Protocol Number: IM101611
IND Number: BB-IND 9391
Ex-US Non-IND
EUDRACT Number 2016-002269-77
Date: 08-Jul-2016
Revised Date: 01-Feb-2019

Clinical Protocol IM101611

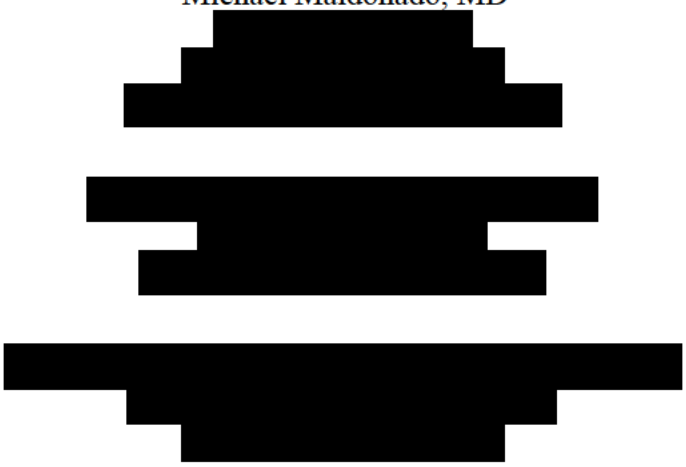
A Phase 3, Randomized, Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of Abatacept SC with Standard Treatment Compared to Standard Treatment Alone in Improving Disease Activity in Adults with Active Idiopathic Inflammatory Myopathy (IIM)

Revised Protocol Number: 04

Incorporates Amendments 03, 04, 05 and 06

Study Director/Medical Monitor

Michael Maldonado, MD



Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04	01-Feb-2019	Incorporates Amendments 03, 04, 05, and 06.
Revised Protocol 03	09-May-2018	This protocol revision is to clarify language, adjust criteria to improve subject selection and clarify allowable concomitant medication.
Revised Protocol 02	10-Mar-2017	Incorporates Amendment 02 and Administrative Letter 01
Amendment 02	10-Mar-2017	This amendment clarifies the target population (Inclusion/Exclusion criteria), randomization stratification criteria [redacted], study procedures and sub-studies, training requirements for site staff, the process for adjudication, the duration of samples retention for additional research and the duration of post drug follow-up. This amendment also updates the IND number and contact information for a new medical monitor..
Administrative Letter 01	26-Jan-2017	This administrative letter corrects the study schematic, eliminates inconsistencies in the standard treatment instructions and sample collection conditions and clarifies that exploratory sub-study results for the MRI muscle biopsies will not be provided to the sites or subjects.
Revised Protocol 01	20-Oct-2016	Incorporates Amendment 01
Amendment 01	20-Oct-2016	This amendment corrects several inconsistencies and clarifies several study procedures. It also incorporates feedback from the FDA and CHMP regarding the study population and study design
Original Protocol	08-Jul-2016	Not applicable

OVERALL RATIONALE FOR THE REVISED PROTOCOL 04

The protocol is being revised to incorporate Amendments 03, 04, 05, and 06 at the request of several IRBs/IECs. Also the changes provide some clarity in language and correct inadvertent errors in several sections of the document.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04

Section Number & Title	Description of Change	[redacted]
Synopsis	Updated duration of the study treatment from 1 year to 4.5 years (from Amendment 06).	
Synopsis, Study Design and Section 3.1, Study Design and Duration, Figure 3.1-1	The description of study design was updated and the schematic was updated to reflect the new study duration (from Amendment 06).	
Synopsis, Study Design	Descriptions for the Open Label Extension Period for Japan and the Long Term Extension Period were added (from Amendments 04 and 06).	
Synopsis, Analyses	Two sentences were added for the Open Label Extension Period for Japan subjects and the Long Term Extension Period were added (from Amendments 04 and 06).	
[redacted]	[redacted]	
Section 2.3, Informed Consent	Added information regarding minors (from Amendment 03).	
Section 3.1.3, Open Label Period (Week 24-Week 52) and Open Label Extension Period (Week 52-Week 76) for Japan	Updated section description and added a new second paragraph to describe the open label extension period for Japan. Added Wk 76 for repeat PFT and HRCT testing (from Amendment 04).	
Section 3.1.4, Long Term Open Label Extension for Subjects Randomized in Countries Other than the U.S. and the Czech Republic	New section was added. Sections were renumbered from this point (from Amendment 06).	
Renumbered Section 3.1.5, Rescue Therapy	Added information on rescue and background treatment for the Open Label Extension Period for Japan and the Long Term Extension Period (from Amendments 04 and 06).	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	[redacted]
Renumbered Section 3.1.6, Post-Treatment Follow-up Period	Added information for the Open Label Extension Period for Japan and the Long Term Extension Period (from Amendments 04 and 06).	
Section 3.3.1, Inclusion Criteria, 2) Target Population, e)ii)	Added MPA is a formulation for mycophenolate and therefore acceptable as an allowed immunosuppressant (from Amendment 06).	
Section 3.3.2, Exclusion Criteria, 3) Physical and Laboratory Test Findings, a)	Added information regarding hepatitis B exclusion (from Amendment 03).	
Section 3.4.1.1, Standard Treatment, second bullet	Added MPA is a formulation for mycophenolate and therefore acceptable as an allowed immunosuppressant (from Amendment 06).	
Section 3.4.2.1, Prohibited Medications	Added statement that provisions for prohibited medication will continue during the long-term open label extension period (Amendment 05).	
Section 3.5, Discontinuation of Subjects following any Treatment with Study Drug, 4th paragraph, 10th bullet	Added information that subjects missing 5 or more consecutive doses of abatacept for any reason between Week 24 and Week 76 should be discontinued (from Amendment 04)..	
Section 4.4, Method of Assigning Subject Identification	Added information for subjects in the Open Label Extension Period for Japan and the Long Term Extension Period (from Amendments 04 and 06).	
Section 4.5.1, Abatacept Treatment, 2nd paragraph	Added information for subjects in the Open Label Extension Period for Japan and the Long Term Extension Period (from Amendments 04 and 06).	
Section 5.1, Flow Chart/Time and Events Schedule, Table 5.1-1	Added autoantibody testing at screening to be tested centrally if requested by sites in Brazil, Mexico, and the U.S. (from Amendment 06).	
Section 5.1, Flow Chart/Time and Events Schedule	Added Tables 5.1-5 and 5.1-6 and renumbered former 5.1-5 to be 5.1-7 (from Amendment 06).	
Section 5.1, Flow Chart/Time and Events Schedule, Table 5.1-5, Open Label Extension for Japan, Table Note c	Modified information to indicate the efficacy assessments may be recorded on paper if the electronic tablet (ePRO) is unavailable/not functioning for transmission of the data (from Amendment 06).	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	[redacted]
Section 5.1-6, Long Term Open Label Period (all countries except the U.S. and the Czech Republic)	Added dispense pregnancy kits at Quarterly Visits (Days 85 and 253) and 6 Months (Days 533 and 729) (from Amendment 06).	
Section 5.1-6, Long Term Open Label Period (all countries except the U.S. and the Czech Republic)	Added dispense SC abatacept and diary cards at 6 Months (Days 533 and 729) (from Amendment 06).	
Section 5.2, Study Materials	Added metronome, wrists weights, and step stool (from Amendment 06).	
Section 5.3, Safety Assessments, 2nd paragraph	Added cross-references to Table 5.1-5 and 5.1-6 (new periods for Open Label Extension Period for Japan and the Long Term Extension Period) (from Amendments 04 and 06).	
Section 5.3.2, Physical Measurements	Updated table references (from Amendment 04).	
Section 5.3.5.6 Hepatitis Screen	Added information regarding hepatitis B screening (from Amendment 03).	
Section 5.3.5.7, Pregnancy Tests	Added new periods for Open Label Extension Period for Japan and the Long Term Extension Period). Updated table references (from Amendments 04 and 06).	
Sections 5.3.6, Pulmonary Function Testing, and Section 5.3.7.2, High-Resolution Computed Tomography (HRCT) Chest, 3rd and 5th paragraphs	Added Week 76 (from (Amendment 04).	
Section 5.4.1.1, IMACS Definition of Improvement (DO), 3rd and 4th paragraphs	Updated table reference (from Amendment 04).	
Section 5.4.1.3, Patient Reported Outcomes, 1st paragraph	Indicated the information will be recorded in the ePRO device and deleted the sentence regarding pages being source documents (Amendment 06).	
[redacted]	[redacted]	
[redacted]	[redacted]	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	[redacted]
Section 5.8.4, Actigraphy, 2nd paragraph, c)	Deleted duplicate information (from Amendment 06).	
Section 6.7, Other Safety Considerations	Added information for malfunction of the pre-filled syringes (from Amendment 03).	
Section 8.2, Populations for Analyses	Added new periods for Open Label Extension Period for Japan and the Long Term Extension Period) (from Amendments 04 and 05)	
[redacted]	[redacted]	
Section 8.4, Analyses	Updated to indicate 4 analyses are planned, not 2. Described plans for analyses of new periods for Open Label Extension Period for Japan subjects and the Long Term Extension Period) (from Amendments 04 and 05).	
Section 8.4.7, Week 52 Analysis	Updated Section Title (from Amendment 06).	
Sections 8.4.8 and 8.4.9, Week 76 Japan Only Analysis and Long Term Open Label Extension (3 Years)	Added new sections for Open Label Extension Period for Japan subjects and the Long Term Extension Period) (from Amendments 04 and 05).	
Appendix 4, Revised Protocol Summary of Change History	Added new appendix (from Amendment 06).	

SYNOPSIS

Clinical Protocol IM101611

Protocol Title: A Phase 3, Randomized, Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of Abatacept SC with Standard Treatment Compared to Standard Treatment Alone in Improving Disease Activity in Adults with Active Idiopathic Inflammatory Myopathy (IIM)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Subjects receive investigational products for a period of 4.5 years. Investigational products are defined as:

- Abatacept SC 125 mg in 1 ml pre-filled syringes
- Placebo to match abatacept SC in 1 ml pre-filled syringes [24 weeks (6 months) in the double-blind period]

Study Phase: III

Research Hypothesis: Subcutaneous abatacept (125 mg weekly) in combination with standard treatment will achieve a higher rate of responders, defined as the percentage of subjects who achieve the IMACS DOI (International Myositis Assessment and Clinical Studies - definition of improvement), after 24 weeks of treatment versus standard treatment alone in adult subjects with active IIM.

Objectives:

Primary Objective

The primary objective for this study is to compare the clinical efficacy of weekly abatacept in combination with standard treatment to standard treatment alone by assessing the percentage of subjects who achieve the IMACS DOI by Wk 24 compared to baseline, defined as:

- An improvement of ≥ 20% in 3 IMACS core measures, AND
- No more than 2 IMACS core measure scores worsen by ≥ 25%, AND
- Manual Muscle Test (MMT-8) may not decrease by ≥ 25%

Secondary Objectives

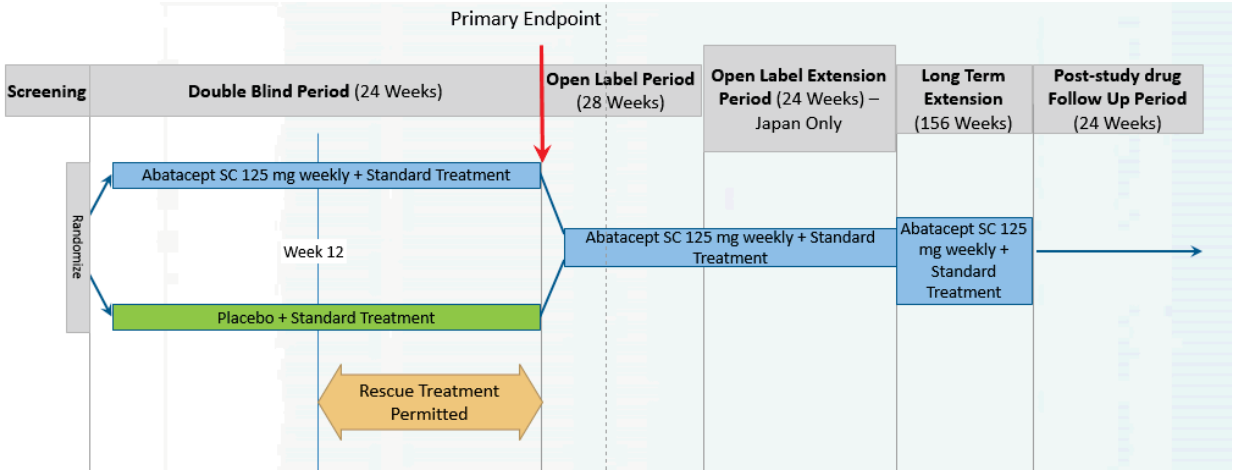
1) To assess the clinical efficacy of weekly abatacept in combination with standard treatment to standard treatment alone by assessing the change in muscle endurance test using the Myositis Function Index (FI-2) from baseline to Wk 24.
2) To assess the efficacy of abatacept in combination with standard treatment to standard treatment alone by assessing the mean change in functional disability using the Health Assessment Questionnaire-Disability Index (HAQ-DI) from baseline to Wk 24.
3) To assess the efficacy of abatacept in combination with standard treatment to standard treatment alone by assessing the mean change in extra-muscular disease activity as defined by Myositis Disease Activity Assessment Tool (MDAAT) from baseline to Wk 24.
4) To assess the efficacy of abatacept in combination with standard treatment to standard treatment alone in achieving improvement on the Myositis Response Criteria by assessing the mean change from baseline to Wk 24.

Study Design: This is a 24 week, randomized, double-blind, placebo-controlled, multicenter, study in subjects with active Idiopathic Inflammatory Myopathy (IIM: eg, Dermatomyositis [DM], Polymyositis [PM], autoimmune necrotizing myopathy; see Section 3.3.1 Inclusion Criteria, (2) Target Population), on standard background treatment.

In addition to the 24 week double blind period, the study includes a 28 week open-label treatment period during which all subjects will receive SC abatacept, an additional 24 weeks open label period of SC abatacept with continued therapy

from the original OL period for sites in Japan, and a 3 year long term extension of SC abatacept (156 weeks) with background treatment for all subjects except subjects in the U.S. and the Czech Republic.

The Primary Endpoint occurs at Wk 24, however assessments will be made throughout both periods to evaluate safety and efficacy.



Double-Blind Period (Day 1 - Week 24)

During this period, approximately 150 subjects will be randomized to one of two parallel treatment arms in a 1:1 ratio. The treatment arms are as follows:

Arm A: Active abatacept SC (125 mg) weekly + standard treatment

Arm B: Placebo abatacept SC weekly + standard treatment

Open-Label Period (Week 24 - Week 52)

After Week 24, all subjects will receive abatacept plus standard therapy.

Open-Label Extension Period (Week 52-Week 76 -- for Japanese only subjects

For Japan subjects will receive abatacept plus standard therapy.

Long Term Extension (3 years)

All subjects (excluding subjects randomized from the U.S. and the Czech Republic) will receive abatacept plus standard therapy.

Rescue Therapy

Subjects who meet the criteria for worsening between Wk 12 and Wk 24 will be eligible for rescue therapy. See Section 3.1.4 for details. In the Open-Label Period, subjects may adjust background treatment at any time.

Study Population: Men and women (not nursing or pregnant) ≥ 18 years old who have active idiopathic inflammatory myositis.

Key Inclusion criteria: Target population

a) Diagnosis of Definite or Probable IIM (DM or PM) based on the Bohan and Peter classification criteria (outlined in Appendix 3)
   i) Subjects with dermatomyositis (DM) must also have a confirmed myositis-associated rash (Gottron's papules or a heliotrope rash preferably confirmed by skin biopsy) and 2 or more of the remaining 4 criteria.
   ii) Subjects with a diagnosis of IIM other than DM include PM, autoimmune necrotizing myopathy, myositis in association with another connective tissue disease (overlap myositis) and juvenile myositis subjects above the age of 18. These subjects must have a prior muscle biopsy diagnostic for IIM *or* a

positive test for at least one myositis-specific autoantibody (anti-aminoacyl-tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, YRS), anti-Mi-2, anti-SRP, anti-TIF1-γ, anti-NXP-2, anti-MDA5, anti-SAE, anti-HMGCR). For subjects with overlap myositis, the myositis must be the principal clinically active manifestation of their disease.

Where applicable, documentation of prior skin biopsy, muscle biopsy, and autoantibody results must be obtained and retained by the site

b) Demonstrable muscle weakness measured by the MMT-8 of ≤ 135 units *and* any 3 of the following:
   i) MMT-8 ≤ 125 units
   ii) Physician's global assessment (PGA) VAS ≥ 2 cm
   iii) Subject's global assessment (SGA) VAS ≥ 2 cm
   iv) HAQ-DI ≥ 0.5
   v) One or more muscle enzyme (CK, aldolase, LDH, AST, ALT) ≥ 1.3 times upper limit of normal (ULN)
   vi) MDAAT Extramuscular Global Activity VAS ≥ 2 cm
c) Demonstration of currently active IIM will be determined by an adjudication committee (Section 7.1) unless the subject has any one of the following:
   i. an active myositis-associated rash (Gottron's papules or heliotrope rash), *or*
   ii. a recent (within 3 months prior to signing informed consent) biopsy, magnetic resonance imaging (MRI), or electromyogram (EMG) demonstrating active disease, *or*
   iii. an elevated CK > 5 times the upper limit of normal at screening with no alternate explanation or cause
d) Active disease despite adequate prior treatment experience with corticosteroids, immunosuppressants, or biologics as determined by the investigator
e) The subject must be on background standard treatment for IIM (Section 3.4.1.1). The standard treatments that are allowed as background treatment for IIM includes:
   i. Corticosteroids alone (Section 3.4.1.2), *or*
   ii. One of the following immunosuppressants: methotrexate, azathioprine, mycophenalate mofetil, tacrolimus, or cyclosporine (combinations of these treatments are not allowed), *or*
   iii. A combination of corticosteroids and one of the above immunosuppressants

   - If using corticosteroids for IIM, the subject must have been on corticosteroids for at least 12 weeks prior to randomization and a stable dose of corticosteroids for at least 4 weeks prior to randomization.
   - If using immunosuppressants other than azathioprine, the subject must have been on the same medication for at least 12 weeks and a stable dose for at least 4 weeks prior to randomization.
   - If using azathioprine, the subject must have been on azathioprine for at least 24 weeks with a stable dose for at least 12 weeks prior to randomization.

Key Exclusion criteria: Medical history and concurrent diseases

a) Subjects with Inclusion Body Myositis or myositis other than IIM, e.g. drug-induced myositis and PM associated with HIV.

b) Subjects treated with penicillamine or zidovudine in the past 3 months.

c) Subjects treated with rituximab in the 6 months prior to randomization (there must be laboratory results indicating the presence of circulating B cells [CD19+]). Any other biologic treatment in the past 3 months or immune globulin (intravenous [IVIG] or subcutaneous [SCIG]) in the past 3 months prior to randomization..

d) Subjects with uncontrolled or rapidly progressive interstitial lung disease (at the discretion of the investigator)

e) Subjects with severe muscle damage (Myositis Damage Index > 7/10), permanent weakness due to a non-IIM cause, or myositis with cardiac involvement

f) Cancer-associated myositis (myositis diagnosed within 2 years of a diagnosis of cancer). See criteria (2i)

g) Subjects who are known to be positive for the anti-TIF-1 (p155/140) autoantibody prior to randomization who were diagnosed with IIM < 1 year prior to randomization.

h) Subjects at risk for tuberculosis

i) Subjects with recent acute infection requiring antibiotics

j) Subjects with history of chronic or recurrent bacterial or viral infections

k) Subjects with active systemic fungal infections (eg, histoplasmosis, blastomycosis, or coccidiomycosis)

l) Subjects who have a present malignancy or have had a previous malignancy within the last 5 years prior to screening (except for a documented history of cured non-metastatic squamous or basal cell skin carcinoma or cervical carcinoma in situ). Additional screening requirements for malignancy are outlined in Sections 3.3.2 and 3.3.4.

Study Assessments: See Section 5 of the protocol for detailed information regarding study assessments.

Statistical Considerations:

Sample Size: A sample size of 150 subjects (75 subjects per treatment group) is planned based on the primary comparison of the proportion of subjects with IMACS DOI (as defined under the primary objective) at Day 169 (Week 24) between the SC abatacept group and the placebo group on a background of standard treatment.

A sample size of 150 subjects randomized in a 1:1 ratio to the SC abatacept group and placebo group will yield a power of approximately 90% to detect a treatment difference of 27% in the rate of IMACS DOI between the 2 treatment groups based on a continuity corrected chi-squared test. This power estimate assumes a two-sided alpha level of 5%, IMACS DOI rate of 60% in the abatacept group and 33% in the placebo group.

The 60% estimate of IMACS DOI in the abatacept group was based on reported rates of IMACS DOI in studies of patients with Myositis on combination therapy with another biologic agent[36]. It is expected that the rate of IMACS DOI on abatacept in combination with standard treatment should be similar to that observed with the use of another biologic agent in combination with standard treatment. Randomization will be stratified globally by 3 stratification variables: (1) Dermatomyositis (DM) vs non-DM IIM, (2) presence or absence of Interstitial Lung Disease (ILD), (3) Japan vs rest of world (ROW).

***Endpoints*:**

Primary Endpoint

- Proportion of subjects who achieve IMACS DOI at Week 24 without rescue

Secondary Endpoints

- Mean change in muscle endurance using the myositis function index (FI-2) from baseline to Weeks 12 and 24.
- Mean change in Health Assessment Questionnaire-Disability Index (HAQ-DI) from baseline to Weeks 12 and 24.
- Mean change in Myositis Disease Activity Assessment Tool (MDAAT) from baseline to Weeks 12 and 24.
- Mean change in Myositis Response Criteria score from baseline to Weeks 12 and 24.

Safety Endpoints

- All adverse events (AEs/SAEs)
- AEs of interest (serious infections, malignancies, injection site reactions, systemic reactions)
- Laboratory test abnormalities

***Analyses*:**

To assess the primary endpoint for this study an analysis (Week 24 Analysis) will be performed once all subjects complete their Week 24 visit assessments or discontinue prematurely prior to Week 24. The Week 24 analysis will

include analyses of the primary, secondary and exploratory endpoints. The primary comparison of proportion of subjects in IMACS DOI at Week 24 between the abatacept and placebo arms will be assessed using a logistic regression model. The logistic regression model will include baseline IMACS (continuous variable) and randomization stratification variables of diagnosis (Dermatomyositis [DM] vs non-DM IIM), Interstitial Lung disease status (present vs. absent), Japan vs. ROW to account for randomization stratification. All subjects who discontinue prematurely prior to reaching the Week 24 assessment visit, will be considered as not achieving IMACS DOI for the primary analysis. No formal statistical testing will be conducted for analyses related to the secondary and exploratory endpoints. Appropriate summary statistics will be provided for the analysis of each endpoint.

Safety summaries for the Week 24 analysis will include all adverse events (AEs) reported during the Double-Blind Period and presented by treatment groups (abatacept vs. placebo). AEs will be summarized from the first dose date in the study up to first dose date in the Open-Label Period or last dose date in the Double-Blind Period + 56 days for subjects who prematurely discontinued the study during the Double-Blind Period.

In accordance with an intent-to-treat approach, all available data from all subjects who receive at least one infusion of a treatment regimen being assessed at any time will be included in the safety and efficacy analyses. Detailed definition of population for analyses will be included in the protocol.

An analyses will be performed for the study once all subjects complete their week 52 assessment and/or all follow-up visits up to 168 days post last dose visit.

An analysis for the long-term efficacy and safety for subjects from Japan will be performed including data collected up to Week 76.

A final analysis will be performed for the study when all subjects complete the long-term open label extension and/or the follow-up period of the study.

TABLE OF CONTENTS

1 INTRODUCTION [redacted]

[redacted]

1.2 Research Hypothesis

Subcutaneous abatacept (125 mg weekly) in combination with standard treatment will achieve a higher rate of responders, defined as the percentage of subjects who achieve the IMACS DOI, after 24 weeks of treatment versus standard treatment alone in adult subjects with active IIM.

1.3 Objectives(s)

1.3.1 Primary Objectives

The primary objective for this study is to compare the clinical efficacy of weekly abatacept in combination with standard treatment to standard treatment alone by assessing the percentage of subjects who achieve the IMACS DOI by Wk 24 compared to baseline, defined as:

- An improvement of ≥ 20% in 3 IMACS core measures, AND
- No more than 2 IMACS core measure scores worsen by ≥ 25%, AND
- Manual Muscle Test (MMT-8) may not decrease by ≥ 25%

1.3.2 Secondary Objectives

1) To assess the clinical efficacy of weekly abatacept in combination with standard treatment to standard treatment alone by assessing the change in muscle endurance test using the Myositis Function Index (FI-2) from baseline to Wk 24.
2) To assess the efficacy of abatacept in combination with standard treatment to standard treatment alone by assessing the mean change in functional disability using the Health Assessment Questionnaire-Disability Index (HAQ-DI) from baseline to Wk 24.
3) To assess the efficacy of abatacept in combination with standard treatment to standard treatment alone by assessing the mean change in extra-muscular disease activity as defined by Myositis Disease Activity Assessment Tool (MDAAT) from baseline to Wk 24.
4) To assess the efficacy of abatacept in combination with standard treatment to standard treatment alone in achieving improvement on the Myositis Response Criteria by assessing the mean change from baseline to Wk 24.

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (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) and applicable local requirements.

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

All potential serious breaches must be reported to Sponsor or designee immediately. If required as per local regulation, serious breaches will be reported by Sponsor or designee to applicable authorities. A breach of the conditions and principles of Good Clinical Practice (GCP) (occurring in any country) in connection with that trial or the protocol related to the trial which is likely to affect to a significant degree the safety or physical or mental integrity of 1 or more subjects of the trial or the scientific value of the trial.

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).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The investigator, Sponsor or designee should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

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

In situations where consent cannot be given by subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for the subject or the subject's legally acceptable representative to inquire about the details of the study.

- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (e.g., due to stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

For minors, according to local regulations, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. In such cases, records on the relationship between the subject and the proxy consenter should be maintained with those of the consent. The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigation.

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

3 INVESTIGATIONAL PLAN

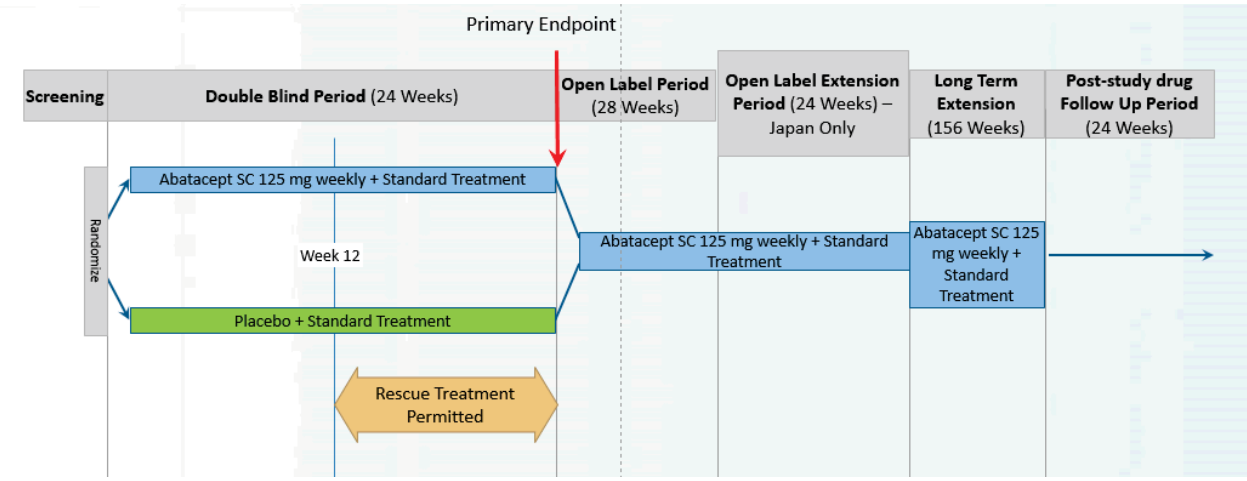
3.1 Study Design and Duration

This is a 24 week, Phase 3, randomized, double-blind, placebo-controlled, multicenter, study in subjects with active Idiopathic Inflammatory Myopathy (IIM; eg, DM, PM, autoimmune necrotizing myopathy; see Section 3.3.1) on standard background treatment.

In addition to the 24-week double-blind period, the study includes a 28 week open-label treatment period during which all subjects will receive SC abatacept with background treatment, an additional 24 weeks open label of SC abatacept with continued therapy from the original OL period for subjects in Japan, and a 3 year long term extension of SC abatacept (156 weeks) with background treatment for all subjects except subjects in the U.S. and the Czech Republic.

The primary objective for this study is to compare the clinical efficacy of weekly abatacept in combination with standard treatment to standard treatment alone by assessing the percentage of subjects who achieve the IMACS DOI after 24 weeks of treatment versus standard treatment alone in adult subjects with active IIM. The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



The start of the trial is defined as the first visit for the first subject screened. The end of the trial is defined as the last visit or scheduled procedure shown in the Time & Events schedule for the last subject. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected.

3.1.1 Screening Period

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity and safety assessments (see Table 5.1-1). Randomization must occur within four weeks of signing the informed consent. However, subjects may extend the screening period beyond 4 weeks, but not beyond a total of 6 weeks (42 days), from the signing of the informed consent.

Subjects who extend the screening period beyond 4 weeks may be required to repeat some screening assessments. If more than 6 weeks is required, e.g. initiation of treatment for latent TB,

a subject should be screen failed and re-enrolled when appropriate. Screening for malignancy is expected to have been performed prior to the Screening Period (Section 3.3.4).

3.1.2 Double-Blind Period (Day 1 - Week 24)

During this period, approximately 150 subjects will be randomized in a 1:1 ratio to one of two parallel arms in a double-blinded manner as follows (see Table 5.1-2):

Arm A: Active abatacept SC (125 mg) weekly + standard treatment

Arm B: Placebo abatacept SC weekly + standard treatment

At the time of randomization, subjects must be on a stable background treatment ("standard treatment" see Section 3.4.1.1) for IIM. No adjustment in background treatment will be allowed during this Period. Randomization will be stratified globally by 3 stratification variables: (1) Dermatomyositis (DM) vs non-DM IIM, and (2) presence or absence of interstitial lung disease (ILD), (3) Japan vs Rest of World (ROW).

Rescue therapy will be available for subjects who meet the disease worsening criteria during the double-blind period as defined in Section 3.1.4.

During this period, subjects who have clinically active or relevant interstitial lung disease (ILD) or anti-synthetase syndrome as determined by the investigator must undergo pulmonary function testing and high-resolution CT (HRCT) scan of the chest during screening (prior to Day 1) and may have repeat pulmonary function testing (PFT) and HRCT scan at Wk 24. (See Section 5.3.6 and Section 5.3.7.2)

Subjects who participate in the sub-study of MRI muscle (thighs) imaging will have an MRI performed during screening (prior to Day 1) and Wk 24. See Section 5.8.2

Subjects who participate in the sub-study of muscle biopsy will have a muscle biopsy performed during screening (prior to Day 1) and Wk 24. See Section 5.8.3

Subjects who discontinue treatment with study medication during the Double-blind Period will complete the Early Termination visit (which is the same visit as Day 169 visit) (See Table 5.1-2). These subjects must also return on the previously scheduled Double-blind Period Day 169 to complete the Post-Study Drug Efficacy Visit (see Table 5.1-4). The purpose of this visit is to assess all aspects of disease activity to ascertain the impact of study participation for regulatory review. Subjects must also complete 2 follow-up visits (85 and 169 days after the last dose) during the 24 week post-treatment follow-up period, to perform safety and laboratory assessments (See Table 5.1-7 Post-Treatment Follow-Up Period). This Period begins on the day of the Early Termination visit and applies only to subjects who do not start commercial abatacept therapy.

3.1.3 Open-Label Period (Week 24 - Week 52) and Open-Label Extension Period (Week 52 - Week 76) for Japan

The 24-week Double-Blind Period is followed by a 28 week open-label abatacept treatment period (Open-Label Period, see Table 5.1-3). During this period, subjects initially randomized to receive

the combination of abatacept and standard treatment will continue this regimen. Subjects who are initially assigned to receive standard treatment alone will be switched to standard treatment plus abatacept.

There will also be a 24 weeks (168 days) open label extension for subjects randomized in Japan.

Background treatment may be adjusted (including the dose of corticosteroids and immunosuppressants) at any time during this period. Use of immune globulin (intravenous [IVIG] or subcutaneous [SCIG] is permitted during this period. Addition of any other prohibited medication (Section 3.4.2.1) is not permitted.

During this period, subjects who have clinically active or relevant interstitial lung disease (ILD) or anti-synthetase syndrome as determined by the investigator, may have to repeat pulmonary function testing and HRCT scan of the chest at Wk 52. (See Section 5.3.6 and Section 5.3.7.2) and at Wk 76 for Japan.

Subjects who participate in the sub-study of MRI muscle (thigh) imaging will have an MRI performed at Wk 52. See Section 5.8.2

Subjects who discontinue treatment with abatacept during the Open-Label Period or Open Label Extension for Japan will complete the Early Termination visit for the OL (See Table 5.1-3 day 365 is also the OL ET) and 2 follow-up visits during the 24 week post-treatment follow-up period, to perform safety and laboratory assessments. (See Table 5.1-7). If the subject receives treatment with an alternate source of abatacept (Post-Study Drug Program [PSDP] or Commercial), completing this post-treatment follow-up period is not required.

Treatment with other biologic therapy is not recommended for at least 70 days (~5 half-lives of abatacept follow-up period.

3.1.4 Long Term Open Label Extension for Subjects Randomized in Countries Other than the U.S. and the Czech Republic

There will be a three year long term extension period for subjects randomized in countries other than the U.S. and the Czech Republic.

All subjects alone will receive standard treatment plus abatacept.

Subjects who discontinue treatment with abatacept during the Long Term Extension Open-Label Period will complete the Early Termination visit for the OL and two follow-up visits to perform safety and laboratory assessments. (See Table 5.1-7). If the subject receives treatment with an alternate source of abatacept (Post-Study Drug Program [PSDP] or Commercial), completing this post-treatment follow-up period is not required.

3.1.5 Rescue Therapy

Double-Blind Period (Day 1 to Wk 24)

Subjects in either treatment group who meet the criteria for worsening at any visit between Weeks 12 and 24 are permitted to use rescue therapy. Rescue is not permitted before Week 12 and

subjects who require a change in therapy due to worsening of their disease must discontinue from the study. Beginning at Week 12, if a subject meets criteria for worsening, the investigator will be notified by means of a Disease Worsening Report generated after efficacy assessments are completed and uploaded via an electronic tablet (ePRO).

The use of rescue therapy is at the discretion of the investigator; however, rescue treatment may not be abatacept or a prohibited medication (See Section 3.4.2.1). Allowable medication are restricted to allowable concomitant medication (Section 3.4.1.1 Standard Treatment). Rescue therapy includes increases in dose of current therapy, addition of therapy and change in therapy, all with some restrictions such that allowable rescue therapy meets the criteria for allowable standard treatment. The following changes are allowable as rescue therapy:

1) Subjects on corticosteroid (CS) alone can:
   a) increase dose (to no more than 30 mg/day of prednisone or prednisone equivalent [3.4.1.2 Corticosteroid medications]), or
   b) initiate an allowable immunosuppressant, with or without increase in CS, or
   c) discontinue CS and initiate an allowable immunosuppressant (Section 3.4.1.1 Standard Treatment)
2) Subjects on allowable immunosuppressant (MTX, AZA, MMF, MPA, tacrolimus, or cyclosporine) alone can:
   a) increase dose of the current immunosuppressant, or
   b) stop current immunosuppressant and start a new allowable immunosuppressant, or
   c) add CS (Section 3.4.1.2 Corticosteroid medications)
3) Subjects on allowable immunosuppressant and CS can:
   a) increase dose of immunosuppressant, or
   b) increase dose of CS (Section 3.4.1.2 Corticosteroid medications) , or
   c) increase dose of both (following guidelines), or
   d) stop current immunosuppressant and start a new allowable immunosuppressant with or without increase in CS.

Rescued subjects will remain blinded to study medication through Week 24 and will begin Open-Label abatacept after Week 24, however they will be considered not to have achieved the IMACS DOI for the purpose of the primary efficacy analysis.

The criteria for worsening are:

1) Physician's global assessment worsening by ≥ 2 cm on the VAS *and* worsening of ≥ 20% on the MMT-8 score compared to baseline, *or*
2) Physician's global assessment worsening by ≥ 2 cm on the VAS *and* global extramuscular activity worsening by ≥ 2 cm on the MDAAT Extramuscular Global Activity VAS compared to baseline, *or*
3) Any 3 of 6 IMACS components worsening by ≥ 30% compared to baseline on 2 consecutive visits

Subjects who fail rescue therapy, as determined by the investigator, must discontinue from the study. These subjects must follow the same T&E schedule for other subjects who early terminate in the double-blind treatment period (see Section 3.1.2)

Open-Label Period (Wk 24 to Wk 52 or to Wk 76 for Japan)

There is no rescue treatment in the Open-Label Period. Background treatment may be adjusted as described in Section 3.1.3.

Long Term Extension (3 Years Treatment for subjects randomized in countries other than the U.S. and the Czech Republic)

Background treatment may be adjusted as described in Section 3.1.3.

3.1.6 Post-Treatment Follow-Up Period

The Post-Treatment Follow-Up Period (see Table 5.1-7) will last 24 weeks (169 days). The Post-Treatment Follow-Up is required for subjects who discontinue study treatment and do not start abatacept from an alternative source. This applies to subjects who either complete or early terminate any of the study periods (DB, OL, OL-EXT, or LTE). The purpose of this Period is to perform safety and laboratory assessments.

3.2 Post-Study Access to Study Drug

At the conclusion of the study, participants who continue to demonstrate clinical benefit with study drug, ie abatacept, will be eligible to receive BMS supplied study drug as part of the a Post-Study Drug Program (PSDP). Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the study is terminated due to safety concerns; b) the development of abatacept for this indication is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulation.

Treatment codes will be provided to the investigators after completion of the study.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subject is willing to participate in the study and has signed the informed consent. See Section 2.3

2) Target Population

a) Diagnosis of Definite or Probable IIM (DM or PM) based on the Bohan and Peter classification criteria (outlined in Appendix 3)

i) Subjects with dermatomyositis (DM) must also have a confirmed myositis-associated rash (Gottron's papules or a heliotrope rash preferably confirmed by skin biopsy) and 2 or more of the remaining 4 criteria.

ii) Subjects with a diagnosis of IIM other than dermatomyositis include PM, autoimmune necrotizing myopathy, myositis in association with another connective tissue disease (overlap myositis) and juvenile myositis subjects above the age of 18. These subjects must have a prior muscle biopsy diagnostic for IIM *or* a prior positive test for at least one myositis-specific autoantibody (anti-aminoacyl-tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, YRS), anti-Mi-2, anti-SRP, anti-TIF1-γ, anti-NXP-2, anti-MDA5, anti-SAE, anti-HMGCR). For subjects with overlap myositis, the myositis must be the principal clinically active manifestation of their disease.

Where applicable, documentation of prior skin biopsy, muscle biopsy, and autoantibody results must be obtained and retained by the site

b) Demonstrable muscle weakness measured by the MMT-8 of ≤ 135 units *and* any 3 of the following:

i) MMT-8 ≤ 125 units

ii) Physician's global assessment (PGA) VAS ≥ 2 cm

iii) Subject's global assessment (SGA) VAS ≥ 2 cm

iv) HAQ-DI ≥ 0.5

v) One or more muscle enzyme (CK, aldolase, LDH, AST, ALT) ≥ 1.3 times upper limit of normal (ULN)

vi) MDAAT Extramuscular Global Activity VAS ≥ 2 cm

c) Demonstration of currently active IIM will be determined by an adjudication committee (Section 7.1) unless the subject has any one of the following:

i) an active myositis-associated rash (Gottron's papules or heliotrope rash), *or*

ii) a recent (within 3 months prior to signing informed consent) biopsy, magnetic resonance imaging (MRI), or electromyogram (EMG) demonstrating active disease (documentation must be obtained and retained by the site), *or*

iii) an elevated CK > 5 times the upper limit of normal at screening with no alternate explanation or cause

d) Active disease despite adequate prior treatment experience with corticosteroids, immunosuppressants, or biologics as determined by the investigator

e) The subject must be on background standard treatment for IIM (Section 3.4.1.1). The standard treatments that are allowed as background treatment for IIM includes:

i) Corticosteroids alone (Section 3.4.1.2), *or*

ii) One of the following immunosuppressants: methotrexate, azathioprine, mycophenolate [any formulation of mycophenolate mofetil (MMF) or mycophenolic acid (MPA)],

tacrolimus, or cyclosporine (combinations of these treatments are not allowed during the Double-Blind Period), *or*

iii) A combination of corticosteroids and one of the above immunosuppressants

- If using corticosteroids for IIM, the subject must have been on corticosteroids for at least 12 weeks prior to randomization and a stable dose of corticosteroids for at least 4 weeks prior to randomization.
- If using immunosuppressants other than azathioprine, the subject must have been on the same medication for at least 12 weeks and a stable dose for at least 4 weeks prior to randomization.
- If using azathioprine, the subject must have been on azathioprine for at least 24 weeks with a stable dose for at least 12 weeks prior to randomization.

f) Subject Re-enrollment: This study permits one re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, "screen failure", the subject has not been randomized /has not been treated) for any reason (see Section 5.1.1).

3) Age and Reproductive Status

a) Men and Women, age ≥ 18 or age of majority

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) (abatacept) plus 5 half-lives of study drug (70 days) plus 30 days (duration of ovulatory cycle) for a total of 100 days post-treatment completion

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) (abatacept) plus 5 half-lives of the study drug (70 days) plus 90 days (duration of sperm turnover) for a total of 160 days post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male subjects who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 1), which have a failure rate of < 1% when used consistently and correctly. It is expected that investigators will refer to the Product Insert, as well as local regulations and guidelines for prevention of pregnancy appropriate for the standard background treatment being used by individual subjects.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with Inclusion Body Myositis, or myositis other than IIM, eg, drug-induced myositis and PM associated with HIV.

b) Subjects treated with penicillamine or zidovudine in the past 3 months.

c) Subjects treated with rituximab in the 6 months prior to randomization (there must be laboratory results indicating the presence of circulating B cells (CD19+). Any other biologic treatment in the past 3 months or immune globulin (intravenous [IVIG] or subcutaneous [SCIG]) in the past 3 months prior to randomization.

d) Subjects with uncontrolled or rapidly progressive interstitial lung disease (at the discretion of the investigator).

e) Subjects with severe muscle damage (Physician VAS for muscle damage in Myositis Damage Index > 7 cm on a 10 cm scale), permanent weakness due to a non-IIM cause (eg. stroke), or myositis with cardiac involvement.

f) Cancer-associated myositis (myositis diagnosed within 2 years of a diagnosis of cancer). See criteria (2i)

g) Subjects who are known to be positive for the anti-TIF1-γ (p155/140) autoantibody prior to randomization who were diagnosed with IIM < 1 year prior to randomization.

2) Medical History and Concurrent Diseases

a) Subjects with severe pulmonary disease due to IIM requiring supplemental oxygen or who have required mechanical breathing assistance (ventilator) within 1 year of signing informed consent.

b) Subjects who, at the discretion of the investigator, have severe muscle damage evidenced by severe, clinically apparent muscle atrophy, or persistent weakness without evidence of active inflammatory disease.

c) Subjects at risk for tuberculosis (TB) defined as follows:

i) Current clinical, radiographic or laboratory evidence of active TB, even if currently being treated. Chest X-rays (posterior/anterior and lateral) obtained within the 6 months prior to screening and TB testing (IFN-γ release assay or PPD) performed in the past month prior to screening will be accepted; however, a copy of the reports must be placed in the subject binder.

ii) A history of active or latent TB unless there is documentation that the subject had received prior anti-TB treatment that was appropriate in duration and type according to local health authority guidelines.

iii) Subjects with a positive TB screening test indicative of latent TB will not be eligible for the study unless they:

(1) Have no evidence of current TB based on chest X-ray performed during the screening period and by history and physical exam, and

(2) They are currently being treated for latent TB or the site has documentation of successful prior treatment of latent TB. Treatment regimens should be dictated by local guidelines as long as the treatment dose and duration meet or exceed local health authority guidelines. If permitted by local guidelines regarding treatment

with biologic medications, subjects with latent TB may be randomized prior to completion of treatment as long as they have completed at least 4 weeks of treatment and they have no evidence of current TB on chest X-ray at screening.

iv) In some cases, subjects with a positive TB screening test, but no clinical or radiologic evidence of active disease may not require treatment to be eligible for the study (eg, positive TB screening test due to fully treated prior infection). All such cases require approval by the Medical Monitor.

d) Subjects with recent acute infection defined as:

i) Any acute infection within 60 days prior to randomization that required hospitalization or treatment with parenteral antibiotics

ii) Any acute infection within 30 days prior to randomization that required oral antimicrobial or antiviral therapy

e) Subjects with history of chronic or recurrent bacterial infection (such as chronic pyelonephritis, osteomyelitis, bronchiectasis, infection of a joint prosthesis or artificial joint) or serious latent viral infections at the time of enrollment, including subjects with evidence of Immunodeficiency Virus (HIV) infection

f) Subjects with active systemic fungal infections (eg, histoplasmosis, blastomycosis, or coccidiomycosis)

g) Subjects with history of recurrent herpes zoster (more than 1 episode/year) or disseminated (more than 1 dermatome) herpes zoster or disseminated herpes simplex, or ophthalmic zoster will be excluded. Symptoms of herpes zoster or herpes simplex must have resolved more than 60 days prior to signing informed consent.

h) Subjects with history of primary or secondary immunodeficiency

i) Subjects who have 1) a present malignancy or 2) a previous malignancy within the last 5 years prior to screening (except documented history of cured non-metastatic squamous or basal cell skin carcinoma or cervical carcinoma in situ). Subjects who had a screening procedure that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations. Additional screening recommendations for malignancy are outlined in Section 3.3.4.

j) Current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, psychiatric, cardiac, neurological, or cerebral disease including severe and uncontrolled infections, such as sepsis and opportunistic infections. Concomitant medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study

k) Subjects who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines during the study. Study subjects also should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication. Subjects who are in close contact with others who have received a live vaccine (e.g., live polio vaccine) may be enrolled at the investigator's discretion.

l) Subjects who have undergone a major surgical procedure, or any surgery that involves the placement of a device or implant, within the 60 days prior to randomization.

m) Subjects with a history of (within 12 months of signing informed consent), or known current problems with drug or alcohol abuse history or known cirrhosis including alcoholic cirrhosis

n) Subjects who are impaired, incapacitated, or incapable of completing study related assessments

o) Subjects who have previously been treated with abatacept.

3) Physical and Laboratory Test Findings

a) Hepatitis B surface antigen (HBsAg)-positive, *or* Hepatitis B core antibody (HBcAb)-positive subjects with detectable Hepatitis B viral DNA, *and* where required by local regulations or standard practice Hepatitis B surface antibody (HBsAb)-positive subjects with detectable Hepatitis B viral DNA.

NOTE: For Japan only subjects

Subjects at risk for Hepatitis B virus (HBV), specifically subjects with:

(1) Hepatitis B surface antigen (+)

(2) Hepatitis B surface antigen (-) but Hepatitis B surface antibody (+) or Hepatitis B core antibody (+) with Hepatitis B virus DNA $\geq$ 1.1 Log copy /mL(20 IU /mL).

Subjects who are negative HBs antigen but positive anti-HBs antibody or positive anti-HBc antibody with Hepatitis B virus DNA < 2.1 Log copy /mL (20 IU /mL) can be enrolled in the study but must undergo periodic monitoring of HBV DNA and liver enzumes such as AST and ALT. Monitoring should be performed on a monthly basis after initiation of treatment, for six months. After 6 months, interval and duration should be decided at the investigator's discretion and in accordance with local guidelines.

b) Hepatitis C antibody (HcAb)-positive subjects with detectable Hepatitis C viral RNA

c) Hemoglobin (Hgb) < 8.5 g/dl

d) White Blood Count (WBC) < 3,000/mm^3 (3 x 10^9/L)

e) Platelets < 100,000/mm^3 (100 x 10^9/L)

f) Creatinine clearance < 50 mL/min (Cockroft-Gault method)

g) Serum ALT or AST > 2 times upper limit of normal not due to IIM.

h) Any laboratory test results that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study

4) Allergies and Adverse Drug Reaction

a) Hypersensitivity to abatacept or one of its excipients

5) Other Exclusion Criteria

a) Subjects who are unable to complete study procedures

b) Subjects with a history or suspicion of unreliability, poor cooperation, or non-compliance with medical treatment

c) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required.

d) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

6) MRI Contraindications (for MRI sub-study only)

For a subject who intends to participate in the MRI sub-study, the radiologist at the site's MRI facility is responsible for determining if a subject is contraindicated from having this procedure. If the subject is contraindicated, the subject must be dropped from the MRI sub-study. The following is a list of some common conditions that may preclude the subject from having MRI of the hands or wrists. However, this should not be used as a substitute for local clinical standards of care. The ultimate decision to perform an MRI on an individual subject in the MRI sub-study rests with the site radiologist, the investigator, and the standard set by the local Ethics Committee:

a) Subjects who have a history of claustrophobia.
b) Subjects who have a physical limitation related to fitting in the bore of the magnet (ie, body weight in excess of 250 pounds or 113.4 kilograms).
c) Subjects with tattoos on the area to be imaged.
d) Subjects who have a history of allergic reaction to contrast agents
e) Subjects who had exposure to a radiological contrast agent within the 72 hours prior to the MRI examination.
f) Subjects who have joint replacements in the leg that is being evaluated by the MRI examination.
g) Subjects with a pacemaker, epicardial pacemaker wires, MRI-incompatible cardiac valve prostheses, MRI-incompatible vascular clips less than two-months old, or MRI-incompatible aneurysm clips of any age.
h) Subjects with MRI-incompatible cochlear implants.
i) Subjects with spinal nerve stimulators.
j) Subjects with an infusion pump.
k) Subjects with metallic fragments in the eyes/orbits or in the vicinity of the brain or major neurovascular structures of the body, subjects with an employment history which involves exposure to welding, or subjects who have shrapnel any place in their body.

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

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

3.3.4 Screening for Malignancy

It is recommended that all subjects should have been assessed for age and gender appropriate malignancy (e.g. breast cancer, gynecologic cancers, prostate cancer, and colon cancer) and any other malignancy for which an individual subject is at an increased risk at the investigator's discretion (e.g., lung cancer) prior to enrollment.

All subjects who were diagnosed with IIM in the past year must have been screened for occult malignancy at the discretion of the investigator.

Subjects who are anti-TIF1-γ (p155/140) autoantibody positive and are more than 1 year from IIM diagnosis must also have undergone screening for occult malignancy in the last year at the discretion of the investigator.[58] .

Testing can include any of the following, at the discretion of the investigator:

- Chest imaging (chest CT required for subjects with a history of smoking, CXR acceptable for all other subjects)
- Abdominal imaging (CT or ultrasound)
- Laboratory testing: alpha-fetoprotein, CA-125
- Documented skin exam for malignancy
- Screening for gastrointestinal malignancy (e.g., stool analysis for occult blood, colonoscopy, sigmoidoscopy)
- Screening for breast cancer (e.g., imaging [mammography or MRI]) for female subjects over the age of 40
- Screening for cervical cancer (e.g., Pap test and human papillomavirus [HPV] testing) for all female subjects
- Screening for prostate cancer (e.g., digital rectal exam, Prostate Specific Antigen testing) for all male subjects over the age of 40

For prior testing results, a copy of the report must be obtained and reviewed by the investigator and placed in the subject binder.

In some cases, subjects who are determined by the investigator to be at low risk of malignancy may not require any of the above testing. All such cases may be discussed with the medical monitor.

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3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects who discontinue treatment with investigational product during the Double-Blind Treatment Period (Day 1 - Week 24) must be assessed for all efficacy measures and for safety at the originally scheduled Week 24 (Day 169 from baseline) time-point (see Post-Study Drug Efficacy Visit - Table 5.1-4).

All subjects who discontinue study drug at any time throughout the study, require visits to assess safety and immunogenicity at Day 85 and Day 169 after the last dose of study drug (see Table 5.1-7). For subjects who discontinue during the Double-Blind Period, if either the Day 85 or Day 169 visit falls within ± 14 days of the Week 24 Post-Study Drug Efficacy Visit (Table 5.1-4), only perform immunogenicity and pharmacokinetic blood samples (Table 5.1-7) along with the Post-Study Drug Efficacy Visit.

The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Subject withdraws consent
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy (see additional instruction below)
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Use of prohibited medication
- Subjects who fail rescue therapy, as judged by the investigator, between Wk 12 and Wk 24
- Subjects who, during the course of the study, require mechanical breathing assistance (ventilator) due to myositis, ILD, or another pulmonary cause. Temporary mechanical breathing assistance during a procedure or elective surgery is permitted.
- Missed Doses
  - Missed 4 or more doses of abatacept/placebo for any reason during the first 24 weeks (Double-Blind Period)
  - Missed 3 or more consecutive doses of abatacept/placebo for any reason during the first 24 weeks (Double-Blind Period)
  - Missed 6 or more doses of abatacept for any reason between Week 24 and Week 52 (Open-Label Period)
  - Missed 5 or more consecutive doses of abatacept for any reason between Week 24 and Week 52 (Open-Label Period) or Week 76 (for subjects randomized in Japan)
- Significant non-compliance with protocol (i.e., procedures, assessments, medication, etc.). The investigator should discuss such issues with the BMS Medical Monitor.
- Participation in another clinical trial with an investigational product.

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post-Study Drug Study Follow up

Subjects who withdraw consent (according to Section 3.6.1) or are lost to follow-up (according to Section 3.6.2) will not be followed in this study; all other subjects will continue to be followed for collection of follow-up data as required and in line with Section 5, Study Procedures and Assessments.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, if possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts,

the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

Table 4-1: Study Drugs for IM101611

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open-Label	Packaging / Appearance	Storage Conditions (per label)
Abatacept Injection / Subcutaneous	125 mg/syringe (125 mg/mL)	IP	Blinded/Open Label	Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated, 2-8 °C (36-46 °F); protect from light; protect from freezing
Placebo to match Abatacept Injection / Subcutaneous	NA	IP	Blinded	Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated, 2-8 °C (36-46 °F); protect from light; protect from freezing

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined 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) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are:

- Abatacept SC 125 mg in 1 ml pre-filled syringes
- Placebo to match abatacept SC in 1 ml pre-filled syringes

BMS will supply the investigational products (also referred to as "study medication"), described above.

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

4.3 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Please refer to Section 9.2.2 for guidance on IP records and documentation.

Investigational product documentation (whether supplied by BMS or not) must be maintained which includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

4.4 Method of Assigning Subject Identification

At the time of enrollment, immediately after written informed consent is obtained and before performing any study-related procedures, each subject will be assigned a unique sequential subject number for identification throughout the study. Any subject number must not be reused for any other participant. The physician/coordinator must contact the Central Randomization System (IVRS) to enroll each subject into a centralized database at the time of signing consent.

After completion of all screening evaluations, concomitant medication adjustment and/or stabilization, all eligible subjects will be randomized into the 24-week double-blinded treatment period (Double-Blind Period), followed by a 28 week open-label abatacept treatment period (Open-Label Period). Subjects randomized in Japan will have an additional 24 week open label period. Also subjects from all countries except the U.S. and the Czech Republic will have a 3 years long term open label extension with SC abatacept.

Randomization schedules will be generated and kept by the Randomization Group within Drug Supply Management of Bristol-Myers Squibb. Randomization treatment will be assigned using a Central Randomization System in the order in which subjects qualify for treatment, not in the order of study enrollment. Subjects will be randomized to abatacept SC or abatacept SC placebo in a 1:1 ratio. To maintain a 1:1 randomization between the abatacept SC and placebo SC arms within subjects from Japan, the study randomization will be stratified by Japan vs. Rest of World (ROW).

Specific instructions for randomization into the Central Randomization System will be provided in a separate manual.

4.5 Selection and Timing of Dose for Each Subject

On "Office Visit" days, study medication should be administered AFTER all assessments, including blood draws for assessment of immunogenicity and drug concentrations.

4.5.1 Abatacept Treatment

Abatacept (125 mg) or matching placebo will be administered subcutaneously (SC) once per week. See Section 5.1.1.1 for dosing windows. On Day 1, subjects and/or personal caregivers will be trained in self-administration of SC injections using pre-filled syringes. Administration of abatacept may be performed by the physician or medical staff at the study site for training purpose through Week 4 if needed. All subsequent injections will be self-administered or administered by a personal caregiver. Medical staff can act as a caregiver only when the subject cannot self-administer and does not have access to a personal caregiver. Training should be performed by investigational site personnel that are considered qualified trainers by the Investigator. Subjects or their caregivers will be trained using instructions that will be provided by BMS or designee.

The last dose of SC abatacept/placebo for the Double-Blind Period will be administered in Week 23 while the last dose of SC abatacept for the Open-Label Period will be administered in Week 51. For subjects randomized from Japan, the last dose of SC abatacept in the Open Label Period will be at Week 75. Also, for subjects (all countries except the U.S. and the Czech Republic) participating in the long term open label extension period, the last dose of SC abatacept will be at Day 1086.

Injections sites may include the upper arms (outside area), thigh, or abdomen. When possible, injection sites and/or sides of the body should be rotated every week. The upper arm injection site should be used only by caregivers and not for self-administration.

To ensure compliance and to monitor technique "office visit" SC injections should be administered in the presence of a qualified investigational staff.

4.5.2 Standard Treatment

Subjects must be on background standard treatment for IIM (see Section 3.4.1).

4.5.3 Dose Modifications

4.5.3.1 Dose Modifications in the Absence of Adverse Events

Every effort should be made to give all study medications within ± 3 days of the target date during the treatment periods. The last dose before each office visit should be administered at least 4 days before the scheduled visit date. If study medication is not received within the dosing window, this dose should be skipped and the next dose must then be administered on the next scheduled target administration day.

4.5.3.2 Dose Modifications Due to Adverse Events

If abnormal laboratory test results or clinical adverse events indicate toxicity that, in the judgment of the investigator, could place the subject at risk, study drug administration should be interrupted and the investigator should notify the BMS Medical Monitor. Subjects may receive further study medication treatment only if full resolution of the adverse event or abnormal laboratory finding is documented.

If a dose is skipped, the next SC injection should be administered on the subsequent targeted administration day.

4.6 Blinding/Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

For this study, the method of unblinding for emergency purposes is the Central Randomization System (IVRS).

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

4.7 Treatment Compliance

Treatment compliance for study medication will be assessed by the following:

1) Phone call reminders by the site staff.
2) Visual inspection of the contents of the sharps containers, which subjects will bring to their office visits.
3) Completion of subject diary cards to document administration of study medications between office visits.
4) Review and monitoring of proper administration technique by investigational site staff at office visits.

Subjects who miss doses may be required to discontinue from the study (see Section 3.5). Therefore, reinforcement of proper treatment compliance at every study visit is encouraged.

4.8 Destruction or Return of Investigational Product

For this study, IP (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

If...	Then...
IP supplied by BMS (including its vendors)	Any unused IP supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless IP containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If IP will be returned, the return will be arranged by the responsible Study Monitor.
IP sourced by site, not supplied by BMS (or its vendors) (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for the return of IP provided by BMS (or its vendors). Destruction of non-IP sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

Please refer to Section 9.2.2 for additional guidance on IP records and documentation.

4.9 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (IM101611)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Call IVRS to Enroll Subject	X	
Inclusion/Exclusion Criteria	X	See Section 3.3
Submit documentation to Adjudication Committee	X	Complete the Active Disease Adjudication Form and submit with supporting documentation, as necessary, see eligibility criteria Section 3.3.1, 2)c)
Medical History	X	
[redacted]	X	
Safety Assessments		
Physical Examination	X	
Vital Signs	X	Body temperature, seated blood pressure, and heart rate.
Weight and Height	X	
Chest X-ray	X	Required only if the results of a CXR performed within the 6 months prior to screening are not available. A copy of the report must be filed in the subject binder.
Pulmonary Function Testing	X	For subjects with ILD (See Section 5.3.6)
Serious Adverse Events Assessment		To be reported after signing informed consent
Laboratory Assessments		
TB Screening	X	TB testing (IFN-γ release assay or PPD) performed locally within 4 weeks prior to Screening will be accepted. A copy of the report must be filed in the subject binder. See Section 5.3.4 for important details

Table 5.1-1: Screening Procedural Outline (IM101611)

Procedure	Screening Visit	Notes
Hematology Panel	X	
Chemistry Panel	X	
Urinalysis	X	
Pregnancy Test	X	Testing performed locally on WOCBP subjects only
Hepatitis Screening	X	See Section 5.3.5.6
HIV Testing	X	Testing performed unless prohibited by local regulations
Fungal infection testing (1-3 β-D-glucan & KL-6)	X	Where required by local regulation or standard practice. See Section 5.3.5.9
Autoantibody Panel	X	Will be performed centrally when requested by sites in Brazil, Mexico, and the U.S.
Additional Assessments	X	
Physician Global Assessment	X	IMACS Core Component
Manual Muscle Test (MMT-8)	X	IMACS Core Component
Myositis Disease Activity Assessment Tool (MDAAT)	X	IMACS Core Component
Subject Global Assessment	X	IMACS Core Component
HAQ-DI	X	IMACS Core Component
Obtain Muscle Biopsy and Skin Biopsy reports	X	Confirmation if performed to support diagnosis (biopsy is not mandatory at screening)
Obtain documentation for malignancy screening	X	As appropriate (Section 3.3.4)
[redacted]	[redacted]	[redacted]
HRCT	X	For subjects with clinically active or relevant ILD or anti-synthetase syndrome (See Section 5.3.7.2)

Table 5.1-1: Screening Procedural Outline (IM101611)

Procedure	Screening Visit	Notes
[redacted]	[redacted]	[redacted]

Table 5.1-2: Study Evaluations - Double-Blind Period (IM101611)

Study Day [a]	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	
Procedure	**Randomization**	**Wk 4/ Mo 1**	**Wk 8**	**Wk 12/ Mo 3 [b]**	**Wk 16**	**Wk 20**	**Wk 24 / Mo 6 or DB ET [c]**	**Notes**
Study Administration								
Confirm Inclusion/Exclusion Criteria	X							
Call IVRS	X	X	X	X	X	X		
Train subjects how to self-inject and how to fill in diary cards	X							
Dispense diary cards	X	X	X	X	X	X		
Collect and review diary cards		X	X	X	X	X	X	
Dosing of weekly abatacept/placebo	X	X	X	X	X	X		Must be administered weekly between visits. See Section 4.5 No dose administered at the Early Termination visit
Reconciliation of abatacept/placebo		X	X	X	X	X	X	
Dispense Study Drug	X	X	X	X	X	X		
Dispense Actigraphy device and train subjects on use	X							
Safety Assessments								
Vital Signs	X	X	X	X	X	X	X	
Weight				X			X	
Targeted Physical Examination	X			X			X	
Adverse Events Monitoring	X	X	X	X	X	X	X	

Table 5.1-2: Study Evaluations - Double-Blind Period (IM101611)

Study Day [a]	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	
Procedure	**Randomization**	**Wk 4/ Mo 1**	**Wk 8**	**Wk 12/ Mo 3 [b]**	**Wk 16**	**Wk 20**	**Wk 24 / Mo 6 or DB ET [c]**	**Notes**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pulmonary Function Testing							X	For subjects with ILD (See Section 5.3.6)
Laboratory Assessments								
Hematology Panel	X	X	X	X	X	X	X	
Chemistry Panel	X	X	X	X	X	X	X	IMACS Core Component
Total Cholesterol and Triglycerides	X						X	Nothing to eat/drink, except water, for 8 hours prior to sample collection
Urine pregnancy test	X	X	X	X	X	X	X	Testing performed locally on WOCBP subjects only
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antibody Panels	X						X	See Section 5.3.5.3
Complement (C3, C4, CH50)	X	X		X			X	
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]			[redacted]	[redacted]
PBMCs (Peripheral Blood Mononuclear Cells)[d]	X						X	(US sites only)

Table 5.1-2: Study Evaluations - Double-Blind Period (IM101611)

Study Day [a]	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	
Procedure	**Randomization**	**Wk 4/ Mo 1**	**Wk 8**	**Wk 12/ Mo 3 [b]**	**Wk 16**	**Wk 20**	**Wk 24 / Mo 6 or DB ET [c]**	**Notes**
DNA for genotyping[d]	X							Optional collection. See Section 5.6.1.3
Efficacy Assessments								
Physician Global Assessment	X	X	X	X	X	X	X	IMACS Core Component
Subject Global Assessment	X	X	X	X	X	X	X	IMACS Core Component
Manual Muscle Test (MMT-8)	X	X	X	X	X	X	X	IMACS Core Component
Myositis Disease Activity Assessment Tool (MDAAT)	X	X	X	X	X	X	X	IMACS Core Component
Myositis Function Index (FI-2)	X			X			X	
Myositis Damage Index	X						X	
Cutaneous Disease Activity Index (CDASI)	X			X			X	For subjects with DM
[redacted]							[redacted]	[redacted]
Actigraphy data collection		X	X	X	X	X	X	
Imaging Assessments								
HRCT Chest							X	For all subjects with clinically active or relevant ILD or anti-synthetase syndrome. (See Section 5.3.7.2).
[redacted]							[redacted]	[redacted]

Table 5.1-2: Study Evaluations - Double-Blind Period (IM101611)

Study Day [a]	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	
Procedure	**Randomization**	**Wk 4/ Mo 1**	**Wk 8**	**Wk 12/ Mo 3 [b]**	**Wk 16**	**Wk 20**	**Wk 24 / Mo 6 or DB ET [c]**	**Notes**
Outcomes Research Assessments								
HAQ-DI	X	X	X	X	X	X	X	IMACS Core Component
PROMIS Fatigue	X			X			X	
SF-36	X			X			X	

[a] All visits and procedures must occur within ± 3 days of the expected visit

[b] For subjects who are Rescued the visit schedule shall not change

[c] For subjects who discontinue study drug during this period, the Early Termination visit (DB ET) visit, Post-Study Drug Efficacy visit (Table 5.1-4) and the Post Treatment Follow-Up Period (Table 5.1-7) visits must be done.

[d] If a subject does not consent to the use of their samples for additional research, their samples will be discarded after all protocol-specified testing has been completed (not to exceed 5 years).

Table 5.1-3: Study Evaluations - Open-Label Period (IM101611)

Study Day [a]	Day 169[b]	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365	
Procedure		**Wk 28**	**Wk 32 (Phone)**	**Wk 36/ Mo 9**	**Wk 40 (Phone)**	**Wk 44**	**Wk 48 (Phone)**	**Wk 52 Mo 12 or OL ET**	**Notes**
Study Administration									
Call IVRS	X	X		X		X		X	
Dispense diary cards	X	X		X		X			
Collect and review diary cards		X		X		X		X	
Dosing of weekly abatacept	X	X	X	X	X	X	X	X	Must be administered weekly between visits. See Section 4.5 No dose administered at the Early Termination visit
Reconciliation of abatacept		X		X		X		X	
Dispense urine pregnancy kits for WOCBP		X		X		X			For home use every 4 weeks
Dispense Study Drug	X	X		X		X			
Safety Assessments									
Vital Signs		X		X		X		X	
Weight				X				X	
Targeted Physical Examination				X				X	
Adverse Events Monitoring		X	X	X	X	X	X	X	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 5.1-3: Study Evaluations - Open-Label Period (IM101611)

Study Day [a]	Day 169[b]	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365	
Procedure		**Wk 28**	**Wk 32 (Phone)**	**Wk 36/ Mo 9**	**Wk 40 (Phone)**	**Wk 44**	**Wk 48 (Phone)**	**Wk 52 Mo 12 or OL ET**	**Notes**
Pulmonary Function Testing								X	For subjects with ILD (See Section 5.3.6)
Laboratory Assessments									
Hematology Panel		X		X		X		X	
Chemistry Panel		X		X		X		X	IMACS Core Component
Total Cholesterol and Triglycerides								X	Nothing to eat/drink, except water, for 8 hours prior to sample collection
Urine pregnancy test		X	X	X	X	X	X	X	Testing performed locally on WOCBP subjects only
[redacted]								[redacted]	[redacted]
Antibody Panels								X	See Section 5.3.5.3
Complement (C3, C4, CH50)								X	
[redacted]								[redacted]	[redacted]
[redacted]								[redacted]	[redacted]

Table 5.1-3: Study Evaluations - Open-Label Period (IM101611)

Study Day [a]	Day 169[b]	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365	
Procedure		**Wk 28**	**Wk 32 (Phone)**	**Wk 36/ Mo 9**	**Wk 40 (Phone)**	**Wk 44**	**Wk 48 (Phone)**	**Wk 52 Mo 12 or OL ET**	**Notes**
PBMCs (Peripheral Blood Mononuclear Cells)[c]								X	(US sites only)
Efficacy Assessments									
Physician Global Assessment		X		X		X		X	IMACS Core Component
Subject Global Assessment		X		X		X		X	IMACS Core Component
Manual Muscle Test (MMT-8)		X		X		X		X	IMACS Core Component
Myositis Disease Activity Assessment Tool (MDAAT)		X		X		X		X	IMACS Core Component
Myositis Function Index (FI-2)				X				X	
Myositis Damage Index								X	
Cutaneous Disease Activity Index (CDASI)				X				X	For subjects with DM
Imaging Assessments									
HRCT Chest								X	For subjects with clinically active or relevant ILD or anti-synthetase syndrome. (See Section 5.3.7.2).
[redacted]								[redacted]	[redacted]

Table 5.1-3: Study Evaluations - Open-Label Period (IM101611)

Study Day [a]	Day 169[b]	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365	
Procedure		**Wk 28**	**Wk 32 (Phone)**	**Wk 36/ Mo 9**	**Wk 40 (Phone)**	**Wk 44**	**Wk 48 (Phone)**	**Wk 52 Mo 12 or OL ET**	**Notes**
Outcomes Research Assessments									
HAQ-DI		X		X		X		X	IMACS Core Component
PROMIS Fatigue				X				X	
SF-36				X				X	

[a] All visits and procedures must occur within ± 3 days of the expected visit

[b] Same visit as Double-blind Day 169

[c] If a subject does not consent to the use of their samples for additional research, their samples will be discarded after all protocol-specified testing has been completed (not to exceed 5 years)

Table 5.1-4: Post-Study Drug Efficacy Visit (Discontinued Subjects Between Baseline and Wk 24)

Visit (± 14 days)	169 Days (24 Weeks) Post-Baseline	Notes
Safety Assessments		
Vital Signs	X	
Adverse Event Monitoring	X	
[redacted]	[redacted]	
Pulmonary Function Testing	X	For subjects with ILD (See Section 5.3.6)
Efficacy Assessments		
Physician Global Assessment	X	IMACS Core Component
Subject Global Assessment	X	IMACS Core Component
Manual Muscle Test (MMT-8)	X	IMACS Core Component
Myositis Disease Activity Assessment Tool (MDAAT)	X	IMACS Core Component
Myositis Function Index (FI-2)	X	
Myositis Damage Index	X	
Cutaneous Disease Activity Index (CDASI)	X	
Muscle biopsy (optional - for histopathology and RNA)	X	
Imaging Assessments		
HRCT Chest	X	For subjects with clinically active or relevant ILD or anti-synthetase syndrome. (See Section 5.3.7.2)
[redacted]	[redacted]	[redacted]
Outcomes Research Assessments		
HAQ-DI	X	IMACS Core Component
PROMIS Fatigue	X	
SF-36	X	

Table 5.1-4: Post-Study Drug Efficacy Visit (Discontinued Subjects Between Baseline and Wk 24)

Visit (± 14 days)	169 Days (24 Weeks) Post-Baseline	Notes
Laboratory Assessments		
Hematology Panel	X	
Chemistry Panel	X	IMACS Core Component
Antibody Panels	X	
Complement (C3, C4, CH50)	X	
[redacted]	[redacted]	
PBMCs (Peripheral Blood Mononuclear Cells)[a]	X	(US sites only)

[a] If a subject does not consent to the use of their samples for additional research, their samples will be discarded after all protocol-specified testing has been completed (not to exceed 5 years).

Table 5.1-5: Open Label Extension for Japan

Study Day[a]	Day 365[b]	Day 393	Day 421	Day 449	Day 477	Day 505	Day 533	
Procedure	**Wk 52/ Mo 12**	**Wk 56 (Phone)**	**Wk 60**	**Wk 64/ Mo 15 (Phone)**	**Wk 68**	**Wk 72 (Phone)**	**Wk 76/ Mo 18 or OL-EXT ET**	**Notes**
Study Administration								
Call IVRS			X		X		X	
Dispense diary cards	X		X		X			
Collect and review diary cards			X		X		X	
Dosing of weekly abatacept	X	X	X	X	X	X	X	Must be administered weekly between visits. See Section 4.5. No dose administered at the Early Termination visit
Reconciliation of abatacept			X		X		X	
Dispense urine pregnancy kits for WOCBP	X		X		X			For home use every 4 weeks
Dispense Study Drug	X		X		X			
Safety Assessments								
Vital Signs			X		X		X	
Weight			X		X		X	
Targeted Physical Examination			X		X		X	
Adverse Events Monitoring		X	X	X	X	X	X	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pulmonary Function Testing							X	For subjects with ILD (See Section 5.3.6)

Table 5.1-5: Open Label Extension for Japan

Study Day[a]	Day 365[b]	Day 393	Day 421	Day 449	Day 477	Day 505	Day 533	
Procedure	**Wk 52/ Mo 12**	**Wk 56 (Phone)**	**Wk 60**	**Wk 64/ Mo 15 (Phone)**	**Wk 68**	**Wk 72 (Phone)**	**Wk 76/ Mo 18 or OL-EXT ET**	**Notes**
Laboratory Assessments								
Hematology Panel			X		X		X	
Chemistry Panel			X		X		X	IMACS Core Component
Total Cholesterol and Triglycerides							X	Nothing to eat/drink, except water, for 8 hours prior to sample collection
Urine pregnancy test		X	X	X	X	X	X	Testing performed locally on WOCBP subjects only
Pharmacokinetic (PK) Sampling in Blood							X	All samples must be collected prior to dosing. See Section 5.5.1 for sub-study sample times
Complement (C3, C4, CH50)							X	
[redacted]							[redacted]	[redacted]
Efficacy Assessments								
Physician Global Assessment[c]			X		X		X	IMACS Core Component
Subject Global Assessment[c]			X		X		X	IMACS Core Component
Manual Muscle Test (MMT-8)[c]			X		X		X	IMACS Core Component

Table 5.1-5: Open Label Extension for Japan

Study Day[a]	Day 365[b]	Day 393	Day 421	Day 449	Day 477	Day 505	Day 533	
Procedure	**Wk 52/ Mo 12**	**Wk 56 (Phone)**	**Wk 60**	**Wk 64/ Mo 15 (Phone)**	**Wk 68**	**Wk 72 (Phone)**	**Wk 76/ Mo 18 or OL-EXT ET**	**Notes**
Myositis Disease Activity Assessment Tool (MDAAT)[c]			X		X		X	IMACS Core Component
Myositis Function Index (FI-2)[c]							X	
Myositis Damage Index[c]							X	
Cutaneous Disease Activity Index (CDASI)[c]							X	For subjects with DM
Imaging Assessments								
HRCT Chest							X	For subjects with clinically active or relevant ILD or anti-synthetase syndrome. (See Section 5.3.7.2).
Outcomes Research Assessments								
HAQ-DI[c]			X		X		X	IMACS Core Component

[a] All visits and procedures must occur within ± 3 days of the expected visit

[b] Same visit as Open-Label Period Day 365

[c] Assessments may be recorded on paper if the electronic tablet (ePRO) is unavailable/not functioning for transmission of the data.

Table 5.1-6: Long Term Open-Label Period (all countries except U.S. and the Czech Republic)

	Day 1 (same day as last visit in OL Period)	Phone Visits (Day 29, 57, 113, 141, 197, 225. 281, 309, and 337)	Quarterly Visits (Days 85 and 253)	6 Months Visits(Day 169 and 365)	Phone Visits (Day 393, 421, 477, 505, 561, 589, 645, 673, and 701)	Quarterly Visits (Days 449 and 617)	6 Months Visits (Day 533 and 729)	Phone Visits (Day 757, 785 , 841, 869, 925, 953, 1009. 1037, and 1065)	Quarterly Visits Visit (Day 813 and 981)	6 Month Visit (Day 897)	Day 1093/ET Visit	Notes
Study Administration												
Informed Consent	X											
Enroll subject in the 3 Year Extension Period through IWRS	X											
Dispense pregnancy kits for home use to WOCBP	X		X	X		X	X		X	X		Sufficient pregnancy kits should be dispensed to subjects to allow for pregnancy testing every 4 weeks.
Dispense SC abataept and diary kits	X		X	X		X	X		X	X		Sufficient SC abatacept should be dispensed to allow for weekly SC dosing.
Review of diary cards		X	X	X	X	X	X	X	X	X	X	
Dosing of SC Abatacept	X	X	X	X	X	X	X	X	X	X		SC Abatacept will injected weekly.
Reconciliation of SC Abatacept			X	X		X	X		X	X	X	
Safety Assessments												
Targeted Physical Examination			X	X		X	X		X	X	X	

Table 5.1-6: Long Term Open-Label Period (all countries except U.S. and the Czech Republic)

	Day 1 (same day as last visit in OL Period)	Phone Visits (Day 29, 57, 113, 141, 197, 225. 281, 309, and 337)	Quarterly Visits (Days 85 and 253)	6 Months Visits(Day 169 and 365)	Phone Visits (Day 393, 421, 477, 505, 561, 589, 645, 673, and 701)	Quarterly Visits (Days 449 and 617)	6 Months Visits (Day 533 and 729)	Phone Visits (Day 757, 785 , 841, 869, 925, 953, 1009. 1037, and 1065)	Quarterly Visits Visit (Day 813 and 981)	6 Month Visit (Day 897)	Day 1093/ET Visit	Notes
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Testing												
Hematology Panel				X			X			X	X	
Chemistry Panel				X			X			X	X	

Table 5.1-7: Post-Treatment Follow-Up Period (only performed for subjects that discontinue study treatment and do not start Post-Study Drug Program (PSDP) or commercial abatacept)

Visit (± 14 days)	85 Days after Last Dose	169 Days after Last Dose	Notes
Safety Assessments			
Vital Signs	X	X	
Adverse Event Monitoring	X	X	
[redacted]	[redacted]	[redacted]	
Laboratory Assessments			
Urine pregnancy test	X	X	Testing performed locally on WOCBP subjects only
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

5.1.1 Retesting During Screening or Lead-in Period / Rescreening

Retesting

Retesting of laboratory parameters and/or other assessments within any single Screening period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (i.e., the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. The Medical Monitor can be consulted if needed to discuss whether repeat testing of any particular parameter is clinically relevant.

Rescreening

Subjects that are screen failures may be considered for re-screening if the investigator feels a change in status may render the subject eligible. Medical monitor approval is required if screen failure was related to safety concern. Rescreens are not permitted within the four weeks after signing the first informed consent. The subject will need to sign a new informed consent and be re-enrolled with a new subject number via the IVRS. Some tests, such as chest X-ray, may not need to be repeated if they were performed within the protocol defined window.

5.1.1.1 Study Drug Administration Windows

SC injections of study medication may be administered ± 3 days of the target day. Subjects who miss the dose window should skip the SC injection and wait until the next targeted administration day.

If abnormal laboratory test results or clinical AEs indicate toxicity that, in the judgment of the investigator, could place the subjects at risk, study medication administration should be withheld. Subjects may receive further study medication only if resolution of the AE or abnormal laboratory finding is documented or, at a minimum, the subject's status returns to what it was at baseline. The investigator can contact the BMS Study Medical Monitor to discuss as needed.

5.1.2 Order of Study Assessments

It is strongly encouraged that study assessments be performed in the following order:

1) Patient reported outcomes (PROs) questionnaires
2) AE collection
3) Vital signs
4) Muscle strength assessments
5) Other investigator assessments
6) Blood draws
7) Study drug administration (when applicable)

5.2 Study Materials

- Diary cards to record SC weekly dosing administration and the monthly pregnancy test results for WOCBPs (mandatory)
- Written instructions on how to use the SC syringes
- eCRF instructions
- Pregnancy Surveillance Forms
- Source documents (paper or electronic device)
- Drug Inventory binder (optional)
- Interactive Voice Response System (IVRS) worksheets
- Laboratory test kits for all required laboratory testing
- Cooler bags and gel packs will be provided to assist subjects in transporting study drug
- Sharps containers will be provided to assist subjects in disposing of used SC syringes
- Tote bags to transport cooler bags, sharp containers and study drug
- For WOCBP urine pregnancy kits/instructions will be provided to be used between office visits.
- HRCT and MRI Imaging Manuals
- Actigraphy device Manuals
- Metronome, wrist weights, step stool

5.3 Safety Assessments

On Day 1, the results of all assessments must be reviewed to assure that eligibility requirements are met before contacting the Central Randomization System for the subject's randomization assignment.

Subjects who terminate treatment early should complete the appropriate Early Termination Visit (Table 5.1-2, Table 5.1-3, Table 5.1.-5, and Table 5.1-6) and the Post Treatment Follow-up Visits (Table 5.1-7). The Early Termination Visit should be as soon as possible after the last dose of study medication.

All assessments should be performed or administered prior to study drug administration unless otherwise indicated.

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of the standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from BMS.

Only results of central laboratory assessments relevant to clinical care will be sent to the sites (Section 5.3.5). All other clinical assessments done as part of this study, including PFTs, HRCT, MRI of the thighs and muscle biopsies will not be read centrally for return to the site. These must be read locally following usual and customary practices for clinical assessments and reviewed by

investigators as required by the protocol for safety assessments (ie, PFT and HRCT) or as deemed necessary by investigators for those not required by the protocol (ie, MRI or muscle biopsy). Reports generated from central analysis of these will not be clinical in nature and will not be sent to sites for review.

Subjects who have clinically active or relevant Interstitial Lung Disease (ILD) as determined by the investigator prior to randomization must undergo pulmonary function testing (PFT) and imaging by High Resolution CT scan (HRCT). The target populations are described and the testing are outlined in Section 5.3.6 and Section 5.3.7.2, respectively.

5.3.1 Physical Examination

Physical examinations preferably should be performed by a qualified physician or Doctor of Medicine (MD). Where permitted by local practice and guidelines a qualified Doctor of Osteopathy (DO), Physician Assistant (PA), or Nurse Practitioner (NP) may perform the physical examination.

The physical examination should include examination of the heart, lungs, abdomen, the lymph nodes, liver, spleen and skin. A physical examination may note any changes in the subject's condition (body systems) since the last assessment and does not preclude examination of any other body systems as clinically indicated. Any new findings after Day 1 should be reported as (S)AE.

5.3.2 Physical Measurements

Weight and height is to be recorded at screening. Weight is to be recorded as noted in Table 5.1-2, Table 5.1-3, and Table 5.1-5, thereafter.

5.3.3 Vital Signs

Vital signs (seated blood pressure, heart rate, and temperature) will be recorded during every office visit and prior to dose administration, when applicable. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.

5.3.4 TB Screening

A chest X-ray and physical examination are considered part of the process to assess a subject's eligibility. In addition to a chest X-ray that does not show any evidence or suspicion of latent TB, a tuberculin test will be performed and interpreted according to local country Health Authorities and/or Medical Society guidelines. Some guidelines have specific recommendations for subjects who are to receive biologics or immunosuppressant therapies (eg, RA experience with biologic agents),[60,61] (outside the US sites, local guidelines endorsed by medical societies on PPD testing in subjects with RA being treated with biologics may also apply) or who are immunocompromised and who have had prior BCG vaccination(s).[62] Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG. An interferon gamma release assay (eg, QuantiFERON Gold or Tspot/ELISpot) is an acceptable alternative when skin testing for tuberculosis (ie, PPD) is not appropriate. TB screening test may be performed by qualified personnel at the central laboratory or by a qualified local laboratory. If TB test has been performed

within 4 weeks prior to informed consent and clear documentation is available, the test result may be used to screen for eligibility.

5.3.5 Laboratory Assessments

All laboratory assessments will be analyzed centrally except where noted.

Blood and/or urine samples will be obtained at all visits noted in Time and Events Schedule. Any laboratory test result that the investigator considers clinically relevant should be recorded on the appropriate Adverse Event page of the CRF (see Appendix 2).

5.3.5.1 Hematology Panel

- Hemoglobin
- Total WBC count, including differential
- Platelet count

5.3.5.2 Chemistry Panel

- Sodium
- Potassium
- Chloride
- Total Protein
- Albumin
- Calcium
- Phosphorus
- Glucose
- Aldolase
- Creatinine
- Blood urea nitrogen (BUN)
- Total bilirubin
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma-glutamyltransferase (GGT)
- Alkaline phosphatase
- LDH
- Creatine kinase (CK)

5.3.5.3 Antibody Panels

- Quantitative Immunoglobulins (IgG, IgA, IgM)
- Anti-nuclear antibody (ANA) panel
- Myositis-specific autoantibodies (eg. Jo-1, PL-12, PL-7, OJ, EJ, SRP, Mi-2, TIF1-γ, MDA5, NXP2)
- Myositis-associated autoantibodies (eg. PM/Scl, Ku, SS-A, U1 RNP, U2 snRNP, fibrillarin U3 RNP)

5.3.5.4 Complement

- C3
- C4
- CH50

5.3.5.5 Urinalysis

- pH
- Protein
- Glucose
- Blood

5.3.5.6 Hepatitis Screen

- Hepatitis B surface antigen, hepatitis B core antibody. If positive, reflex Hepatitis B viral DNA testing must be performed. Where required by local regulations or standard practice Hepatitis B viral DNA testing also must be performed on Hepatitis B suface antibody (HBsAb)-positive subjects.
- Hepatitis C antibody. If positive, reflex HCV RNA testing must be performed

NOTE: For Japan only subjects

- Hepatitis B surface antigen, hepatitis B core antibody (hepatitis B surface antibody, where required by local guidelines). If negative HBs antigen but positive anti-HBc antibody or positive anti-HBs antibody, reflex Hepatitis B viral DNA treating must be performed.

5.3.5.7 Pregnancy Tests

Urine/serum pregnancy tests (minimum sensitivity 25 IU/L of β-HCG) must be performed, with a negative result, for all WOCBP within 24 hours prior to dosing for visits specified in Table 5.1-2, Table 5.1-3, Table 5.1-5, Table 5.1-6 and every 4 weeks in the Follow up period, Table 5.1-7. Urine tests are the preferred method and must be performed unless serum is required by local regulations. A serum test must be performed for confirmation of any positive urine test result. Urine tests can be processed locally and can be self-administered by the subject between office visits, if permitted by local regulations. If any female subject becomes pregnant, she will stop receiving study treatment immediately and enter the Post Treatment Follow-up Period. A pregnancy surveillance form will be completed and submitted to Bristol-Myers Squibb. Serum pregnancy tests will be processed centrally.

5.3.5.8 HIV Testing

HIV testing will be performed centrally unless prohibited by local regulation, guidelines, or standard practice.

5.3.5.9 Fungal Infection and Pulmonary Fibrosis Test

The (1 to 3)-β-D-glucan and KL-6 test will only be performed in regions and/or countries where it is considered the local standard of care at the screening visit. This test should be analyzed locally.

5.3.6 Pulmonary Function Testing

To assess the safety and efficacy of abatacept in IIM subjects with interstitial lung disease (ILD), pulmonary function testing including FEV1, FVC, and DLCO will be performed on all subjects who have clinically active or relevant Interstitial Lung Disease (ILD) or anti-synthetase syndrome at baseline (define in 5.3.7.2). Testing will be obtained at baseline (prior to Day 1), Week 24, Week 52 and Week 76 (or early termination) for subjects with ILD. PFT will be performed and read locally and reviewed by the sites for clinical decision making. No central clinical report will be generated for return to the site.

5.3.7 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment. Images will be submitted to the imaging core lab for central analysis as specified below.

5.3.7.1 X-ray Assessment

A posterior-anterior and lateral chest X-ray, performed during screening, is required for all subjects unless performed within 6 months prior to obtaining written informed consent and documentation of the earlier X-ray is on file. Investigators must ensure that the results of the chest X-ray satisfy criteria for eligibility. The chest X-ray result will be recorded on the appropriate page of the eCRF. This assessment will not be evaluated by a central lab.

5.3.7.2 High-Resolution Computed Tomography (HRCT) Chest

HRCT of the chest will be obtained to evaluate the extent of lung fibrosis at baseline (prior to Day 1) for subjects who are identified by the investigator as having clinically active or relevant Interstitial Lung Disease (ILD) or anti-synthetase syndrome at baseline (defined as the presence of anti-synthetase autoantibody and at least 2 of the following: ILD, inflammatory myositis or inflammatory polyarthritis).

Subjects with clinically active or relevant ILD will be defined as those who have:

1) clinical symptoms of ILD at baseline and/or during the study, or
2) worsening ILD, at baseline and/or during the study, as per the treating physician assessment necessitating a treatment change (with documented worsening of at least 2 the following 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, or
3) new onset of ILD (within 3 months of study entry), or
4) a clinically relevant decrease in lung function on Pulmonary Function Testing (at the discretion of the investigator)

Subjects with ILD who are evaluated with a HRCT at baseline will also have repeat HRCT performed at Weeks 24, 52, and 76 (or early termination).

In this study, full-chest HRCT should be performed on CT scanners deemed qualified by BMS/assigned imaging core lab. If qualification is not possible, CT scanners approved by local regulations for clinical use can be used to obtain the required images for local review. To ensure comparability, the same scan, equipment, method, and technique used during the baseline HRCT scan should be used for the follow-up HRCT scans (Wk 24, Wk 52, Wk 76, or ET if applicable). At early termination, HRCT conducted only if subject received ≥ 8 weeks of study drug and was ≥ 8 weeks from previous HRCT. For each subject, HRCT scans will be performed at total lung capacity and residual volume, with no contrast agent (CA) administration, reconstructed every 1 to 1.5 mm, using a low-dose protocol.

The baseline HRCT is to be performed within 28 days prior to the first study drug treatment but after all other eligibility criteria have been met. If necessary, the screening period may be extended by 14 days to accommodate HRCT scheduling.

All HRCT must be read locally and reviewed by site clinical personnel. No central clinical report will be generated for return to the site. For efficacy assessment, HRCT images of baseline, Week 24, Week 52, and Week 76 (or early termination [ET], if applicable) will be processed and analyzed by centralized blinded reader(s). Only HRCTs performed on CT scanners deemed qualified by BMS/assigned imaging core lab will be used for central review. The HRCT analysis will focus on visual and CAD scores for regional lung fibrosis evaluation. Changes in the lung fibrosis scores from the baseline HRCT will be used to evaluate the treatment responses. Detailed HRCT imaging procedures will be defined in an IM101611 imaging manual.

Suggestive or typical features of UIP, NSIP or OP on HRCT may suffice for the detection and characterization of ILD and eliminate the need for an invasive and potentially harmful surgical lung biopsy.[65] In IIM-ILD, HRCT parenchymal changes are fairly heterogeneous including basilar and posterior infiltrates, with various patterns that commonly include consolidation rather than

honeycombing in non-septal, linear, plate-like, and sub-pleural patterns.[66] However, it is not uncommon for consolidation to progress to frank fibrosis.[67]

HRCT has been applied in multiple clinical studies of lung fibrosis for drug development, serving as an inclusion criterion, a predictive marker of positive treatment response, and/or efficacy readout. A computer-assisted diagnosis (CAD) score to quantify lung fibrosis as the percentage involvement of reticulation patterns based on texture measures from HRCT has been developed and validated as a measure of quantitative lung fibrosis (QLF) and a potential surrogate imaging marker. CAD scores of QLF have been successfully applied as outcome measurements to test treatment efficacy in ILD trials. Compared with visual assessments, CAD scores have been shown to improve objectivity, sensitivity, and repeatability when measuring quantitative changes in lung features.

5.4 Efficacy Assessments

Questionnaires and investigator/subject assessments will be completed prior to study drug administration. If captured on an electronic tablet (ePRO), this device will serve as the source document.

5.4.1 Clinical Assessments for the Study

5.4.1.1 IMACS Definition of Improvement (DOI)

The IMACS DOI is:

- An improvement of ≥ 20% from baseline in 3 IMACS core measures, AND
- No more than 2 IMACS core measure scores worsen by ≥ 25% from baseline, AND
- Manual Muscle Test (MMT-8) may not decrease by ≥ 25% from baseline

IMACS core measures are:

- Physician Global Assessment of Disease Activity (PGA)
- Patient (Subject) Global Assessment of Disease Activity (SGA)
- Manual Muscle Test (MMT-8)
- Health Assessment Questionnaire-Disability Index (HAQ-DI)
- Muscle Enzyme levels
- Myositis Disease Activity Assessment Tool (MDAAT) Extramuscular Global Activity

The muscle enzymes of interest are creatine kinase (CK), aldolase, AST, ALT, and LDH. To assess the DOI the most abnormal lab value (% above ULN) at baseline will be determined. The subsequent change from baseline for this lab value will be used to determine if the patient has met the DOI at each time point indicated (Table 5.1-2, Table 5.1-3, and Table 5.1-5).

To assess the criteria for worsening, the change from baseline will be determined for all 5 lab values at each time-point indicated (Table 5.1-2, Table 5.1-3. and Table 5.1-5). The lab value with

the greatest percent increase from baseline for each will be used to determine if the patient has met the criteria for worsening respectively (Section 3.1.5).

Descriptions of the other core measures are below.

5.4.1.2 Assessments Performed by Medical Staff

The investigator or sub-investigator performing this assessment should have appropriate medical credentials and/or should be individuals with appropriate scientific/medical background who are experienced in performing myositis disease activity assessments. The sub-investigator preferably should be a qualified physician or Doctor of Medicine (MD). Where permitted by local practice and guidelines, a qualified Doctor of Osteopathy (DO), Physician Assistant (PA), or Nurse Practitioner (NP) may perform the Physicians Global Assessment if they have substantial experience assessing patients with IIM. All other non-PGA assessments may be performed by study site personnel that have appropriate relevant clinical or technical training (eg, RN or physical therapist) and are trained to perform the specific IIM study assessments. All individuals that perform study assessments must be recorded in the study file along with their educational background, work experience and training.

Physicians Global Assessment of Disease Activity (PGA)

This tool 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 that can be performed by the investigator or sub-investigator.

Manual Muscle Test (MMT-8)

This tool assesses muscle strength using a 0 - 10 point scale. A set of 7 designated muscles is tested bilaterally plus axial (neck flexor) testing, so that the potential MMT-8 score ranges from 0 - 150. The designated muscles tested will be:

- Neck flexors
- Deltoid middle
- Biceps brachii
- Gluteus maximus
- Gluteus medius
- Quadriceps
- Wrist extensors
- Ankle dorsiflexors

Myositis Disease Activity Assessment Tool (MDAAT)

This is a combined tool that captures the physician's assessment of disease activity of various organ systems using (1) a 0-4 scale and (2) a visual analog scale (VAS). It assesses the clinical features of each organ system based upon:

a) The presence of clinical features or symptoms within the previous 4 weeks that are due to active disease (i.e., use your clinical judgment to determine how active the myositis-associated clinical feature has been within the previous 4 weeks)
b) The judgment that the feature is due to the myositis disease process (ie, clinical findings known or suspected to be due to another disease process or due to therapy should NOT be considered in this evaluation)
c) The concept that disease activity is defined as a potentially reversible finding
d) A clinical, functional, and laboratory assessment for each organ system

The scoring system is based primarily on the physician's intention to treat (Categories A – E). In some cases, a patient may meet the clinical manifestations of a particularly category, but the treatment does not match the intention to treat of that particular category; in those cases, the category matching the clinical symptoms should be marked. If more than one clinical symptom is present within a system, and different categories would be scored for each, mark the category that is most severe.

Myositis Function Index (FI-2)

The FI-2 is a functional outcome developed for patients with adult polymyositis or dermatomyositis assessing muscle endurance in seven muscle groups. Each muscle group is scored as the number of correctly performed repetitions with 60 or 120 maximal number of repetitions depending on muscle group. The FI-2 is a further development of the original Functional Index (FI) and has been validated as to content and construct validity and intra- and inter-rater reliability. The FI-2 can be performed on both right and left sides requiring a maximum of 33 minutes, or just on the dominant side which takes 21 minutes

Myositis Damage Index (MDI)

This tool measures the degree of disease damage of all organ systems. It is composed of a series of organ-specific questions relating to the presence or absence of a given sign or symptom or problem to measure the extent of damage, and an overall rating of the disease damage of each system using a 10 cm. visual analogue scale to measure the severity of damage

Myositis Response Criteria (MRC)[68]

This Myositis Response Criteria (MRC) algorithm generates a continuous total improvement score (range 0-100) based on the sum of the absolute % change in the 6 core domains (weighted) used in the IMACS DOI. It also defines cut points for minimal (≥ 20 point increase), moderate (≥ 40 points), and major (≥ 60 points) improvement in disease.

Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)

This tool assesses the improvement in skin disease activity in subjects with dermatomyositis. Four domains are evaluated including 1) disease activity and damage in 15 anatomic locations, 2) presence of Gottron's papules on the hands, 3) periungual changes, and 4) alopecia. A total activity score and damage score are calculated.

5.4.1.3 Patient Reported Outcomes

Subjects will complete the Patient Global Assessment of Disease Activity, HAQ-DI, PROMIS Fatigue, and SF-36 in the ePRO device. All of these patient reported outcomes should be performed prior to all other assessments.

Patient (Subject) Global Assessment of Disease Activity (SGA)

This tool measures the global evaluation by the subject of their overall disease activity at the time of assessment using a 10 cm visual analogue scale.

Health Assessment Questionnaire Disability Index (HAQ/HAQ-DI)

Scoring conventions are based on the Standard Disability Index of HAQ/HAQ-DI, using the 20 response items. The HAQ-DI takes into account the subject's use of aids, devices, or assistance in the scoring algorithm for a disability category. For each of the 8 disability categories there is an "aids/devices" companion variable that is used to record the type of assistance, if any, a subject uses for his/her usual activities. If either "aids/devices" and/or "assistance from another person" are checked for a disability category, the score for this category is set to "2" (much difficulty), if the original score was "0" (no difficulty) or "1" (some difficulty). The HAQ-DI is then calculated by summing the adjusted categories scores and dividing by the number of categories answered. Details of the HAQ-DI scoring conventions are documented in Fries *et al*[69] and Ramey *et al*[70].

The HAQ is based on a scale of 0-3.

Patient Reported Outcomes Measurement Information System (PROMIS) - SF Fatigue v1.0 Adult Form 8a

The Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 8a will be used to capture fatigue. The PROMIS project was established as part of the National Institutes of Health Roadmap Initiative to create item banks which are publically available, efficient, precise, and valid across a variety of diseases to assess PROs (www.nihpromis.org).

The PROMIS Fatigue instrument evaluates 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.

In this study, the static form of eight questions will be used. The Fatigue short form is universal rather than disease-specific. It assesses fatigue over the past seven days.

[redacted]

[redacted]

5.7 Outcomes Research Assessments

The following assessments will be performed (see Section 5.4.1):

a) Patient (Subject) Global Assessment of Disease Activity (SGA).
b) Subject assessment of physical function (HAQ-DI).
c) Subject assessment of fatigue (PROMIS Fatigue).
d) Subject assessment of quality of life (SF-36).

[redacted]

[redacted]

6 ADVERSE EVENTS

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

The causal relationship to study drug is determined by a physician 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 study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration 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.)

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A S***erious Adverse Event (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 (see **NOTE** below)
- 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.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

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 SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not 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 (eg, 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 reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Section 5.5.1 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. 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 during the screening period through 24 weeks after discontinuation of dosing.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its 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 must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study treatment, and Pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.

SAEs must be recorded on the SAE Report Form. The required method for SAE data reporting is through the eCRF. The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable /not functioning for transmission of the eCRF to BMS (or designee). In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission. When paper forms are used, the original paper forms are to remain on site.

Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission.

[redacted]

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must 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, the SAE report must be updated and submitted within 24 hours to Sponsor or designee using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious 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.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as

appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

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

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the Sponsor or designee within 24 hours of awareness of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject.

The investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to Sponsor or designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for BMS to collect any pregnancy surveillance information from the

female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 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 (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, X-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

For Japan only subjects, malfunctions of the pre-filled syringes containing study drug should be reported to the sponsor via designated form (electronic system). SAEs or events that could lead to an SAE that occurred as a result of the malfunction should be reported to the sponsor within 24 hours of awareness of the event.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Adjudication Committee

An adjudication committee will be established to determine eligibility of subjects with regard to the requirement that subjects have active disease at the time of screening when they do not have at least one of the 3 identified clinical findings: 1) active myositis-associated rash (Gottron's papules or heliotrope rash), or 2) a muscle biopsy, MRI or EMG within 3 months demonstrating active disease or 3) elevated CK > 5 times the upper limit of normal with no alternate explanation or cause (see Section 3.3.1). The committee will be composed of experts in the treatment and study of IIM who will evaluate all relevant material including, but not limited to, medical history, IIM history (such as disease duration and type), laboratory results (including muscle enzyme levels and auto-antibodies), medication history (including dose, duration, number of current and prior therapies), and available imaging, EMG, and biopsy results. Sites will complete the Active Disease Adjudication Form and submit with supporting documentation. Further details on the processes and procedures the committee will follow will be outlined in the Charter of that committee.

7.2 Data Monitoring Committee

A Data Monitoring Committee will be established to provide oversight of safety and efficacy considerations in Study IM101611 and to provide advice to BMS regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the study. Further details on the content and method of data reports to the DMC will be outlined in the Charter of that committee along with the processes and procedures the committee will follow.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

A sample size of 150 subjects (75 subjects per treatment group) is planned based on the primary comparison of the proportion of subjects with IMACS DOI (as defined under the primary objective) at Day 169 (Week 24) between the SC abatacept group and the placebo group on a background of standard treatment.

A sample size of 150 subjects randomized in a 1:1 ratio to the SC abatacept group and placebo group will yield a power of approximately 90% to detect a treatment difference of 27% in the rate of IMACS DOI between the 2 treatment groups based on a continuity corrected chi-squared test. This power estimate assumes a two-sided alpha level of 5%, IMACS DOI rate of 60% in the abatacept group and 33% in the placebo group.

The 60% estimate of IMACS DOI in the abatacept group was based on reported rates of IMACS DOI in studies of patients with Myositis on combination therapy with another biologic agent[36]. It is expected that the rate of IMACS DOI on abatacept in combination with standard treatment should be similar to that observed with the use of another biologic agent in combination with standard treatment. Table 8.1-1 below presents the power estimates for other considerations of proportion of subjects in IMAC DOI in the abatacept group assuming the total sample size of 150 subjects. Randomization will be stratified globally by 3 stratification variables: (1) disease diagnosis (Dermatomyositis [DM] vs non-DM IIM), (2) Interstitial Lung Disease (ILD) (present vs absent), (3) Japan vs ROW.

Table 8.1-1: Estimates of Power for Various Assumed Rates of IMACS DOI at Week 24 Assuming Total Sample Size of 150

Aba Rate	Placebo Rate	Delta	Power (%)
50%	20%	30%	96
	25%	25%	85
55%	25%	30%	95
	30%	25%	84
60%	25%	35%	~ 99
	30%	30%	95
	35%	25%	83

8.2 Populations for Analyses

Efficacy endpoints will be summarized according to the Intent-to-Treat (ITT) population and safety endpoints will be summarized according to the As-Treated population. These populations are described briefly below along with the Per-protocol population [redacted].

- Intent-to-Treat Analysis Population

The Intent-to-Treat (ITT) Analysis Population is defined to include all subjects randomized into the study for whom Case Report Form (CRF) data indicate that at least one dose of study medication (abatacept or placebo) is administered during the Double-Blind Period.

All subjects who are randomized but never received study medication are to be excluded. Given the blinded nature of this study, it is reasonable to assume that subjects who discontinue prior to the receipt of study medication do so for reasons unrelated to study medication. Subjects are grouped according to the treatments to which they are randomized by IVRS.

ITT Analysis Population is also referred to as 'All Randomized and Treated Subjects'.

- As-Treated Analysis Population

  The As-Treated Analysis Population contain all subjects for whom CRF data indicate that at least one dose of study medication was administered during Double-Blind Period.

  Subjects are grouped according to the treatments to which they are randomized, except in cases where information are available, which indicate that a subject receives a different treatment for the entire course of Double-Blind Period. In this case, the subject will be presented by the treatment they actually received.

  The As-Treated Analysis Population will also be referred as 'All Treated Subjects'.

- Per-Protocol Analysis Population

  The Per-protocol Analysis Population is defined as a subset of the ITT Analysis Population which excludes subjects who have relevant protocol deviations during the double-blind study period. Relevant protocol deviations are those protocol deviations that might affect the primary efficacy endpoint of the study. A programmable list of relevant protocol deviations will be included in the Statistical Analysis Plan and approved prior to the Double-Blind Period database lock.

  The Per-protocol Analysis Population will only be used if more than 10% of the subjects in either treatment group have relevant protocol deviations. In such a case, the analysis of the primary efficacy endpoint will be repeated in the Per-protocol Analysis Population.

[redacted]

- Open-label Abatacept Treated Population

  The open-label abatacept treated population will contain all subjects for whom CRF data indicate that at least one dose of study medication was administered during the Open-Label Period. All Week 52 analyses will be performed using this population.

- Subjects randomized in Japan Open-label Abatacept Treated Population

The Japan open-label abatacept treated population will contain all subjects from Japan for whom CRF data indicate that at least one dose of study was administered during the Open-Label Period. All Week 76 analysis will be performed using this population.

- Long Term Open-label Extension Abatacept Treated Population

  The long term open-label abatacept treated population will contain all subjects for whom CRF data indicate that at least one dose of study medication was administered during the long term open-label extension period. All Year 3 analysis will be performed using this population.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint for this study is the proportion of subjects who achieve IMACS DOI (as defined in Section 5.4.1) at Day 169 (Week 24) without rescue.

8.3.2 Secondary Endpoint(s)

Secondary Efficacy Endpoints

- Mean change in muscle endurance using the myositis function index (FI-2) from baseline to Day 169 (Week 24).
- Mean change in Health Assessment Questionnaire-Disability Index (HAQ-DI) from baseline to Day 169 (Week 24).
- Mean change in Myositis Disease Activity Assessment Tool (MDAAT) from baseline to Day 169 (Week 24).
- Mean change in Myositis Response Criteria (MRC) score from baseline to Day 169 (Week 24).

Safety Endpoints

- All adverse events (AEs/SAEs)
- AEs of interest (serious infections, malignancies, injection site reactions, systemic reactions)
- Laboratory test abnormalities

[redacted]

8.4 Analyses

The analyses for this study is scheduled to be performed at 4 separate time points: 1) end of Double-Blind Period (Week 24), and 2) end of Week 52 (open-label period for all subjects), 3) end of open-label extension (Week 76) for Japan, and 4) end of the study (completion of follow-up period).

The Double-Blind Period (Week 24) analysis will be performed once all subjects complete their Week 24 visit assessment or discontinue prematurely prior to Week 24. The Week 24 analysis will include the analyses of the primary efficacy endpoint, secondary and exploratory efficacy endpoints up to Week 24 and safety analyses. Safety analyses will include all the adverse events (AEs) reported in the study up to first dose date in the Open-Label Period, or 56 days after the last dose date in the Double-Blind Period whichever is earlier. Nominal p-values will provided for the

secondary endpoint measures at Day 169 (week 24), no formal statistical testing will be conducted for any of the efficacy analyses related to the secondary endpoints at other time points and on any of exploratory endpoints. Appropriate summary statistics will be provided for the analysis of each endpoint.

The Week 52 analysis will be performed once all subjects complete 52 weeks of treatment in the study and/or follow-up visits whichever is later. The Week 52 analysis will include summaries of AEs reported during the study up to 56 days post last dose date in the study for all subjects. Efficacy endpoints will be summarized over time during the open-label period for the week 52 analysis. The 52 week analysis will be performed using the open-label treated analysis population. Nominal p-values will provided for the secondary endpoint measures at Day 169 (week 24), no formal statistical testing will be conducted for any of the efficacy analyses related to the secondary endpoints at other time points and on any of exploratory endpoints. Appropriate summary statistics will be provided for the analysis of each endpoint.

An analysis using only Japanese sites will performed once all subjects complete 76 weeks of treatment in the study.

A final analysis will be performed when subjects complete the 3 year long term extension and/or follow-up visits whichever is later.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions and summary statistics of all demographic variables and baseline characteristics will be presented by treatment arm using the ITT population. Detail of baseline characteristics to be presented will be included in the SAP.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Efficacy Analysis

The primary comparison of proportion of subjects in IMACS DOI at Week 24 between the SC abatacept and placebo groups will be assessed using a logistic regression model. To account for randomization stratification, the logistic regression model will adjust for the randomization stratification variables of disease diagnosis (Dermatomyositis [DM] vs non-DM IIM), Interstitial Lung disease status (present vs. absent), and Japan vs. ROW; baseline MMT8, baseline MDAAT, baseline PGA (continuous) and treatment group will also be included in the model. Point estimate of the adjusted Odds Ratios (OR) of the odds of achieving IMACS DOI in the abatacept arm compared to the placebo arm, corresponding 95% CI and p-value will be provided. The proportion of subjects in IMACS DOI in each treatment group and corresponding 95% CI will also be provided. All subjects who discontinue study medication prematurely prior to reaching the Week 24 assessment visit, will be considered as not achieving IMACS DOI for the primary analysis. Efficacy assessments collected at week 24 on subjects who discontinue study medication prior to week 24 will not be included in the primary analysis of the primary endpoint, but will be included in a sensitivity analysis of the primary endpoint. Specification of sensitivity analyses of the primary endpoint under different assumptions for missing data at week 24 will be provided in the Statistical Analysis Plan (SAP).

8.4.2.2 Secondary Efficacy Analysis

In addition to the primary efficacy endpoint, analyses related to the secondary and exploratory endpoints will also be included in the Week 24 analysis. The secondary efficacy assessment of change from baseline in muscle endurance using FI-2 up to Day 169 (Week 24) will be assessed using a longitudinal (repeated measure) mixed model including treatment group, baseline FI-2 value and randomization stratification factors: diagnosis (DM vs non-DM IIM), ILD, Japan vs ROW, time (study days in which FI-2 is measured), time by baseline FI-2 and time by treatment interactions as fixed effects and subject as a random effect. Adjusted mean, SE, 95% CI for adjusted mean difference between treatment arms will be provided. A similar mixed model will also be used to assess the change from baseline in HAQ-DI up to Day 169 (Week 24). The model will include treatment group, baseline value HAQ-DI value, randomization stratification factors: disease diagnosis (DM vs non-DM IIM ILD, Region (Japan vs ROW), time (study days in which HAQ-DI is measured), time by baseline HAQ-DI and time by treatment interactions as fixed effects and subject as a random effect. Adjusted mean, SE, 95% CI for adjusted mean difference between treatment arms will also be provided.

The secondary efficacy assessment of change from baseline in MDAAT value will also be assessed using a longitudinal (repeated measure) mixed model including treatment group, baseline value MDAAT value, randomization stratification factors: disease diagnosis (DM vs non-DM IIM), ILD, Region (Japan vs ROW), time (study days in which MDAAT is measured), time by baseline MDAAT and time by treatment interactions as fixed effects and subject as a random effect. Adjusted mean, SE, 95% CI for adjusted mean difference between treatment arms will also be provided.

A similar mixed model will also be used to assess the change from baseline in Myositis Response Criteria (MRC) score up to Day 169 (Week 24). The mixed model will include treatment arm, baseline MRC score and randomization stratification factors: disease diagnosis (DM vs non-DM IIM), ILD (absent vs present), Region (Japan vs ROW), time (study days in which MRC is measured), time by baseline MRC score and time by treatment interactions as fixed effects and subject as a random effect. Adjusted mean, SE, 95% CI for adjusted mean difference between treatment arms will be provided.

Nominal p-values will be provided for the secondary efficacy endpoints at Day 169 ie, mean change from baseline at Day 169 for each of the secondary endpoints: FI-2, HAQ-DI, MDAAT and MRC. The mixed longitudinal model will account for any missing values on any of the secondary efficacy endpoints. All construction of CIs for differences in response rates between treatment groups will be based on minimum risk weights to account for randomization stratification factors, unless otherwise noted. All construction of CIs for response rates within treatment group will be based on normal approximation, unless otherwise noted.

Efficacy assessments collected at week 24 on subjects who discontinue study medication prior to week 24 will not be included in the primary analyses of the secondary endpoints, but will be included in a sensitivity analysis of the secondary endpoints. The mixed longitudinal model will be considered the primary analyses for all the continuous secondary endpoints, specifications of

sensitivity analyses of the secondary endpoints under different assumptions for missing data, including the use of efficacy data collected after discontinuation from the study, will be provided in the SAP.

A summary of the analysis methods to be used for the analysis of the primary, secondary and exploratory efficacy endpoints are presented in Table 8.4.2.2-1 below. Further details on the primary and secondary analyses along with exploratory evaluations, any sensitivity analyses and data handling details regarding issues such as missing data will be provided in the Statistical Analysis Plan. Analyses specific to the MRI sub-study, Muscle Biopsy sub-study, and Actigraphy will be presented in the Statistical Analysis Plan.

Table 8.4.2.2-1: Planned Efficacy Analyses

Measure of Interest	Analysis Method
IMACS DOI at Day 169 (Week 24)	Primary Analysis: Using a logistic regression model that includes treatment group, stratification factors: disease diagnosis (DM vs non-DM IIM), ILD (absent vs present), Region (Japan vs ROW), and baseline MMT8, baseline MDAAT, and baseline PGA as continuous variable. Point estimate of adjusted ORs, corresponding 95% CI and p-value will be provided. The proportion of subjects in IMACS DOI in each treatment group and corresponding 95% CI will also be provided.
Time to event (IMACS DOI at 2 consecutive time points) up to Day 169 (Week 24)	Point estimates and 95% CIs for the hazard ratio of abatacept versus placebo will be based on Cox proportional hazards models. The stratification factors: disease diagnosis (DM vs non-DM IIM), ILD (absent vs present), Region (Japan vs ROW) and baseline MMT8, baseline MDAAT, and baseline PGA (continuous) will be included in the model. Observations from subjects who discontinue due to lost to follow-up will be censored at the time of last available data in the study. The date of the first IMACS DOI of the 2 consecutive IMACS DOI events will be used in the analysis. Estimate the distribution of time to first occurrence of event using Kaplan-Meier method/curve.
Changes from baseline in continuous variables (ie, FI-2, MDAAT, MRC score, IMACS core components, SF-36, HAQ-DI, PROMIS, CDASI, MDI, etc)	Longitudinal (repeated measure) mixed model [including treatment group, baseline value of variable and randomization stratification factors: diagnosis (DM vs non-DM IIM), ILD (absent vs present), Region (Japan vs ROW), time (categorical as study visit at which variable was measured), time by baseline value of variable and time by treatment as fixed effects and subject as a random effect], adjusted mean, SE, 95% CI for adjusted mean difference between treatment groups will be provided. Nominal p-values will be provided for the change from baseline at Day 169 (week 24) analysis.
[redacted]	[redacted]
Differences in proportions (i.e., proportion of subjects achieving IMACS DOI in myositis Ab negative subjects, etc.)	Point estimate of response rate, 95% CI, point estimates and 95% CI of treatment difference adjusted for randomization stratification factors: diagnosis (DM vs non-DM IIM), ILD (absent vs present), Region (Japan vs ROW) (based on minimum risk weights)

8.4.3 Safety Analyses

For the Week 24 analysis, frequency distribution of all adverse events (AEs) reported during Period I of the study will be presented by the 2 treatment arms (abatacept vs. placebo). AEs will be summarized from the first dose date in the study up to first dose date in the Open-Label Period or last dose date in the Double-Blind Period + 56 days for subjects who prematurely discontinued the study during the Double-Blind Period. Summary of AEs of special interest will also be provided, details and analyses of the AEs of special interest will be provided in the SAP. Individual listings of AEs indicating treatment arms will also be generated. Changes in clinical laboratory test results from baseline will be summarized by treatment group. Laboratory marked abnormality using pre-defined abnormality criteria will also be descriptively summarized by treatment group. In general, there will be no statistical testing of group difference with respect to frequencies of AEs or laboratory marked abnormalities, except otherwise specified in the SAP. All safety analyses in the Week 24 analysis will be performed using the as-treated analysis population.

8.4.6 Outcomes Research Analyses

The changes from baseline in Fatigue (PROMIS) and SF-36 will be summarized by treatment group. The treatment differences in adjusted mean changes from baseline for each measure, along with the corresponding 95% two-sided CI, will be based on a repeated measure mixed model and will be presented at each scheduled study visit at which the PROMIS Fatigue or SF-36 assessment was done. The mixed model will include baseline measurement, treatment group, randomization stratification factors: diagnosis (DM vs non-DM IIM), ILD (present vs absent), Japan vs ROW, time (study days in which variable was measured), time by baseline value of variable and time by treatment as fixed effects and subject as a random effect], adjusted mean, SE, 95% CI for adjusted mean difference between treatment groups will be provided.

8.4.7 Week 52 Analysis

The final study (Week 52 analysis) for all study sites will be performed when all subjects have completed a total of 52 weeks on treatment in the study (ie. completed the Open-Label Period) and/or the follow-up period of the study. The Week 52 analysis will include efficacy and safety

analyses. No formal statistical testing will be conducted for any of the efficacy analyses included in the final Week 52 analysis, appropriate summary statistics will be provided. Safety summaries will include events reported from the start of the Open-Label Period up to 56 days post last dose date in the Open-Label Period. Cumulative abatacept safety summaries will also be provided for all subjects who received abatacept at any time during the study. The cumulative safety summaries will include all AEs reported from the first dose date of abatacept up to 56 days post the last dose date of abatacept in the study. [redacted] The Week 52 analyses will be based on open-label treated analysis population except for the cumulative abatacept safety summaries which will be based all subjects who received at least one dose of abatacept at any time during the study.

8.4.8 Week 76 Japan Only Analysis

The analysis for the assessment of long-term efficacy and safety for subjects from Japan will be performed including data collected up to Week 76.

8.4.9 Long Term Open Label Extension (3 Years)

The analysis will be performed when all subjects have completed a total of 3 years open label treatment in the Long Term Open-Label Extension and/or the follow-up period of the study. The analysis will include safety. No formal statistical testing will be conducted; appropriate summary statistics will be provided. Safety summaries will include events reported from the start of the Long Term Open-Label Period up to 56 days post last dose date.

Cumulative abatacept safety summaries will also be provided for all subjects who received abatacept at any time during the study. The cumulative safety summaries will include all AEs reported from the first dose of abatacept up to 56 days post the last dose of abatacept in the study.

The analyses will be based on open-label treated analysis population except for the cumulative abatacept safety summaries which will be based on all subjects who received at least one dose of abatacept at any time during the study.

8.5 Interim Analyses

Not Applicable

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

- IRB/IEC

- Regulatory Authority(ies), if applicable by local regulations per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority, must be sent to BMS. If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by BMS or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS or designee.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.2 Records

9.2.1 Records Retention

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS or designee prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

9.2.2 Study Drug Records

Records for IP (whether supplied by BMS, its vendors, or the site) must substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If...	Then...
Supplied by BMS (or its vendors):	• and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • non-study disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply,	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers

If...	Then...
or a specialty pharmacy)	• date and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor of designee.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
ACR	American College of Rheumatology
ACTH	adrenal corticotropic hormone
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase (SGPT - serum glutamic pyruvate transaminase)
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase (SGOT - serum glutamic oxaloacetic transaminase)
AZA	Azathioprine
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
BCG	Bacillus Calmette–Guérin
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CA	Contrast Agent
CAD	Computer assisted diagnosis
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CDC ACIP	Center for Disease Control Advisory Committee on Immunization Practices
CFR	Code of Federal Regulations
CI	confidence interval
cm	Centimeter
COPD	Chronic Obstructive Pulmonary Disease
CPK/CK	creatine phosphokinase
CRF	Case Report Form, paper or electronic
CT	computed tomography
CXR	chest X-ray

Term	Definition
DAD	diffuse alveolar damage
D/C	Discontinue
DILI	Drug Induced Liver Injury
DLCO	diffuse capacity for carbon monoxide
DM	Dermatomyositis
DMARD	disease-modifying antirheumatic drug
DNA	Deoxyribonucleic Acid
DOI	Definition of Improvement
ECG	Electrocardiogram
ECL	Electrochemiluminescence
eCRF	electronic Case Report Form
EDC	electronic Data Capture
e.g.	exempli gratia (for example)
EIA	Enzyme Immunoassay
EMG	Electromyography
ER	exposure response
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FI-2	Myositis Function Index
FSH	follicle stimulating hormone
FVC	forced vital capacity
g	Gram
GCP	Good Clinical Practice
GGO	Ground Glass Opacities
GGT	gamma-glutamyl transferase
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HcAb	Hepatitis C antibody

Term	Definition
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPV	Human papilloma virus
HRCT	high-resolution computed tomography
HRT	hormone replacement therapy
ICH	International Conference on Harmonization
i.e.	id est (that is)
IEC	Independent Ethics Committee
IIM	Idiopathic Inflammatory Myopathy; Idiopathic Inflammatory Myositis
ILD	interstitial lung disease
IMACS	International Myositis Assessment and Clinical Studies group
IMACS DOI	IMACS Definition of Improvement
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
INH	Isoniazid
IRB	Institutional Review Board
ISR/T	investigator sponsored research/trial
ITT	intent-to-treat
IU	International Unit
IV	Intravenous
IVIG	Intravenous Immunoglobulin
IVRS	interactive voice response system
JIA	juvenile idiopathic arthritis
Kg, kg	Kilogram
L	Liter
LDH	lactate dehydrogenase
LT	long term
MDAAT	Myositis Disease Activity Assessment Tool
MDI	Myositis Damage Index

Term	Definition
mg	Milligram
μg	Microgram
MHC	major histocompatibility complex
min	Minute
mL	Milliliter
mmHg	millimeters of mercury
MMR	Measles, mumps and rubella
MMT	Manual Muscle Test
MOA	Mode of Action
MRC	Myositis response criteria
MRI	magnetic resonance imaging
MSD	meso-scale discovery
MTX	Methotrexate
N	number of subjects or observations
N/A	not applicable
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NSIP	nonspecific interstitial pneumonia
OP	organizing pneumonia
OR	odds ratio
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
PFT	Pulmonary Function Testing
PGA	Physician Global Assessment of Disease Activity
PK	Pharmacokinetics
PM	Polymyositis
PPD	Purified Protein Derivative
PRO (ePRO)	Patient-Reported Outcomes (electronic Patient-Reported Outcomes)
PROMIS	Patient-Reported Outcomes Measurement Information System
QLF	quantitative lung fibrosis

Term	Definition
RA	Rheumatoid Arthritis
RBC	red blood cell
RNA	Ribonucleic Acid
ROW	Rest of World
SAE	serious adverse event
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
SD	standard deviation
SGA	Patient (Subject) Global Assessment of Disease Activity
SOC	system organ class
ST	short term
Subj	Subject
TB	Tuberculosis
UIP	usual interstitial pneumonia
ULN	Upper-Limit of Normal
UV	Ultraviolet
VAS	visual analog scale
WBC	white blood cell
Wk, wk	Week
WOCBP	women of childbearing potential

APPENDIX 1 HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation.
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as MirenaÒ
3. Nonhormonal IUDs, such as ParaGardÒ
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure
    - Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
6. Intrauterine hormone-releasing system (IUS).
7. Complete abstinence
    - Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
    - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
    - It is not necessary to use any other method of contraception when complete abstinence is elected.
    - Subjects who choose complete abstinence must continue to have pregnancy tests as specified in Section 5.1.
    - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Local laws and regulations may require use of alternative and/or additional contraception methods.

UNACCEPTABLE METHODS OF CONTRACEPTION

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)

2. Withdrawal (coitus interruptus)
3. Spermicide only
4. Lactation amenorrhea method (LAM)

TREATMENT WITH TERATOGENIC CONCOMITANT MEDICATION

Males and females taking a concomitant teratogenic medication should follow contraception guidelines and duration described in the label for the concomitant medication in addition to those required for abatacept.

[redacted]

APPENDIX 2 LABORATORY GUIDELINES: PATIENT STUDIES (REVISED AUGUST 13, 1999)

Laboratory test results, which meet these criteria, and the Investigator feels is clinically relevant should be described on the Adverse Event Form. Those which are judged to be SERIOUS events require the completion of a Serious Adverse Event Form (see Sections 6.1.1 and 6.3).

[NOTE: LLN = lower limit of normal; ULN = upper limit of normal.]

albumin - < 0.9 x LLN or if pretreatment value is < LLN, < 0.75 x pretreatment

alkaline phosphatase - > 2 x ULN; or if pretreatment >ULN, 3 x pretreatment value

basophils (%) - > 3% if 0-1% pretreatment, > 3 x pretreatment value if pretreatment > 1%

bilirubin

a. direct - > 1.5 x ULN, or if pretreatment above ULN, > 2 x pretreatment

b. total - > 2 x upper limit of normal, or if pretreatment above ULN, > 4 x pretreatment value

blasts - > 0

blood urea nitrogen (BUN) - > 2 x pretreatment

calcium - < 0.8 x LLN or > 1.2 x ULN; < 0.75 x pretreatment if pretreatment below LLN, or > 1.25 x pretreatment if pretreatment above ULN; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

chloride - < 0.9 x LLN or > 1.1 x ULN; or < 0.9 x pretreatment if pretreatment below LLN, or > 1.1 x pretreatment if pretreatment above ULN; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

creatinine - > 1.5 x pretreatment value

eosinophils (%) - > 3 x pretreatment and > 8% if pretreatment normal; if pretreatment > ULN, > 3 x pretreatment

erythrocytes - < 0.75 x pretreatment value

glucose - < 0.8 x LLN or > 1.5 x ULN; if pretreatment < LLN then < 0.8 x pretreatment; if pretreatment > ULN then > 2 x pretreatment; < LLN if > ULN pretreatment, or > ULN if < LLN pretreatment

hematocrit - < 0.75 x pretreatment

hemoglobin - > 3 g/dL decrease from pretreatment value

lactic dehydrogenase (LDH) - > 1.5 x ULN; if pretreatment value is above ULN, > 3 x pretreatment value

leukocyte (WBC) count - < 0.75 x LLN or > 1.25 x ULN; < 0.8 x pretreatment if pretreatment < LLN or > 1.2 x pretreatment if pretreatment > ULN; > ULN if pretreatment < LLN or < LLN if > ULN pretreatment

lymphocytes (%) - < 0.5 x LLN or > 2.0 x ULN, or < 0.5 x pretreatment if below LLN pretreatment; > 2.0 x pretreatment if above ULN pretreatment. > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

monocytes (%) - > 2 x ULN; > 2 x pretreatment if pretreatment above ULN

neutrophil count (neutrophils+bands) - < 0.67 x pretreatment if pretreatment < 1000/mm^3; otherwise, < 1000/mm^3.

phosphate - < 0.75 x LLN or > 1.25 x ULN; < 0.67 x pretreatment value if below LLN pretreatment, or > 1.33 x pretreatment if above ULN pretreatment; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

platelet count - < 0.67 x LLN or > 1.5 x ULN; if below normal pretreatment, < 0.5 x pretreatment value and < 100,000/mm^3

potassium - < 0.9 x LLN or > 1.1 x ULN; < 0.9 x pretreatment if pretreatment below LLN, or > 1.1 x pretreatment if pretreatment above ULN; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

protein, total - < 0.9 x LLN or > 1.1 x ULN; <0.9 x pretreatment if below LLN pretreatment, or > 1.1 x ULN if above ULN pretreatment; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

SGOT and SGPT (ASAT and ALAT) - > 3 x upper limit of normal; if pretreatment above ULN, > 4 x pretreatment value

sodium - < 0.95 x LLN or > 1.05 x ULN; < 0.95 x pretreatment if below LLN pretreatment, > 1.05 x pretreatment if above ULN pretreatment; > ULN if < LLN pretreatment, or < LLN if > ULN pretreatment

uric acid - > 1.5 x ULN; if pretreatment above ULN, > 2 x pretreatment value

urinalysis

a) urinary protein - > 1 gram/24 hours and 2 x pretreatment value

b) urinary RBC - > 5/HPF or, > 4 x pretreatment if pretreatment value 5/HPF

c) urinary WBC - > 5/HPF or, > 4x pretreatment if 5/HPF pretreatment

d) creatinine clearance (glomerular filtration rate) - < 0.67 x pretreatment value

e) urine dipstick measurements: Protein, blood, sugar, and acetone- 2+, or if 1+ pretreatment, 2 x pretreatment. Do not evaluate protein if quantitative protein determination done

stool hemoccult - positive if negative pretreatment

APPENDIX 3 BOHAN AND PETER CLASSIFICATION CRITERIA

1. Symmetrical weakness, usually progressive, of the limb-girdle muscles
2. Muscle biopsy evidence of myositis
   - Necrosis of type I and type II muscle fibers
   - Phagocytosis
   - Degeneration and regeneration of myofibers with variation in myofiber size
   - Endomysial, perimysial, perivascular or interstitial mononuclear cells
3. Elevation of serum levels of muscle-associated enzymes
   - CK, Aldolase, LD, Transaminases (ALT/SGPT and AST/SGOT)
4. Electromyographic triad of myopathy
   - Short, small, low-amplitude polyphasic motor unit potentials
   - Fibrillation potentials, even at rest
   - Bizarre high-frequency repetitive discharges
5. Characteristic rashes of dermatomyositis

Definite Polymyositis = all first 4

Probable Polymyositis = 3 of first 4

Possible Polymyositis = 2 of first 4

Definite Dermatomyositis = rash + 3 other

Probable Dermatomyositis = rash + 2 other

Possible Dermatomyositis = rash + 1 other

[redacted]

APPENDIX 4 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

[redacted]

Summary of Key Changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	[redacted]
Synopsis, Secondary Objectives & 1.3.2 Secondary Objectives & 8.3.2 Secondary Endpoint(s)	Removed 'Wk 12' time-points from (1), (2), (3) & (4) or the four bullet-points.	
Synopsis, Key Inclusion Criteria: (c-ii) & 3.3.1 Inclusion Criteria: (2) Target Population (c-ii) & 7 .1 Adjudication Committee	Modified '1 month' to '3 months'.	
Synopsis, Key Exclusion Criteria: (c) & 3.3.2 Exclusion Criteria: (1) Target Disease Exceptions (c)	Reduced treatment-free period(s) with rituximab, IVIG, SCIG or any other biologic treatment.	
[redacted]	[redacted]	

Summary of Key Changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	[redacted]
2.1 Good Clinical Practice (3rd paragraph)	Incorporated • 'If required as per local regulation, serious breaches will be reported by Sponsor or designee to applicable authorities' • '(occurring in any country)' • and 'of 1 or more subjects'.	
2.2 Institutional Review Board/Independent Ethics Committee	Removed 'BMS' notation and added 'Sponsor' & 'designee'.	
3.1.2 Double-Blind Period (Day 1 - Week 24)	Additional text:' Rescue therapy will be available for subjects who meet the disease worsening criteria during the double-blind period as defined in Section 3.1.4.' & Subjects who discontinue treatment with study medication during the Double-blind Period will complete the Early Termination visit (which is the same visit as Day 169 visit) (See Table 5.1-2). These subjects must also return on the previously scheduled Double-blind Period Day 169 to complete the Post-Study Drug Efficacy Visit (see Table 5.1-4). The purpose of this visit is to assess all aspects of disease activity to ascertain the impact of study participation for regulatory review. Subjects must also complete 2 follow-up visits (Day 85 and 169) during the 24 week post-treatment follow-up period, to perform safety and laboratory assessments (See Table 5.1-5 Post-Treatment Follow-Up Period). This Period begins on the day of the Early Termination visit and applies only to subjects who do not start commercial abatacept therapy.'	
3.1.3 Open-Label Period (Week 24 - Week 52)	Supplementary text 'Use of immune globulin (intravenous [IVIG] or subcutaneous [SCIG] is permitted during this period.' & 'Subjects who discontinue treatment with abatacept during the Open-Label Period will complete the Early Termination visit for the OL (See Table 5.1-3 day 365 is also the OL ET) and 2 follow-up visits during the 24 week post-treatment follow-up period, to perform safety and	

Summary of Key Changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	[redacted]
	laboratory assessments. (See Table 5.1-5). If the subject receives treatment with an alternate source of abatacept (Post-Study Drug Program [PSDP] or Commercial), completing this post-treatment follow-up period is not required. Treatment with other biologic therapy is not recommended for at least 70 days (~5 half-lives of abatacept follow-up period.'	
3.1.4 Rescue Therapy	Removed the following text 'The choice of rescue therapy is at the discretion of the investigator; however, rescue treatment may not be abatacept or a prohibited medication (See Section 3.4.2.1).' & Later in the segment, added 'The use of rescue therapy is at the discretion of the investigator; however, rescue treatment may not be abatacept or a prohibited medication (See Section 3.4.2.1). Allowable medication are restricted to allowable concomitant medication (Section 3.4.1.1 Standard Treatment). Rescue therapy includes increases in dose of current therapy, addition of therapy and change in therapy, all with some restrictions such that allowable rescue therapy meets the criteria for allowable standard treatment. The following changes are allowable as rescue therapy:' and sections (1), (2) & (3).	
3.1.5 Post-Treatment Follow-Up Period	Removed sections: • Double-Blind Period (Day 1 to Wk 24) • Open-Label Period (Wk 24 to Wk 52) • Study Completion (After Wk 52).	
3.2 Post Study Access to Therapy	Amended title to '3.2 Post Study Access to Study Drug', and included 'with study drug, ie abatacept'.	
3.3.4 Screening for Malignancy	Added the text 'It is recommended that all' & 'at the discretion of the investigator', at several points. & Last paragraph, removed 'require approval by' and added 'may be discussed with'.	

Summary of Key Changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	[redacted]
3.4.1.1 Standard Treatment	Added the text 'Use of immune globulin (intravenous [IVIG] or subcutaneous [SCIG] is permitted during this period. Addition of any other prohibited medication (Section 3.4.2.1; except IVIG3.4.2.1) is not permitted' to the last paragraph.	
3.4.1.3 Immunosuppressant medications	Provided substantial text revision to clarify what immunosuppressants are permitted	
3.4.2.1 Prohibited Medications	Added text 'All prohibited medication must have been discontinued at least 4 weeks prior to randomization with the exception of immune globulin, rituximab and d-penicillamine which have longer exclusion periods (see 3.3.2). Prohibited medication in this contest refers to immunomodulatory medications for the treatment of IIM which are not included as immunosuppressant medications (Section 3.4.1.3). The following list includes examples of specific prohibited medications.' Also added/removed several therapies.	
3.4.2.2 Restricted Medications	Developed second bullet-point.	
3.5 Discontinuation of Subjects following any Treatment with Study Drug	Second paragraph: Provided substantial text revision to clarify the requirements for subjects that discontinue	
Table 4-1: Study Drugs for IM101611	Added 'Open Label'.	
Table 5.1-2 Study Evaluations - Double-Blind Period (IM101611)	Added Wk 8 assessments for MMT-8 & MDAAT	
Table 5.1-5	Revised Schedule/T&E 'Title'.	
5.4.1.2 Assessments Performed by Medical Staff: Myositis Response Criteria	Added a 'continuous total improvement score' range '0-100'.	
Table 5.5.1-1 Sampling Schedule	Amended Study Days to reflect '85 Days & 169 Days after Last Dose	
6.1.1 Serious Adverse Event Collection and Reporting	Text revised to clarify the reporting of SAEs and Pregnancies immediately.	

Summary of Key Changes of Revised Protocol 03		
Section Number & Title	**Description of Change**	[redacted]
[redacted]	[redacted]	
[redacted] 8.4.7 Final Study (Week 52) Analysis	Amended [redacted] Section 8.4.7 to reflect 85 days and 169 days post last dose in study	
8.4.2.1 Primary Efficacy Analysis & Table 8.4.2.2-1 Planned Efficacy Analyses	Replaced 'IMACS score' with 'MMT8, baseline MDAAT, baseline PGA'. Clarifying also' Time to event (IMACS DOI at 2 consecutive time points) up to Day 169 (Week 24)'	
11. LIST OF ABBREVIATIONS	Additional abbreviations added.	
[redacted]	[redacted]	
Throughout Revised Protocol 03	Amended 'anti-TIF1-c' 'to anti-TIF1-γ'.	
Throughout Revised Protocol 03	Grammatical and spelling corrections throughout the document. Also addition of other minor clarifications and correction of typographical errors.	