our guidance, after failure to suppress JDM disease activity with corticosteroids, IVIG, cyclosporine, methotrexate, rituximab, etanercept, and other agents, had a dramatic response to Abatacept within 6 months of beginning infusions, including clearing of her refractory skin disease, normalization of her muscle strength and function, and ability to reduce daily prednisone down to 10 mg daily; she achieved clinical remission with abatacept. A third patient that Dr. Rider was involved with at the NIH was a teenager who failed multiple medications (steroids, methotrexate, cyclosporine, cyclophosphamide, IVIG, mycophenolate mofetil, azathioprine, tacrolimus and had a hypersensitivity reaction to rituximab). Only after the addition of intravenous infusions with abatacept, she achieved marked clinical and laboratory parameters, with near normalization of her muscle strength, function and serum levels of muscle enzymes. An adult patient at an academic

center in France (35) with severe treatment- refractory myositis who had failed to the combination of methotrexate and azathioprine, responded to the addition of abatacept with a significant improvement in muscle strength and function and was able to reduce daily prednisone. A Japanese patient with refractory anti-signal recognition particle myopathy achieved remission following treatment with abatacept (36). Dr. Rider is aware of at least 10 other refractory JDM patients under treatment with abatacept who have experienced an excellent response. All patients have received the dosing regimen used in JIA patients (37).

1.4 ETHICAL CONSIDERATIONS

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 will 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).

1.5 RATIONALE

JDM is an autoimmune disease involving specific immunity, including plasmacytoid dendritic cells, B and CD4+ T lymphocytes. We postulate that the immunomodulatory action of abatacept in JDM will inhibit the co-stimulatory signal from CD80 and CD86, by inhibiting dendritic-cell mediated T cell activation. Our hypothesis is that treatment refractory patients with JDM will respond to abatacept and that abatacept will also be safe for use in this population.

2.0 OBJECTIVES

This open label non-randomized trial will assess the safety and efficacy of subcutaneous abatacept in 10 patients ≥ 7 years of age with refractory JDM.

2.1 PRIMARY OBJECTIVE

AIM: To assess the safety and efficacy of subcutaneous abatacept in an open-label trial of refractory JDM in 10 adults and children.

- **Hypothesis A:** ***Abatacept will be well-tolerated and safe in treatment–refractory JDM patients.*** For this, the NCI Common Terminology criteria version 4.0 June 2010 will be applied. Medical records will be reviewed for the 6 months prior to enrollment to obtain adverse events prior to beginning abatacept, which will be compared to any adverse events that develop after abatacept was initiated. Particular attention will be given to serious adverse events and infections. Patient evaluations will include: vital sign measurement, physical examination, and laboratory parameters for hematology and routine chemistries.

- **Hypothesis B**: ***Patients will clinically improve after treatment with abatacept.*** We hypothesize that at least 6 of 10 patients will meet the myositis preliminary definition of improvement after receiving 24 weeks of therapy with abatacept.

  Definitions of improvement (DOIs) for clinical trials in IIM have recently been proposed by the IMACS Group (International Myositis Assessment and Clinical Studies) for adult and pediatric myositis utilizing six core set measures among five domains of myositis disease activity (38) **(see Appendix C**). They are:
  a) Physician global disease activity;
  b) Parent/patient global disease activity;
  c) Muscle strength, utilizing manual muscle strength testing (MMT8);
  d) Physical function assessment using the (Childhood) Health Assessment Questionnaire (CHAQ);
  e) Laboratory assessment using the most abnormal serum muscle enzyme level; and
  f) Extra-muscular disease activity using the Myositis Disease Activity Assessment Tool (MDAAT). (see section 14.0: assessment tools: description) (39)

  For this clinical trial, the primary endpoint will be the published Definition of Improvement (DOI): 3 of any of the 6 core set measures improved by ≥ 20%, with no more than 2 of the core set measures worsening by ≥25% (worsening measures cannot include the muscle strength). (Appendix D1) (38)

  The PRINTO Group (Pediatric Rheumatology International Trials Organization) has developed and validated a core set of outcome variables for the evaluation of response to therapy in JDM. (40) (Appendix C)

  The additional PRINTO core set activity measures are:

1) Childhood Myositis Assessment Scale is used as a measure of strength;
2) A health related quality of life measure, CHQ-PF50, is used and
3) Disease Activity Score (DAS) is used as a measure of global activity (42)

PRINTO also has a definition of minimal clinical improvement (20%), moderate (50%) and major (70%) improvement (41) (Appendix D).

PRINTO has also defined clinically inactive disease (41) as creatine kinase ≤150 (within normal limits), CMAS ≥48, MMT ≥78 and Physician Global Activity VAS ≤0.2. (41) (Appendix D)

The frequency of minimal, moderate and major improvement by the DOIs, with 20%, 50% and 70% change, as well as clinically inactive disease by the PRINTO criteria will also be examined in this trial.

Finally, the DOIs are currently undergoing revision in an ACR-EULAR project that is combining the efforts of IMACS and PRINTO. New definitions of minimal, moderate and major improvement have been developed and are expected to be finalized within the coming year. These newly-developed definitions will be added to the criteria as a secondary efficacy outcome measures for this trial (**Appendix D2**). Other criteria found to perform very highly in the ACR-EULAR project will be used as secondary endpoints in this trial (Appendix D2).

2.2 SECONDARY OBJECTIVES

Steroid-sparing benefit will be obtained. ***We hypothesize that we can reduce daily corticosteroid therapy by <u>at least 20%</u> in this population of treatment-refractory patients.***

To this end, a standardized corticosteroid tapering regimen will be utilized (Section 5). All subjects will remain on their initial prednisone dose until at least the first follow-up visit (week 6) and until they meet the definition of improvement and are rated as 'much improved' by both the physician and the patient or parent. The prednisone dose may then be reduced according to the standardized steroid tapering schedule in Section 5.

a) To examine response to treatment in individual core set measures of disease activity as developed by IMACS, including Physician and Patient/Parent global activity, Muscle strength (by manual muscle testing, MMT-8), Physical function (by HAQ/CHAQ), Muscle enzymes, and Extra-muscular activity (by the Myositis Disease Activity Assessment Tool, MDAAT).

b) To examine other core set activity measures as developed by PRINTO, including the Childhood Myositis Assessment Scale (CMAS), the Disease Activity Score (DAS) and Health Related Quality of Life Questionnaire (Childhood Health Questionnaire (CHQ-PF50) for children or SF-36 for adults.

c) To examine improvement in patient reported outcomes, including health-related quality of life and fatigue measures, including the PROMIS fatigue questionnaire and PedsQL fatigue questionnaire. Both patient and parent questionnaires will be obtained, for patients < 18 years of age.

d) (optional Assessment by Dermatology) To examine improvement in cutaneous activity, using the Cutaneous Dermatomyositis Area and Severity Index (CDASI) and the Dermatology Life Quality Index (DLQI), as well as periungual nailfold capillary density. To document changes in cutaneous findings by standardized photography.

e) To examine improvement in muscle inflammation by examining a thigh/pelvis STIR MRI at baseline and 6 month follow-up.

f) To examine that disease damage does not increase while under treatment with abatacept, by examining the Myositis Damage Index (MDI) at baseline and 6 month follow-up.

g) To examine improvement of biomarkers that may relate to disease pathogenesis and the mechanism of action of abatacept in JDM, including:
   i. Immunophenotyping for CD4, CXCR3, IFNγ (TH1), CD4, CCR4, CRTH2, IL4 (TH2), CD4, CCR6, IL17a (TH17), CD4, CD25, Foxp3 (T regulatory cells), B cell markers and macrophage markers along with B71, B72, CTLA4, CT28 on fresh lymphocytes
   ii. Isolation of T cells, B cells, dendritic cells, monocyte and macrophages, and freeze the isolated cells for subsequent molecular and functional analysis, including gene expression profiling
   iii. Cytokine 30-plex panel on serum samples
   iv. Peripheral blood mononuclear cells for RNA gene expression using a gene bead chip panel.

h) To evaluate immunogenicity and the pharmacokinetics of SC abatacept by the trough concentrations at steady state.

3.0 STUDY DESIGN

TREATMENT PHASE

This study will employ an open label nonrandomized design in the treatment of subjects with JDM. Study participation will consist of a screening visit and 5 protocol visits over six months (week 0, week 6, week 12, week 18, and week 24) for each subject, and phone follow-up in between in-person visits (week 2, week 4, week 8, week 10, week 14, week 16, week 20, and week 22). Some patients will undergo some of the screening tests at home, and present results at a screening visit. This will enable them to move to the week 0 visit simultaneously and begin treatment.

At Visit 1, which will be treatment initiation, eligible subjects will be instructed on the use and side effects of subcutaneous abatacept. Patients will be started on the study drug (abatacept) 125 mg SQ weekly for subjects with body weight ≥ 50KG and 87.5 mg SQ for subjects with weight <50 KG. For patients not improving with therapy by at least 5% on

at least 3 of 6 core set measures (IMACS or PRINTO measures) at week 12, they would be offered the opportunity to increase their dose of treatment to abatacept 212.5 mg SQ weekly (125 mg prefilled syringe plus 87.5 mg prefilled syringe) for subjects with weight ≥ 50KG and 137.5 mg SQ weekly (87.5 mg prefilled syringe plus 50 mg prefilled syringe) for subjects with weight <50KG, or to continue on their present dose.

At each study visit, patients will undergo assessment and questionnaires to include the core set myositis activity measures (both IMACS and PRINTO core set measures), patient questionnaires (including patient/parent global activity, [Childhood] Health Assessment Questionnaire **([C]HAQ**), Health Related Quality of Life Questionnaire (Childhood Health Questionnaire **(CHQ-PF50**) for children or **SF-36** for adults) and **PROMIS** and **PedsQL** fatigue questionnaires; at Visit 1 (week 0) and Visit 5 (week 24), the **Myositis Damage Index**- performed by a pediatric or adult rheumatologist; at visit 1 (week 0) and visit 5 (week 24); **Cutaneous Dermatomyositis Activity and Severity Index** and **Dermatology Life Quality Index**, by our affiliated dermatologist Dr. Allison Ehrlich or Dr. Rider on interim visits. (The dermatologic assessments will be optional) (Section 14). An open label extension of 6 months will be offered to subjects who met the primary study endpoint and are rated by the study physician as at least minimally improved from baseline visit. During this period, patients will be evaluated twice a year.

3.1 ENDPOINTS

Primary

The *primary endpoint* of this trial is to establish safety and efficacy of Abatacept in patients with refractory Juvenile Dermatomyositis

a) Safety: Abatacept will be well-tolerated and safe.
b) Improvement in myositis disease activity: the published IMACS myositis definition of improvement will be achieved in at least 6 of 10 patients at the end of the trial (38).

Secondary

a) To evaluate the response rate to Abatacept in JDM using the PRINTO definition of improvement, including criteria for minimal, moderate and major clinical response (40, 41).
b) To evaluate the response rate to Abatacept using newly developed criteria for myositis clinical response, which are pending ACR-EULAR approval (Appendix D2), as well as other top performing criteria considered at the International Myositis Response Criteria Consensus Conference.
c) To examine response to treatment in individual core set measures of disease activity as developed by IMACS, including physician and patient/parent global activity, muscle strength (by manual muscle testing), physical function (by HAQ/CHAQ), muscle enzymes, and extra-muscular activity (by the Myositis Disease Activity Assessment Tool)

d) To examine other core set activity measures as developed by PRINTO, including the Childhood Myositis Assessment Scale, the Disease Activity Score and CHQ-PF50
e) Steroid-sparing benefit: 20% reduction of the corticosteroid therapy will be achieved in 6 of 10 patients at the end of the trial
f) To examine improvement in patient reported outcomes, including health-related quality of life and fatigue measures, including the PROMIS and PedsQL fatigue questionnaires. Both patient and parent questionnaires will be obtained, for patients < 18 years of age.
g) To examine improvement in cutaneous activity, using the Cutaneous Dermatomyositis Area and Severity Index (CDASI) and the Dermatology Life Quality Index, as well as periungual nail fold capillary density. To document changes in cutaneous findings by standardized photography.
h) To examine improvement in muscle inflammation by examining a thigh/pelvis STIR MRI at baseline and 6 month follow-up. MRI readings will be blinded to the clinical assessment information, including, if possible, date of assessment, and study drug dose.
i) To examine that disease damage does not increase while under treatment with abatacept, by examining the Myositis Damage Index at baseline and 6 month follow-up.
h) To examine at baseline, 3 and 6 months biomarkers of disease including:
    i. Immunophenotyping for CD4, CXCR3, IFNγ (TH1), CD4, CCR4, CRTH2, IL4 (TH2), CD4, CCR6, IL17a (TH17), CD4, CD25, Foxp3 (T regulatory cells), B cell markers and macrophage markers along with B71, B72, CTLA4, CT28 on fresh lymphocytes
    ii. Isolation of T cells, B cells, dendritic cells, monocyte and macrophages, and freeze the isolated cells for subsequent molecular and functional analysis, including gene expression profiling
    iii. Cytokine 30-plex panel on serum samples
    iv. Peripheral blood mononuclear cells for RNA gene expression using a gene bead chip panel.

Biomarker studies will be blinded to the clinical assessment information and drug dose.

To evaluate immunogenicity and the pharmacokinetics of SC abatacept by the steady-state trough concentrations of abatacept at week 0, week 12 and week 24

3.2 SAFETY ENDPOINTS

Safety assessment will include adverse events, vital signs, physical examination findings, laboratory parameters and NCI common terminology safety assessment, including focus on serious adverse events and the infection module. This will be collected in person during study visits, but in between study visits, a phone call will be made at weeks 2, 4,8,10,14,16, 20 and 22 to review adverse events.

Patient evaluations include:
1. Vital sign measurement, physical examination

2. Laboratory parameters for hematology, routine chemistry, muscle enzymes and urinalysis
3. NCI Common Toxicity assessment (version 4.0 June 2010) including focus on serious adverse events and the infection module.
4. Adverse event monitoring
5. Assessment of primary and secondary efficacy endpoints

4.0 SUBJECT POPULATION

Enrolled patients will include male and female, adults with a definite or probable diagnosis of JDM and pediatric patients ≥ seven years of age and older with definite or probable JDM (using the criteria of Bohan and Peter-Appendix A) [33] with greater than four months of disease duration. Patient body weight will be at least 25 kg. Patient enrolment will occur at the GWU Myositis Center of the Medical Faculty Associates. The total number of subjects will be 10. A diagnosis of DM prior to age 18 is considered JDM; patients with JDM enrolled after age 18 will continue to be classified as JDM.

A log will be kept of all patients screened for study enrollment and will document the reasons for exclusion for each subject not entered. Every effort will be made to keep patients in the study until they complete all study procedures. We plan to screen up to 30 patients in clinic to enroll 10 patients. Additional patients may be screened by phone and not seen in clinic if not qualified for the protocol.

4.1 Inclusion Criteria:

In order to qualify for participation, a subject must meet all of the following criteria:

1	**Considering 1A-1F below, does the subject have documented criteria for probable (2 + rash) or definite (3-4 + rash) juvenile DM by the criteria of Bohan and Peter?**
	a. Does the subject have documented symmetric proximal muscle weakness on exam? b. Does the subject have documented Gottron's papules or Heliotrope rash on exam? c. Does the subject have documented elevations of any of the following muscle enzymes (CK, LD, AST, ALT or aldolase)? d. Was the age at diagnosis < 18 years? e. Has the subject had an EMG and if so, if so, does the subject have documented EMG evidence for myopathy f. Does the subject have documented muscle biopsy evidence of dermatomyositis?
2	**Is the body weight at least 25 kg or over?**
3	**Is the subject at least 7 years or older?**
4	**Does the patient reside within the United States or Canada?**
5	**Considering 5A-5J below, Does the patient have refractory myositis? (As defined by the intolerance to or an inadequate response to corticosteroids plus at least one other IS agent?)**
	a. Has the patient had intolerance or an inadequate response to prednisone for at least one month?
	b. Has the patient had intolerance at any time, or an inadequate response for at least 3 months to azathioprine at least 2 mg/kg/d or 150 mg/day?
	c. Has the patient had intolerance or an inadequate response to methotrexate at least 15 mg/week or 0.3 mg/kg or 15 mg/m^2/ week for at least 3 months?
	d. Has the patient had intolerance or an inadequate response to mycophenolate mofetil at least 30 mg/kg/d or 1000 mg bid for at least 3 months?
	e. Has the patient had intolerance or an inadequate response to cyclophosphamide at least 1.0 mg/kg/d poor 500 mg/m^2/month IV for at least 3 months?
	f. Has the patient had intolerance or an inadequate response to oral tacrolimus for at least 3 months?
	g. Has the patient had intolerance or an inadequate response to cyclosporine at least 2.5 mg/kg/d for at least 3 months?
	h. Has the patient had intolerance or an inadequate response to IVIG at least 1.0 g/kg/month for at least 3 months?

	i. Has the patient had intolerance or an inadequate response to an anti-TNF agent (including Etanercept, Infliximab, Humira, etc) for at least 3 months?
	j. Has the patient had intolerance or an inadequate response to 2 infusions of Rituximab (375mg/m^2 (for 4 doses), or 500 mg/m^2 or 1000 mg for 2 doses)?
6	**Considering 6a-6f, Does the patient have a moderately active disease (MD global VAS with a minimum value of 2,5 cm on a 10 cm scale plus another 2 other abnormal Core set Measures as listed above (7b-7f)**
	a. Does the MD global VAS have a minimum value of 2.5 cm on a 10 cm scale
	b. Is the MMT-8 score no greater than 125/150
	c. Does the Patient/parent Global VAS have a minimum value of 2.0 cm on a 10 cm scale
	d. Does the CHAQ/HAQ disability index have minimum value of 0.25
	e. Is at least one of the muscles enzymes (including CK, aldolase, LDH, AST and ALT) elevated at a minimum level of 1.3 times the upper limit of normal. If more than one muscle enzyme is identified as being elevated and meeting the above guidelines, then the most abnormal will be selected and this enzyme will be the target enzyme followed to evaluate disease improvement or worsening.
	f. Does the Global extra-muscular disease have a score with a minimum value of 2 cm on a 10 cm VAS scale.
7	Is the prednisone dose stable for 4 weeks prior to the screening visit? (recommended dose ≤ 1.0 mg/kg/day)
8	Background therapy with at least 1 non-corticosteroid immunosuppressive agent is required at a stable dose (timeframe mentioned below) prior to the screening visit with the following exception: • *There is written documentation in the medical record that the patient is intolerant of an IS agent which is defined as side effects that require discontinuation of the medication(s) or an underlying condition that precludes the further use of the IS medication*. Stable dose for 4 weeks: Prednisone, IVIG, IV Methylprednisolone Stable dose for 6 weeks: Methotrexate, Azathioprine, mycophenolate mofetil, leflunomide, cyclophosphamide, tacrolimus or cyclosporine
9	Did an immunosuppressive agent, discontinued prior to the screening visit, have the required washout period: • 4 weeks for prednisone, IV methylprednisolone and methotrexate • 8 weeks for other IS agents including IVIG, Azathioprine, mycophenolate, mofetil, leflunomide, cyclophosphamide, tacrolimus or cyclosporine. • For discontinuation of biologic therapies-with the required washout period

	Half-life	Waiting period before enrollment (5 half-lives)	Washout Period
Etanercept	70 hours	15 days	1 month
Adalimumab	14 days	70 days	2 months

	washout period for Rituximab is 3 month+ and CD19 has to be detectable and IgG level is within normal limits (normal serum levels of IgG per reference lab: 7-9 years ≥572 mg/dl, 10-11 yrs ≥698 mg/dl, 12-13 yrs ≥759 mg/dl, 14-15 yrs ≥716 mg/dl,16-19 yrs ≥549 mg/dl, >19 yrs ≥700 mg/dl).
10	If on hydroxychloroquine or colchicine, the dose should be stable for 6 weeks prior to Visit 1
11	Is the statin or fibric acid derivative drug dose stable for 6 weeks prior to the screening visit?
12	Ability of patient or parent to complete self-report questionnaires.
13	If of reproductive potential**, does the patient agree to use a reliable method of birth control during the 24 week duration of the trial and for 100 days after the last dose of study drug was administrated?
14	Does patient agree to forgo immunization with a live vaccine during the course of the study and for at least 3 months after discontinuation of study drug?
15	Patients must have a letter from the referring rheumatologist or specialist supervising the care of the JDM, agreeing to the patient's participation in the study and to continuing to provide care for the patient, including emergency care during the trial.
16	Has the patient or parent provided informed consent, and assent when applicable for patients ages 8-17 or younger, for participation in study?
17	For children of divorced or separated parents: A copy of the parental custody papers will be received. One parent has sole custody and will sign the consent, OR There is joint custody and 1 parent gives permission for the other parent to sign consent/be in charge of medical decisions, OR Both parents sign the consent

****Age and Reproductive Status Reproductive Status: Definition of Women of Child-Bearing Potential (WOCBP).** WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who are not post-menopausal.

The following women are WOCBP:

- Women using the following methods to prevent pregnancy: Oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as intrauterine devices or barrier methods (diaphragm, condoms, spermicides).
- Women who are practicing abstinence.
- Women who have a partner who is sterile (e.g., due to vasectomy).

WOCBP must be using an acceptable method of contraception to avoid pregnancy throughout the study and for up to 10 weeks after the last dose of study drug in such a manner that the risk of pregnancy is minimized.

WOCBP must have a negative urine pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of HCG) within 0 to 48 hours before the first dose of study drug.

Women must not be breast-feeding.

Sexually active fertile men must use effective birth control if their partners are WOCBP.

4.2 Exclusion Criteria

In order to qualify for participation, subjects must not meet any of the following criteria:

1	Drug-induced myositis (myositis in patients taking medications known to induce myositis-like syndromes, including, but not limited to, statin agents, fibric acid derivatives, and colchicine).
2	Juvenile polymyositis; inclusion body myositis; cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer except basal or squamous cell skin cancer or carcinoma in situ of the cervix if at least 5 years since excision

3	Myositis in overlap with another connective tissue disease (CTD) that precludes the accurate assessment of a treatment response (for example, difficulty in assessing muscle strength in a scleroderma patient with associated myositis)
4	History of receiving a live vaccine 4 weeks prior to initiation of study treatment
5	Does the patient have any of the following concomitant illnesses that would prevent adequate assessments or in the opinion of the investigator pose an added risk to patient: a. Joint disease, severe calcinosis, or other musculoskeletal condition which precludes the ability to quantitate muscle strength b. Wheelchair bound c. Recurrent or chronic infections, including HIV, hepatitis B or C, TB (incl contact with household contact with active TB and no prophylaxis), or recurrent or active infections with calcinosis d. Symptomatic herpes zoster or herpes simplex (not including just simple oral HSV lesions) within past 12 weeks e. Disseminated/complicated herpes zoster (multi-dermatomal involvement, ophthalmic zoster, CNS involvement, post-herpetic neuralgia f. Known liver disease (i.e. cirrhosis or other conditions compromising the synthetic function of the liver) g. Disorder that would preclude accurate assessment of neuromuscular function? h. Cardiomyopathy or arrhythmias that in the investigators opinion poses an additional risk for study participants. i. New York Heart Association Classification III or IV for congestive heart failure. j. Psychiatric illness that precludes compliance or neuromuscular assessment k. Life threatening non-myositis illness that would interfere with the patient's ability to complete the study l. History of cancer within the last 5 years
6	Known hypersensitivity to abatacept or prior receipt of abatacept
7	Serum creatinine > 2.0mg/dl
8	Pregnant females or nursing mothers
9	Known or suspected history of drug or alcohol abuse within the past 6 months as determined by the medical record or patient interview
10	Anticipated poor compliance
11	Participation in another clinical experimental therapeutic study within 30 days of screening visit.
12	Any history or evidence of severe illness or any other condition that would make the patient, in the opinion of the investigator unsuitable for the study.
13	Low total WBC <2.000, platelets ≤ 100,000/mm^3; hemoglobin ≤10 gm/dl

14	History of recurrent infection including active skin infections with calcinosis
15	Is the patient receiving and concomitant treatment with anti-TNF therapies, rituximab or anakinra or other biologic therapies? Washout period for etanercept is 1 month and anakinra is 1 week Washout period for adalimamub and infliximab is 2 months Washout period for Rituximab is 3 and CD19 has to be detectable and IgG level is within normal limits (normal serum levels of IgG per reference lab: 7-9 years ≥572 mg/dl, 10-11 yrs ≥698 mg/dl, 12-13 yrs ≥759 mg/dl, 14-15 yrs ≥716 mg/dl,16-19 yrs ≥549 mg/dl, >19 yrs ≥700 mg/dl).
16	Initiation of colchicine and hydroxychloroquine as new drugs during study participation is not allowed.
17	Initiation of statins or fibric acid derivatives during study participation is not allowed.
18	Initiation of an exercise program within 4 weeks of the screening visit. Only a stretching program may be initiated during the study
19	Prisoners or subjects who are involuntarily incarcerated.
20	Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

5.0 CONCOMITANT MEDICATIONS

One of the important issues of trial design involves the use of concomitant medications. IMACS has addressed this by survey and consensus conference format and both adult and pediatric specialists agreed that concomitant corticosteroids should be allowed in a clinical trial, but tapering should follow a standardized reduction regimen. If the patient has achieved the Definition of Improvement (DOI) at week 6 (visit 2) or at any point **thereafter rated moderate improvement compared to the baseline visit and/or mild improvement compared to the last**

visit, tapering of corticosteroids may commence using a dose reduction schedule as follows:

- For patients taking 36 to 60 mg daily, prednisone will be tapered by 10 mg , if they meet the DOI and are rated as at least “at least “mild improvement” compared to the last visit and/or “Moderate improvement” compared to the baseline visit ” by both the physician and the patient or parent (if patient is less than 18 years of age).

- For patients taking 16 to 35 mg daily, prednisone will be tapered by 5 mg , if they meet the DOI and are rated as at least “at least “mild improvement” compared to the last visit and/or “Moderate improvement” compared to the baseline visit ” by both the MD and the patient or parent (if patient is less than 18 years of age).

- For patients taking 6 to 15 mg daily, prednisone will be tapered by 2.5 mg , if they meet the DOI and are rated as at least “at least “mild improvement” compared to the last visit and/or “Moderate improvement” compared to the baseline visit ” by both the MD and the patient or parent (if patient is less than 18 years of age).

- For patients taking 1 to 5 mg daily, prednisone will be tapered by 1 mg if they meet the DOI and are rated as at least “at least “mild improvement” compared to the last visit and/or “Moderate improvement” compared to the baseline visit ” by both the MD and the patient or parent (if patient is less than 18 years of age).

- For patients receiving intravenous pulse methylprednisolone therapy, they may alternatively reduce the dose of IV therapy, instead of oral by a decrease of 25% if they meet the DOI and are rated as at least “at least “mild improvement” compared to the last visit and/or “Moderate improvement” compared to the baseline visit ” by both the MD and the patient or (parent if patient is less than 18 years of age).

- Corticosteroid tapering using the aforementioned guidelines can be commenced at any time on or after week 6 if (a) the patient achieves the DOI and **is rated as at least “mild improvement” compared to the last visit and/or “Moderate improvement” compared to the baseline visit** by both the MD and the patient or parent (for patients less than 18 years of age) or (b) there are complications or circumstances that, in the investigator’s opinion, necessitate the tapering of corticosteroids. The taper schedule is at each visit and the corticosteroid dose will remain stable between study visits. As noted above under Inclusion Criteria #6, it is recommended that patients be on less than 1 mg/kg/day of prednisone at study entry.

Corticosteroid dosing in disease flare:

If in the clinical investigator’s opinion, there are complications or worsening of disease that necessitate an increase in the corticosteroid dose, then the smallest reasonable increase should be considered.

A stable dose of an immunosuppressive (IS) agent must be maintained for a period of 4-6 weeks prior to Visit 1. The dose(s) should be held constant without tapering (unless there is a serious adverse event).

Medications known to induce myositis-like syndromes, including but not limited to, statin agents, fibric acid derivatives, colchicine, and hydroxychloroquine will be subject to the following restrictions. See Tables 1, 2 & 3 below.

5.1 Pre-study drug restrictions

Table 1

Drug	**Restrictions**
Biologic Agents	See Table Below for washout period.
Prednisone	Stable dose for 4 weeks prior to Visit 1 If discontinued, a washout of 4 weeks is required
IVIG (JDM)	Stable regimen 4 weeks prior to Visit 1. If discontinued a washout period of 8 weeks is required.
IV methylprednisolone (pulse therapy)	Stable regimen 4 weeks prior to Visit 1 If discontinued, a washout of 4 weeks is required
Methotrexate	Stable dose for 6 weeks prior to Visit 1 If discontinued, a washout of 4 weeks is required
Other immunosuppressive agents including: azathioprine, mycophenolate mofetil, leflunomide, cyclophosphamide, tacrolimus or cyclosporine	Stable dose for 6 weeks prior to Visit 1 If discontinued, a washout of 8 weeks is required
Statin agents: Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin and Fibric acid derivatives: Fenofibrate (Lipidil™, Lipidil micro™, Tricor), Gemfibrozil (Lopid™), Benafibrate (Bezalip™), Clofibrate (Atromid-S)	Stable dose for 6 weeks prior to Visit 1
Colchicine	Stable dose for 6 weeks prior to Visit 1
Hydroxychloroquine	Stable dose for 6 weeks prior to Visit 1

	Half-life	Waiting period before enrollment (5 half-lives)	Washout Period
Etanercept	70 hours	15 days	1 month
Adalimumab	14 days	70 days	2 months
Rituximab	32 days	160 days	3 months
Infliximub	9 days	45 days	2 months
Anakinra	6 hours	1 day	1 week

*For rituximab, CD19 has to be detectable and IgG level is within normal limits (normal serum levels of IgG per reference lab: 7-9 years ≥572 mg/dl, 10-11 yrs ≥698 mg/dl, 12-13 yrs ≥759 mg/dl, 14-15 yrs ≥716 mg/dl,16-19 yrs ≥549 mg/dl, >19 yrs ≥700 mg/dl).

5.2 Concomitant Medications Allowed for the Duration of the Study

Table 2

Drug	Restrictions
Prednisone	Stable dose for 4 weeks prior to Visit 1 (see tapering/escalation guidelines above under section 5.0)
IVIG	Stable regimen for 4 weeks prior to Visit 1
IV methylprednisolone (pulse therapy)	Stable regimen for 4 weeks prior to Visit 1
Methotrexate and other IS agents including azathioprine, mycophenolate mofetil, leflunomide, cyclophosphamide, tacrolimus or cyclosporine	Stable dose for 6 weeks prior to Visit 1
Statin agents: Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin and Fibric acid derivatives: Fenofibrate (Lipidil ™, Lipidil micro ™, Tricor), Gemfibrozil (Lopid ™), Benafibrate (Bezalip ™), Clofibrate (Atromid-S)	Stable dose for 6 weeks prior to Visit 1
Colchicine	Stable dose for 6 weeks prior to Visit 1
Hydroxychloroquine	Stable dose for 6 weeks prior to Visit 1

*When possible, patients will take no more than 2 immunosuppressive agents, not including prednisone, IVIG, colchicine, hydroxychlorloquine

5.3 Concomitant Medications Not Allowed for the Duration of the Study

Table 3

Drug	Restrictions
Biologic agents	Not allowed throughout study
Colchicine	Initiation of new therapy is not allowed after Visit 1 or throughout enrollment.

Fibric acid derivatives: Fenofibrate (Lipidil™, Lipidil micro™, Tricor), Gemfibrozil (Lopid™), Benafibrate (Bezalip™), Clofibrate (Atromid-S)	Initiation of new therapy is not allowed after Visit 1 or throughout enrollment
Statin agents: Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin	Initiation of new therapy is not allowed after Visit 1 or throughout enrollment
Hydroxychloroquine	Initiation of new therapy is not allowed after Visit 1 or throughout enrollment.

IVIG and IV methylprednisolone use throughout the trial:

- These medications will be allowed during the trial.
- Patients must be on a stable regimen of 4 weeks prior to Visit 1.
- Dose of IVIG and dosing interval of both agents must remain stable.
- Suggested guidelines for IVIG: one (1) - two (2) grams / kg monthly

Suggested guidelines for IV methylprednisolone or equivalent 10 - 30 mg/kg: IV once weekly to IV once per month.

5.4 Other Restrictions

- A patient may continue with an exercise program that was initiated before the 4 week period prior to the screening visit, regardless of the components of the program (stretching, muscle building, etc.)
- A stretching program may be initiated during the 4 week period prior to the screening visit or during the study period as long as there is no muscle building component to the program.

6.0 STUDY MEDICATION

Study Treatment: **Abatacept**

Definition of Investigational Product: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way

different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.
In this protocol, the investigational product is abatacept. Abatacept will be provided by BMS in 50 mg pre-filled syringes, 87.5 mg pre-filled syringes and 125 mg prefilled syringes.

6.1 Study Medication Description

Abatacept Injection, 125 mg/Syringe (125 mg/mL), is a sterile solution for SC administration, which contains approximately 125 mg abatacept, 171 mg sucrose, 8 mg Poloxamer 188, 0.29 mg monobasic sodium phosphate, monohydrate, and 0.84 mg dibasic sodium phosphate, anhydrous, in Water for Injection. 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.

Two presentations of Abatacept Injection 125 mg/Syringe are currently commercialized:

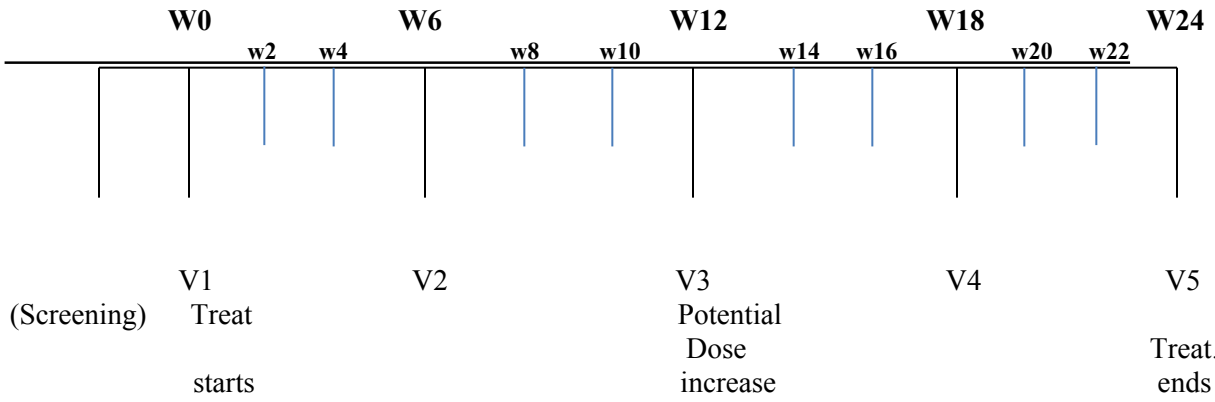
- Abatacept injection prefilled syringe with UltraSafe Passive Needle Guard (SSI NeedleGuard) and flange extenders
- Abatacept injection prefilled syringe with flange bags have been observed.

Abatacept injection, 50 mg/syringe (50 mg/ml) and Abatacept injection, 87.5 mg/syringe (87.5 mg/ml) will also be available for subjects with body weight <50 kg

6.2 Study Medication Schedule

At Visit 1 (week 0), eligible subjects will be instructed on the use and potential side effects of subcutaneous abatacept and will be started on the study drug (abatacept 125 mg SQ weekly for subjects with body weight ≥ 50, or abatacept 87.5 mg SQ weekly for subjects with body weight < 50 kg)). Subjects will be on weekly Abatacept for the duration of the study (from week 0 through week 24). For patients not improving with therapy by at least 5% on at least 3 of 6 core set measures at week 12 (visit 3), and rated as unchanged or worsened from visit 1 by the study physician, they would be offered the opportunity to increase their dose of treatment to abatacept 212.5 mg (125 mg prefilled syringe plus 87.5 mg prefilled syringe) weekly subcutaneously for subjects with body weight ≥ 50 kg or to abatacept 137.5 mg (87.5 mg prefilled syringe plus 50 mg prefilled syringe) for subjects withy body weight < 50 kg, or to continue on their present dose.

STUDY SCHEMATIC



The short lines indicate phone follow-ups, which will occur at weeks 2, 4, 8, 10, 14, 16, 20 and 22

An open label extension phase will be offered for up to 6 months (visit could be in time less than that) for patients meeting the definition of improvement and who are rated by their study physician as at least minimally improved.

6.3 Drug Ordering and Accountability

Initial Orders: The BMS project manager will be contacted for study drug requirements.

Re-Supply: The BMS project manager will be contacted for study drug requirements.

Packaging and Labeling: Abatacept SC is supplied in a box of 4 syringes.

Handling and Dispensing:

Administration of Study Medication
The investigational product will 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 by authorized personnel, as dictated by local regulations.

The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity), as described below:

Abatacept SC formulations (prefilled syringes) will be stored under refrigeration (approximately 2 to 8°C) and protected from long-term (more than 24 hours) exposure to light.

Abatacept injection, 125 mg/syringe (125 mg/mL) is ready to use solutions provided in pre-filled siliconized syringes with a 29 gauge needle.

Abatacept injection, 50 mg/syringe (50 mg/ml) and Abatacept injection, 87.5 mg/syringe (87.5 mg/ml) will also be available for subjects with body weight <50 kg

Care will be taken when handling the injectable drug products that are used in this protocol. Proper aseptic techniques will be used
Patients will be instructed to inject the full amount in the syringe (1 mL), which provides either 125 mg of Abatacept or 87.5 mg. At week 12 and weekly until the end of the study, some patients (those without improvement by at least 5% who are rated as unchanged or worsened by the study physician and those who agreed to this dose change) will be instructed to inject the full amount of a second syringe (1 ML) containing 87.5 mg of abatacept for subjects with body weight ≥ 50 kg or a second syringe containing 50 mg of abatacept for subjects with body weight < 50 kg.
Abatacept injection should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ABATACEPT prefilled syringes should not be used if exhibiting particulate matter or discoloration. ABATACEPT should be clear and colorless to pale yellow, according to the directions provided in the Instructions for Use.

Injection sites (abdomen, thigh, upper arms) should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

6.4 Storage and Accountability

All study drugs must be kept in a secure location under appropriate storage conditions (see investigator brochure). The medication provided for this study is for use only as directed in the protocol. GWU Medical Faculty Associates will be responsible for the storage, handling, and dispensing of study drug. GWU Medical Faculty Associates will monitor all documentation related to drug handling activities to ensure adherence to proper procedures. At each study visit, GWU Medical Faculty Associates will dispense the required study medication needed until the next study visit.

All used and unused study drugs must be retained at the clinic for reconciliation and accountability and should be destroyed at the study site by authorized personnel according to approved procedures or collected by the monitor for disposal.

7.0 TREATMENT PLAN

All subjects must sign the informed consent form (ICF) and if applicable privacy authorization for release of health information prior to initiating any screening procedures including: discontinuing/changing or withholding (washout) of any medication. It is expected that after being consented, if any subject is using a

concomitant medication where his/her dosage has not met the stable dose time frame outlined in Section 5.0 the subject will be asked to return to the site after the appropriate timeframe to complete the Visit 1 procedures. This return to the site would be considered a continuation of screening visit. At no time should a subject withhold medication prior to signing the ICF. The visit schedule is outlined in "Treatment Protocol Schedule."

The original signed patient consent form will be kept in the patient's source document study folder and maintained at the clinical site. A copy of the signed patient consent form will be given to the study participant.

7.1. Details on Treatment Schedule and Procedures

A schedule of all study visits and assessments is provided in Appendix E, table 1. Appendix E, Table 2 provides all laboratory studies being performed on screening and throughout the trial. **Patient should be encouraged to adhere to the study visit schedule unless an emergency occurs preventing compliance.**

Screening/enrollment
Subjects will be screened at the screening visit to determine their eligibility for enrollment. The following data are to be collected at Screening Visit for every patient and recorded in the CRF.

- Obtain written informed consent for screening and treatment phase of study, and privacy authorization for release of medical information to include muscle biopsy results and tissue if done previously.
- Demographics: date of birth, sex, race
- Diagnosis of definite or probable JDM by Bohan and Peter criteria (or JDM by newly-developed myositis classification criteria after approval by American College of Rheumatology), and date of diagnosis
- Review inclusion and exclusion criteria for eligibility for study and verify that inclusion/exclusion criteria have been met
- Obtain and record medication history
- Obtain referring physician's contact information, patient release to share information, and agreement with patient's potential entry into trial
- Medical and surgical history: past and current medical and surgical history relevant for purpose of the study.
- Vital signs: height (m), weight (kg), pulse (beats/min), blood pressure (mmHg), and pulse oximetry
- History and physical examination
- Core set measures: CMAS, MMT-8, MDAAT (Extra-muscular Global activity), MD global activity (VAS), MD global damage (VAS), Patient-parent global activity (VAS), CHAQ/HAQ

- Obtain laboratory samples for clinical chemistry (Chem-20, GGT), complete blood count (CBC) with differential, urinalysis, muscle enzymes (CK, LDH, aldolase, AST, ALT), GGT; serologies: HIV antibody, Hepatitis B surface antigen, Hepatitis B core antigen, and hepatitis C antibody , CD19 (for those who received rituximab before) Quantiferon will be completed at the screening visit. If the Quantiferon is indeterminate, then a T spot or PPD will be done.
- Urinalysis
- Collect urine sample for pregnancy for females of child bearing potential (where applicable) Post-menopausal females defined as ≥ age 60 and twelve (12) consecutive months of amenorrhea (lack of menstruation) will not be required to undergo pregnancy testing
- Perform radiographic examination of chest

Some patients may wish to obtain screening labs at home and present the results at the screening visit. This would enable them to enter the intervention phase at the same visit as the screening visit. Results dated within 6 weeks prior to screening visit will be accepted to satisfy eligibility criteria.

All safety labs during the regular study visit may be completed at the home institution up to 10 days prior to the visit and reports sent to GW.

A re-screen protocol will be followed if a period of greater than 45 days elapses between the screening visit and start of treatment.

Visit 1/Week 0 (Intervention phase)

Visit 1(week 0) will occur 0- 45 days after all initial screening evaluations are concluded and the results of screening testing procedures are completed. The subject must remain in the clinic for 15 minutes following administration of study drug. The following evaluations/procedures will be performed at this visit.

- Review of inclusion/exclusion criteria
- NCI Common Toxicity Assessment
- Obtain vital signs (HR,BP,RR, oral temperature and weight, and if indicated , by history of shortness of breath or lung disease, pulse oximetry)
- Medical history and perform a full physical examination
- Collect urine sample for pregnancy test for females of child bearing potential prior to administration of study medication (where applicable)
- Core set activity measures: physician global activity, patient/parent global activity, manual muscle testing (MMT-8), CMAS, HAQ/CHAQ, MDAAT, muscle enzymes, CHQ PF-50/SF- 36, and Disease Activity Score (DAS)
- Myositis Damage Index (MDI): assessment of disease damage completed by the physician during physical examination.
- Physician global damage (VAS)
- Dermatology assessment: CDASI, MD Global Skin Activity + Damage (Optional)
- CDASI, photographs of skin rashes, periungual nailfold capillary assessment.

- Quality of life questionnaires: CHQ PF-50/SF- 36,Dermatology Life Quality Index (DLQI), PROMIS/fatigue, Peds QL fatigue
- Muscle MRI: bilateral thighs and pelvis, axial STIR and T1 images
- Plain radiographs for calcinosis for patients with calcinosis
- Obtain blood samples for Chem-20,GGT, CK, aldolase, LDH, CBC with diff., TSH, anti-thyroid antibodies, von Willebrand Factor antigen level, quantitative immunoglobulins (IgG, IgM, IgA), ANA, ENA, dsDNA, Lymphocyte flow cytometry (TBNK cells)
- Urinalysis
- Collect pre -treatment research blood samples for Immunophenotyping (T, B cells and macrophages), gene expression, and cytokine/chemokine analysis (see Section 3.1.h)
- Myositis specific and associated autoantibody testing
- Collect pre -treatment blood samples for immunogenicity
- Pregnancy test for females of child bearing potential (where applicable)
- Administer first dose of study medication and observe after the injection for at least 15 minutes
- Schedule and instruct the subject to return for the next visit, teaching injection technique, review medication administration log.

Phone follow-up #1 (14 days (+/- 7 days after visit 1)

- Adverse events will be reviewed and recorded (NCI Common Toxicity criteria version 4.0).

Phone follow-up #2 (**will occur 28 days (+/- 7 days) after visit 1.**

- Adverse events will be reviewed and recorded.

Visit 2 (week 6) will occur 42 days (+/-10 days) after visit 1

- Review concomitant medication and query for adverse events and document in CRF
- NCI Common Toxicity Assessment
- Obtain vital signs (HR,BP,RR, oral temperature and weight) and if indicated , by history of shortness of breath or lung disease, pulse oximetry)
- Medical history and perform a full physical examination
- Collect urine sample for pregnancy test for females of child bearing potential prior to administration of study medication (where applicable)
- Core set activity measures: physician global activity, patient/parent global activity, manual muscle testing (MMT-8), CMAS, HAQ/CHAQ, MDAAT, muscle enzymes, CHQ PF-50/SF- 36, and Disease activity score (DAS), physician global damage (VAS)
- Dermatology assessment: CDASI, photographs of skin rashes
- Quality of life questionnaires: CHQ PF-50/SF- 36,DLQI, PROMIS/fatigue, and Peds QL fatigue
- Physician and patient/parent assessment of study outcome

- Obtain blood samples for Chem-20, GGT, CK, aldolase, LDH, CBC with diff., von Willebrand Factor antigen level ***[may be performed at home institution, up to 10 days before the visit date]***
- Urinalysis
- Collect urine sample for pregnancy test for females of child bearing potential (where applicable)
- Prednisone taper may commence using a predetermined schedule (section 5) If the patient has achieved the Definition of Improvement (DOI) and is rated by the study physician as at least minimally improved.
- Review log of medication self-administration and pharmacy to dispense study medication needed before next visit
- Administer dose of study medication and observe after the injection for at least 15 minutes
- Schedule and instruct the subject to return for the next visit

Phone follow-up #3 (14 days (+/- 7 days after visit 2)

- Adverse events will be reviewed and recorded (NCI Common Toxicity criteria version 4.0).

Phone follow-up #4 (**will occur 28 days (+/- 7 days) after visit 2.**

- Adverse event will be reviewed and recorded.

Visit 3 (week 12) will occur 42 days (+/- 10) days after Visit 2

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- Review concomitant medication and query for adverse events and document in CRF.
- NCI Common Toxicity Assessment
- Obtain vital signs (HR,BP,RR, oral temperature and weight) and if indicated , by history of shortness of breath or lung disease, pulse oximetry)
- Medical history and perform a full physical examination
- Collect urine sample for pregnancy test for females of child bearing potential prior to administration of study medication (where applicable)
- Core set activity measures: physician global activity, patient/parent global activity, manual muscle testing (MMT-8), CMAS, HAQ/CHAQ, MDAAT, muscle enzymes, CHQ PF-50/SF- 36, and Disease activity score (DAS), physician global damage (VAS)
- Quality of life questionnaires: CHQ PF-50/SF- 36,DLQI , PROMIS/fatigue and Peds QL fatigue
- Physician and patient/parent assessment of study outcome
- Dermatology assessment performed by Rheumatologist : CDASI, photographs of skin rashes, periungual nailfold capillary assessment Dermatology Assessment Performed by Derm: CDASI, MD Global Skin Activity + Damage (Optional)

- Obtain blood samples for Chem-20,GGT, CK, aldolase, LDH, CBC with diff., von Willebrand Factor antigen level, Lymphocyte flow cytometry (TBNK cells) ***[may be performed at home institution, up to 10 days before the visit date]***
- Urinalysis
- Collect research blood samples for Immunophenotyping (T, B cells and macrophages), gene expression and cytokine/chemokine analysis (see Section 3.1.h)
- Review if patient improved by ≥ 5% in at least 3 of 6 core set measures (by IMACS or PRINTO measures). If patient did not meet this criterion and was rated by the study physician as unchanged or worsened since visit 1, an option to increase the dose to 212 mg (87.5 + 125 mg) SQ weekly for subjects with body weight ≥ 50 kg or to increase the dose to 137.5 mg (87.5 mg + 50 mg) for subjects with body weight < 50 kg will be presented.
- Prednisone taper may commence using a predetermined schedule (section 5) If the patient has achieved the Definition of Improvement (DOI) and is rated by the study physician as at least minimally improved.

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- Collect blood samples prior to the injection at Week 12 for PK and immunogenicity assessment

- Review log of medication self-administration and pharmacy to dispense study medication needed before next visit
- Administer dose of study medication and observe after the injection for at least 15 minutes
- Schedule and instruct the subject to return for the next visit

Phone follow-up #5 (14 days (+/- 7 days after visit 3)

- Adverse events will be reviewed and recorded (NCI Common Toxicity criteria version 4.0).

Phone follow-up #6 (**will occur 28 days (+/- 7 days) after visit 3.**

- Adverse event will be reviewed and recorded.

Visit 4 (week 18) will occur 42 days (+/-10 days) after visit 3

- Review concomitant medication and query for adverse events and document in CRF.
- NCI Common Toxicity Assessment
- Obtain vital signs (HR,BP,RR, oral temperature and weight) and if indicated , by history of shortness of breath or lung disease, pulse oximetry)

- Medical history and perform a full physical examination
- Collect urine sample for pregnancy test for females of child bearing potential prior to administration of study medication (where applicable)
- Core set activity measures: physician global activity, patient/parent global activity, manual muscle testing (MMT-8), CMAS, HAQ/CHAQ,MDAAT, muscle enzymes, CHQ PF-50/SF- 36, and Disease activity score (DAS), physician global damage (VAS)
- Quality of life questionnaires: CHQ PF-50/SF- 36,DLQI, PROMIS/fatigue and Peds QL fatigue
- Physician and patient/parent assessment of study outcome
- Obtain blood samples for Chem-20, GGT, CK, aldolase, LDH, CBC with diff., von Willebrand Factor antigen level ***[may be performed at home institution, up to 10 days before the visit date]***
- Urinalysis
- Prednisone taper may commence using a predetermined schedule (section 5) If the patient has achieved the Definition of Improvement (DOI) and is rated by the study physician as at least minimally improved.
- Review log of medication self-administration and pharmacy to dispense study medication needed before next visit
- Administer dose of study medication and observe after the injection for at least 15 minutes
- Schedule and instruct the subject to return for the next visit

Phone follow-up #7 (14 days (+/- 7 days after visit 4)

- Adverse events will be reviewed and recorded (NCI Common Toxicity criteria version 4.0).

Phone follow-up #8 (**will occur 28 days (+/- 7 days) after visit 4.**

- Adverse event will be reviewed and recorded.

Visit 5 (week 24) will occur 42 days (+/- 10) days after Visit 4 (End of Study Treatment or Early Termination)

- Review concomitant medication and query for adverse events and document in CRF.

- NCI Common Toxicity Assessment
- Obtain vital signs (HR,BP,RR, oral temperature and weight) and if indicated , by history of shortness of breath or lung disease, pulse oximetry)
- Medical history and perform a full physical examination
- Collect urine sample for pregnancy test for females of child bearing potential prior to administration of study medication (where applicable)
- Core set activity measures: physician global activity, patient/parent global activity, manual muscle testing (MMT-8), CMAS, HAQ/CHAQ, MDAAT, muscle enzymes, CHQ PF-50/SF- 36, and Disease activity score (DAS)
- Quality of life questionnaires: CHQ PF-50/SF- 36, DLQI , PROMIS/fatigue and Peds QL fatigue
- Myositis Damage Index (MDI): assessment of disease damage completed by the physician during physical examination. Physician global damage (VAS)
- Physician and patient/parent assessment of study outcome
- Dermatology assessment performed by Rheumatologist: CDASI, photographs of skin rashes, periungual nailfold capillary assessment
- Dermatology Assessment performed by Dermatologist: CDASI, MD Global Skin Activity + Damange (Optional)
- Prednisone taper may commence using a predetermined schedule (section 5) If the patient has achieved the Definition of Improvement (DOI) and is rated by the study physician as at least minimally improved..
- Muscle MRI: bilateral thighs and pelvis, axial STIR and T1 images
- Plain radiographs for calcinosis for patients with calcinosis
- Obtain blood samples for Chem-20,GGT, CK, aldolase, LDH, CBC with diff., TSH, anti-thyroid antibodies, von Willebrand Factor antigen level, quantitative immunoglobulins (IgG, IgM, IgA), ANA, ENA, dsDNA, Lymphocyte flow cytometry (TBNK cells) ***[may be performed at home institution, up to 10 days before the visit date]***
- Collect research blood samples for Immunophenotyping (T, B cells and macrophages), gene expression and cytokine/chemokine analysis (see Section 3.1.h)
- Urinalysis
- Review log of medication self-administration
- Collect blood samples prior to the injection at Week 24 for PK and immunogenicity assessment
- Prednisone taper may commence using a predetermined schedule (section 5) if the patient has achieved the Definition of Improvement (DOI) and is rated by the study physician as at least minimally improved.
- Administer dose of study medication (abatacept) and observe after the injection for at least 15 minutes
- Patient terminates study enrollment and all study supplies are returned, or patient will continue on open-label extension: schedule and instruct the subject to return for the next visit

- An open label extension phase will be offered for up to 6 months for patients meeting the definition of improvement and who are rated by their study physician as at least minimally improved.
- If the subject chooses not to continue to be in the open label extension phase of the trial, the subject will be referred back to his/her local rheumatologist for further care. Subject terminates study enrollment and all study supplies are returned
- Subjects will receive their last injection of abatacept at week 24 even if they do not want to continue in the open label extension phase of the trial

Open label extension Visit (will occur within 6 months of visit 5)
An open label extension phase of up to 6 months duration will be offered to all patients meeting the definition of improvement and who are also rated as at least minimally improved from the baseline visit (visit 1). Patients must commit to at least one follow-up visit within 6 months of visit 5, which will be at their own expense for travel and testing costs. At each follow-up visit, the following will be performed:

- Review concomitant medication and query for adverse events and document in CRF.
- NCI Common Toxicity Assessment
- Obtain vital signs (HR,BP,RR, oral temperature and weight) and if indicated , by history of shortness of breath or lung disease, pulse oximetry)
- Medical history and perform a full physical examination
- Collect urine sample for pregnancy test for females of child bearing potential prior to administration of study medication (where applicable)
- Core set activity measures: physician global activity, patient/parent global activity, manual muscle testing (MMT-8), CMAS, HAQ/CHAQ,MDAAT, muscle enzymes, CHQ PF-50/SF- 36, and Disease activity score (DAS), physician global damage (VAS)
- Physician and patient/parent assessment of study outcome
- Obtain blood samples for Chem-20, GGT, CK, aldolase, LDH, CBC with diff.,
- Urinalysis
- Review log of medication self-administration
- Prednisone taper may commence using a predetermined schedule (section 5) If the patient has achieved the Definition of Improvement (DOI) and is rated by the study physician as at least minimally improved.
- Administer dose of study medication and observe after the injection for at least 15 minutes
- Patient terminates open-label extension. Patient is referred back to referring rheumatologist.

7.2 Laboratory Sample Collection
In case staff at the GW-MFA unable to get a reliable venous access for blood sample, the subject will be taken to the George Washington University Hospital to undergo ultrasound guided phlebotomy. The sample will then be carried to 2300 M Street location and processed there as per protocol.

8.0 DOSE MODIFICATION

The dose of abatacept will remain constant until week 12. For patients not improving with therapy by at least 5% on at least 3 of 6 core set measures at week 12, they would be offered the opportunity to increase their dose of treatment to abatacept 212 mg (87.5 + 125 mg) for subjects with body weight ≥ 50 kg or to abatacept 137.5 mg (87.5 mg+ 50 mg for subjects with body weight of < 50 kg) weekly subcutaneously, or to continue on their present dose.

9.0 DISCONTINUATION OF SUBJECTS

Subjects in this study may be discontinued for any of the following reasons:

- Severe allergic reaction to the study medication
- Participation in another investigational drug study
- Any medical condition which, in the opinion of the investigator, warrants discontinuation from the study for the safety of the patient, either as a cause of the study drug or Protocol violations, including non-compliance or inability to perform protocol-required procedures
- Voluntary withdrawal (withdrawal of consent)
- Pregnancy
- Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (e.g., 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 will notify BMS if a study subject becomes pregnant.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- If 3 or more patients develop a serious adverse event thought to be related to study drug, no new patients will be enrolled into the study until the adverse events have been reviewed by the Medical Safety Officer and/or Data Safety Monitoring Board.

Criteria for Disease Worsening (Appendix F):
Criteria for disease worsening in a clinical trial, by which patients could be termed treatment failures and offered alternative therapies, were preliminarily defined by IMACS. They will be incorporated into this trial and include:

- Physician global worsening of ≥ 2 cm on the 10 cm visual analog scale (VAS) and a worsening of the manual muscle testing by ≥ 20%, or
- Global extra muscular organ disease activity (a composite of constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiac activity) worsening by ≥ 2 cm on a 10 cm VAS, or
- 3 of any 6 IMACS core set activity measures worse by ≥ 30%.

In order to be classified as "worsening" in this trial, subjects will have to meet the above criteria and be classified by the physician as at least moderately worse (on the Assessment of Study Outcome form). It was also noted by IMACS that significant worsening in cardiac, pulmonary (interstitial lung disease) or GI organs (dysphagia or vasculitis), which, based on the opinion of the treating protocol physician, requires alternate therapy, should be considered as alternate worsening criteria, potentially leading to patients being removed from a trial or considered treatment failures.

All subjects who leave the trial after receiving study drug, regardless of cause, are recommended to obtain a termination evaluation prior to study termination. All patients receiving at least one dose of abatacept will be encouraged to remain in the trial and complete all study visits and phone follow-up evaluations to continue to assess safety.

Continuation of subjects after a serious adverse-event will be based on discussions between the Principal Investigator and Medical Safety Officer and/or Data Safety Monitoring Board. If 3 or more patients develop a serious adverse event thought to be related to study drug, no new patients will be enrolled into the study until the adverse events have been reviewed by the Medical Safety Officer and/or Data Safety Monitoring Board.

10.0 Treatment Compliance

All study drugs must be kept in a secure location under appropriate storage conditions. Access must be restricted to authorized personnel. The intake of all study drugs will be recorded in the Case Report Form (CRF) in a medication administration log. Patients will take home the medication needed until next protocol visit in a safe container box. Used vials must be returned for accountability. The medication provided for this study is for use only as directed in the protocol. GWU Medical Faculty Associates will be responsible for the storage, handling, and dispensing of study drug. The GWU Medical Faculty Associates will monitor all documentation related to drug handling activities to ensure adherence to proper procedures.

All unused study drugs must be returned to GWU Medical Faculty Associates for reconciliation and accountability and should be destroyed at the study site by authorized personnel according to approved procedures or collected by the monitor for disposal.

Study drugs are to be prescribed only by a physician named in the study form. Under no circumstances will the investigator allow the study drug to be used other than as directed by the protocol.

11.0 SAFETY ISSUES

SAFETY ASSESSMENTS

General
Safety assessments will include adverse events, vital signs, physical examination findings, laboratory parameters (hematology, serum chemistry, including BUN, creatinine, urinalysis) and NCI common toxicity safety assessment.

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12.0 ADVERSE EVENT REPORTING

12.1 Adverse Events

An adverse event (AE) is any reaction, side effect, or other undesirable or unexpected experience that occurs in conjunction with the use of the study drug, whether or not the experience is considered drug-related. New or worsening signs and symptoms of underlying or emerging disease are also considered adverse events. Adverse events will be tracked through routine communication with the subjects and the family.

12.1.1 Study Drug Relationship

The clinical site investigator will determine which events are associated with the use of study drug. For reporting purposes, an AE should be regarded as possibly related to the use of the investigational product if the investigator believes:

- There is a clinically plausible time sequence between onset of the AE and abatacept administration; and/or
- There is a biologically plausible mechanism for causing or contributing to the AE; and
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

An AE is deemed associated with the use of the study drug "if there is a reasonable possibility that the AE may have been caused by the drug" (21 CFR 312.32)

12.2 Immediately Reportable Events

There are 2 categories of medical events that could occur during participation in this clinical trial that must immediately be reported to Dr. Curiel. The categories are as follows:

- Death or other serious adverse experience (SAE)
- Pregnancy

A serious adverse event is any experience that results in one of the following: hospitalization or prolonged hospitalization, a life threatening event resulting in: death, significant or permanent disability, congenital anomaly/birth defect (in the case of unanticipated birth to a study participant), or requires intervention to prevent permanent damage.

Dr. Curiel will distribute reports of SAEs, which are both unexpected and related to the study medication, to the DSMB, the FDA, BMS Drug Safety, and to the Institutional Review Board. Reporting of adverse events will follow all applicable regulatory laws, guidelines and timeframes. Procedures for reporting adverse events are detailed in the Manual of Operations for this study.

12.3 Physical Examination Observations

Baseline observations from the Screening physical examination that worsen during the study will be recorded on the Adverse Event CRF page. Every effort should be made for the same physician to conduct all physical examination assessments on each subject. Care will be taken to avoid reporting worsening of initial physical examination observations which may result only from differing medical opinions when the same physician is not available to conduct pre-study, interim and end of study physical examinations.

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

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. Potential drug induced liver injury (DILI) us also considered an important medical event (see Section 7.6 for the definition of potential DILI).
- Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is a SAE.
- Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. An SAE report should be completed for any event where doubt exists regarding its status of seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

All SAEs, whether related or unrelated to abatacept, and all pregnancies must be reported to BMS and the Data Safety Monitoring Board (by the investigator or designee) within 24 hours.
All SAEs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:
SAE Email Address: Worldwide.Safety@BMS.com
SAE Fax Number: 609-818-3804

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

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

13.0 DATA SAFETY MONITORING PLAN

The Data Safety and Monitoring Board (DSMB) will be appointed under the direction of (to be named). DSMB members have no potential financial conflicts of interest. Written documentation attesting to the absence of conflict of interest will be required of all DSMB members on an annual basis. The ongoing review of data by this independent committee assures the investigators that the trial can continue without jeopardizing patient safety.

The DSMB will review the study protocol, recommend recruitment initiation, monitor all aspects of study (e.g., recruitment, protocol deviations, adverse events, data quality, descriptive characteristics, efficacy) and recommend protocol modifications, including early study termination.

Meetings of the DSMB will occur on an annual basis to review all aspects of the study (e.g., recruitment, adverse events, and efficacy). In addition, reports will be produced to show study progress according to a set schedule dictated by the DSMB. The DSMB will also receive reports of any serious adverse events within 24 hours and review together if 3 or more patients develop SAEs thought likely to be related to study drug.

14.0 ASSESSMENT TOOLS: description

The core assessment tools are available on the International Myositis Assessment and Clinical Studies (IMACS) Group website at:

1. IMACS website:
http://www.niehs.nih.gov/research/resources/imacs/imacsforms/
2. Disease activity core set measures:
http://www.niehs.nih.gov/research/resources/imacs/diseaseactivity/index.cfm
3. Disease damage core set measures:
http://www.niehs.nih.gov/research/resources/imacs/diseasedamage/index.cfm

Manual Muscle Testing. (MMT): MMT has been widely used in myositis therapeutic trials and clinical studies, previously as a primary end point (17) and more recently as part of a composite end point of core set measures (38). MMT has been modified to a shorter version called MMT-8, in which quantitative testing of eight proximal, distal and axial muscle groups tested unilaterally (using a 0-10 point scale) closely approximate a total MMT score of 26 groups tested bilaterally(42).

MMT- 8 is a set of 8 designated muscles tested unilaterally (potential score 0-80) or bilaterally (potential score 0-150)

Muscle Groups	**Right (0 – 10)**	**Left (0 – 10)**	**Axial (0 – 10)**
Axial Muscles (0 – 10)			
Neck Flexors	**X**	**X**	**0-10**
Proximal Muscles (0 – 100)			
Deltoid	**0-10**	**0-10**	**X**
Biceps brachii	**0-10**	**0-10**	**X**
Gluteus maximus	**0-10**	**0-10**	**X**
Gluteus medius	**0-10**	**0-10**	**X**
Quadriceps	**0-10**	**0-10**	**X**
Distal Muscles (0 – 40)			
Wrist Extensors	**0-10**	**0-10**	**X**
Ankle dorsiflexors	**0-10**	**0-10**	**X**
MMT-8 score (0 – 150)	**0-70**	**0-70**	**0-10**

Myositis Disease Activity Assessment Tool (MDAAT). This tool has been developed by IMACS. This is a comprehensive tool that captures the physician's assessment of disease activity of muscle, skin, joints, gastrointestinal tract, lung, and other organ systems. The MDAAT is a combined tool that includes the Myositis Disease Activity Assessment Visual Analog Scale (MYOTAC) and the Myositis Intention to Treat activities Index (MITAX).

The MYOACT is a series of physician's assessments of disease activity in various organ systems using a VAS to assess severity of activity that has been modified from the Vasculitis Activity Index (42) The MYOACT consists of a 10-cm VAS for each organ system to score the overall severity of activity in each and a global extra-muscular VAS. For the MYOTAC, each organ system has a single VAS; a global extra-muscular activity VAS is also scored.

The MITAX assesses specific manifestations in 7 organs/systems, including constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiac, and muscle. For the MITAX each question is answered as 0= not present; 1= improving, 2= the same, 2= worse, 4=new.

The key issue in relation to the MDAAT is to ensure that the items recorded are, in view of the physician, actually due to the active myositis and not due to disease damage, another unrelated process, or a side effect of medication.

Disease Activity Score (DAS): this tool assesses muscle and cutaneous manifestations, including vasculopathic features, based on bedside clinical assessment. The DAS consists of 19 items, resulting in a score of 0-20: 1) the presence or absence of weakness is assessed via 8 variables: neck flexors muscles, abdominal muscles, upper extremity proximal muscles, lower extremity proximal muscles, Gower's sign, abdominal gait, difficulty swallowing, and nasal speech. 2) Functional status consists of a 4-point scale, ranging from normal function to severe limitations in daily life functions. 3) The presence or absence of vasculitis is assessed by determining the presence of any one of the following: eyelid erythema, eyelid vessel dilatation, eyelid thrombosis, nailfold erythema, nailbed telangiectasia, dilatation of blood vessels on the palate, and "other vasculitis". 3) The presence of rashes is rated using polychotomous scales: the distribution of the involved skin is rated on a 4-point scale ranging from none to generalized, while the severity of skin involvement is rated on a 5-point scale, ranging from absent to severe. Gottron's papules are rated on a 4-point scale,(42)

Muscle Enzymes**:** Activity of at least one serum muscle enzyme from the following: creatine kinase (CK), aldolase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The most abnormal muscle enzyme will be chosen as the core measure to be followed.

MDI: Myositis Damage Index: The MDI scores damage, which is defined as persistent or permanent change in anatomy, physiology, and function that develops from previously active disease, complications of therapy, or older events.(42). The MDI measures specific manifestations in 11 organ systems. The MDI also includes a series of visual analog scales (VAS) to quantify damage severity in a given organ system.

Stanford HAQ/CHAQ: Health Assessment Questionnaire: The Stanford HAQ is a brief self-report questionnaire assessing physical function pertaining to activities of daily living in a variety of domains (42). Originally developed for use in rheumatoid arthritis, it has been successfully applied inflammatory myopathies. The C-HAQ was adapted directly from the HAQ and it has also been successfully applied to patient with juvenile myositis. (42).

Physician Global Assessment (MD Global Activity): It is a tool that measures the global evaluation by the treating physician of the overall disease activity of the patient at the time of assessment using a 10 cm. visual analogue scale and a 5 point Likert scale, validated by JDM study group.(43)

Patient/Parent Global Assessment Patient/Parent Global Activity, 0- 10 cm VAS.
It is a tool that measures the global evaluation by the patient, or by the parent if the patient is a minor, of the patient's overall disease activity at the time of assessment using a 10 cm. visual analogue scale. (Validated by JDM study group (43)

Childhood Myositis Assessment Score (CMAS) is validated tool to assess muscle strength, physical function, and endurance. Items of the CMAS include upper and

lower extremity muscle groups, simple and compound movements, and timed items to evaluate endurance. The tool is weighted toward lower extremity proximal and axial muscle groups more than upper extremity and distal muscle groups. The CMAS consists of 14 items. The CMAS has been included as a core set activity measure by both the IMACS and PRINTO (42)

Assessment to be performed by the Dermatologist is Optional: Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) It measures activity and damage in the skin. The modified CDASI (version 2) is the one in current use. It has 3 activity scales (erythema, scale, erosion/ulceration) and 2 damage measures (poikiloderma and calcinosis). In addition, Gottron's papules on the hands are evaluated in terms of activity (erythema/ulceration) and damage (dyspigmentation or scarring). Activity in terms of periungal changes and alopecia is also measured. Each of the 3 activity scales and 2 damage measures is assessed over 15 body areas; the worst level of activity is scored, whereas the damage measures is scored for their presence or absence. It will be performed by both Rheumatology and Dermatology. (42)

Childhood Health Questionnaire (CHQ) is validated tool to assess health related quality of life, physical and psychosocial well-being of children at least 5 years of age. The CHQ consists of 14 health concepts: global health, physical functioning, role/social limitations-emotional/behavioral, role/social limitations-physical, bodily pain/discomfort, behavior, general behavior, mental health, self-esteem, general health perception, parent impact-emotional. Parent impact-time, family activities, and family cohesion. In addition, there are 2 summary measures, the Physical summary score (PhS) and the Psychosocial summary score (PsS). The CHQ- PhS has been selected by PRINTO as a core set of measures to be used to evaluate response to therapy in JDM. (42)

SF-36 is a widely used tool that assesses the global medical quality of life, functional health and well-being. It has been used in several small natural history studies of PM and DM (44)

Dermatology Life Quality Index (DLQI). It is a simple questionnaire to assess quality of life in skin disease. The measure consists of 10 questions related to skin symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the side effects of treatment. Each item is scored on a Likert scale, where 0= not at all/not relevant, 1= a little, 2= a lot, 3=very much. (42)

PROMIS and Peds QL Fatigue Questionnaires: The PROMIS Fatigue instruments evaluate a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities. The fatigue short form is generic rather than disease-specific. It assesses fatigue over the past seven days.

The PedsQL Multidimensional Fatigue Scale was designed to measure fatigue in pediatric patients, but can also be used in adults. It is comprised of the General Fatigue Scale (6 items), Sleep/Rest Fatigue Scale (6 items), and Cognitive Fatigue Scale (6 items).

Fatigue instruments are available for adults (ages 18+), pediatric self-report (ages 8-17) and for parents serving as proxy reporters for their child (youth ages 5-17).

Assessment of Study Outcomes: A physician assessment of whether the patient has improved or worsened from baseline, and by how much (mild, moderate, great degree of change) will be made at each follow-up visit, using the IMACS assessment tool available for this outcome.

15.0 STATISTICS/DATA ANALYSIS

Statistical Plan:
This is an open label nonrandomized trial to assess the safety and efficacy of subcutaneous abatacept in 10 patients (children and adults) with juvenile onset refractory dermatomyositis (JDM).

We postulate that at least 6 of 10 patients with JDM will meet the myositis preliminary definition of improvement (DOI) after receiving 24 weeks of therapy with abatacept. Data will be entered and stored in the RedCap database,licensed to George Washington University. Primary analyses will be performed using intention to treat regardless of compliance with therapy or trial protocol. We will also perform analyses that include only those participants with known outcome data.
Summary statistics will be generated to describe the study samples. Descriptive statistics, including measures of central tendency (e.g. means, medians) and estimates of spread (e.g. standard deviations) will be used for continuous variables, including reporting of adverse event frequencies, core set measure assessments, and demographic and clinical variables. Non-parametric Wilcoxon signed rank tests will be used to investigate changes in continuous variables. 95% confidence intervals will be calculated for all point estimates.

We will examine the percentage of subjects meeting the DOI (20%),as well as moderate (DOI 50%) or major improvement criteria (DOI 70%), as well as frequency of patients achieving clinically inactive disease.

Due to the small number of subjects, it is unlikely that any statistical test would have the power to detect significant differences in any of the measured variables. We will therefore look not only at the percentage of subjects meeting improvement criteria by the DOIs, but also look for an improvement in individual core set myositis disease activity measurements of muscular and extra-muscular disease activity, as well as the in the patient- reported outcome measures, cutaneous assessments and MRI. We will also examine responsiveness after treatment using standardized response means and correlation degree of change between the measures. Differences between initial

and 24 weeks values will be analyzed by Student t distribution and Wilcoxon matched pair tests.

Statistical analyses will be performed by using GraphPad InStat version 3.00 for Windows 95 (GraphPad, San Diego, CA) and/or SAS System for Windows, version 9.1.3 (SAS Institute, Cary, NC). For all statistical tests, a P-value of < 0.05 will be utilized to indicate statistical significance.

Results of this project may lead to the development of larger study that will have the statistical power to detect significant differences in the measured variables after treatment of JDM with abatacept.

16.0 COSTS AND PAYMENTS

16.1 Research Study Costs

The study drug, abatacept will be provided at no cost to participants or their insurance companies. The study will cover the costs of the study drugs laboratory testing, examinations and clinic visits and the patients insurance will not be billed for these. However, patients participating in the open-label extension phase of the study will be responsible for these costs, and their insurance companies will be billed. Routine care not associated with research will be billed to the subject or third party payer and the subject will be responsible for costs not covered, including any applicable copays, coinsurances and deductibles.

Emergent care will be billed to the subject or third party payer and the subject will be responsible for costs not covered, including any applicable copays, coinsurances and deductibles.

Patients and their families will be paid a participation fee for time and inconvenience associated with participation in the trial. They will receive $150 upon completion of visit 1 and visit 5 $100 upon completion of visit 3, and $50 upon completion of visit 2 and visit 4, for a total of $500 per patient.

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APPENDIX A.

BOHAN AND PETER CLASSIFICATION CRITERIA for Diagnosis of Dermatomyositis

Criterion	Definition
1. Symmetric weakness	Weakness of proximal limb-girdle muscles, progressing over weeks to months
2. Muscle Biopsy evidence	Evidence of necrosis of Type I and II fibers, phagocytosis, regeneration with basophilia, large vesicular sarcolemmal nuclei and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size, and an inflammatory exudate, ofte perivascular
3. Elevation of Serum Muscle Enzymes level	Elevation in serum of any skeletal muscle enzyme, particularly creatine phosphokinase , aldolase, lactate dehydrogenase, aspartate aminotransferase and alanine amintransferase
4. EMG	Electromyographic triad of short, small, polyphasic motor units, Evidence fibrillations, positive sharp waves, and insertional irritability, and bizarre, high frequency repetitive discharges
5. Dermatologic Changes	A lilac discoloration of the eyelids (heliotrope rash) with periorbital edema (heliotrope rash), or a scaly, erythematous dermatitis over the dorsum of the hands, especially the metacarpophalangeal and proximal inter phalangeal joints, knees, elbows, and medial malleoli (Gottron's papules or sign)

[a] Confidence limits can be defined as follows. For a definite diagnosis of dermatomyositis, three of four criteria plus the rash must be present. For a probable diagnosis of dermatomyositis, two criteria plus the rash must be present. Patients must be < 18 years of age at time of diagnosis to meet criteria for juvenile dermatomyositis.

The following findings exclude a diagnosis of dermatomyositis:

- Evidence of central or peripheral neurologic disease, including motor-neuron disorders with fasiculations or long-tract signs, sensory changes, decreased nerve conduction times, and fiber-type atrophy and grouping on muscle biopsy.

- Muscle weakness with a slowly progressive, unremitting course and a positive family history or calf enlargement to suggest muscular dystrophy
- Biopsy evidence of granulomatous myositis such as with sarcoidosis.
- Infection, including trichinosis, schistosomiasis, trypanosomiasis, staphylococcosis, and toxoplasmosis
- Recent use of various drugs and toxins, such as clofibrate and alcohol
- Rhabdomyolysis as manifested by gross myoglobinuria related to strenuous exercise, infections, crush injuries, occlusions of major limb arteries, prolonged coma or convulsions, high-voltage accidents, heat stroke, the malignant-hyperpyrexia syndrome, and envenomation by certain sea snakes.
- Metabolic disorders such as McArdle's syndrome.
- Endocrinopathies such as thyrotoxicosis, myxedema, hyperparathyroidism, hypoparathyroidism, diabetes mellitus, or Cushing's syndrome.
- Myasthenia gravis with response to cholinergics, sensitivity to d-tubocurarine, and decremental response to repetitive nerve stimulation.

Data from Bohan A. Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344-347,

APPENDIX B: Proposed New classification criteria for IIM *

Variable	Score	
	Without muscle biopsy data	**With muscle biopsy data**
18 ≤ Age of onset of first symptom assumed to be related to the disease < 40	1.3	1.5
Age of onset of first symptom assumed to be related to the disease ≥ 40	2.1	2.2
Muscle weakness		
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin manifestations		
Heliotrope rash	3.1	3.2
Gottron´s papules	2.1	2.7
Gottron's sign	3.3	3.7
Other clinical manifestations		
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory measurements		
Anti-Jo-1 (anti-Histidyl-tRNA synthetase) autoantibody positivity	3.9	3.8
Serum creatine kinase activity (CK) activity *or* Serum lactate dehydrogenase (LDH) activity *or* Serum aspartate aminotransferase (ASAT/AST/SGOT) activity *or* Serum alanine aminotransferase (ALAT/ALT/SGPT) activity	1.3	1.4
Muscle biopsy features		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1

Risk score ≥ 5 (without biopsy) or ≥ 6 (with muscle biopsy) classified as myositis.

*A Tjärnlund, M Bottai, LG Rider et al. The International Myositis Classification Criteria Project Progress Report on Development of Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies. Arthritis and Rheumatism. 2012. 64(suppl). 23-324.

APPENDIX C : IMACS AND PRINTO CORE SET ACTIVITY MEASURES

IMACS Core Set Disease Activity Measures for Juvenile Dermatomyositis*

Core Set Variables	Core Set Measures
MD Global Activity	Physician global disease activity assessment by Likert or VAS
Patient/parent global activity	Parent/patient global disease activity assessment by Likert or VAS
Muscle strength	MMT(manual muscle test) by a 0-10 point or expanded 0-5 point scale to include proximal , distal, and axial muscles
Physical Function	Validated patient/parent questionnaire of activities of daily living (HAQ/CHAQ)
Laboratory Assessment	At least 1 serum muscle enzyme activity level from the following: CK, creatine kinase, aldolase, LDH, lactate dehydrogenase, AST, aspartate aminotransferase, ALT, alanine aminotransferase
Extra skeletal Muscle Disease Activity Assessment	MDAAT, Myositis Disease Activity Assessment Tool, extra muscular global activity assessment (constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiac) assessment score

*IMACS, International Myositis Assessment and Clinical Studies Group

**Rider LG, Giannini EH, Harris-Love et al. Defining clinical improvement in adult and juvenile myositis. J of Rheumatol 2003; 30(3): 603-617

PRINTO Core Set Disease Activity Measures for Juvenile Dermatomyositis *

Core Set Variables	Core Set Measures
MD Global Activity	Physician global disease activity assessment by Likert or VAS
Patient/parent assessment of overall well being	Parent/patient global disease activity assessment by Likert or VAS
Muscle strength	MMT(manual muscle test) by a 0-10 point or expanded 0-5 point scale to include proximal, distal, and axial muscles, or Validated observational tool of function, strength, and endurance, Childhood Myositis Assessment Scale (CMAS)
Physical Function	Validated patient/parent questionnaire of activities of daily living (HAQ/CHAQ)
Global Disease Activity	Disease Activity Score (DAS) or Myositis Disease Activity Assessment Tool (MDAAT)
Health Related Quality of Life	Childhood Health Questionnaire (CHQ) or SF-36 in adult patients

*PRINTO, Pediatric Rheumatology International Trials

***Ruperto A, Pistorio A, Ravelli et al. The Paediatric Rheumatology International Trials Organization provisional criteria for the evaluation of response to therapy in juvenile dermatomyositis. Arthritis Care & Res 2010; 62 (11): 1533-41.

APPENDIX D1.
IMACS definition of minimal clinical improvement, PRINTO definition of minimal, moderate, and major improvement and PRINTO criteria of inactive disease**

IMACS definition of minimal improvement	PRINTO definition of minimal improvement	PRINTO definition of moderate clinical improvement	PRINTO definition of major clinical improvement	PRINTO definition of inactive disease
≥ 20% of improvement in at least 3 of 6 core set measures, with ≤ 2 of the remaining worsening by > 25% (muscle strength cannot worsen)	≥ 20% of improvement in at least 3 of 6 core set measures, with ≤ 1 of the remaining worsening by ≥ 30% (muscle strength cannot worsen).	≥ 50% of improvement in at least 3 of 6 core set measures, with ≤ 1 of the remaining worsening by ≥ 30% (muscle strength cannot worsen).	≥ 70 of improvement in at least 3 of 6 core set measures, with ≤ 1 of the remaining worsening by ≥ 30% (muscle strength cannot worsen).	At least 3 of 4 criteria: CMAS≥ 48; MD global Activity VAS ≤ 0.5 cm; CK ≤ 150; MMT ≥ 78.

*IMACS, International Myositis Assessment and Clinical Studies Group
**PRINTO, Pediatric Rheumatology International Trials

References:

**Rider LG, Giannini EH et al. International consensus on preliminary definitions of improvement in adult and juvenile myositis. International Myositis Assessment and Clinical Studies Group. Arthritis Rheum. 2004 Jul;50(7):2281-90. Review.
**Ruperto N, Pistorio A et al. The Paediatric Rheumatology International Trials Organisation provisional criteria for the evaluation of response to therapy in juvenile dermatomyositis. Arthritis Care Res (Hoboken). 2010 Nov;62(11):1533-41
**Lazarevic D, Pistorio A, Palmisani E et al. The PRINTO criteria for clinically inactive disease in juvenile dermatomyositis. Paediatric Rheumatology International Trials Organisation (PRINTO). Ann Rheum Dis. 2013 May;72(5):686-93

Appendix D2. Newly Developed Criteria for Myositis Clinical Response (pending ACR-EULAR approval).

Definition 20: 1000 Minds Model 3 (absolute % change)	
Core Set Measure	**Improvement score for each level**
MD Global Absolute % Change	
Up to <=5%	**0**
>5% up to <=15%	**7.5**
>15% up to <=25%	**15**
>25% up to <=40%	**17.5**
>40%	**20**
Pt Global/Par Global Absolute % Change	
Up to <=5%	**0**
>5% up to <=15%	**2.5**
>15% up to <=25%	**5**
>25% up to <=40%	**7.5**
>40%	**10**
MMT/CMAS Absolute % Change	
Up to <=2%	**0**
>2% up to <=10%	**10**
>10% up to <=20%	**20**
>20% up to <=30%	**27.5**
>30%	**32.5**
HAQ/CHAQ Absolute % Change	
Up to <=5%	**0**
>5% up to <=15%	**5**
>15% up to <=25%	**7.5**
>25% up to <=40%	**7.5**
>40%	**10**
Enzyme/CHQ-PF50 Absolute % Change	
Up to <=5%	**0**
>5% up to <=15%	**2.5**
>15% up to <=25%	**5**
>25% up to <=40%	**7.5**
>40%	**7.5**
ExtraMusc/DAS Absolute % Change	
Up to <=5%	**0**
>5% up to <=15%	**7.5**
>15% up to <=25%	**12.5**
>25% up to <=40%	**15**
>40%	**20**

Improvement Score (sum of all CSM)

Profile	Improvement Category	Cutpoint
Adult	Minimal	20
	Moderate	40
	Major	60
Pediatric (IMACS/PRINTO)	Minimal	30
	Moderate	45
	Major	70

APPENDIX E TABLE 1 AND TABLE 2 /2a: STUDY SCHEDULE OF EVENTS

Table 1.

Study Events	Treatment Week														
	Screening	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W25-W48
Visit		V1			V2			V3			V4			V5	V6 (extension)
Phone f/up*			X	X		X	X		X	X		X	X		
Informed Consent/Assent	X														
Inclusion/Exclusion Criteria	X														
Vital signs, Weight, (pulse oximetry) is changed to screening evaluation	X	X			X			X			X			X	X
Brief physical evaluation		X			X			X			X			X	X
CMAS	X	X			X			X			X			X	X
MMT8	X	X			X			X			X			X	X
MDAAT (EM Global only at Screening)	X	X			X			X			X			X	X
Disease Activity Score		X			X			X			X			X	X
MD Global Activity (VAS)	X	X			X			X			X			X	X
Patient/Parent Global Activity (VAS)	X	X			X			X			X			X	X
CHAQ/HAQ	X	X			X			X			X			X	X
CHQ-PF50/SF36		X			X			X			X			X	
Myositis Damage Index		X												X	
Urine Pregnancy , UA,	X	X			X			X			X			X	X
Screening Blood Tests	X														
Research Blood Tests form is changed to blood sample tracking form (regular and research blood test)		X						X						X	
Chest X-ray	X														
Plain radiograph for calcinosis (calcinosis pts only)		X												X	
Muscle MRI (bilateral, Axial and T1)		X												X	
MD Global Disease Damage (VAS)		X			X			X			X			X	X
Physician Assessment of Study Outcome					X			X			X			X	X

Dermatology assessment (Includes CDASI, MD Global Skin Activity/Damage performed by Dermatologist) *Optional*		X						X						X	
CDASI (performed by Rheumatologist)		X			X			X			X			X	X
DLQI, skin itch, Patient and MD skin global activity/damage (performed by Rheumatologist)		X			X			X			X			X	X
Photograph Documentation (if applicable)		X			X			X			X			X	X
Nailfold capillaries photograph (Optional)		X						X						X	X
PROMIS and PedsQL fatigue		X			X			X			X			X	X
Review medication log and self-administration log		X			X			X			X			X	X
NCI CTC Assessment		X			X			X			X			X	X
Adverse Events assessments		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prednisone taper if meet DOI and rated at least minimally improved					X			X			X			X	X
Increase Abatacept dose if ≤ 5% improved by DOI and rated as unchanged or worsened								X							
Administer Abatacept medication		X			X			X			X			X	X
Visit		**V1**			**V2**			**V3**			**V4**			**V5**	**V6**
Week	**Screening**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W25-W48**

*Phone f/up at W2, 4, 8, 10, 14, 16, 20, and 22 will consist of evaluation of Adverse Events.

Abbreviations: CMAS, Childhood Myositis Assessment Scale; MMT8, manual muscle testing 8 muscle groups; MDAAT, Myositis Disease Activity Assessment Tool; EM Global, Extra muscular Global; CHAQ/HAQ, Childhood Health Assessment Questionnaire/Health Assessment Questionnaire; CHQ-PF50, Childhood Health Questionnaire, parent form 50; SF36, Short Form 36; CDASI, Cutaneous Dermatomyositis Assessment and Severity Index; DLQI, Dermatology Life Quality Index

Table 2 (*)

Test	Collection Date	Collection Tube	Matrix	Required volume (ml) for Children	Adults
Comprehensive Metabolic Panel (Chem 14)	Screen, W0, 6,12,18,24, 25-48	Gold SST top tube	Serum	2.5	4.0
Complete blood count (CBC) with diff	Screen, W0, 6,12,18,24, 25-48	Lavender top tube	Whole Blood	1.5	3.0
Von Willebrand Factor Antigen	W0,6,12,18,24	Blue top tube	Plasma	1.0	1.0
Thyroid function test, TSH, Thyroid Abs	W0, 24	Red top tube	Serum	4.0	4.0
Glutamyl Transferase (GGT)	Screen, W0,6,12,18,24, 25-48	Green or Red top tube	Serum	0.6	0.6
Creatine Kinase (CK)	Screen, W0,6,12,18,24, 25-48	Gold SST tube/Red top	Serum	5.0	5.0
Aldolase	Screen, W0,6,12,18,24, 25-48	Red top tube	Serum	3.0	3.0
Lactate Dehydrogenase (LDH)	Screen, W0,6,12,18,24, 25-48	Red top tube	Serum	1.0	1.0
HIV Ab	Screen	Lavender top tube	Serum	2.0	2.0
Hepatitis panel (HBsAg, Anti-HBc, Anti-HepC) ,CD19 (for those who received rituximab before)	Screen	Red /black SST tube	Serum	8.0	12.0
Quantiferon-gold TB test	Screen	Test Special kit	Whole blood	3.0	3.0
Lymphocyte Phenotyping-TBNK/Flow cytometry	W0,12,24	Lavender top tube	Whole blood	2.0	2.0
Antinuclear Abs (ANA) and ENA (extractable nuclear Abs) comprehensive panel	W0,24	Red (stopper) tube	Serum	2.0	2.0
PK, immunogenicity	W0.12.24			10.0	10.0
Quantitative Immunoglobulins G and M	W0	Red top tube	Serum	2.0	2.0
Myositis-Specific and Myositis-Associated Ab (MSA and MAA) test	W0	Red (stopper) tube	Serum	5.0	5.0
Research Immunology Tests at Ross Hall: 1. FACS Immunophenotyping for CD4, CXCR3, IFNγ (TH1), CD4, CCR4, CRTH2, Il4(TH2), CD4, CCR6, Il17α (TH17), CD4, CD25, Foxp3 (T regulatory cells), B cell markers, macrophage markers along with B71, B72, CTLA4, CT28 2. Cytokine Human Magnetic 30-Plex Panel 3. RNA isolation and RNA Quality Check 4. Illumina Human Gene Bead Chip Panel	W0,12,24	Heparinized tube	Whole blood	60.0	60.0

5. Illumina Data Analysis and Ingenuity Pathways Analysis					
Urinalysis	Screen, W0,6,12,18,24, 25-48	Urine cap	Urine	1.0	1.0
Urine pregnancy Test	Screen, W0,6,12,18,24, 25-48	Urine cap	Urine	1.0	1.0

(*) NIH guidelines for limits of blood drawn for research purposes will be followed:

Adult Patients and Volunteers: Blood Drawing Limits for Research Purposes

The amount of blood that may be drawn from adult patients and volunteers (i.e., those persons 18 years of age or older) for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period. The amount of blood to be drawn from volunteers and the frequency of collection shall be specified in the clinical research protocol, and exceptions to the 10.5 mL/kg or 550 mL limitations shall be approved by the IRB.

Pediatric Patients: Blood Drawing Limits for Research Purposes

For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period.

Table 2a : Summary of blood collection

	Blood Volume (ml)	
	Children	Adult
Screen	**28.6**	**35.6**
W0	**105.7**	**114.2**
W6	**14.6**	**17.7**
W12	**86.6**	**89.6**
W18	**14.6**	**17.7**
W24	**92.6**	**95.6**
W 25-48	**13.5**	**16.6**

APPENDIX F ACTION PLAN FOR TREATMENT OF WORSENING OF DISEASE:

Criteria for disease worsening in a clinical trial, by which patients could be termed treatment failures and offered alternative therapies, were preliminarily defined at an IMACS Workshop. These criteria will be incorporated into this trial.

. In order to be classified as "worsening" in this trial subjects will have to meet the following criteria:
(1) Physician global worsening of ≥ 2 cm on the 10 cm visual analog scale (VAS) and a worsening of the manual muscle testing by ≥ 20%, or

(2) Global extra muscular organ disease activity (a composite of constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiac activity) worsening by ≥ 2 cm on a 10 cm VAS, or

(3) 3 of any 6 IMACS core set activity measures worse by ≥ 30%. And

(4) Subjects will have to meet the above criteria and be classified by the investigator as at least moderately clinically worse.

Patients who improve by less than 5% in at least 3 of 6 core set measures by week 12, will be considered to be not improved : These patients may be offered higher dose therapy at 212 mg (87.5 + 125 mg) for subjects with body weight ≥ 50 kg or 137.5 mg for subjects with body weight < 50 kg abatacept weekly.

APPENDIX G CLINICAL LABORATORY EVALUATIONS

HEMATOLOGY	SERUM CHEMISTRY	URINALYSIS
Total white blood cell count Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Hematocrit Hemoglobin Platelet Count Lymphocyte phenotypingperifascicular (TBNK by flow cytometry) Von Willebrand Factor antigen	Electrolytes: Bicarbonate Chloride Potassium Sodium Calcium Magnesium Phosphorus (inorganic) Enzymes: Aldolase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) LDH CPK GGT CPK Other: BUN Creatinine QIG panel (IGM, IGG) Hepatitis B surface antigen Hepatitis C antibody TSH HIV Quantiferon Gold ANA/ENA	pH Blood Glucose Protein Ketones Nitrites Bilirubin Urobilinogen Leukocyte esterase Microscopic exam if dipstick positive Urine Pregnancy

	MSA/MAA Immunogenicity (HAHA) pK	

Laboratory test results will be reviewed by the Investigator or Sub-Investigator as they become available. The Investigator or Sub-Investigator must determine the clinical significance of all out-of- range laboratory values. Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

Appendix H. Study Personnel and Roles

Rodolfo Curiel, MD, Associate Professor of Medicine, George Washington University, is the Principal Investigator, of the study. He will be responsible for the oversight of all study personnel, procedures and logistics. He will assist with patient recruitment, screening and assessment, and oversee data management and analysis.

Lisa Rider, MD, Deputy Chief, Environmental Autoimmunity Group, NIEHS, NIH and Adjunct Clinical Professor of Medicine, George Washington University, will be an Associate Investigator for the study. She will assist with patient recruitment, screening and assessment, and oversee analysis.

Olcay Jones, MD, PhD**,** Chief of Pediatric Rheumatology, Walter Reed National Military Medical Center and Adjunct Clinical Associate Professor of Medicine, George Washington University, will be an Associate Investigator for the study. She will assist with patient screening and assessment.

Alison Ehrlich, MD, Professor of Dermatology and Chair, Department of Dermatology, George Washington University, will be an Associate Investigator for the study. She will assist with dermatologic assessment of the patients, including photographing skin rashes.

Kathleen Brindle, MD, Associate Professor of Radiology, George Washington University, will be an Associate Investigator for the study. She will read and score the magnetic resonance imaging studies of the thighs/pelvis and also plain x-rays of calcinosis.

Victoria Shanmugan, MD Associate Professor of Medicine. George Washington University. She will oversee the performance of the research blood samples, including lymphocyte flow cytometry, cytokine production, gene expression profiling, and Ingenuity Pathway Analysis.

Gulnara Mamyrova, MD, PhD, Researcher/GWU Myositis Center Coordinator, Division of Rheumatology, will be an associate investigator for the study. She will be responsible for the oversight of all study procedures and logistics. She will assist with patient recruitment and screening, regulatory submissions and preparation of reports for the DSMB, as well as data management and analysis.

Hassan Awal**,** MD Clinical Research Coordinator, Department of Medicine, The GW MFA, will be an associate investigator for the study. He will be responsible for the oversight of all study procedures and logistics. She will assist with patient recruitment and screening, regulatory submissions and preparation of reports for the DSMB, as well as assist with data management.

Other personnel involved with the study include:

Dr. Ira Targoff and staff, Oklahoma Medical Research Foundation, Oklahoma City, OK, will perform the myositis autoantibody testing. They will have access to identifiable patient information in their clinical fee for testing program.

Appendix I: COVID19 Addendum San Diego subsite

Due to current state of national emergency due to COVID19 Pandemic, special consideration applies to the protocol as per guidance set by Department of Health and Human services, George Washington University Office of Human Research, and Research Guidance set by GW Medical Faculty Associates.

We will be enrolling one patient from San Diego, California with help from Dr Robert Sheets at Rady's Children's Hospital's/ UCSD. University of California San Diego will be effectively added as a subsite of The George Washington University Medical Faculty Associates.

The visit that will take place will be run virtually, with Dr Sheets performing the visit assessments with Dr Curial and Dr Rider present via ZOOM telemedicine video call. Labs will be collected and processed at UCSD, along with the imagine needed for enrollment visit (chest X-Ray and pelvis/thigh MRI). Study drugs will be shipped to UCSD Investigational Drug Services and will be dispensed there to the patient as per guidelines. Due to the uncertainty of the pandemic, all the follow up visit might need to be done in San Diego. IRB have approved this plan.

This change in research plan is approved by BMS, the funder of the study.