University of Pittsburgh School of Medicine

Study Title

Abatacept for the **T**reatment of **My**ositis-associated **I**nterstitial **L**ung **D**isease (**AT**tack**My-ILD**)

Study Drug

Abatacept

A randomized, controlled pilot trial to evaluate the efficacy and safety of subcutaneous Abatacept in treating interstitial lung disease associated with the anti-synthetase syndrome

Support Provided By

Bristol Myers Squibb

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Identifiers: NCT03215927
Protocol Number: BMS: IM101-657
Protocol Version Date: Version 2.0 07Jan2019

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1.0 INTRODUCTION

1.1 Disease Background

Idiopathic Inflammatory Myopathy (IIM) or myositis is a heterogeneous group of disorders with an autoimmune pathogenesis characterized by muscle inflammation leading to muscle weakness. Many patients with IIM [primarily polymyositis (PM) and dermatomyositis (DM)] develop interstitial lung disease (ILD), a leading cause of morbidity and mortality in these patients. The prevalence of ILD varies in myositis, but in certain subsets (e.g. the antisynthetase syndrome), ILD can occur in up to 80-90% of patients and be the first and most prominent feature. ILD is the most common cause of mortality and morbidity in myositis. There are currently no approved treatments for myositis-associated ILD (Myositis-ILD) or anti-synthetase syndrome associated ILD (Syn-ILD). A T cell mediated pathogenesis has been posited for Myositis-ILD with bronchoalveolar lavage (BAL) showing activated T cells[1]. There is strong biological plausibility for considering ABT in Myositis-ILD. In a mouse model of hypersensitivity pneumonitis (HP), characterized by activated T cells in the lung parenchyma (similar to Myositis-ILD), blockade of T cell co-stimulation by CTLA-4 Ig (CD28/B7 antagonist) ameliorated lung inflammation[2]. Moreover, treatment with CTLA-4 Ig led to a significant decrease in lung damage and less inflammatory cells in the BAL fluid as well as a diminished CD4/CD8 T cell ratio [3]. CTLA-4 Ig ligands are present in autoinvasive CD8+ T cells in biopsies of PM-scleroderma patients[4]. CTLA-4 and CD28 are over-expressed on inflammatory cells and muscle cells in muscle biopsies of PM and DM patients [4,5]. The goal of this proposal is to perform a collaborative multi-center trial among adult rheumatologists and pulmonologist to examine the efficacy and safety of ABT as a potentially important new therapeutic advance for Syn-ILD.

1.2 Abatacept Background and Rationale in IIM

ABT not only down-regulated T cells, thereby directly affecting lung and muscle inflammation in myositis, but also decreased the antigen-presenting capability of myocytes, inhibited macrophages and led to decreased pro-inflammatory cytokines (specifically IL-6, TNF alpha, and others), all of which are strongly implicated in the pathogenesis of myositis[6]. Moreover, CD80 and CD86 are expressed in antigen-presenting B lymphocytes and ABT decreases B lymphocyte expression, of importance in the pathogenesis of myositis and Myositis-ILD given the beneficial effects of rituximab for Myositis-ILD [7-9]. Anti-T cell therapy (e.g. tacrolimus and cyclosporine) has been shown by our investigative group and others to be effective in refractory patients with Myositis-ILD especially in those with the antisynthetase syndrome[10-15]. However, its use is limited by established toxicity, patient intolerance and the need for complex monitoring. Other case reports suggest that ABT has efficacy in treating the muscle and skin features of refractory PM and DM[16-19], and the pathogenesis of Myositis-ILD is similar to that of muscle disease in myositis except that the target of inflammation and subsequent damage is different. There is encouraging evidence of the amelioration of Rheumatoid Arthritis (RA) associated ILD using ABT[20] as well as the lack of ILD worsening when RA is treated with ABT, a somewhat unique effect not shared with other biologics currently FDA-approved for RA. Given the rarity, heterogeneity and complexity of myositis and Myositis-ILD, any clinical study or trial is very difficult to perform and should only be done in specialized centers seeing such patients. Moreover, it is essential for clinical trials that myositis and ILD outcome measures be appropriately assessed.

1.2.1 Abatacept

ABT is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). It is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of ABT is 92 kilodaltons. It is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the solution of ABT is clear, colorless to pale yellow, with a pH range of 7.0 to 8.0. Each single-use vial of ORENCIA provides 250 mg ABT, 500 mg maltose, 17.2 mg monobasic sodium phosphate, and 14.6 mg sodium chloride for administration. The efficacy and safety of ABT was assessed in five randomized, double-blind, placebo-controlled studies in patients ≥ age 18 with active RA diagnosed according to American College of Rheumatology (ACR) criteria.

Further information on ABA can be found in the Investigator's Brochure (IB).

1.3 Other Study Drug(s) Background

Not applicable

1.4 Study Rationale

There are currently no approved treatments for myositis-associated ILD (Myositis-ILD) or anti-synthetase syndrome associated ILD (Syn-ILD). A T cell mediated pathogenesis has been posited for Myositis-ILD with bronchoalveolar lavage (BAL) showing activated T cells[1]. There is strong biological plausibility for considering ABT in Myositis-ILD. In a mouse model of hypersensitivity pneumonitis (HP), characterized by activated T cells in the lung parenchyma (similar to Myositis-ILD), blockade of T cell co-stimulation by CTLA-4 Ig (CD28/B7 antagonist) ameliorated lung inflammation[2]. Moreover, treatment with CTLA-4 Ig led to a significant decrease in lung damage and less inflammatory cells in the BAL fluid as well as a diminished CD4/CD8 T cell ratio [3]. CTLA-4 Ig ligands are present in autoinvasive CD8+ T cells in biopsies of PM-scleroderma patients[4]. CTLA-4 and CD28 are over-expressed on inflammatory cells and muscle cells in muscle biopsies of PM and DM patients [4,5]. The goal of this proposal is to perform a collaborative multi-center trial among adult rheumatologists and pulmonologist to examine the efficacy and safety of ABT as a potentially important new therapeutic advance for Syn-ILD.

2.0 OBJECTIVES

2.1 Primary

The primary objective is to evaluate the efficacy, safety and tolerability of ABT (125 mg SQ weekly) and standard of care (SOC) vs. SOC in patients with Syn-ILD in a multi-center, double-blind, randomized placebo-controlled proof of concept clinical trial.
Hypothesis: ABT will be efficacious, safe and tolerable in Syn-ILD patients.

2.2 Secondary

The secondary objectives include assessing: (a) radiographic improvement, (b) improvement in other PFT variables like FEV1 and DLCO, (c) time to improve in composite outcome for ILD by OMERACT, (d) death/transplant, (d) patient-reported outcomes of dyspnea, (c) rapidity and magnitude of response to ABT, (d) steroid-sparing effect of ABT, (e) durability of response, and (f) assessment of drug effect on other muscle or skin manifestations using standard myositis response criteria.

2.3 Exploratory

We plan to identify predictors of treatment response to ABT in Syn-ILD which will include the concomitant blood repository along with collection of clinical and demographic data collected during the course of the trial to study clinical, pathologic and immunologic factors associated with a response or lack of response to the study drug. This objective will be achieved in the future using a separate study after the completion of the clinical trial, but the samples will be collected as part of the current trial.

3.0 STUDY DESIGN

3.1 Description of the Study

This is a proof of concept study to evaluate the efficacy, safety and tolerability of ABT in Syn-ILD in a multi-center randomized, placebo-controlled 6-month (24-week) pilot study followed by a 24 week open label extension phase.

3.1.1 Study Schema

We will enroll 20 adult subjects with Syn-ILD across 5 clinical sites. We expect enrollment to be completed within 15 months. A 1:1 randomization scheme for active drug: placebo as a weekly SQ injection with their SOC for 24 weeks. All patients can then enter an optional open label follow-up after the 24-week randomized, controlled phase, during which all subjects receive 24 weeks of ABT in the same fashion as the initial study phase. This follow-up phase will assess durability, long term response and safety in patients who were in the active treatment arm while allowing the placebo arm to receive active drug, thus improving recruitment and study power.

Patient must have active ILD associated with anti-synthetase syndromes (a subset of myositis) that are being given SOC treatment for ILD. Patients could have refractory disease with flare up or new onset disease. Patient may or may not have active myositis (PM/DM). We anticipate the continued participation of all subjects in open label extension phase.

Open label phase: At the end of the active study period (week 24 closing visit), patients in either arm can enroll into the optional open-label phase of 24-week ABT therapy (125 mg SQ injection weekly).

a. **Standard of Care (SOC):** The SOC of patients with Syn-ILD includes steroids OR another IS agentOR a combination of steroid and another IS agent. Thus, we will allow steroids and/or only 1 additional IS agent. **Additional IS agent can be either mycophenolate mofetil (MMF) or azathioprine (AZA), but not both.** Patients on steroids alone can be enrolled without additional IS agent. Maximum dose allowed for MMF is 3 gms/day and for AZA is 200 mg/day. Patient should be on stable dose of MMF or AZA for 4 weeks and/or stable dose of steroids 2 weeks prior to Visit 1. Visit 1 is the time of first ABT/placebo dosing. Overall goal is to enroll patients into the trial as soon as the SOC drug has achieved stable dosing. Prednisone taper will be allowed at maximum dose of 60 mg at baseline (Visit 1), at which time a forced prednisone taper will commence as outlined below. Dose of concomitant medication cannot change throughout the phase I of the trial (24 weeks) unless safety/toxicity issues supervene.

No other concomitant IS agent is allowed (e.g. IVIG, plasmapharesis, rituximab, methotrexate, tacrolimus, cyclosporine, other biologics. Hydroxychloroquine and pirfenidone **are permitted** during the trial if on a stable dose for 4 weeks prior to trial entry.

Forced steroid taper (Prednisone or other steroid in prednisone equivalent doses) in subject on a stable dose of steroid 2 weeks prior to visit 1.

a. Steroid Tapering: May begin within or at 1 week after beginning study drug. Goal is to taper steroid to 5 mg or lower dose within 8 weeks. Recommended daily prednisone taper (or other forms of steroid in equivalent doses)
    i. 60 mg decreased to 40 mg after 1 week
    ii. 40 mg decreased to 30 mg after 1 week
    iii. 30 mg decreased to 20 mg after 1 week
    iv. 20 mg decreased to 15 mg after 1 week
    v. 15 mg decreased to 10 mg after 1 week
    vi. 10 mg decreased to 7.5 mg after 1 week
    vii. 7.5 mg decreased to 5 mg after 1 week
    viii. Further decrease as per treating physician.
b. Steroid at Entry: Maximum steroid dose allowed at study entry is ≤ 60 mg/day prednisone (or other forms of steroid in equivalent doses). If on a lower dose then the tapering scheme noted above should be employed based on the entry dose. Patients not on steroids are allowed in the study and are not allowed to start new steroids unless there is a disease flare.
c. Steroid Dosing During Flare: If in the clinical site investigator's opinion there are complications or worsening of disease that necessitate an increase in the prednisone dose (or other forms of steroid in equivalent doses) then the smallest reasonable increase should be considered (maximum increase of prednisone equivalent of 20 mg/day is allowed). After the increase, subjects should resume the prednisone taper noted above.

Concomitant medications will remain unchanged throughout Phase I, except changes made per the rescue medication protocol. During the open label Phase II, concomitant medications adjustments are permitted even if the subject has not met the definition of worsening.

Active ILD: Defined as (a) new onset of ILD (within 3 months of ILD diagnosis) or (b) worsening ILD as per the treating physician assessment necessitating a treatment change within last 3 months (with documented worsening of at least 2 of the 3 parameters: patient's report of worsening dyspnea, worsening in severity of ground glass opacities (GGO), reticulation or honeycombing or fibrosis on chest HRCT or a decline in the FVC% > 10% within last 6 months.)

Active Study Drug: A weekly dose of 125 mg SQ will be used in this 24-week trial and open label phase of 24 weeks.

Specimens (serum, cells etc.) collected and stored in a biospecimen repository at each study visit for future experimental studies. The repository will be located at the University of Pittsburgh, Division of Rheumatology. We will consider submission of ancillary proposals to conduct experiments designed to further elucidate biomarkers and basic physiologic and cellular mechanisms of disease resulting from Abatacept therapy.

Strategies for (1) allowing "rescue" therapies and (2) insuring that the original randomization treatment scheme is not revealed are discussed in Section 4.4.

Future Tests:
The Specimen Repository samples will be used in the future for two types of research:
1) immunologic and 2) genetic.

Immunology Research

Tests to be performed on the stored blood include the following: RNA-Seq analysis, autoantibody testing for the presence of myositis associated autoantibodies, serum interferon (IFN)-inducible chemokines, Th1, Th2, Th17, innate, and regulatory cytokines at baseline and later time points in this clinical trial to identify a biomarker signature predicting responsiveness to Abatacept. These immunology tests will be conducted in a research laboratory, not a public certified laboratory. Therefore, subjects will not be informed of these results.

Genetic Research

Genetic analysis. While the exact nature of the genetic research studies is not fully known, they may involve identifying genes that can: 1) increase the risk of developing autoimmune illnesses such as myositis, 2) modify the severity of autoimmune disease, or 3) control components of the immune system (immunogenetic studies).

3.2 Rationale for the Study Design and Dose

It is difficult to estimate the timing of response to abatacept but given the general timing of response to biologic therapy in rheumatic disease patients we anticipate that a 24-week trial is adequate in this pilot study Syn-ILD. In addition, we will employ the dose of ABT that has been used in most of the RA trials to date. For a pilot, proof of concept study we will not employ a dose escalation design.

3.3 Outcome Measures

The outcome measures used in this trial will include:

- Pulmonary Function Test - change in FVC%, FEV1%, DLCO%
- University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ)

- Qualitative changes in HRCT
- Six minute walk distance (6MWD)
- Mean daily step count on Fitbit One®.

The Myositis Clinical Core Set Measures (CSM) used in this trial are those agreed upon by IMACS include:

- The MMT-8 (Manual muscle testing)
- Patient global VAS recorded on a 10cm scale
- MD global VAS recorded on a 10cm scale
- HAQ disability index
- At least one of the muscle enzymes (CK, aspartate aminotransferase (AST), alanine aminotransferase (ALT), aldolase, lactate dehydrogenase (LDH))
- Global extramuscular disease activity (a composite of constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiac activity) score recorded on a 10 cm VAS scale on the Myositis Disease Activity Assessment Tool (MDAAT)

3.3.1 Primary Outcome Measures

The primary outcome criteria for efficacy will be the FVC% change from the baseline visit to week 24 between the 2 treatment arms (SOC/placebo vs. SOC/ABT). An intention to treat analysis will be used. Ranked ANCOVA will be used with average standardized rank change in the predicted FVC% as the outcome measure and the standardized rank baseline as a covariate. Primary outcome criteria for safety and tolerability will be adverse events (routine adverse events or tolerability issues and serious adverse event) between the 2 treatment arms (SOC/placebo vs. SOC/ABT). Chi-square (or Fischer exact test) and t-test (or Mann-Whitney) will be used based on data variable and distribution.

3.3.2 Secondary Outcome Measures

(SOC/placebo vs. SOC/ABT) for Syn-ILD:

a. Time to progression free survival where progression is defined as the first occurrence of any of the following: death or lung transplant or FVC ≥10% decline *or* FVC ≥5% decline with DLCO ≥15% decline.
b. Change in dyspnea, as measured by University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) (range 0-120, higher score is worsening dyspnea).
c. Time to improvement in FVC% by ≥10%.
d. Rates of death or requiring lung transplant.
e. Other individual PFT variables (FEV1%, DLCO%)
f. Qualitative changes in HRCT chest over 6 and 12 months in the two arms. Changes in semi-qualitative scoring of fibrosis over 6 months based on HRCT chest scan images collected from all sites and centrally read by an expert blinded radiologist, will be done as a separately and analyzed.
g. Steroid-sparing effect (calculated using prednisone dose equivalents)
h. Frequency of treatment failures: a) patient meeting worsening criteria or withdrawal due to worsening ILD anytime during the trial or b) FVC% worsening by 10% at 6 months, c) death or transplant within 6 months.
i. Quantitative changes in mean Six minute walk distance (6MWD)

j. Quantitative changes in mean daily step count on Fitbit One®.

Secondary outcome criteria for myositis: Myositis response will be evaluated among patients with concomitant active myositis. Active myositis is defined based on MDAAT at baseline muscle or cutaneous skin disease activity of ≥ 3 on 10 cm visual analogue scale (VAS).

New myositis response criteria (table 1) and International Myositis Assessment & Clinical Studies Group (IMACS) definition of improvement (DOI) (given below) will be used to assess myositis response in drug + SOC vs. placebo + SOC.

IMACS DOI: 3 of 6 core set measures (CSM) improved by ≥ 20%, with no more than 2 CSM worsening by ≥ 25% (a worsening measure cannot be the manual muscle testing (MMT).

Table 1. New Myositis Response criteria (based on conjoint analysis continuous definition using absolute % change in six core set measures)

1000Minds Model (absolute % change)	
Core Set Measure	**Improvement score for each level of CSM**
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
Patient Global/Parent 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
Muscle 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
Extra Muscular VAS/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
Total Improvement Score is sum of score achieved in each CSM	

Total improvement score ≥ cut points determines Minimal, Moderate and Major Improvement

Profile	Improvement Category	Cut point on total improvement score
Adult	Minimal	≥20
	Moderate	≥40
	Major	≥60

3.3.3 Safety Outcome Measures

Safety is being assessed in one of the secondary endpoints listed above in Section 3.3.2. We will statistically compare the frequency of the following adverse events between the treatment and placebo arms.

Similarly, we will analyze the proportion of serious adverse events between the treatment and placebo arms. In addition, the number and percent of patients with AEs during the treatment period will be summarized.

3.4 End of Study

As described above, the end of the study (closing visit) is week 24 for Phase I. An optional open label phase (Phase II) with 2 additional visits 3 months and 6 months after the closing visit at week 24 have been added to assess durability of ABT response and safety. This follow-up phase will assess durability, long term response and safety in patients who were in the active treatment arm while allowing the placebo arm to receive active study drug.

4 STUDY POPULATION

4.0.1 Overview: Target Population

20 patients with Syn-ILD will be enrolled. Patients must have active ILD associated with anti-synthetase syndrome (a subset of myositis) that is being given SOC treatment for ILD. It will be randomized for patients to receive the drug vs. placebo as weekly SQ injections with their SOC treatment for 24 weeks. Patients could have refractory disease with flare up or new onset disease. They may or may not have active myositis (PM/DM). Given our current cohort of Syn-ILD

patients, we expect enrollment to be completed within 15 months. We anticipate the continued participation of all subjects in open label extension phase (Phase II).

4.1 Inclusion Criteria

Patients will be included in the trial based on the following criteria:

1. Age ≥ 18 years.
2. Anti-synthetase syndrome defined as the patient possessing 1 antisynthetase autoantibody (Jo-1, PL-12, PL-7, KS, OJ, EJ, Zo) in the presence of autoimmune ILD.
3. ILD defined by radiographic (HRCT chest) findings of reticulation, honeycombing or ground glass opacities (GGO) without another plausible explanation. HRCT chest defining ILD for inclusion criteria, should be within last 1 year done as SOC.
4. Active ILD (see Section 4.2).
5. Baseline FVC % :
6. a) FVC <80% OR b) FVC 80-100% with >=10% decline in FVC in last 12 months as minimal threshold of ILD severity (PFT done within last 3 months is acceptable for inclusion criteria determination).
7. SOC immunosuppressive therapy (IS) therapy:
    a. Steroids (prednisone or other forms of steroid in equivalent doses) OR one of the other immunosuppressive agent (either Mycophenolate (MMF) or Azathioprine) OR a combination of steroid and an immunosuppressive agent. MMF (maximum of 3 gm/day) or azathioprine (maximum of 200 mg/day).Goal is to start the trial drug (or placebo) soon after starting SOC (MMF/AZA/Steroids) and their doses are stable. Note that patients on steroids alone as well as not on steroids can be enrolled in the trial as well.
    b. Desired dose of the SOC therapy should be reached 4 weeks prior to first study visit (Visit 1). No dose changes are allowed 4 weeks prior to first study visit.
    c. Dose of concomitant therapy (SOC) cannot be changed during the 24 weeks of the trial unless safety/toxicity issues supervene.
    d. If on steroid, the steroid dose must be stable for 2 weeks prior to Visit 1.
8. No other concomitant IS medications including methotrexate, cyclosporine, IVIG, tacrolimus, cyclophosphamide or tofacitinib.
9. No concomitant biologic agents (i.e. rituximab, anti-TNF agents, tocilizumab).
10. Additional IS therapy: Patient cannot begin any new IS therapy or new steroid taper for the 24-week study period, except if severe clinical worsening (flare up) of the disease requiring rescue therapy occurs (i.e. documentation of worsening of PFT/HRCT ***and*** patient and physician determination of worsening). See section of rescue medication below for details.
11. If the enrolling physician is planning to discontinue current IS agent or steroid before clinical trial, then following washout period is required prior to Visit 1.

Medication	**Washout Period**

Methotrexate	4 weeks
Other IS agent (e.g. azathioprine, cyclosporine, tacrolimus, leflunomide, mycophenolate mofetil)	4 weeks
IVIg or cyclophosphamide	3 months
Rituximab	6 months
infliximab or adalimumab	8 weeks
Glucocorticoids	2 weeks
Etanercept	2 weeks
Anakinra	1 week
Pirfenidone	4 weeks

12. Men and women of reproductive potential must agree to use an acceptable method of birth control during the trial period.
13. Subject has provided written informed consent.

4.2 Exclusion Criteria

A patient will be excluded if any of the following Exclusion Criteria are met:

1. Severe end stage lung disease:
    a. FVC ≤30% *or* FEV1 ≤ 30% *or*
    b. Requirement of high O_2 requirement ≥ 6 L/min at rest for >1 month before the study enrollment *or*
    c. Listed for lung transplantation *or*
    d. PI feels that ILD is severe and end stage fibrosis is such that there is low potential for improvement with any disease modifying intervention.
2. Subjects under the age of 18.
3. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease, hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds).
4. Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening.
5. Active TB requiring treatment within the previous 3 years. Patients should be screened for latent TB using PPD/or quantiferon gold within last 1 year and, if positive, treated following local practice guidelines prior to initiating ABT. Patients treated for active tuberculosis with no recurrence in 3 years are permitted.
6. Primary or secondary immunodeficiency (history of or currently active) unless related to primary disease under investigation.
7. Pregnant women or nursing (breast feeding) mothers.
8. History of alcohol, drug or chemical abuse within 1 year prior to screening or any medical condition or physical or psychological state that the PI feels would not allow the subject to safely complete the study.
9. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization.
10. Treatment with any other investigational agent within 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of screening.

11. Previous treatment with the following cell-depleting therapies, including investigational agents or approved therapies: CAMPATH, anti-CD4, anti-CD5, and anti-CD3.
12. Previous treatment with ABT.
13. History of severe allergic or anaphylactic reactions to monoclonal antibodies.
14. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, renal, hepatic, endocrine (include uncontrolled diabetes mellitus) or gastrointestinal disease (including complicated diverticulitis, ulcerative colitis, or Crohn's disease.)
15. Evidence of concomitant lung disease which PI feels may interfere with clinical assessment of ILD for example severe active COPD, asthma, occupational lung disease, pulmonary sarcoidosis, etc.
16. Prisoners or subjects who are compulsory detained.

4.3 Immunization during Abatacept therapy

Live vaccines should not be given concurrently with ABT or within 3 months of its discontinuation.

4.4 Criteria for Premature Withdrawal

Patients have the right to withdraw from the study at any time for any reason. Every attempt will be made to have all patients complete the remaining study visits as detailed in the Study Schema (Appendix A).

If the patient decides to prematurely discontinue study treatment ("refuses treatment"), he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the CRF. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

Before categorizing a patient as lost to follow-up, the investigator must attempt to contact the patient or a responsible relative by telephone followed by registered mail to determine if any new adverse events (AEs) occurred, follow-up of any ongoing AE and to establish as completely as possible the reason for the withdrawal.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the investigator without the patient's consent. The investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is felt by the investigator that it is in the best interest of the patient to be terminated from the study. The reason(s) for withdrawal must be documented and explained to the patient.
If the reason for removal of a patient from the study is an adverse event, the specific event will be recorded in the study database. There should be an attempt to follow the patient until the event has resolved or stabilized.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

4.5 Definition of Worsening Criteria

4.5.1 Myositis Worsening Criteria

If any one of the criteria is met after 8 weeks of therapy:

a. Physician global worsening of ≥ 2 cm on the 10 cm VAS and/or worsening of the manual muscle testing by ≥ 20%, or
b. Global extra muscular organ disease activity worsening by ≥ 2 cm on a 10 cm VAS on MDAAT, or
c. 3 of 6 CSM worse by ≥ 30%.

4.5.2 ILD Worsening Criteria

If any one of the criteria is met after 8 weeks of therapy:

a. FVC% decline >= 30% from baseline PFT
b. HRCT chest suggesting severe worsening in the ILD as compared to baseline (clinician/radiologist interpretation
c. Hospitalization with severe ILD with new or increased long term O2 requirement related to worsening ILD
d. Severe worsening in clinical dyspnea due to ILD as determined by patient and treating physician. Note that meeting "worsening criteria" doesn't automatically mean administration of rescue therapy. Rescue therapy is given if patient meeting worsening criteria AND treating physician believe clinical disease warrants a change in therapy.

Subjects meeting these criteria will be considered treatment failures but can continue to receive study drug if deemed reasonable by the managing clinician or investigator. If at any time a worsening in condition occurs, the subject should be seen for an unscheduled study visit. A subject irrespective of worsening or rescue medication use, can enter the open label phase (II) of the study at the end of the 24 week period of phase I.

4.5.3 Rescue Medications

If in the clinical site investigator's opinion there are complications or worsening of disease (meeting worsening criteria) that necessitate an increase in concomitant immunosuppressive therapy the following guidelines should be followed:

- The steroid dose may be increased by ≤20 mg (prednisone equivalent) daily. After 2 weeks of increase the forced corticosteroid taper will commence as noted above. Such patients will remain on the trial protocol (on study drug), and it will not be considered as treatment failure.
- Requirement of additional non-steroid IS therapy or requirement of increase of steroids dose > 20 mg equivalent of prednisone for worsening ILD as rescue therapy (after initial 8 weeks of study drug) will be considered a treatment failure. Such patients can be continued on the trial protocol (on study drug) only if rescue drug include either one of them: MMF, AZA, tacrolimus, cyclosporine, IVIG, methotrexate AND maximum of one non-steroid IS

therapy is given during the trial. Steroids can be concomitantly increased with non-IS agent.

- Note if additional non-steroid IS therapy or increase of steroid dose > 20 mg equivalent of prednisone occurs <8 weeks on study drug, then these patients are not considered treatment failure as not enough time to have outcome assessment.
- Biological drugs, cyclophosphamide, plasmaphresis, are not allowed as rescue therapy and will lead to withdrawal from the trial drug/placebo protocol (i.e stopping trial drug/placebo) for safety reasons. Similarly, more than one non-steroid IS agent is not allowed as rescue therapy and will lead to withdrawal from the trial drug/placebo protocol (i.e. stopping trial drug/placebo). But all patients despite withdrawal from trial drug/placebo will be followed for at least 24 weeks for clinical evaluation. Note withdrawal from trial drug/placebo as above is not considered with withdrawal from the study.

For example: If a patient is having severe worsening at 3 months while on AZA and the study drug; investigator/treating physician can give rescue steroid increase by 20 mg prednisone (or new prednisone 20 mg if patient was not on steroid) without any changes in the outcome or trial protocol. However, if for some reason the investigator/treating physician needs to start MMF on the patient, then the patient can continue on the trial protocol (on study drug) as long as AZA is stopped (so only one non-steroid immunosuppressive drug is given concomitantly with study drug). Concomitant increase of steroid is OK. Such scenarios should be avoided as these patients will be considered as treatment failure.

Specifically related to this trial, there are several scenarios for subjects as they are followed through the 6 month trial:

1. Subjects can withdraw from the study drug (active drug/placebo) at any time for various reasons deemed appropriate by PI. They are then treated at the discretion of the PI off the study drug, but should continue to be followed at the regular study time points for the duration of the trial for efficacy and safety data monitoring. No randomization scheme will be broken/revealed. Withdrawal from study drug doesn't mean withdrawal from the study.
2. If the criteria for the worsening are formally met but the subject and PI do not feel it is necessary to change therapies other than allowed rescue therapies (as above), then the subject will remain on the trial protocol (study drug). No randomization scheme will be broken/revealed.
3. If criteria for the worsening is formally met and the subject and/or the PI feel that "escape" therapy other than allowable rescue agents is necessary, then the subject will be treated at the discretion of the PI off the trial protocol (withdrawal from study drug), but should continue to be followed at the regular study time points for the duration of the trial for efficacy and safety data monitoring. No randomization scheme will be broken/revealed. Withdrawal from study drug doesn't mean withdrawal from the study.

Refer to Appendix C for rescue medication diagram.

5.0 STUDY MEDICATION

5.1 Abatacept

ABT is a fully human soluble fusion protein of the extracellular domain of cytotoxic T lymphocyte

antigen 4 (CTLA-4) linked to a modified Fc portion of human IgG1, a physiological antagonist of the T cell co-stimulatory molecule CD28 by binding to CD80/CD86 with higher affinity than CD28. By this action, ABT inhibits T cells as a costimulatory signal is needed for full T cell activation. Activated T lymphocytes are implicated in the pathogenesis of My-ILD (see above). ABT decreases T cell proliferation and inhibits the production of the cytokines TNF alpha (TNFα), interferon-γ, IL-2, IL-6, some of which are also linked to the pathogenesis of myositis.

5.1.1 Abatacept Dosage and Administration

A self-administered weekly dose of 125 mg SQ will be used in this 24-week trial and open label phase of 24 weeks. Abatacept is supplied in prefilled syringes or ClickJect™ prefilled autoinjectors for Subcutaneous (SC) injections. The clinical site will provide instructions to the subject how to safely administering the study medication subcutaneously at the Visit 1 time-point.

5.1.2 Abatacept Storage

Abatacept subcutaneous syringes or autoinjectors should be stored under refrigeration (2-8°C) and protected from light. Do not allow the pre-filled syringe or autoinjector to freeze and do not use beyond the expiration date on the syringe or autoinjector. If frozen, do not use.

Access must be restricted to authorized personnel. The intake of all study drugs will be recorded in the Case Report Form (CRF). The medication provided for this study is for use only as directed in the protocol. Clinical center pharmacies will be responsible for the storage, handling, and dispensing of study drug. The Coordinating Center will monitor all documentation related to drug handling activities to ensure adherence to proper procedures.
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.

Study drugs are to be prescribed only by a physician named in the Form FDA-1572. Under no circumstances will the investigator allow the study drug to be used other than as directed by the protocol.

5.1.3 Study Drug Labeling

Bristol Myers Squibb will provide study drug and placebo. The kits and pre-filled syringes will contain the same labeling to ensure blinding of the subject. Study drug should dispensed at the clinical site by the unblinded investigational pharmacist. Study medication will be labeled with the following information:

- Subject ID
- Study protocol number
- Investigational new drug statement
- Storage conditions and expiration date

5.1.3 Abatacept Overdosage

Doses up to 50 mg/kg have been administered intravenously without apparent toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

5.2 Other Study Drug(s)

Placebo will be prepared as described above in 5.1.3.

6.0 RISK AND BENEFITS

6.1 Study Medication Risks

A cumulative review of serious and non-serious ADRs was performed from completed double blind, placebo-controlled studies for the RA indication (7 IV and 2 SC studies) and also from ongoing studies where the unblinded data are available, which included studies in psoriatic arthritis (PsA). Assessment of ADRs from one ongoing study in PsA was also performed. The ADRs in patients with PsA are similar to those reported in patients with RA in terms of type, severity, and nature of ADRs. As of 30-Jun-2016, the following serious and non-serious ADRs have been reported in clinical studies with abatacept treatment.

Serious and non-serious infections with common pathogens such as bacterial, viral, and fungal are considered expected in patients treated with abatacept, since abatacept modulates the immune system. The list is presented by SOC and frequency using the following categories: very common (≥ 10%); common (≥ 1% to < 10%); uncommon (≥ 0.1% to < 1%); rare (≥ 0.01% to < 0.1%), or very rare (< 0.01%).

The following is an integrated summary of the Adverse Drug Reactions in Subjects Treated with Abatacept in Clinical Studies

Common Adverse Events (≥ 1% to < 10%):

Administration Site Reactions: Generalized fatigue and injection site reactions
Gastrointestinal Disorders: abdominal pain, diarrhea, dyspepsia, mouth ulceration and nausea
General Disorders and Infestations: asthenia, bronchitis, urinary tract infection, upper respiratory tract infection, herpes simplex, ear infections and oral herpes
Nervous System Disorders: dizziness and headache
Respiratory, Thoracic and Mediastinal Disorders: cough

Uncommon Adverse Events (≥ 0.1% to < 1%)

Administration Site Conditions: influenza-like illness
Blood and Lymphatic System Disorders: leukopenia and thrombocytopenia
Cardiac Disorders: bradycardia, palpitations and tachycardia
Ear and Labyrinth Disorders:vertigo
Eye Disorders: conjunctivitis and reduced visual acuity
Gastrointestinal Disorders: gastritis and aphthous stomatitis
Immune System Disorders: urticaria
Infections and Infestations: pneumonia, herpes zoster, cellulitis, lower respiratory tract infections, tuberculosis, nasopharyngitis, sinusitis, tracheitis, rhinitis, infected skin ulcer, onychomycosis, tooth infection and pylenephritis
Investigations: increased weight, Transaminases increased
Nervous system disorders: paraesthesia
Malignancies: basal cell carcinoma
Psychiatric Disorders: anxiety, depression and insomnia

Reproductive System and Breast Disorders: amenorrhea, menorrhagia
Respiratory, Thoracic and Mediastinal Disorders: wheezing, chronic obstructive pulmonary disease and dyspnea
Skin and Subcutaneous Tissue Disorders: alocpecia, dermatitis, dry skin, hyperhidrosis, increased tendency to bruise, pruritis, erythema and acne
Vascular Disorders: flushing, hot flush and hypotension
Immune System Disorders: drug hypersensitivity
Musculoskeletal and Connective Tissue Disorders: pain in extremity, arthralgia

Very Rare Adverse Events (< 0.01%)

Infections and Infestations: sepsis and diverticulitis
Psychiatris Disorders: sleep disorders
Investigations: abnormal liver function test
Malignancies: lymphoma

Antirheumatic therapies have been associated with hepatitis B reactivation.

Adult COPD patients treated with abatacept in RA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. Use of abatacept in patients with COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status.

6.2 Other Risks

Physical Activity Monitor (PAM) Use: There is the possibility of minor skin irritation associated with wearing the PAM device. There may be minor risk of skin irritation from use of the elastic belt if used with the PAM device. Keeping the band clean, dry and loosely fitting will help reduce this risk.

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.

Risk of Breach of Confidentiality: Study data and blood specimens collected during the course of this trial will be labeled with a study code and contain no personal subject identifiers that could directly identify the subject and will be stored in a secure location; however there is a chance that a breach of confidentiality will occur and the subject personal or medical health information may be inappropriately distributed.

Data that is transferred from your FitBit One ® device will not contain any identifiable personal information. The data will be stored on a secure network server located in the Department of Medicine, Division of Rheumatology. Study data will be stored in the Rheumatic Disease Management System (RDMS) located at the University of Pittsburgh, Division of Rheumatology which is located on a secure server behind a network firewall. There is the possibility that if the results of the research studies involving biologic samples or genetic material were to become known this information could affect the subjects ability to be insured or employed, reputation, and future plans for children, or family relationships. Although every reasonable effort has been taken,

confidentiality during Internet communication activities cannot be guaranteed and it is possible that additional information beyond that collected for research purposes may be captured and used by others not associated with this study.

Reproductive Risks: The effect of the study drug on the unborn child is unknown.

Consequences of additional therapy restrictions: There is a risk for deterioration in the subjects' condition. New symptoms occurring during the treatment period requiring an unscheduled physician visit, emergency department evaluation, hospitalization or change in immunosuppressive therapy will be evaluated by the principal investigator. Determination will then be made by the principal investigator if additional medication is necessary.

Genetic Samples: It would be rare (less than 1% of cases or in less than 1 out of 100 cases) that if the results of the research studies involving genetic material were to become generally known the information could affect the subjects ability to be insured, ability to be employed, r future plans for children, or family relationships.

7.0 OBSERVATIONS PER VISIT

7.1 Screening Visit (Visit 0)

The following assessments will be performed during the Screening Visit:

Screening Visit (Visit 0)

1. Obtain informed consent from the subject.
2. Review concomitant medications for defined study washout and restriction of immunosuppressive (IS) medications.
3. Urine Pregnancy (if applicable) for all females of childbearing potential.
4. Obtain safety screening tests to include: serologies for Hepatitis B (Hep B surface Ab, surface antigen and core antibody), Hepatitis C (Qualitative HCV antibody) and tuberculosis (Quantiferon TB Gold) if a negative result was not obtained **within the last year.** If Quantiferon gold is non-interpretable or cannot be done, then skin PPD test for tuberculosis should be done.
5. Pulmonary Function Test (PFT) with DLCO should be obtained.
6. If a High-Resolution Computed Tomography (HRCT) chest has been completed as part of the patients' standard of care the results should be recorded on the HRCT chest ILD Assessment Form.
7. Brief Evaluation (history/physical)
8. Obtain and record vital sign measurements.
9. Complete screening evaluation, demographics and screening criteria assessments.

7.2 Other Study Visits

Study Visits 1, 2 and 3 (Weeks 0, 12, and 24)
Subjects who are eligible will visit the study site and enter the randomized treatment phase after randomization. Visit 1 should take place within 21 days after the Screening Visit.

All eligible subjects will receive their first injection of either abatacept 125mg SQ injection or placebo as per randomization at Visit 1. The following assessments will be performed:

The following research procedures will be conducted at Visits 1, 2 and 3 unless otherwise noted:

- Review concomitant medications
- A urine pregnancy (if applicable) will be performed for all females with child bearing potential.
- Site pharmacist will randomize subject to receive either study drug or placebo.
- Perform and record functional test (6 minute walk distance test - 6MWD)
- Administer patient questionnaires to include: dyspnea, patient global, SF-36 and health assessment questionnaires and patient assessment of change
- Site Investigator to perform Manual Muscle Test (MMT-8)
- Site Investigator to complete MDAAT, brief physical exam and physician assessment of change
- Obtain safety screening tests to include: creatine kinase(CK), aldolase, complete blood count with differential, serum creatinine and liver function tests
- Obtain research repository blood per study schema (Appendix A)
- Instruct the subject on how and when to use the FitBit One ® device. Patient will wear FitBit device for 7 consecutive days one a month for 6 months. Refer to Manual of Operations for specific procedures for syncing the device. - **visit 1 only**
- A pulmonary function test will be performed at **visits 2 and 3 only**
- Assess and record adverse events (if applicable) – **visits 2 and 3 only**
- If a High-Resolution Computed Tomography (HRCT) chest has been completed as part of the patient standard of care, the research coordinator will obtain and record the results of this test for research purposes at **visit 1 and 3 only**. A CD of HRCT chest (at baseline and follow up) should be mailed to coordinating center for centralized evaluation in future.
- **At visit 1 only**, you will instruct the subject on how to do the subcutaneous injection of the study drug. The subject will self-administer the study drug at Visit 1 to ensure adequate knowledge. Study drug will be dispensed to the subject at study **visits 1 and 2** (approximately 11 - 12 pre-filled syringes) to continue weekly at home. Note at study **visit 3**, that open label drug should be dispensed to the subject if continuing into the open label Phase II of the study.

Subjects will be informed that the FitBit device must be returned to the research team once they have completed the trial. The FitBit device will be then be re-assigned to future subjects at your site. The FitBit device is setup with individual accounts therefore no data from a previous participant will remain on the device. Please refer to the Manual of Operations for further guidance on setting up a de-identified account for each participant.

The following research activities will occur in between study visits 1, 2, 3 and 4:

- Approximately one week after the subject has been randomized (Visit 1) at the study center, you should call the subject to determine if the subject has experienced any adverse

events, difficulty with administering the self-injection and to confirm steroid taper compliance. This call should be documented in your site source documentation.

- To insure that we are capturing and addressing potential side effects or deterioration in condition, the coordinators were instructed to call the subject monthly to review for adverse events, steroid taper compliance, and any signs of deterioration from the steroid taper. The call will be documented in the sites source documentation.

Unscheduled Visits: The subject should be seen for an unscheduled visit if any worsening in condition has occurred.

The following research procedures will be conducted at an unscheduled visit:

- Review concomitant medications
- Administer patient questionnaires to include: dyspnea, patient global, and health assessment questionnaires and patient assessment of change
- Site Investigator to perform Manual Muscle Test (MMT-8)
- Site Investigator to complete MDAAT, brief physical, physician global assessment exam and physician assessment of change
- A pulmonary function test (PFT) will be performed as SOC for worsening condition as deemed necessary by investigator.
- Assess and record adverse events (if applicable)
- High-Resolution Computed Tomography (HRCT) will be performed as SOC for worsening condition as deemed necessary by investigator.
- The research coordinator will obtain and record the results of HRCT or PFT if any of these tests are conducted as standard of care.

7.3 Open Label Phase Study Visits

Optional Open Label Follow Up Phase - Visits 4 and 5 (weeks 36 and 48)
The subject will continue in the open label phase of the trial if:

- The subject has completed the 24 week randomized treatment phase
- The subject has provided consent to participate in the open label phase

The following study procedures would be performed at Visits 4 and 5:
The same study procedures that were performed at visits 1, 2 and 3 would be performed at these visits with the following exceptions:

- A pulmonary function test will be performed at **visits 5 only**.
- If HRCT was performed as standard of care, the results should be recorded at **visit 5 only.**
- The physical activity monitor, FitBit One ® will not be used in the open label phase of the trial.

8.0 DOSE MODIFICATION/TOXICITY MANAGEMENT

A number of measures will be taken to ensure the safety of patients participating in this study. These measures will be addressed through exclusion criteria (see Section 4.2) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

9.0 CRITERIA FOR SUBJECT DISCONTINUATION

9.1 Abatacept-Specific Criteria

Subjects who meet the following criteria should be discontinued from the study:

- Anaphylaxis or hypersensitivity reaction or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity (ABT should be permanently discontinued from these patients)
- If, following initiation of study drug, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of study drug administration, including at least 5 half-lives administration, the study drug will be permanently discontinued.

9.2 General Criteria

- Inability of subject to comply with study requirements

Determination by the investigator that it is no longer safe for the subject to continue therapy**10.0 CLINICAL AND LABORATORY EVALUATIONS**

Refer to Appendix B.

10.1 Pre-Treatment Evaluations

Unless otherwise specified, the following evaluations must be performed within two weeks prior to the date of each patient's initial treatment with Abatacept:

- Urine Pregnancy (if applicable)
- Serologies (HCV, HBV) or TB screening if not done within last 1 year
- Screening demographics, evaluation, and criteria
- PFT (FVC, FEV1, DLCO)
- HRCT chest (SOC)

Brief Evaluation (history/physical)

10.2 Evaluations During Treatment

- PFT (FVC, FEV1, diffusing capacity of the lungs for carbon monoxide (DLCO)) will be evaluated at baseline (accepted if within prior 1 month of screening visit), 3, 6 months (+/- 2 weeks). If patient opts into the open label phase, then additional PFT at 12 months will be done.
- HRCT chest at baseline i.e. visit 0/1 (accepted within 3 months of screening visit if no significant change in clinical status has occurred in 3 months) will be done as standard of care (SOC) in clinical practice. HRCT chest at 6 month (+/- 1 month) follow up i.e visit 3 will be done as SOC as well. In patients opting for open label phase, additional HRCT at 12 months (+/- 1 month) follow up i.e visit 5 will be collected if done as SOC.

- Muscle enzyme: creatine kinase (CK) and aldolase levels at baseline, 3, 6 months. If open label phase – then additional 9 and 12 months will be obtained.
- Safety monitoring labs – complete blood count (CBC), liver function test (LFT), serum creatinine will be done at baseline, 3 and 6 months. If patient opts for open label phase, these safety labs will also be done at 9 and 12 months.
- Research specimens (serum, cells, etc) collected at each study visit for future experimental studies.

Refer to study schema in Appendix B

11.0 REPORTING OF ADVERSE EVENTS

11.1 Adverse Event and Reporting Definitions

An adverse event (AE) is any new untoward medical occurrence or worsening of a preexisting medical condition in a patient or clinical investigation subject who has been administered a study drug and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Data on adverse events will be collected and reported regardless of relation to the study drug. Moreover, relatedness of these AE to the use of BMS drugs associated with this study (where applicable) will be assessed.
Note: Although not always considered adverse events by regulatory definition, the following events associated with a BMS product must be reported.

- Exposure (to fetus) during pregnancy, exposure (to infant) during lactation, and paternal exposure
- Overdose
- Lack of efficacy
- Abuse
- Misuse
- Off-label use
- Occupational exposure
- Medication error and potential medication error
- Suspected transmission of an infectious agent, e.g., any organism, virus or infectious particle pathogenic or non-pathogenic, via the medicinal product.

The causal relationship to the study drug associated with this study is determined by the PI and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between the BMS product associated with this study and the AE.
- Not related: There is not a reasonable causal relationship between the BMS product associated with this study and the AE.
- The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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

NON-SERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A ***non-serious adverse event*** is an AE not classified as serious.

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:
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 (PI determines if the hospitalization event is considered SAEs); results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.); suspected transmission of an infectious agent, pathogenic or nonpathogenic, via the BMS product associated with this study is an SAE.

An ***overdose*** is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.
Although pregnancy, overdose; potential drug-induced liver injury (DILI) and cancer are not always serious by regulatory definition, these events are handled as SAEs.

The following hospitalizations are <u>not</u> considered SAEs in BMS clinical studies:

- A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event).
- Elective surgery, planned prior to signing consent.
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reasons).
- Admission for administration of subsequent anti-cancer therapy in the absence of any other SAEs (applies to oncology protocols).

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.
The following laboratory abnormalities should be documented and reported appropriately:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

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

Potential Drug Induced Liver Injury (DILI)
Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN) AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, active myositis with elevated CK, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Pregnancy
If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).
The investigator must immediately notify Worldwide.Safety@bms.com of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.
Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.
Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]
Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

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

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

11.2 Reporting of Serious Adverse Events Associated with Abatacept

Immediate Reporting Requirements:

Non-serious AEs and SAEs whether or not related to the BMS product associated to this study, pregnancies, AEs associated with maternal exposure, and pregnancy outcomes ascertained in the study must be reported individually in the time frames noted below. All AEs collected will also be reported in aggregate in the final study report. Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE.

Serious Adverse Event Collection and Reporting

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).
- The MedWatch form 3500A will be to report SAEs. The form will be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator. The form can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. For drugs with potential for delayed SAEs (e.g., delayed excretion of the parent or active metabolites), a longer follow-up period may be warranted to allow collection of these SAEs Laboratory tests, and other assessments.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection.
- The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). *Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.*
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of SUSAR Report.
    - Other important findings which may be reported by BMS as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered

associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

Investigators should report to the responsible regulatory authority as appropriate.
All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 1-609-818-3804

SAEs, whether related or not related to study drug, as well as pregnancies, must be reported to BMS within 24 hours. SAEs must be recorded on the MedWatch form; pregnancies must be reported on a Pregnancy Surveillance Form.

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- 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.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

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 BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

Non-serious Adverse Event Collection and Reporting
The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

All non-serious AEs must be reported by confirmed fax transmission or reported via electronic mail to:

Non-serious AE Email Address: Worldwide.Safety@BMS.com
Non-serious AE Facsimile Number: 1-609-818-3804

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of the BMS product associated with this study and for those present at the end of the study, as appropriate.

MedWatch 3500A Reporting Guidelines
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

12.0 STATISTICAL CONSIDERATIONS

12.1 Determination of Sample Size

The sample size is 20 patients with 10 patients in each arm for a 24-week randomized double blind clinical trial. The sample size is justified based on this trial being a proof of concept pilot study. This study will allow us to determine an initial signal for possible efficacy of ABT in Myositis-ILD (Syn-ILD) as well as give safety and tolerability data. Moreover, it will allow us to determine an estimate of the effect size of the study drug and placebo to design a more definitive phase II/III clinical trial. In our cohort about 25% patients with SOC decline by FVC% of ≥15% or death or

transplant. Assuming FVC decline by mean of 10% on SOC therapy and trial drug + SOC leads to improvement in FVC% (Even by mean of 5%) we will have >90% power to detect the difference with sample size proposed. Based on our database there is about 25% patients that decline FVC > 10% on SOC for myositis ILD.

12.2 Planned Efficacy Evaluations

12.2.1 Primary Efficacy Variables

The primary end point for statistical analysis will be the percent FVC changes from baseline to week 24 between the 2 treatments arms (SOC/placebo vs. SOC/ABT).

Primary outcome criteria for safety and tolerability will be adverse event (routine adverse events or tolerability issues and serious adverse event) between the 2 treatment arms (SOC/placebo vs. SOC/ABT).

12.2.2 Secondary Efficacy Variables

a. Time to progression free survival where progression is defined as first occurrence of any of the following: death or lung transplant or FVC ≥10% decline *or* FVC ≥5% decline with DLCO ≥15% decline.
b. Change in dyspnea, as measured by University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) (range 0-120, higher score is worsening dyspnea).
c. Time to improvement in FVC% by ≥10%.
d. Rates of death or requiring lung transplant..
e. Other individual PFT variables (FEV1%, DLCO%).
f. Qualitative changes in HRCT chest over 6 months in the two arms using chi-square (or Fischer exact) test. Changes in semi-qualitative scoring of fibrosis over 6 months based on HRCT chest scan images collected from all sites and centrally read by an expert blinded radiologist, will be done as a separately.
g. Steroid-sparing effect (calculated using prednisone dose equivalents)
h. Frequency of treatment failures: a) patient meeting worsening criteria or withdrawal due to worsening ILD anytime during the trial or b) FVC% worsening by 10% at 6 months, c) death or transplant within 6 months.

Secondary Outcome Myositis: Given that many patients *may* have concomitant active myositis with muscle and/or skin involvement we will assess clinical outcomes related to both muscle and skin using following secondary outcomes (SOC/placebo vs. SOC/ABT):
Active myositis is defined based on MDAAT at baseline muscle or cutaneous skin disease activity of ≥ 3 on 10 cm visual analogue scale (VAS).
New myositis response criteria and IMACS definition of improvement (DOI) will be used to assess myositis response in drug + SOC vs. placebo + SOC.

12.3 Methods of Analysis

Primary End Point:
The primary end point for statistical analysis will be the percent FVC changes from baseline to week 24 between the 2 treatments arms (SOC/placebo vs. SOC/ABT). Ranked ANCOVA, with average standardized rank change in the predicted FVC% as the outcome measure and the standardized rank baseline as a covariate will be used. Primary outcome criteria for safety and

tolerability will be adverse event (routine adverse events or tolerability issues and serious adverse event) between the 2 treatment arms (SOC/placebo vs. SOC/ABT). Chi-square (or Fischer exact test) and t-test (or Mann-Whitney) will be used based on data variable and distribution. Patients will be stratified for sub-analysis based on their SOC drug

Secondary Analysis (SOC/placebo vs. SOC/ABT) for Syn-ILD:

a. Time to progression free survival where progression is defined as first occurrence of any of the following: death or lung transplant or FVC ≥10% decline *or* FVC ≥5% decline with DLCO ≥15% decline. This will be done using Cox proportional hazards model and controlling for baseline demographics and FCV%.
b. Change in dyspnea, as measured by University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) (range 0-120, higher score is worsening dyspnea), will be done using Mann-Whitney test.
c. Time to improvement in FVC% by ≥10%. This will be done using Kaplan Meier survival curve and Cox's proportional hazards model after controlling for co-variates.
d. Rates of death or requiring lung transplant using Chi-square (Fischer exact) test.
e. Other individual PFT variables (FEV1%, DLCO%) similar to analysis done for primary outcome of FVC%.
f. Qualitative changes in HRCT chest over 6 months in the two arms using chi-square (or Fischer exact) test. Changes in semi-qualitative scoring of fibrosis over 6 months based on HRCT chest scan images collected from all sites and centrally read by an expert blinded radiologist, will be done as a separately and analyzed using analysis strategy similar to primary outcome.
g. Steroid-sparing effect (calculated using prednisone dose equivalents) using paired t-test.
h. Frequency of treatment failures: a) patient meeting worsening criteria or withdrawal due to worsening ILD anytime during the trial or b) FVC% worsening by 10% at 6 months, c) death or transplant within 6 months. Chi-square test will be used to compare between the two groups.

Secondary Outcome Myositis:

New myositis response criteria (table 1) and IMACS definition of improvement (DOI) will be used to assess myositis response in drug + SOC vs. placebo + SOC.

a. Comparison of the average Total Improvement Scores during the 6-month treatment period. Repeated measures analysis will be used to compare the two treatment groups and adjustments will be made for the baseline core set measures (CSM) values.
b. Comparison of the proportion of patient meeting IMACS DOI and time to first IMACS DOI between the 2 arms,
c. Comparison of the individual CSM in subjects over time between the 2 arms (repeated measures analysis).
d. Comparison of the magnitude of the effect size between both treatment arms by comparing the proportion of subjects having Total Improvement Scores ≥ 20 (minimal), 40 (moderate) and 60 (major).

13.0 RETENTION OF RECORDS

All study records and source documents will be maintained for 7 years after the completion of the study or for the period specified by agreement with BMS, whichever is longer.

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APPENDIX A: MMT-8

MMT- 8 is a set of 8 designated muscles tested unilaterally (potential score 0-70 and usually

tested on the right side unless contraindicated) or bilaterally (potential score 0-140) and if axial (neck flexor) testing is included, potential score = 150. The scale of 150 is proposed for this trial.

Muscle Groups	Right (0 – 10)	Left (0 – 10)
Axial Muscles (0 – 10)		
Neck Flexors	**0-10**	
Proximal Muscles (0 – 50)		
Deltoid	**0-10**	**0-10**
Biceps brachii	**0-10**	**0-10**
Gluteus maximus	**0-10**	**0-10**
Gluteus medius	**0-10**	**0-10**
Quadriceps	**0-10**	**0-10**
Distal Muscles (0 – 20)		
Wrist extensors	**0-10**	**0-10**
Ankle dorsiflexors	**0-10**	**0-10**
MMT- 8 score (0 – 150)	**0-70**	**0-80**

APPENDIX B: STUDY FLOW CHART/SCHEMA

											Open Label				
Month	**0-21 days before study drug**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Unscheduled Visit**
(weeks)		**0**	**+7 days from V1**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Visit	**Screen or Visit 0**	**1**	**Call**	**Call**	**2**	**Call**	**Call**	**3**	**Call**	**Call**	**4**	**Call**	**Call**	**5**	
Safety Laboratory Testing															
Urine Pregnancy (if applicable)	X	X			X			X			X			X	
CK, Aldolase		X			X			X			X			X	
CBC, Creatinine, LFT		X			X			X			X			X	
Serologies (HCV, HBV) or TB screening if not done within last 1 year	X														
Data Collection															
Screening demographics	X														
Screening evaluation	X														
Screening criteria	X														
Randomization form		X													
PFT (FVC, FEV1, DLCO)	X				X			X						X	**
HRCT chest (if done as SOC) *	X							X						X	**
HRCT ILD Assessment Form (if done as SOC)	X							X						X	
Dyspnea questionnaire		X			X			X			X			X	X
Patient Global Assessment		X			X			X			X			X	X
HAQ		X			X			X			X			X	X
MMT-8		X			X			X			X			X	X

MDAAT		X			X			X			X			X	X
Physician Global Assessment		X			X			X			X			X	X
Physician Assessment of Change					X			X			X			X	X
Patient Assessment of Change					X			X			X			X	X
SF 36 QoL Questionnaire		X			X			X			X			X	
Brief Evaluation (history/physical)	X				X			X			X			X	X
Six Minute Walk Distance (6MWD)		X			X			X			X			X	
Average daily step count on Fitbit One ® (measured for 7 days at baseline and every month for 6 months)		X			X			X							
Adverse Event/Tolerability Monitoring		X			X			X			X			X	X
Follow Up Call (assess AE's.confirm steroid taper per protocol and subjective clinical worsening)			X	X		X	X		X	X		X	X		
Bio-specimen Repository Collection		X			X			X			X			X	
RESEARCH SPECIMEN COLLECTION															
PAXGene tube (ml)		8			8			8			8			8	
Stored cells (ml) Green Top		16			16			16			16			16	
Stored Serum (ml) SST		16			16			16			16			16	

* An HRCT scan done as SOC within the last 6 months is required for entry into the trial to meet eligibility criteria.

** HRCT and PFT done as SOC for worsening condition as deemed necessary by investigator.

APPENDIX C: Rescue Medication for ILD Worsening