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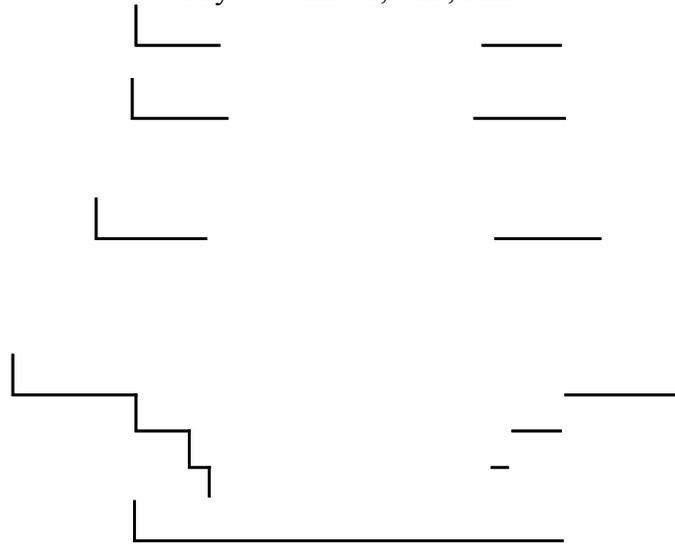
Clinical Protocol IM101603

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Subcutaneous Abatacept in Adults with Active Primary Sjögrens Syndrome

Revised Protocol Number: 01
Incorporates amendment(s) 01

Medical Monitor

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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 01	25-Aug-2016	Incorporates Amendment 01
		<p>Changes to Protocol include:</p> <ul style="list-style-type: none"> • To provide clear differentiate between discontinuation of study treatment from discontinuation from the study. <ul style="list-style-type: none"> ○ Subjects who discontinue investigational product during the Double-Blind Treatment Period should continue to comply with all protocol specified procedures during the Double-Blind Treatment Period. ○ Define the assessments required for the collection of follow-up data. • To clarify inclusion/exclusion criteria • To clarify testing for stimulated salivary flow • Add allowable window for obtaining the optional biopsy samples. • Modify laboratory testing to limit to the most critical tests and to adjust for feasibility issues. • Add additional secondary <input type="checkbox"/> <input type="checkbox"/> • Increase the total number of subjects targeted for enrollment in order to increase statistical power and the overall size of the safety database. • Revise appendices to include most current versions. • Corrections to minor typographical errors
Amendment 01	25-Aug-2016	
Original Protocol	23-Jun-2016	Not applicable

SYNOPSIS

Clinical Protocol IM101603

Protocol Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Subcutaneous Abatacept in Adults with Active Primary Sjögrens Syndrome

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

Subjects receive investigational products for a period of 1 year. Investigational products are defined as:

- Abatacept SC 125 mg in 1 mL pre-filled syringes
- Placebo for abatacept SC in 1 mL pre-filled syringes

Study Phase: III

Research Hypothesis: Abatacept 125 mg, administered subcutaneously (SC) weekly will have greater efficacy than placebo in subjects with moderately to severely active primary Sjögren's Syndrome (pSS) as assessed by the mean change from baseline in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) score after Day 169 of treatment.

Objectives:

Primary Objective

To compare the mean change from baseline (Day 1) to Day 169 in ESSDAI of abatacept versus placebo in subjects with moderate to severe pSS.

Secondary Objective

Key Secondary:

- To compare the mean change from baseline (Day 1) to Day 169 in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) of abatacept versus placebo in subjects with moderate to severe pSS.
- To compare the mean changes from baseline (Day 1) to Day 169 in the stimulated whole salivary flow of abatacept versus placebo in subjects with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline.

Other Secondary:

- To assess the mean change from baseline at all measured time points up to Day 169 in DAS28-CRP among those with a tender joint count plus swollen joint count of at least 3 at baseline, among those with a tender joint count plus swollen joint count of less than 3 at baseline and in the full population.
- To assess the mean change from baseline at all measured time points up to Day 169 in the individual components of DAS28-CRP among those with a tender plus swollen joint count of at least 3 at baseline, among those with a tender joint count plus swollen joint count of less than 3 and in the full population.
- To assess the proportion of subjects who achieve a minimally clinically important improvement in ESSDAI (≥ 3) at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- To assess the proportion of subjects who achieve a minimally clinically important improvement in ESSDAI (≥ 5) at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- To assess the proportion of subjects who achieve a minimally clinically important improvement in ESSPRI (≥ 1) at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary

flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.

- To assess the mean change from baseline at all measured time points up to Day 169 in ESSDAI in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- To assess the mean change from baseline at all measured time points up to Day 169 in ESSPRI in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- To assess the mean change from baseline in the individual components of the ESSDAI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- To assess the mean change from baseline in the individual components of the ESSPRI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- To assess the mean change from baseline in Schirmer's test at all measured time points up to Day 169.
- To assess the mean change from baseline in ocular staining score at all measured time points up to Day 169.
- To assess the mean change from baseline in tear break-up time at all measured time points up to Day 169.
- To assess the mean change from baseline in unstimulated whole salivary flow at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- To assess the mean change from baseline in stimulated whole salivary flow at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- To assess the change in patient symptoms using the Numeric Rating Scale (NRS) for mouth dryness at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- To assess the mean change in patient symptoms using the Numeric Rating Scale (NRS) for eye dryness at all measured time points up to Day 169.
- To assess the mean change in patient symptoms using the patient global assessment of disease activity at all measured time points up to Day 169.
- To assess the mean change in the physician global assessment at all measured time points up to Day 169.
- To assess the mean change in patient fatigue using PROMIS Fatigue assessment at all measured time points up to Day 169.
- To assess the mean change in female sexual function using the Female Sexual Function Index (FSFI) at all measured time points up to Day 169.
- To assess the mean change in patient quality of life using the SF-36 at all measured time points up to Day 169.
- To assess safety and immunogenicity of abatacept.
- To assess the pharmacokinetics of abatacept.

- Subjects should have pSS that is refractory to symptomatic or local therapy (e.g. NSAIDs)
- Subjects having an ESSDAI score of at least 5 at screening.
- Subjects being anti-SS-A/Ro positive at screening.
- Stimulated salivary flow of at least 0.1 mL/min at screening and randomization in at least 124 subjects (72%)

Key Exclusion criteria:

- Subjects who have a systemic autoimmune disease other than Sjögren's syndrome, such as RA, SLE or systemic sclerosis, that can better explain the majority of the symptoms (ie, secondary Sjögren's syndrome).
- Subjects who have another autoimmune disease or inflammatory condition that could interfere with assessment of response of pSS to therapy (eg, systemic sclerosis, inflammatory bowel disease, gout).
- Subjects with any other medical condition associated with clinical features overlapping those of pSS or that would interfere with interpretation of results, including but not limited to a history of head and neck radiation treatment, sarcoidosis, amyloidosis, graft-versus-host disease, hepatitis C, acquired immunodeficiency syndrome, and IgG4-related disease.
- Active life-threatening or organ-threatening complications of Sjögren's-syndrome (SS) disease at the time of screening based on investigator evaluation including but not restricted to the following:
 - Vasculitis with renal, digestive, cardiac, pulmonary or central nervous system (CNS) involvement characterized as severe (note: cutaneous vasculitis is allowed)
 - Active CNS or peripheral nervous system (PNS) involvement requiring high dose steroids
 - Severe renal involvement, e.g., GFR < 60 mL/min, a serum creatinine > 2 mg/dL, or proteinuria > 3 g/day,
 - Severe pulmonary involvement, e.g., shortness of breath at rest, or pulmonary function tests demonstrating DLCO < 40% or FVC < 60%
 - Severe muscular involvement requiring high dose steroids
 - Lymphoma
- Subjects who have previously been exposed to abatacept or anti-CD28 therapy.
- Subjects who have received IV, IM, SC or intra-articular corticosteroids within 4 weeks of randomization (Day 1).
- Subjects who have taken rituximab within 12 months prior to randomization (Day 1).
- Subjects who have taken belimumab within 12 weeks prior to randomization (Day 1).
- Subjects who have taken a biologic therapy other than rituximab or belimumab or any other investigational therapy within 12 weeks or 5 half-lives prior to randomization (Day 1), whichever is longer.
- Subjects who have taken cyclophosphamide, mycophenolate mofetil (MMF)/mycophenolic acid (MPA) or leflunomide within 6 months of randomization (Day 1).
- Subjects who have taken methotrexate within 12 weeks of randomization.
- Subjects who have taken cyclosporine (systemic), azathioprine, tacrolimus, tofacitinib, mizoribine, actarit, or bucillamine within 4 weeks of randomization (Day 1).
- Subjects who have taken Intravenous Immunoglobulin (IVIG) within 4 weeks of randomization (Day 1).
- Subjects who have taken diquafosol or ophthalmic rebamipide within 4 weeks prior to randomization (Day 1)
- Subjects who have taken a tricyclic antidepressant drug within 4 weeks prior to randomization (Day 1).

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for IM101603					
Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Abatacept Injection 125 mg/syringe	125 mg/mL	IP	Blinded	4 syringes per kit Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated 2 – 8 °C Protect from light Protect from freezing
Placebo for abatacept Injection	N/A	IP	Blinded	4 syringes per kit Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated 2 – 8 °C Protect from light Protect from freezing
Abatacept Injection 125 mg/syringe	125 mg/mL	IP	Open-Label	4 syringes per kit Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated 2 – 8 °C Protect from light Protect from freezing

Study Assessments: See [Section 5](#) of the protocol for detailed information regarding study assessments.

Study assessments include the ESSDAI, ESSPRI, whole stimulated and unstimulated salivary flow, ocular staining score, tear break-up time, Schirmer’s test, tender and swollen joint counts, physician global assessment, subject global assessment, numeric rating scale for mouth dryness and for eye dryness, PROMIS Fatigue scale, SF-36, and FSFI.

Statistical Considerations:

Sample Size: A hierarchical testing procedure will be applied for the primary endpoint (mean change from baseline in ESSDAI at Day 169) and the 2 key secondary endpoints (mean change from baseline in ESSPRI at Day 169 and mean change from baseline in the stimulated whole salivary flow at Day 169) to ensure the preservation of the overall type I error of 5%. A sample size of 172 patients (86 per arm) will achieve 98% power to detect a treatment difference of 3 in changes from baseline in ESSDAI at Day 169 between the abatacept and placebo group using a two-sided t-test with a significance level (alpha) of 0.05 and assuming a common SD of 4.8. The sample size of 86 patients per arm will achieve 90% power to detect a treatment difference of 1 in change from baseline in ESSPRI at Day 169 assuming a common SD of 2 and 91% power to detect a treatment difference in mean change from baseline of 0.165 mL/min in salivary flow in subjects with a residual salivary flow of at least 0.1 mL/min at screening and baseline assuming a common SD of 0.275. Taking into account the hierarchical testing procedure, the overall power for the primary and the 2 key secondary endpoints is at least 80%.

Endpoints:

Primary Endpoint

The mean change from baseline (Day 1) in ESSDAI at Day 169.

Secondary Endpoint(s)

Key Secondary Endpoints

- The mean change from baseline in ESSPRI at Day 169
- The mean change from baseline in the stimulated whole salivary flow at Day 169 among subjects with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline.

Other Secondary Endpoints

- The mean change from baseline at all measured time points up to Day 169 in the DAS28-CRP among those with a tender plus swollen joint count ≥ 3 at baseline, among those with a tender plus swollen joint count < 3 at baseline and in the full population.
- The mean change from baseline at all measured time points up to Day 169 in the individual components of DAS28-CRP among those with a tender plus swollen joint count ≥ 3 at baseline, among those with a tender plus swollen joint count < 3 at baseline and in the full population.
- Proportion of subjects who achieve a minimally clinically important change (of at least 3 points) in the ESSDAI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- Proportion of subjects who achieve a minimally clinically important change (of at least 5 points) in the ESSDAI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- Proportion of subjects who achieve a minimally clinically important change (of at least 1 point) in the ESSPRI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline at all measured time points up to Day 169 in the ESSDAI in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline at all measured time points up to Day 169 in the ESSPRI in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline in the individual components of the ESSDAI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline in the individual components of the ESSPRI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline in Schirmer's test at all measured time points up to Day 169.

- The mean change from baseline in ocular staining score at all measured time points up to Day 169.
- The mean change from baseline in tear break-up time at all measured time points up to Day 169.
- The mean change from baseline in unstimulated whole salivary flow at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline in stimulated whole salivary flow at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline in patient symptoms using the Numeric Rating Scale (NRS) for mouth dryness at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline in patient symptoms using the Numeric Rating Scale (NRS) for eye dryness at all measured time points up to Day 169.
- The mean change from baseline in subject assessment of disease activity at all measured time points up to Day 169.
- The mean change from baseline in the physician global assessment of disease activity at all measured time points up to Day 169.
- The mean change from baseline in patient fatigue using PROMIS Fatigue assessment at all measured time points up to Day 169.
- The mean change from baseline in female sexual function using the FSFI at all measured time points up to Day 169.
- The mean change from baseline in patient function using SF-36 at all measured time points up to Day 169.
- Geometric mean of trough concentration (C_{min}) of abatacept at all measured time points.
- Proportion of subjects with at least one positive immunogenicity response up to Day 169 and during 3 months follow up (for subjects who discontinue during the 6-months double-blind) and during the cumulative abatacept period and 3 months follow-up (for the cumulative abatacept population).
- Safety (proportion of subjects with adverse events, deaths, SAEs, and AEs leading to discontinuation and proportion of laboratory marked abnormalities) up to Day 169 and during the cumulative abatacept period and follow-up period.

Analyses:

Efficacy Analyses

Changes from baseline over time for ESSDAI will be analyzed using a longitudinal repeated measures analysis. The model will include the fixed categorical effects of treatment, day (is a windowed time point), baseline corticosteroid use, baseline hydroxychloroquine use, stimulated salivary flow, treatment-by-day interaction, baseline corticosteroid use-by-day interaction, baseline hydroxychloroquine use-by-day interaction, stimulated salivary flow-by-day interaction as well as, the continuous fixed covariate of baseline score and baseline score-by-day interaction. An unstructured covariance matrix will be used to represent the correlation of the repeated measures within each subject. The parameter estimations will be based on the assumption of data being missing at random (MAR) and using the method of restrictive maximum likelihood (REML). The difference in adjusted means (LSMEANS)

between abatacept and placebo at the primary time point, Day 169, and corresponding 95% CI and p-value based on the longitudinal repeated measures above will be provided.

A similar longitudinal repeated measures analysis will be provided for the key secondary endpoints, mean change from baseline in ESSPRI and mean change from baseline in the stimulated whole salivary flow and the other secondary efficacy endpoints including changes from baseline.

The binary secondary efficacy endpoints e.g., the proportion of subjects with a decrease in ESSDAI of at least 3 from baseline to Day 169 and the proportion of subjects with a decrease in the ESSPRI of at least 1 to Day 169 will be analyzed with a logistic regression including treatment, corticosteroid use, hydroxychloroquine use, stimulated salivary flow use and baseline value in the model. The odds ratio along with its 95% confidence interval will be provided. A missing responder value at Day 169 due to discontinuation or for other reasons will be imputed as a non-responder.

Safety Analyses

The proportion (%) of subjects with adverse events, deaths, SAEs, and AEs leading to discontinuation and subjects with laboratory marked abnormalities up to start of the open label period for subjects continuing in the OL or up to last dosing date +56 days for subjects discontinuing during double blind will be provided per treatment group using the as-treated population. These safety endpoints will also be summarized during the cumulative abatacept period (from the first day of abatacept treatment in the study up to 56 days after the last abatacept treatment in the study) for the cumulative abatacept population. For the cumulative abatacept population all subjects will be combined in one group.

The proportion (%) of subjects with at least one positive immunogenicity response (relative to baseline) up to Day 169 and 3 months follow up (for subjects who discontinue in the Day 169 short-term period) and during the cumulative abatacept period and 3 months follow-up (for the cumulative abatacept population) will be summarized using the immunogenicity population.

TABLE OF CONTENTS

TITLE PAGE	1
DOCUMENT HISTORY	3
SYNOPSIS.....	4
TABLE OF CONTENTS.....	12
1	16
1.1.1 <i>Pathophysiology of Sjögren’s Syndrome</i>	16
1.1.2 <i>Mechanism of Action of Abatacept</i>	17
1.2 Research Hypothesis	19
1.3 Objectives(s)	19
1.3.1 <i>Primary Objectives</i>	19
1.3.2 <i>Secondary Objectives</i>	19
1.4 Product Development Background	21
1.5 Overall Risk/Benefit Assessment	22
2 ETHICAL CONSIDERATIONS.....	22
2.1 Good Clinical Practice	22
2.2 Institutional Review Board/Independent Ethics Committee.....	23
2.3 Informed Consent.....	23
3 INVESTIGATIONAL PLAN.....	24
3.1.1 <i>Screening Period</i>	25
3.1.2 <i>Double-Blind Treatment Period (Day 1 to Day 169)</i>	26
3.1.3 <i>Open Label Extension (Day 169 to Day 365)</i>	26
3.1.4 <i>Post-Treatment Follow-up Period</i>	27
3.2 Post Study Access to Therapy.....	27
3.3 Study Population.....	27
3.3.1 <i>Inclusion Criteria</i>	27
3.3.2 <i>Exclusion Criteria</i>	29
3.3.3 <i>Women of Childbearing Potential</i>	32
3.4.1 <i>Prohibited and/or Restricted Treatments</i>	33
3.4.1.1 <i>Prohibited Treatments While Receiving Treatment with Study Drug</i>	33
3.4.1.2 <i>Restricted Treatments While Receiving Treatment with Study Drug</i>	33
3.4.2 <i>Other Restrictions and Precautions</i>	35
3.4.2.1 <i>Immunizations</i>	36
3.4.2.2 <i>Infectious Complications</i>	36
3.4.2.3 <i>Management of Possible Acute Hypersensitivity Reactions</i>	36
3.5 Discontinuation of Study Therapy	37
3.6 Discontinuation from the Study	38

3.7 Post Study Drug Study Follow up	38
3.7.1 <i>Withdrawal of Consent</i>	38
3.7.2 <i>Lost to Follow-Up</i>	38
4 STUDY DRUG.....	40
4.1 Investigational Product	41
4.2 Non-investigational Product	41
4.3 Storage of Study Drug	41
4.4 Method of Assigning Subject Identification.....	42
4.5 Selection and Timing of Dose for Each Subject.....	42
4.5.1 <i>Abatacept Treatment</i>	42
4.5.2 <i>Dose Modifications</i>	43
4.5.2.1 <i>Dose Modifications in the Absence of Adverse Events</i>	43
4.5.2.2 <i>Dose Modifications Due to Adverse Events</i>	43
4.6 Blinding/Unblinding	43
4.7 Treatment Compliance.....	44
4.8 Destruction or Return of Investigational Product	44
4.9 Retained Samples for Bioavailability / Bioequivalence	45
5 STUDY ASSESSMENTS AND PROCEDURES.....	46
5.1 Flow Chart/Time and Events Schedule.....	46
5.1.1 <i>Retesting During Screening or Lead-in Period</i>	59
5.1.2 <i>Order of Study Assessments</i>	59
5.1.3 <i>Study Drug Administration Window</i>	60
5.2 Study Materials	60
5.3 Safety Assessments.....	61
5.3.1 <i>Imaging Assessment for the Study</i>	61
5.3.2 <i>Physical Examination</i>	61
5.3.3 <i>Chest X-ray</i>	61
5.3.4 <i>Physical Measurements</i>	62
5.3.5 <i>Vital Signs</i>	62
5.3.6 <i>TB Screening</i>	62
5.3.7 <i>Laboratory Assessments</i>	62
5.3.7.1 <i>Hematology</i>	62
5.3.7.2 <i>Blood Chemistry</i>	62
5.3.7.3 <i>Immunology</i>	63
5.3.7.4 <i>Urinalysis</i>	63
5.3.7.5 <i>Hepatitis Screen</i>	63
5.3.7.6 <i>Pregnancy Tests</i>	63
5.3.7.7 <i>HIV Testing</i>	64
5.3.7.8 <i>FSH Testing</i>	64
5.4 Efficacy Assessments.....	64
5.4.1 <i>Primary Efficacy Assessment</i>	64
5.4.2 <i>Salivary Flow</i>	65
5.4.3 <i>Ophthalmologic Assessments</i>	66
5.4.4 <i>Physician’s Global Assessment of Disease Activity</i>	67
5.4.5 <i>Joint Count Assessments</i>	67
5.5 Pharmacokinetic Assessments	67

5.5.1 Pharmacokinetic: Blood Collection.....	67
5.5.2 Pharmacokinetic: Blood Sample Processing, Labeling and Shipping	69
5.5.3 Pharmacokinetic Sample Analysis.....	69
5.5.4 Pharmacokinetic Evaluation.....	69
5.6 Biomarker Assessments	69
.....	69
.....	70
.....	70
.....	70
.....	71
.....	71
.....	71
.....	71
5.7 Outcomes Research Assessments	72
5.8 Other Assessments	73
5.8.1 Immunogenicity Assessments	73
5.8.1.1 Immunogenicity: Blood Collection	73
5.8.1.2 Immunogenicity: Blood Sample Processing, Labeling, and Shipping	74
5.8.1.3 Immunogenicity: Sample Analysis	74
5.9 Labial Salivary Gland or Parotid Gland Biopsy (Substudy).....	74
6 ADVERSE EVENTS.....	74
6.1 Serious Adverse Events	75
6.1.1 Serious Adverse Event Collection and Reporting.....	76
6.2 Nonserious Adverse Events	77
6.2.1 Nonserious Adverse Event Collection and Reporting.....	77
6.3 Laboratory Test Result Abnormalities.....	77
6.4 Pregnancy.....	78
6.5 Overdose	78
6.6 Potential Drug Induced Liver Injury (DILI)	78
6.7 Other Safety Considerations	78
7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES	79
8 STATISTICAL CONSIDERATIONS.....	79
8.1 Sample Size Determination.....	79
8.2 Populations for Analyses	80
8.3 Endpoints	80
8.3.1 Primary Endpoint(s)	80
8.3.2 Secondary Endpoint(s).....	80
.....	83
8.4 Analyses.....	83
8.4.1 Demographics and Baseline Characteristics.....	83
8.4.2 Efficacy Analyses	83
8.4.3 Safety Analyses.....	84
8.4.4 Pharmacokinetic Analyses	85
.....	85

1.1.1 Pathophysiology of Sjögren's Syndrome

The salivary glands in pSS are infiltrated by T- and B-lymphocytes as well as by non-lymphoid cells. Epithelial cells of striated ducts are likely the targets of the autoimmune attack. Within the glandular tissue, inflammatory infiltrates can be organized as ectopic lymphoid tissues with segregated T- and B-cell areas, germinal center-like structures and high endothelial venules. B cell hyper-reactivity is a hallmark of pSS.⁶ Autoantibodies directed against the Ro/SSA and

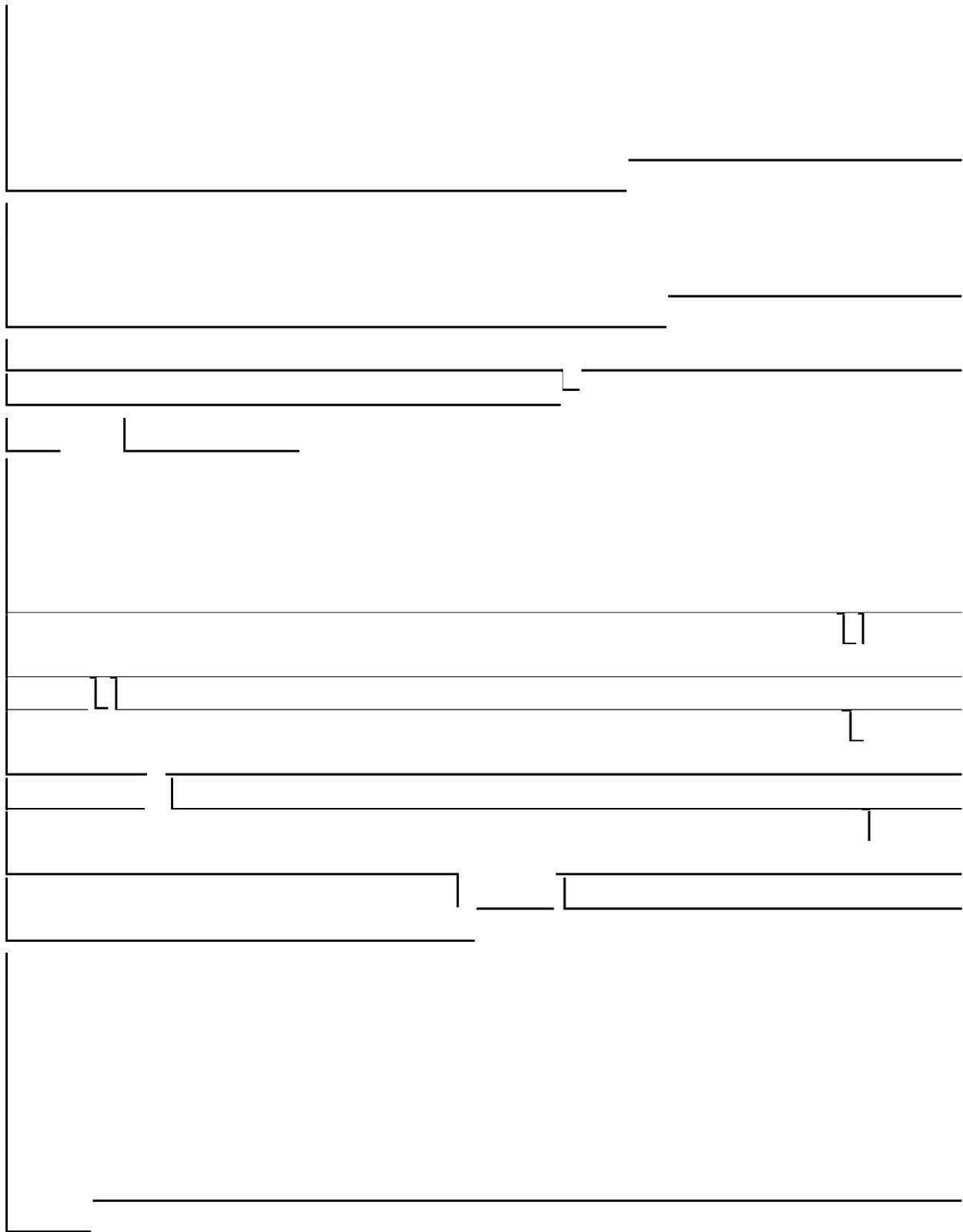
La/SSB ribonucleoproteins and/or the autoantibody, RF, are frequently found in pSS patients, together with elevated levels of serum immunoglobulins (hypergammaglobulinemia). However, the pathogenic role for autoantibodies remains unclear. Effector CD4+ Th cells are known to be required for humoral immune responses to these protein autoantigens.⁷ These CD4+ Th (T follicular helper cells or Tfh) cells are essential for the generation of plasma cells, as well as for the formation of memory cells in the germinal center-like structures in the salivary glands.

[Redacted]

pSS.

[Redacted]

[Redacted]



1.2 Research Hypothesis

Abatacept 125 mg, administered subcutaneously (SC) will have greater efficacy than placebo in subjects with moderately to severely active pSS as assessed by the mean change from baseline in the ESSDAI score after Day 169 of treatment.

1.3 Objectives(s)

1.3.1 Primary Objectives

To compare the mean change from baseline (Day 1) to Day 169 in ESSDAI of abatacept versus placebo in subjects with moderate to severe pSS.

1.3.2 Secondary Objectives

Key Secondary Objectives

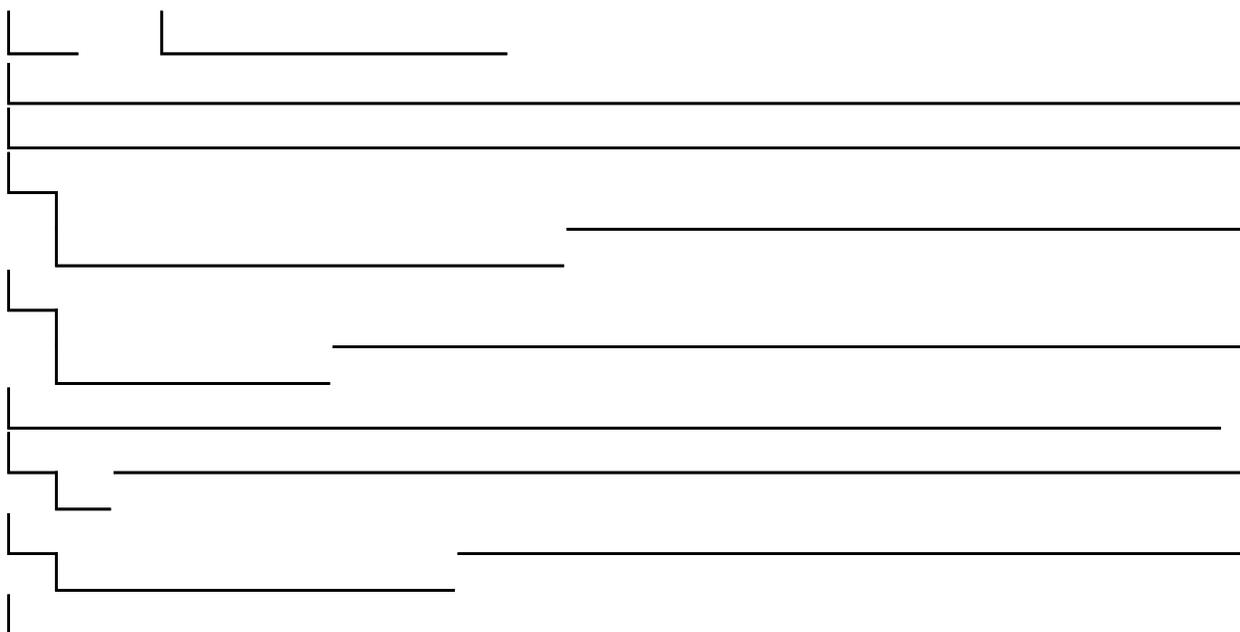
- 1) To compare the mean change from baseline (Day 1) to Day 169 in ESSPRI of abatacept versus placebo in subjects with moderate to severe pSS.
- 2) To compare the mean change from baseline (Day 1) to Day 169 in the stimulated whole salivary flow of abatacept versus placebo in those subjects with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline.

Other Secondary Objectives

- 1) To assess the mean change from baseline at all measured time points up to Day 169 in DAS28-CRP among those with a tender joint count plus swollen joint count of at least 3 at baseline, among those with a tender joint count plus swollen joint count of less than 3 at baseline, and in the full population.
- 2) To assess the mean change from baseline at all measured time points up to Day 169 in the individual components of DAS28-CRP among those with a tender plus swollen joint count of at least 3 at baseline, among those with a tender joint count plus swollen joint count of less than 3, and in the full population.
- 3) To assess the proportion of subjects who achieve a minimally clinically important improvement in ESSDAI (≥ 3) at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- 4) To assess the proportion of subjects who achieve a minimally clinically important improvement in ESSDAI (≥ 5) at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- 5) To assess the proportion of subjects who achieve a minimally clinically important improvement in ESSPRI (≥ 1) at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.

- 6) To assess the mean change from baseline at all measured time points up to Day 169 in ESSDAI in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- 7) To assess the mean change from baseline at all measured time points up to Day 169 in ESSPRI in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- 8) To assess the mean change from baseline in the individual components of the ESSDAI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- 9) To assess the mean change from baseline in the individual components of the ESSPRI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- 10) To assess the mean change from baseline in Schirmer's test at all measured time points up to Day 169.
- 11) To assess the mean change from baseline in ocular staining score at all measured time points up to Day 169.
- 12) To assess the mean change from baseline in tear break-up time at all measured time points up to Day 169.
- 13) To assess the mean change from baseline in unstimulated whole salivary flow at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- 14) To assess the mean change from baseline in stimulated whole salivary flow at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- 15) To assess the change in patient symptoms using the Numeric Rating Scale (NRS) for mouth dryness at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- 16) To assess the mean change in patient symptoms using the Numeric Rating Scale (NRS) for eye dryness at all measured time points up to Day 169.
- 17) To assess the mean change in patient symptoms using the patient global assessment of disease activity at all measured time points up to Day 169.
- 18) To assess the mean change in the physician global assessment at all measured time points up to Day 169.
- 19) To assess the mean change in patient fatigue using PROMIS Fatigue assessment at all measured time points up to Day 169.

- 20) To assess the mean change in female sexual function using the Female Sexual Function Index (FSFI) at all measured time points up to Day 169.
- 21) To assess the mean change in patient quality of life using the SF-36 at all measured time points up to Day 169.
- 22) To assess safety and immunogenicity of abatacept.
- 23) To assess the pharmacokinetics of abatacept.



1.4 Product Development Background

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

Abatacept is the first and currently the only approved drug in a class of agents termed, “selective costimulation modulators”. Activation of naive T cells during an immune response requires 2 stimuli from antigen presenting cells (APC). The first signal is antigen specific and is mediated through the T cell receptor. The second or costimulatory signal is not antigen specific and is delivered following the engagement of a costimulatory ligand on the APC with a cognate receptor on the T cell. A key co stimulatory receptor on T cells is CD28. CD28 is constitutively expressed on resting T cells and binds to both B7-1 (CD80) and B7-2 (CD86) on the APC.^{14,15,16,17} A costimulatory signal is required for the full antigen-induced activation of naive T cells and may be required for the survival of auto-immune effector memory T cells.^{18,19} Abatacept binds specifically to B7-1 and B7-2 and hence inhibits the CD28-mediated co stimulation of T cells by these molecules.

1.5 Overall Risk/Benefit Assessment

Clinical investigation of abatacept has been underway since 15-Aug-1995. Over 15,000 subjects have enrolled in clinical trials, and an estimated 10,771 of these subjects have been exposed to abatacept IV or SC regimens, with the majority of subjects with diagnoses of RA (8,345) or lupus (557).²⁰

There is extensive safety experience with IV and SC abatacept in adults with RA. The safety profile of abatacept is well established and favorable.²¹ The total patient-years (p-y) of exposure in RA, as well as consistent safety profiles in non-RA clinical studies provides a high level of confidence in the assessment of the acceptable safety profile associated with abatacept.

Primary Sjögren's syndrome shares features with other autoimmune diseases, such as systemic lupus erythematosus (SLE). Safety data are available for IV abatacept use in 121 adult subjects with SLE from IM101042 (placebo subjects n = 59).²² This study was a 12-month exploratory Phase 2 study of abatacept at 10 mg/kg IV monthly in SLE subjects experiencing flares with active manifestations of polyarthritis, discoid lesions, or pleuritis/pericarditis. Safety data are also available for IV abatacept in 228 adult subjects with lupus nephritis (LN) in the Phase 2, dose-ranging, placebo-controlled IM101075 study (placebo subjects n = 74).²³ The study was terminated prematurely by the Sponsor during the long term extension period because the main primary and secondary efficacy endpoints were not met for abatacept at the end of the double-blind short term period.^{23,24} The overall safety profile of IV abatacept in SLE and LN did not indicate a different safety profile than in RA.

Two open-label, single-center pilot studies have suggested efficacy of abatacept ~10 mg/kg administered intravenously in pSS with a well-tolerated safety profile (N = 11, N = 15), as noted above.^{4,5}

Based on the safety data of abatacept in RA, SLE, LN and pSS, abatacept is expected to be well-tolerated in this pSS patient population. The mechanism of action of abatacept, as well as its proven efficacy in RA and its efficacy in two different open-label pilot studies in pSS, suggests potential efficacy for patients with pSS. There are currently no approved therapies to manage the systemic manifestations of pSS, and therefore the unmet need is high.

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. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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 (eg, 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 (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS 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 (eg, 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 to 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 (ie, 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 subject or 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.

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 randomized, double-blind, placebo controlled study in subjects who have been diagnosed with active, moderate to severe, primary Sjögren's Syndrome based on the proposed 2015 ACR/EULAR Classification Criteria for pSS and have an ESSDAI disease activity score of at least 5 at screening. The study consists of a 28-day screening period, followed by a 169-day double-blind period, a 197-day open-label abatacept period and a subsequent 84-day follow-up period.

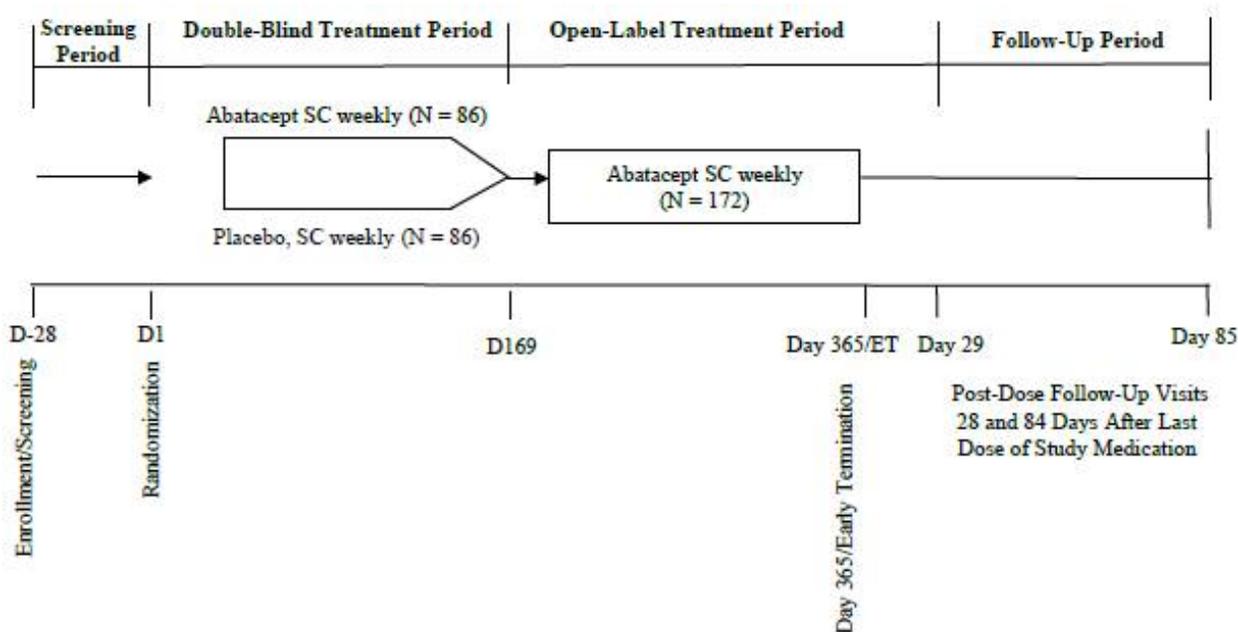
The investigator should accept only those subjects who give a reasonable indication that they will complete the double-blind period of the study. All subjects who discontinue investigational product during the Double-Blind Treatment Period should continue to comply with protocol specified procedures as outlined in [Section 5](#) - Study Assessments and Procedures. 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 (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

Subjects who discontinue treatment with study drug during the Double-Blind Treatment Period must continue to be assessed for all efficacy measures and for safety at all remaining double-blind study visits through Week 24 (Day 169) (see [Table 5.1-2](#)). In addition, subjects who discontinue treatment with the study drug will require visits to assess safety and immunogenicity

28 and 84 days after the last dose of study drug. If these visits will fall within ± 14 days of a scheduled study visit, only an additional laboratory assessment (immunogenicity) may need to be performed at the scheduled study visit. Otherwise, the 28 Day and/or 84 Day After Last Dose of Study Medication follow-up visits need to be performed at the appropriate time.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



A pharmacokinetic sampling sub-study (approximately 40 subjects) will be conducted during the double-blind treatment period to collect additional PK samples from those subjects that sign consent to participate. An optional labial salivary gland or parotid gland biopsy sub-study (Day 1 and Day 169) will also be conducted.

3.1.1 Screening Period

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity and safety assessments. The screening phase will last for a minimum of 7 days and a maximum of 28 days. Subjects who experience an acute infection or initiate treatment for latent TB may extend the screening period to 56 days. If the screening period extends beyond 28 days, a second screening visit will be required within 28 days prior to randomization.

Eligible subjects will have been diagnosed with Sjögren’s syndrome based on the proposed 2015 ACR/EULAR Classification Criteria ([Appendix 3](#)) and will have an ESSDAI score of at least five points at screening ([Appendix 6](#)). Subjects must be anti-SSA/Ro positive at screening and at least 124 subjects (72%) must have a stimulated salivary flow of at least 0.1 mL/min at screening and randomization.

Subjects taking hydroxychloroquine are permitted to continue this medication provided that the therapy has been taken for at least 12 weeks and that the dose is stable for at least 4 weeks prior to randomization and remains stable throughout the study. Decreases in dose or discontinuation is permitted for adverse events or intolerance.

Subjects receiving oral corticosteroids must be on a stable dose and at the equivalent of ≤ 10 mg prednisone daily for at least 4 weeks prior to randomization. Subjects may not have received an IM, IV or IA administration of a corticosteroid within 4 weeks prior to randomization.

Stable doses of pilocarpine, cevimeline, and cyclosporine eye preparations, as well as artificial tears and saliva are permitted, but must not be used for an appropriate period prior to salivary and ocular testing. See [Section 3.4.1.2](#) for specified times for each assessment.

Approximately 172 subjects in total will be randomized in a 1:1 ratio to 125 mg SC weekly of abatacept or placebo (86 subjects per arm). Randomization will be stratified globally by current use of corticosteroids, current use of hydroxychloroquine, and by stimulated salivary flow (< 0.1 mL/min, ≥ 0.1 mL/min).

3.1.2 Double-Blind Treatment Period (Day 1 to Day 169)

On day 1, subjects will be randomized to one of two blinded parallel treatment arms in a 1:1 ratio:

- 1) Abatacept for SC injection 125mg/mL in 1 mL pre-filled syringe
- 2) Placebo for abatacept for SC injection in 1 mL pre-filled syringe

The duration of the treatment period is 169 days.

Abatacept or matching placebo administration:

Abatacept (125 mg) or matching placebo will be administered subcutaneously (SC) once per week. On Day 1, subjects and/or personal caregivers will be trained in self-administration of SC injections using pre-filled syringes. All subsequent injections will be self-administered or administered by a personal caregiver, and should not be administered by the physician or medical staff at the study site. Medical staff can act as a caregiver only when the subject cannot self-administer and does not have access to a personal caregiver, see [Section 4.5.1](#).

On “Office Visit” days, SC injections should occur AFTER all assessments, including blood draws for assessment of immunogenicity and drug concentrations. To ensure compliance and to monitor technique “office visit” SC injections should be conducted in the presence of a qualified investigational staff.

3.1.3 Open Label Extension (Day 169 to Day 365)

At the end of the double blind treatment period there will be a 196 day open label extension (OLE). On Day 169 all subjects continuing on treatment (including those subjects who received placebo during the double blind period) will receive open-label abatacept SC, 125 mg weekly to Day 357.

On “Office Visit” days, SC injections should occur AFTER all assessments, including blood draws for assessment of immunogenicity and drug concentrations.

Subjects not wishing to continue on open-label abatacept have the option of discontinuing treatment at the end of the double-blind period and proceeding to the post-treatment follow-up period.

3.1.4 Post-Treatment Follow-up Period

Subjects who discontinue treatment of study drug during the open-label period or complete the study will have two follow-up visits 28 and 84 days after the last treatment visit, to perform safety and laboratory assessments, including immunogenicity testing. Subjects who discontinue treatment with the study drug during the double-blind period will require two visits to assess safety and immunogenicity 28 and 84 days after the last dose of study drug. If these visits are within ± 14 days of a scheduled study visit, only an additional laboratory assessment (immunogenicity) needs to be performed at the scheduled study visit. Otherwise, the follow-up visits as described in the Time & Events table ([Table 5.1-6](#)) need to be performed.

The start of the trial is defined as the date the first subject signs the informed consent. End of trial is defined as the last visit or scheduled procedure shown in the Time & Events schedule for the last subject. The study will continue beyond primary endpoint collection until the End of Trial.

3.2 Post Study Access to Therapy

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment. Study treatment 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 treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of abatacept 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 regulations.

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 and has signed informed consent.

2. Target Population

- a. Subjects must meet the proposed 2015 ACR/EULAR Classification Criteria for SS (Sjögren’s Syndrome) ([Appendix 3](#)), as specified for pSS (primary Sjögren’s Syndrome).

- i. If a prior labial salivary or parotid gland biopsy was performed, information will be reported in the CRF and the report should be obtained for the source documents.
- b. Subjects should have pSS that is refractory to symptomatic or local therapy (eg, NSAIDs).
- c. ESSDAI \geq 5 at screening.
- d. Positive anti-SSA/Ro at screening.
- e. Stimulated salivary flow of at least 0.1 mL/min at screening and randomization in at least 124 subjects (72%). Enrollment of subjects with less than 0.1 mL/min of stimulated salivary flow at screening and/or randomization may be closed after 48 of such subjects are randomized.
- f. Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, a “screen failure”, the subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented and will receive a new PID.

3. Age and Reproductive Status

- a. Males and Females, ages \geq 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. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) (abatacept/placebo) 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. Males 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/placebo) 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.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

- a. Subjects who have a systemic autoimmune disease other than Sjögren's syndrome (SS), such as RA, SLE, or systemic sclerosis, that can better explain the majority of the symptoms (ie, secondary Sjögren's syndrome).
- b. Subjects who have another autoimmune disease or inflammatory condition that could interfere with assessment of response of primary SS (pSS) to therapy (eg, systemic sclerosis, inflammatory bowel disease, gout).
- c. Subjects with any other medical condition associated with clinical features overlapping those of pSS or that would interfere with interpretation of results, including but not limited to a history of head and neck radiation treatment, sarcoidosis, amyloidosis, graft-versus-host disease, hepatitis C, acquired immunodeficiency syndrome, and IgG4-related disease.
- d. Subjects with severe fibromyalgia that could interfere with the assessment of response of pSS to therapy.
- e. Active life-threatening or organ-threatening complications of SS disease at the time of screening based on investigator evaluation including but not restricted to the following:
 - i. Vasculitis with renal, digestive, cardiac, pulmonary or central nervous system (CNS) involvement characterized as severe (note: cutaneous vasculitis is allowed)
 - ii. Active CNS or peripheral nervous system (PNS) involvement requiring high dose steroids
 - iii. Severe renal involvement, eg, GFR < 60 mL/min, a serum creatinine > 2 mg/dL, or proteinuria > 3 g/day,
 - iv. Severe pulmonary involvement, eg, shortness of breath at rest, or pulmonary function tests demonstrating DLCO < 40% or FVC < 60%
 - v. Severe muscular involvement requiring high dose steroids
 - vi. Lymphoma

2. Medical History and Concurrent Diseases

- a. 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 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.
- b. 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.
- c. Subjects with history of chronic or recurrent bacterial infection (such as chronic pyelonephritis, osteomyelitis, and bronchiectasis etc.).
- d. Subjects who have a history of systemic fungal infections (such as histoplasmosis, blastomycosis, or coccidiomycosis).
- e. Subjects with history of recurrent herpes zoster (more than 1 episode) 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 screening.
- f. Subjects with history of Human Immunodeficiency Virus (HIV) infection or who test positive for HIV at screening.
- g. Subjects with a history of primary immunodeficiency.
- h. Subjects who have a present malignancy or 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. Subjects with a history of lymphoma
- i. Current clinical findings of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, psychiatric, cardiac, endocrine, 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.
- j. 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 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 may be enrolled at the investigator's discretion.

- k. Subjects who have undergone a major surgical procedure within the 60 days prior to randomization.
- l. 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.
- m. Subjects who are impaired, incapacitated, or incapable of completing study-related assessments.

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.
- 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) < 2,500/mm³ (2.5×10^9 /L)
- e. Lymphocytes < 500/mm³ (0.5×10^9 /L)
- f. Platelets < 50,000/mm³ (50×10^9 /L)
- g. Subjects with serum ALT or AST > 3 times upper limit of normal unless in the judgment of the investigator the elevation is explicitly related to pSS and does not pose a risk to participation in the study.
- h. Any 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 and/or its excipients

5. Prohibited Treatments and/or Therapies

- a. Subjects who have previously been exposed to abatacept or anti-CD28 therapy.
- b. Subjects who have received IV, IM, SC or intra-articular corticosteroids within 4 weeks of randomization (Day 1).
- c. Subjects who have taken rituximab within 12 months prior to randomization (Day 1).
- d. Subjects who have taken belimumab within 12 weeks prior to randomization (Day 1).
- e. Subjects who have taken a biologic therapy other than rituximab or belimumab or any other investigational therapy within 12 weeks or 5 half-lives prior to randomization (Day 1), whichever is longer.
- f. Subjects who have taken cyclophosphamide, mycophenolate mofetil (MMF)/mycophenolic acid (MPA) or leflunomide within 6 months of randomization (Day 1).
- g. Subjects who have taken methotrexate within 12 weeks of randomization (Day 1).

- h. Subjects who have taken cyclosporine (systemic), azathioprine, tacrolimus, tofacitinib, mizoribine, actarit, or bucillamine within 4 weeks of randomization (Day 1).
- i. Subjects who have taken Intravenous Immunoglobulin (IVIG) within 4 weeks of randomization (Day 1).
- j. Subjects who have taken diquafosol or ophthalmic rebamipide within 4 weeks prior to randomization (Day 1).
- k. Subjects who have taken a tricyclic antidepressant drug within 4 weeks prior to randomization (Day 1).
- l. Subjects are not permitted to have new installation of lacrimal punctum plugs within 4 weeks of randomization (Day 1). Subjects with existing lacrimal punctum plugs are permitted to enroll, and have these plugs replaced as necessary during the study.

6. Other Exclusion Criteria

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

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.

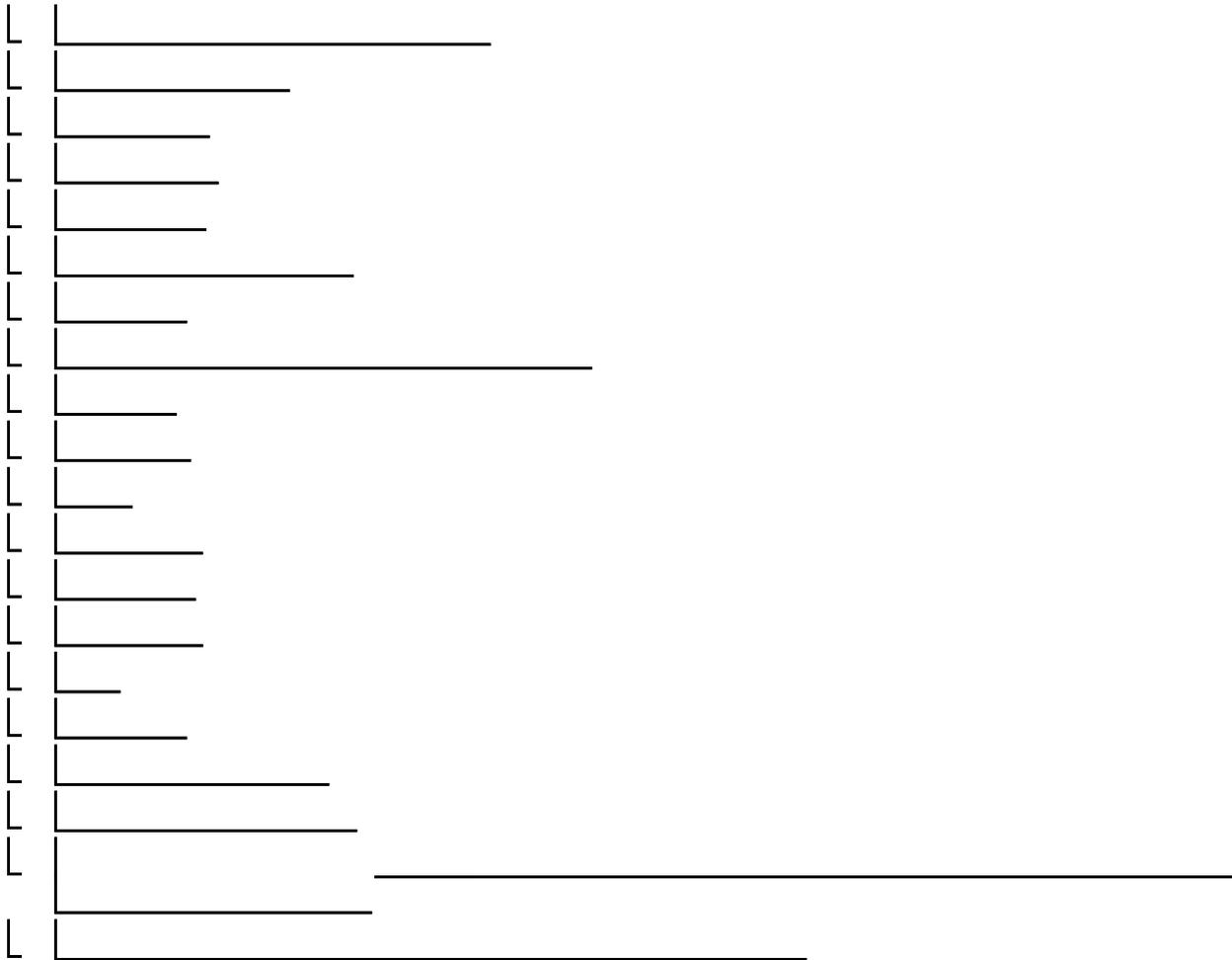
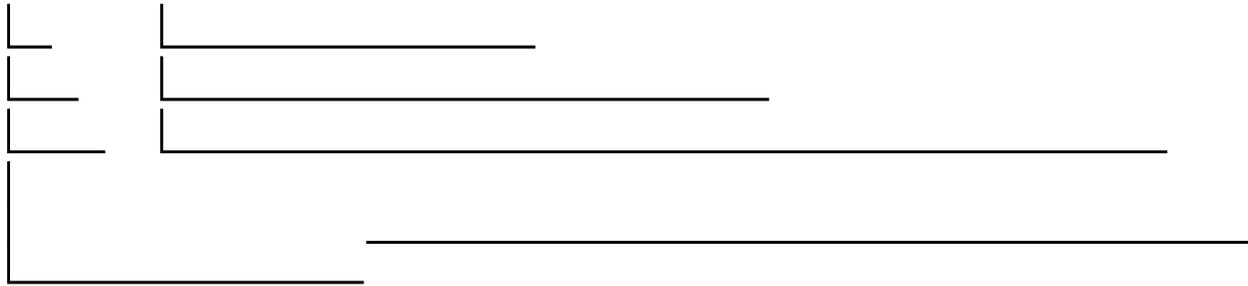
3.3.3 *Women of Childbearing Potential*

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.



Double-blind Period

Subjects are permitted to continue oral corticosteroids at doses of less than or equal to prednisone 10 mg daily (or equivalent) provided that the dose is stable for at least 4 weeks prior to randomization and remains stable throughout the double-blind period. During the double-blind period, decrease in dose or discontinuation of oral corticosteroids is permitted only for adverse events or intolerance. IM, IV, SC and intra-articular corticosteroids are not permitted. Topical corticosteroids are permitted throughout the study.

Open-label Period

During the open-label period, oral corticosteroids at a dose of prednisone, up to 10 mg daily, or equivalent, may be initiated. The dose of oral corticosteroids may be decreased for any reason, but the dose may not be increased above prednisone 10 mg daily (or equivalent). Intra-articular corticosteroids are permitted, but IM, IV and SC corticosteroids are not permitted. Topical corticosteroids are permitted throughout the study.

Analgesics and NSAIDs:

- NSAIDs and analgesics (including topical NSAIDs) are not permitted within 12 hours before a joint assessment
- During the double-blind period for subjects on study therapy, NSAID doses should remain stable, as assessed by the Investigator, with the exception of decreases being permitted due to related AEs, such as gastric toxicity.
- Analgesics
 - Acetaminophen (paracetamol) permitted if
 - ◆ Average dose of ≤ 3 g/day
 - ◆ No single dose exceeding 1 g

NOTE: combination products including acetaminophen and narcotic analgesics (eg, acetaminophen with codeine phosphate, acetaminophen with propoxyphene napsylate, acetaminophen with oxycodone HCl, acetaminophen with hydrocodone bitartrate, etc.) are allowed provided the acetaminophen component dosage is accounted for in the maximum of 3 g/day.

- Narcotic analgesics must not exceed 30 mg/day of morphine or its equivalent.
- Tramadol, gabapentin, and pregabalin are allowed but doses must be stable throughout double blind period for subjects on study therapy.

3.4.2.1 Immunizations

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

Due to the risk of infection, vaccination of subjects with any live vaccine is absolutely contraindicated during the study drug treatment period of the study, as is the administration of LIVE oral polio vaccine to household contacts. The Center for Disease Control Advisory Committee on Immunization Practices (CDC ACIP) recommends that subjects should not be administered a live virus vaccination for at least 3 months after discontinuing high dose corticosteroid therapy (defined as more than 20 mg of prednisone per day for more than 2 weeks). In view of the long half-life of abatacept, study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication.

3.4.2.2 Infectious Complications

Subjects who develop significant infectious complications during the study should be treated appropriately and have study medication withheld, and restarted only when clinically resolved and the investigator considers it appropriate.

3.4.2.3 Management of Possible Acute Hypersensitivity Reactions

Hypersensitivity resulting in severe, acute allergic reactions may occur as a result of the protein nature of abatacept. As defined in a recent consensus statement,²⁵ anaphylaxis is highly likely if 2 or more of the following occur rapidly after administration of the study drug (minutes to several hours):

- Involvement of the skin-mucosal tissue (eg generalized hives; itching or flushing; swollen lips, tongue, or uvula).
- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
- Reduced blood pressure (BP) or associated symptoms (eg, hypotonia/collapse, syncope, and incontinence).
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

Sites must be appropriately prepared to handle medical emergencies such as severe hypersensitivity including anaphylaxis. Subjects must be rapidly assessed and stabilized at the site and transferred to an emergency facility as required. If subjects experience symptoms of severe allergic reactions at home, they should be advised to seek immediate medical attention, including a visit to the local emergency facility, as needed. The site will provide emergency contact information to the subject. A blood sample for analysis of anti-abatacept antibodies should be obtained in case of a hypersensitivity reaction.

The decision whether to continue treatment with the study drug will be left to the medical judgment of the investigator. Care should be taken to treat any acute toxicity, expeditiously,

should they occur. Adequate equipment and trained health care personnel should be available to handle medical emergencies when they occur at the site.

3.5 Discontinuation of Study Therapy

Subjects who discontinue treatment with investigational product during the Double-Blind Treatment Period must continue to be assessed for all efficacy measures and for safety at all remaining double-blind study visits through Week 24 (Day 169) (see [Table 5.1-2](#)). Those subjects who discontinue treatment with the study drug during the double-blind period will also require visits to assess safety and immunogenicity at 28 and 84 days after the last dose of study drug. If these visits fall within ± 14 days of a scheduled double-blind study visit, only an additional laboratory assessment (immunogenicity) needs to be performed at the scheduled study visit. Otherwise, the follow-up visits need to be performed.

Subjects who discontinue study drug during the Open-Label Treatment period should comply with protocol specified follow-up procedures as outlined in [Section 5](#). 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
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continuation of study therapy is not in the best interest of the subject
- Pregnancy
- Missed Doses:
 - During the double-blind period, any subject who misses greater than four consecutive doses or greater than eight total doses must be discontinued from study therapy
 - During the open-label period, any subject who misses greater than six consecutive doses or greater than ten total doses must be withdrawn from the study
- Significant non-compliance with protocol (ie, procedures, assessments, medication, etc). The investigator should discuss such issues with the BMS Medical Monitor.
- Use of prohibited medication. The investigator should discuss the use of a prohibited medication with the Medical Monitor prior to withdrawing a subject from study therapy

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 (eg, dose tapering if necessary for subject safety). 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.

The reason for discontinuation of study drug must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Discontinuation from the Study

Subjects MUST discontinue the study for any of the following reasons:

- 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 (eg, infectious disease) illness
- Subject withdraws consent
- Participation in another clinical trial with an investigational product

The reason for discontinuation from the study must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.7 Post Study Drug Study Follow up

Subjects who discontinue study drug may continue to be followed.

Subjects who withdraw consent (according to Section 3.7.1) or are lost to follow-up (according to Section 3.7.2) 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 Assessments and Procedures.

3.7.1 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.

3.7.2 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 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 IM101603:

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Abatacept Injection 125 mg/syringe	125 mg/mL	IP	Blinded	4 syringes per kit Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated 2 – 8 °C Protect from light Protect from freezing
Placebo for abatacept Injection	N/A	IP	Blinded	4 syringes per kit Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated 2 – 8 °C Protect from light Protect from freezing
Abatacept Injection 125 mg/syringe	125 mg/mL	IP	Open-Label	4 syringes per kit Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated 2 – 8 °C Protect from light Protect from freezing

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as 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 (also described in [Table 4-1](#)) are:

- Abatacept for subcutaneous injection 125mg/mL in 1 mL pre-filled syringe
- Placebo for abatacept for subcutaneous injection in 1 mL pre-filled syringe

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.

In this protocol, non-investigational product(s) include, but are not limited to:

- Hydroxychloroquine
- Prednisone or other oral corticosteroids
- NSAIDs and analgesics
- Pilocarpine, cevimeline, cyclosporine eye drops (Restasis®), lifitegrast
- Ocular and oral lubricants
- Topical lubricants (skin emollients)

The Sponsor will not be providing these medications since they are part of subject's standard of care.

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.

4.4 Method of Assigning Subject Identification

At the time of enrollment, immediately after written informed consent is obtained and before any study-related procedures are performed, each subject will be assigned a unique, sequential five-digit number beginning with 00001, 00002, 00003, and so on, for identification throughout the study. This subject number must not be reused for any other subject. The study physician or research coordinator must contact the Central Randomization System to enroll each subject into a centralized database at the time consent is obtained.

After completion of all screening evaluations and concomitant adjustment or stabilization, all eligible subjects will be randomized into the Double-Blind Treatment Phase of the study. 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 on a 1:1 basis to either the abatacept treatment arm or the placebo treatment arm.

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 have been completed, including blood draws.

For subjects participating in the PK sub-study, the sample collection for PK on Day 15 should occur prior to dose administration.

4.5.1 Abatacept Treatment

Abatacept or matching placebo administration:

Abatacept (125 mg) or matching placebo will be administered subcutaneously (SC) once per week. On Day 1, subjects and/or personal caregivers will be trained in self-administration of SC injections using pre-filled syringes. The subject should be able to self-administer the SC injection between office visits or have an office-trained caregiver do so. 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.

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.

On Day 169, all subjects continuing on in the Open-label treatment period will receive abatacept, 125 mg SC, weekly.

4.5.2 Dose Modifications

4.5.2.1 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.

4.5.2.2 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/IWRS).

In cases of accidental unblinding, the Medical Monitor should be contacted and every attempt should be made to preserve the blind.

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

The BMS Bioanalytical Science Department or its designee will be unblinded to the randomized treatment assignments in order to accurately perform sample analysis for the PK and Immunogenicity samples.

4.7 Treatment Compliance

All subjects are expected to receive study therapy as outlined in the protocol. Subjects will use diary cards to document self-injection of study drug between clinic visits. Permitted dose modifications are described in [Section 4.5.2](#). Conditions under which therapy must be discontinued due to non-compliance are outlined in [Section 3.5](#).

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 (eg, 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 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.

Table 5.1-1: Screening Procedural Outline (IM101603)

Procedure	Screening Visit ^a	Screening Visit 2 ^b	Notes
Urinalysis	X		
HBsAg, anti-HBcAb (anti-HBsAb where required)	X		If positive, obtain HBV DNA (see Section 5.3.7.5)
Hepatitis C Antibody	X		If positive, reflex to HCV confirmation such as PCR
HIV	X		Testing performed locally, if required
Anti-Ro Antibody (anti-SSA)	X		
Quantitative Immunoglobulins (IgG, IgA, IgM)	X		
Urine/Serum Pregnancy Test	X	X	WOCBP only, see Appendix 1 for details
<u>Disease Assessments</u>			
ESSDAI	X	X	
Stimulated Salivary Flow	X	X	See Section 5.4.2

^a The duration of the screening period should not exceed 28 days.

^b Subjects that experience an acute infection or initiate treatment for latent TB may extend the screening period to 56 days. Under these circumstances, all screening procedures except subject consenting, IVRS enrollment, height/weight, immunoglobulins, urinalysis, chest x-ray, TB testing, HepB/C and HIV should be repeated prior to randomization.

Table 5.1-2: Double-Blind Treatment Period - Procedural Outline (IM101603)^{a,b}

Procedure	Day 1	Day 29 (Wk 4)	Day 57 (Wk 8)	Day 85 (Wk 12)	Day 113 (Wk 16)	Day 141 (Wk 20)	Day 169 (Wk 24)/ Early Term.	Notes
Quantitative Immunoglobulins (IgG, IgM, IgA)	X	X		X	X		X	
hsCRP	X	X	X	X	X	X	X	
ESR	X	X	X	X	X	X	X	Performed locally, kits provided centrally.
Rheumatoid Factor, IgM-RF	X	X		X	X		X	
β-2-Microglobulin (B2M)	X	X		X	X		X	
Free Light Chain (FLC)	X	X		X	X		X	
Complement (C3, C4, CH50)	X	X		X	X		X	
Anti-Ro Antibody (anti-SSA)	X	X		X	X		X	
Anti-La Antibody (anti-SSB)	X	X		X	X		X	
Anti-centromere Antibody (ACA)	X	X		X	X		X	
Anti-CCP2	X	X		X	X		X	
	L			L			L	
	L						L	
	L			L			L	
	L							
	L						L	
	L			L			L	

Table 5.1-2: Double-Blind Treatment Period - Procedural Outline (IM101603)^{a,b}

Procedure	Day 1	Day 29 (Wk 4)	Day 57 (Wk 8)	Day 85 (Wk 12)	Day 113 (Wk 16)	Day 141 (Wk 20)	Day 169 (Wk 24)/ Early Term.	Notes
<u>Pharmacokinetic (PK) Assessments</u>								
Pharmacokinetic (PK) Sampling	X	X	X	X	X	X	X	Samples collected predose, except for ET. See additional PK sampling for PK sub-study (Table 5.1-5). See more details in Section 5.5.1 .
Immunogenicity (anti-abatacept antibody) testing	X			X			X	Samples collected pre-dose See more details in Section 5.5.1 . Subjects who discontinue treatment with the study drug will require a visit to assess safety and immunogenicity 28 and 84 days after the last dose of study drug. If the visit is within ± 14 days of a scheduled study visit, only an additional laboratory assessment for immunogenicity needs to be performed at the scheduled visit.
<u>Efficacy Assessments</u>								
ESSDAI	X	X	X	X	X	X	X	

Table 5.1-2: Double-Blind Treatment Period - Procedural Outline (IM101603)^{a,b}

Procedure	Day 1	Day 29 (Wk 4)	Day 57 (Wk 8)	Day 85 (Wk 12)	Day 113 (Wk 16)	Day 141 (Wk 20)	Day 169 (Wk 24)/ Early Term.	Notes
Tender (68)/Swollen (66) Joint Count	X	X	X	X	X	X	X	
Physician's Global Assessment of Disease Activity	X	X	X	X	X	X	X	
ESSPRI	X	X	X	X	X	X	X	
PROMIS Fatigue	X	X	X	X	X	X	X	
Subject's Global Assessment of Disease Activity	X	X	X	X	X	X	X	
Mouth (Oral) Dryness (NRS)	X	X	X	X	X	X	X	
Eye (Ocular) Dryness (NRS)	X	X	X	X	X	X	X	
SF-36	X			X			X	
Female Sexual Function Index (FSFI)	X			X			X	
Unstimulated Salivary Flow	X			X			X	See Section 5.4.2
Stimulated Salivary Flow	X			X			X	See Section 5.4.2
Schirmer Test ^c	X			X			X	
Tear Break-Up Time ^c	X			X			X	
Ocular Staining Score ^c	X			X			X	
Study Drug								
Contact IVRS/IWRS	X	X	X	X	X	X		
Train subjects and/or caregiver on how to self-inject and how to fill out the diary cards	X							
Dispense diary cards	X	X	X	X	X	X		

Table 5.1-2: Double-Blind Treatment Period - Procedural Outline (IM101603)^{a,b}

Procedure	Day 1	Day 29 (Wk 4)	Day 57 (Wk 8)	Day 85 (Wk 12)	Day 113 (Wk 16)	Day 141 (Wk 20)	Day 169 (Wk 24)/ Early Term.	Notes
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
Dispense monthly abatacept/placebo	X	X	X	X	X	X		
Reconciliation of abatacept/placebo monthly kits		X	X	X	X	X	X	

^a All visits and procedures during the Double-Blind Treatment Period must occur within ± 3 days of the expected visit

^b All subjects who discontinue study drug during the double-blind period should continue to comply with protocol specified procedures as outlined in [Table 5.1-2](#). 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 (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

^c Procedure to be performed by an ophthalmologist or optometrist experienced in the diagnosis and treatment of Sjögren’s syndrome patients. Eye assessments must be performed within ± 5 days of the study visit. See [Section 5.4.3](#) for additional detail.

Table 5.1-3: Open-Label Treatment Period Procedural Outline (IM101603)^a

Procedure	Day 169 (WK 24) ^b	Day 197 (Wk 28)	Day 225 (Wk 32)	Day 253 (Wk 36)	Day 281 (Wk 40)	Day 309 (Wk 44)	Day 337 (Wk 48)	Day 365 (Wk 52)/ End of Treatment	Notes
ESR		X	X	X	X	X	X	X	Performed locally, kits provided centrally.
Rheumatoid Factor; IgM-RF				X				X	
Free Light Chain (FLC)				X				X	
β-2-Microglobulin (B2M)				X				X	
Complement (C3, C4, CH50)				X				X	
Anti-Ro Antibody (anti-SSA)				X				X	
Anti-La Antibody (anti-SSB)				X				X	
Anti-centromere Antibody (ACA)				X				X	
Anti-CCP2				X				X	
<u>Pharmacokinetic (PK) Assessments</u>									
Pharmacokinetic (PK) Sampling								X	No sample collection at EOT.
Immunogenicity (anti-abatacept antibody) testing								X	No sample collection at EOT.
<u>Biomarker Assessments</u>									
Serum Biomarkers				X				X	See Section 5.6.3
Saliva Biomarkers				X				X	See Section 5.6.4
Blood Immunophenotyping								X	See Section 5.6.5
PBMCs				X				X	See Section 5.6.5

Table 5.1-3: Open-Label Treatment Period Procedural Outline (IM101603)^a

Procedure	Day 169 (WK 24) ^b	Day 197 (Wk 28)	Day 225 (Wk 32)	Day 253 (Wk 36)	Day 281 (Wk 40)	Day 309 (Wk 44)	Day 337 (Wk 48)	Day 365 (Wk 52)/ End of Treatment	Notes
<u>Efficacy Assessments</u>									
ESSDAI		X	X	X	X	X	X	X	
Tender (68)/Swollen (66) Joint Count		X	X	X	X	X	X	X	
Physician's Global Assessment of Disease Activity		X	X	X	X	X	X	X	
ESSPRI		X	X	X	X	X	X	X	
PROMIS Fatigue		X	X	X	X	X	X	X	
Subject's Global Assessment of Disease Activity		X	X	X	X	X	X	X	
Mouth (Oral) dryness (NRS)		X	X	X	X	X	X	X	
Eye (Ocular) dryness (NRS)		X	X	X	X	X	X	X	
SF-36				X				X	
Female Sexual Function Index (FSFI)				X				X	
Unstimulated Salivary Flow				X				X	
Stimulated Salivary Flow				X				X	
Schirmer Test ^c				X				X	
Tear break-up time ^c				X				X	
Ocular staining score ^c				X				X	

Table 5.1-3: Open-Label Treatment Period Procedural Outline (IM101603)^a

Procedure	Day 169 (WK 24) ^b	Day 197 (Wk 28)	Day 225 (Wk 32)	Day 253 (Wk 36)	Day 281 (Wk 40)	Day 309 (Wk 44)	Day 337 (Wk 48)	Day 365 (Wk 52)/ End of Treatment	Notes
Study Drug									
Contact IVRS/IWRS	X	X	X	X	X	X	X		
Dispense diary cards	X	X	X	X	X	X	X		
Collect and review diary cards		X	X	X	X	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 End of Treatment visit
Dispense monthly abatacept kits	X	X	X	X	X	X	X		
Reconciliation of abatacept monthly kits		X	X	X	X	X	X	X	

^a All visits and procedures during the Open-label Treatment Period must occur within ± 3 days of the expected visit

^b Same Day as Double-Blind Day 169

^c Procedure to be performed by an ophthalmologist experienced in the diagnosis and treatment of Sjögren’s syndrome patients. Eye assessments must be performed within ± 5 days of the study visit.

Table 5.1-6: Follow-Up Period Procedural Outline for IM101603 (After Last Dose of Study Medication)^a

Procedure	28 Days	84 Days	Notes
Adverse Events Assessment	X	X	
<u>Laboratory Tests</u>			
Urine/Serum Pregnancy	X	X	
Serum anti-abatacept antibodies	X	X	
Pharmacokinetic (PK) Sampling ^b	X	X	

^a These visits should occur 28 and 84 days after the last dose of study medication. If study medication is discontinued during the Double-Blind Treatment Period and the subject continues to be followed for the scheduled Double-Blind Treatment Period visits these additional visits may not be required.

^b The samples for PK will be evaluated to determine serum abatacept concentration in the event there is a corresponding positive immunogenicity result

5.1.1 Retesting During Screening or Lead-in Period

All screening procedures are to be performed within 4 weeks of the randomization visit except as described below.

Retesting:

A single retest 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 (ie, 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 Period, may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Extended Screening:

Subjects that experience an acute infection or initiate treatment for latent TB may extend the screening period to 56 days, as long as the infection did not require hospitalization or administration of parenteral antibiotics agents. Under these circumstances, all screening procedures except IVRS enrollment, height/weight, chest x-ray, TB testing, HepB/C, HIV, quantitative immunoglobulins, and anti-SSA should be repeated prior to randomization.

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. Laboratory parameters and/or assessments that are included in [Table 5.1-1](#), Screening Procedural Outline, should be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant. The subject will need to sign a new informed consent and be reenrolled 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.

5.1.2 Order of Study Assessments

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

- 1) Patient reported outcomes (PROs) questionnaires
- 2) Salivary Flow
 - a) Unstimulated salivary flow
 - b) Stimulated salivary flow
- 3) Ophthalmologic Assessments - there is a ± 5 day window for the completion of these assessments
 - a) Schirmer test

- b) Tear break-up time
- c) Ocular staining
- 4) AE collection
- 5) Vital signs
- 6) Joint assessments
- 7) Investigator assessments
- 8) Blood draws
- 9) Study Drug Administration

5.1.3 Study Drug Administration Window

Self-administration must be observed for compliance and technique at office visits.

Administration Windows

SC injections of study medication may be administered ± 3 days around 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 assessment indicate an adverse event that, in the judgment of the investigator, could place the subjects at risk with continued administration of study medication, study medication administration should be skipped. 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.

5.2 Study Materials

The following materials will be provided for use during the trial:

- Diary cards to record SC dosing administration
- Written instructions on how to use the SC syringes
- eCRF instructions
- Pregnancy Surveillance Forms
- Subject and Investigator-rated questionnaires/scales (paper)
- Ruler, 10 cm for measurement of Visual Analog Scales
- 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

5.3 Safety Assessments

On Day 1, the results of all assessments must be reviewed to ensure 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 and the Post Drug Follow-up Visits. 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 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.

5.3.1 Imaging Assessment for the Study

Not Applicable.

5.3.2 Physical Examination

Physical examinations (complete and/or brief) may be performed by a Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physician Assistant (PA), or Nurse Practitioner (NP) as allowable, per local regulations/guidelines.

The physical examination should include examination of the oropharynx, heart, parotid glands, neck (including submaxillary glands), lymph nodes, lungs, abdomen, lymph nodes, liver, spleen, musculoskeletal system, peripheral and central nervous systems, 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.

While the brief interim physical exam may not be as comprehensive as the initial full examination, key aspects of the brief interim examination should evaluate important body systems clinically indicated. The brief physical exam should include examination of the oropharynx, parotid glands, neck, lymph nodes, heart, lungs, and abdomen and may include other relevant body systems such as the skin, musculoskeletal system, central and/or peripheral nervous system, liver, spleen, and breasts, at the discretion of the examiner. A brief 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.

5.3.3 Chest X-ray

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.

5.3.4 Physical Measurements

Weight and height is (are) to be recorded at screening. Weight will also be recorded at Days 1, 169, and 365.

5.3.5 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.

5.3.6 TB Screening

Chest x-ray, history, 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 TB, a tuberculin skin test or an IFN γ release assay 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),^{26,27,28} or who are immunocompromised and who have had prior BCG vaccination(s).^{29,30} 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.

5.3.7 Laboratory Assessments

All laboratory assessments will be analyzed centrally except if noted otherwise.

Blood 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 8](#)).

5.3.7.1 Hematology

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

5.3.7.2 Blood Chemistry

- | | |
|------------------------|----------------------------------|
| • Sodium | Creatinine |
| • Potassium | Blood urea nitrogen (BUN) |
| • Chloride | Bicarbonate |
| • Creatine Kinase (CK) | Total bilirubin |
| • Total Protein | Alanine aminotransferase (ALT) |
| • Albumin | Aspartate aminotransferase (AST) |

- Calcium
 - Phosphorus
 - Glucose
 - hsCRP
 - ESR*
- Gamma-glutamyltransferase (GGT)
Alkaline phosphatase

*Performed locally, kits provided centrally.

5.3.7.3 Immunology

- Quantitative Immunoglobulins (IgG, IgA, IgM)
- anti-CCP2
- anti-dsDNA
- Rheumatoid Factor
- ANA and reflex ENA panels
- β -2-Microglobulin (B2M)
- Free Light Chain (FLC)
- Complement (C3, C4, CH50)
- Anti-Ro Antibody (SSA)
- Anti-La Antibody (SSB)
- Anti-centromere Antibody (ACA)

5.3.7.4 Urinalysis

- pH
- Protein
- Glucose
- Blood

5.3.7.5 Hepatitis Screen

The Laboratory results must be available on Day 1 prior to dosing.

- Hepatitis B surface antigen, hepatitis B core antibody (hepatitis B surface antibody, where required by local guidelines). If positive, reflex HBV DNA testing must be performed
- Hepatitis C antibody. If positive, reflex HCV RNA testing must be performed

5.3.7.6 Pregnancy Tests

Urine/serum pregnancy tests (minimum sensitivity 25 IU/L of β -HCG) must be performed for all WOCBP within 24 hours prior to dosing for visits specified in [Section 5.1](#). 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, if pregnancy is confirmed, 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.

5.3.7.7 HIV Testing

HIV testing (screening) will be performed locally in countries where testing is required.

5.3.7.8 FSH Testing

FSH testing must be performed to confirm menopause for female subjects under the age of 55. The female subject must have a serum FSH level > 40 mIU/mL in screening.

FSH testing will be performed for female subjects who become menopausal after entry into the study.

5.4 Efficacy Assessments

Questionnaires and investigator/subject assessments will be completed prior to study drug administration.

5.4.1 Primary Efficacy Assessment

The primary efficacy endpoint is the mean change from baseline in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) at Day 169 in abatacept vs placebo. The ESSDAI is a systemic disease activity index designed for pSS. It includes 12 domains (cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, lymphadenopathy & lymphoma, and biological). Each domain is divided into 3-4 levels of activity with different weightings at each activity level for individual domains.³¹ The definition of each activity level is provided by a detailed description of what should be considered in that item. When the ESSDAI is used, it should be with the assurance that the signs and symptoms are related to pSS and not to an underlying and/or associated disease. Likewise, patients with pSS may have concomitant illnesses that can mimic SS symptoms and organ involvement, which should be taken into account when scoring the ESSDAI. When assessing disease activity of an individual patient, the physician has to keep in mind that he/she has to exclude damage features that are irreversible.³¹

Some of the activity levels within some of the domains utilize results from tests that are not specifically listed in this protocol. For example, skin biopsy, high-resolution computed tomography (HRCT) scan, pulmonary function tests (PFTs), electromyography (EMG), nerve conduction studies (NCS), muscle magnetic resonance imaging (MRI), muscle biopsy, and brain MRI. If the subject has undergone such testing to evaluate active signs and symptoms related to pSS, the results of these tests should be used for the ESSDAI score at screening and Day 1. If the relevant signs/symptoms have changed since the initial testing was performed, repeat testing during the screening period should be performed.

If the ESSDAI score for a patient at Day 1 has contributions from tests not specifically required in this protocol, such as HRCT, PFTs, EMG, NCS, MRI, and biopsy, these tests should be repeated at Day 169.

If the ESSDAI score for a patient at Day 169 has contributions from tests not specifically required in this protocol, such as HRCT, PFTs, EMG, NCS, MRI, and biopsy, these tests should be repeated at Day 365.

If during the double blind period a subject develops a sign or symptom that necessitates additional testing not required in the protocol (eg, HRCT, PFTs, EMG, NCS, MRI, biopsy), this testing should be performed at the time of the sign/symptom onset, and additionally at Day 169 if at least 8 weeks have elapsed since prior testing. If during the open-label abatacept period a subject develops a sign or symptom that necessitates additional testing not required in the protocol this testing should be performed at the time of the sign/symptom onset, and additionally at Day 365, if at least 8 weeks have elapsed since prior testing.

Training and instruction on the ESSDAI will be provided at the Investigator's Meeting or at other trainings and workshops. ESSDAI Assessors should have appropriate medical credentials, such as a Doctor of Medicine (MD)/Doctor of Osteopathy (DO), Physician Assistant (PA) or Nurse Practitioner (NP), and should be individuals who are experienced in the clinical care of patients with pSS. Visits should be scheduled with the availability of the assessor taken into account. It is strongly recommended that the same assessor evaluates findings in individual subjects throughout the study. If the assessor is unable to complete the evaluation, then another qualified trained individual can take the place of the initial evaluator, as long as the restrictions, described above, are still met. The substitute evaluator will have also examined and reviewed the subject with the initial assessor to ensure consistency between subject evaluations.

5.4.2 Salivary Flow

Whole unstimulated and stimulated salivary flow will be assessed at baseline (Day 1) and Days 85, 169, 253, 365 and early termination. The same assessor should perform salivary testing on the subject at each visit, if possible. Salivary assessments throughout the study should be performed at approximately the same time of day as the baseline salivary assessment. Subjects should be instructed to not use parasympathomimetic (cholinergic) agents, such as pilocarpine and cevimeline for the 48 hours prior to salivary assessments, and not to use artificial saliva on the day of the assessment. Subjects should refrain from eating, drinking, smoking or chewing gum for at least 90 minutes prior to the salivary test procedures.

Unstimulated Salivary Flow:

The subject's unstimulated whole salivary flow rate will be measured for 15 minutes. The subject is advised to rinse his or her mouth several times with deionized (distilled) water and then to relax for five minutes and minimize movement, particularly of his/her mouth. For the collection procedure, the subject should keep his/her head tilted forward and swallow once before starting the procedure to clear the mouth of excess saliva. At this point, the 15-minute collection period is initiated. The subject should lean his/her head forward over a pre-weighed 50 cm³ conical tube. Subjects then expectorate, as needed, any accumulated saliva into the tube. At

the end of the collection period, the subject will be asked to collect any remaining saliva in his/her mouth and spit it into the test tube. |

Refer to [section 5.6.4](#) for additional details

Stimulated Salivary Flow:³²

A sterile 10 x 10-cm gauze sponge is first folded twice at 90 degree angles (final size 5 x 5 cm) and placed in a 50 cm³ conical tube and the gauze and tube are weighed. After swallowing to remove any preexisting oral fluid, saliva is collected by having the subject vigorously chew on the gauze for exactly 2 minutes, 1 chew/minute. After chewing the gauze, it is placed in the same tube. The amount of saliva produced in 2 minutes will be determined by subtracting the original weight from the weight obtained after chewing.

5.4.3 Ophthalmologic Assessments

The following procedures should be performed at baseline/Day 1, and Days 85, 169, 253, 365 and early termination by an ophthalmologist trained in the ophthalmologic assessment of patients with Sjögren's Syndrome. Assessments may also be performed by an optometrist who is familiar with the required testing and experienced in diagnosing and treating patients with dry eyes associated with Sjögren's syndrome. A visit window of 5 days relative to the study visit to perform the ophthalmologic assessments is acceptable, but all ophthalmologic assessments must be performed during the same visit. Subjects should be instructed to not use parasympathomimetic agents, such as pilocarpine and cevimeline for the 48 hours prior to ocular assessments. Subjects should not use cyclosporine, lifitegrast, or corticosteroid eye drops or artificial tears for 12 hours prior to the assessment. Ophthalmologic assessments performed on days 85, 169, 253, 365 and early termination should be performed at approximately the same time of day as the baseline assessment.

- Schirmer's test: The test (without anesthesia) is performed by placing a narrow calibrated filter-paper strip in the inferior cul-de-sac of each eye. Aqueous tear production is measured by the length in millimeters that the strip wets during the 5 minute test period.
- Tear break-up time (TBUT): Determined by instilling fluorescein dye and evaluating the stability of the pre-corneal tear film. After several blinks, the tear film is examined using a broad beam of the slit-lamp (biomicroscope) with a cobalt blue filter. The TBUT, defined as the time in seconds between the subject's last blink and the first appearance of a random dry spot on the corneal surface, is measured 3 times and the mean value is recorded.
- Ocular surface staining: The test is performed by instillation of fluorescein dye and lissamine green dye to stain the cornea and conjunctiva, respectively. After instilling the dye, the ocular surface is examined through a slit lamp (biomicroscope) and the staining pattern is recorded per the method described in Whitcher, et al. (Rose Bengal stain as a substitute for lissamine green is acceptable only in regions in which lissamine green is not available.)

5.4.4 Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity (PGA) should be performed by a Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physician Assistant (PA) or Nurse Practitioner (NP) who has experience caring for patients with pSS. The assessment should be performed by the same individual at every visit for a given subject, if possible.

5.4.5 Joint Count Assessments

The Joint Count Assessor may perform the PGA for the same subject. For both assessments every effort should be made to ensure the same assessor is used for a given subject throughout the study.

Training and instruction on joint count assessments will be provided at the Investigator's Meeting or at other trainings and workshops.

Joint Count Assessors should have appropriate medical credentials and/or should be individuals with appropriate scientific/medical background who are experienced in performing joint assessments for the BMS Phase 3 studies. If the individual does not have medical credentials, documentation of their experience (preferably on a curriculum vitae) must be provided to the BMS site manager, and their eligibility as joint assessor must be confirmed by the BMS Medical Monitor before the individual's participation in the study as Joint Count Assessor.

Visits should be scheduled with the availability of the assessor taken into account. If the assessor is unable to complete the evaluation, then another qualified individual can take the place of the initial evaluator, as long as the restrictions, described above, are still met. The substitute evaluator will have also examined and reviewed the subject with the initial assessor to ensure consistency between subject evaluations.

5.5 Pharmacokinetic Assessments

5.5.1 Pharmacokinetic: Blood Collection

The sampling schedule to be followed for the assessment of pharmacokinetics is listed in [Table 5.5.1-1](#). The actual date and time of sample collection should be recorded. Every effort should be made to collect PK samples as close to the protocol-specified times as possible.

All randomized subjects will have PK samples collected during the Double-Blind Treatment Period, Open-Label Treatment Period and the Post-Treatment Follow-up Period unless the subject discontinues study treatment and starts treatment with commercial abatacept.

In addition, approximately 40 randomized subjects (approximately 20 subjects randomized to active treatment and 20 subjects randomized to placebo) will participate in a PK sub-study. Those subjects that sign consent to participate in the PK sub-study will have samples collected Days 2, 5, 15, 17, 32, and 61 (see [Table 5.5.1-1](#)). Each sub-study visit may be a home visit conducted by a visiting nurse or qualified healthcare professional if approved by the IRB/IEC and investigator.

Table 5.5.1-1: Pharmacokinetic (PK) Sampling Schedule

Study Day	Event	Time (Relative to Dosing) Hour:Min	PK Blood Sample		Immunogenicity Sample
			All Subjects (N=144)	For PK sub-study (N = 40)	All Subjects (N=144)
1	predose	0	X		X
2		24:00		X	
5		96:00		X	
15	predose	0		X	
17 ± 1		24:00 to 72:00		X	
29	predose	0	X		
32 ± 1		48:00 to 96:00		X	
57	predose	0	X		
61 ± 1		72:00 to 120:00		X	
85	predose	0	X		X
113	predose	0	X		
141	predose	0	X		
169 or ET ^a	predose	0	X		X
365 or EOT ^a			X		X
Post-Treatment Follow-up Period ^b					
28		696:00 hrs	X ^c		X ^d
84		2016:00 hrs	X ^c		X ^d

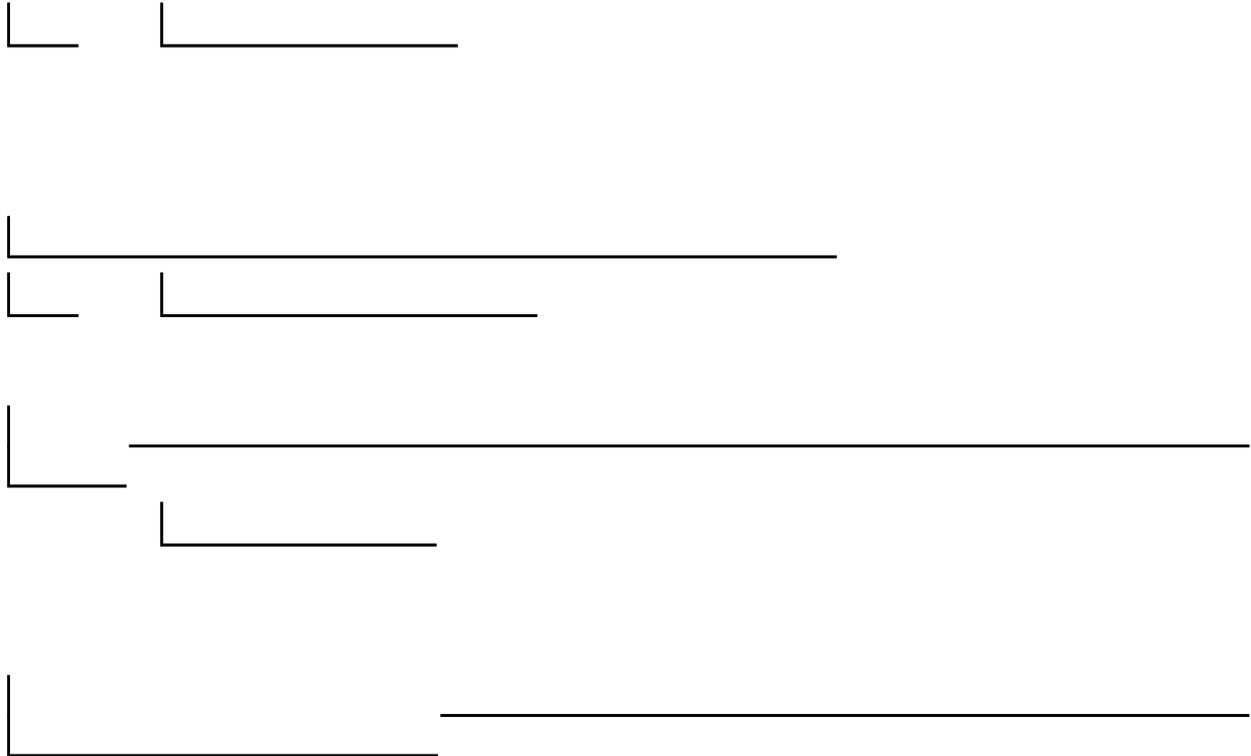
^a Sample collected predose, except for Early Termination (ET) and End of Treatment (EOT).

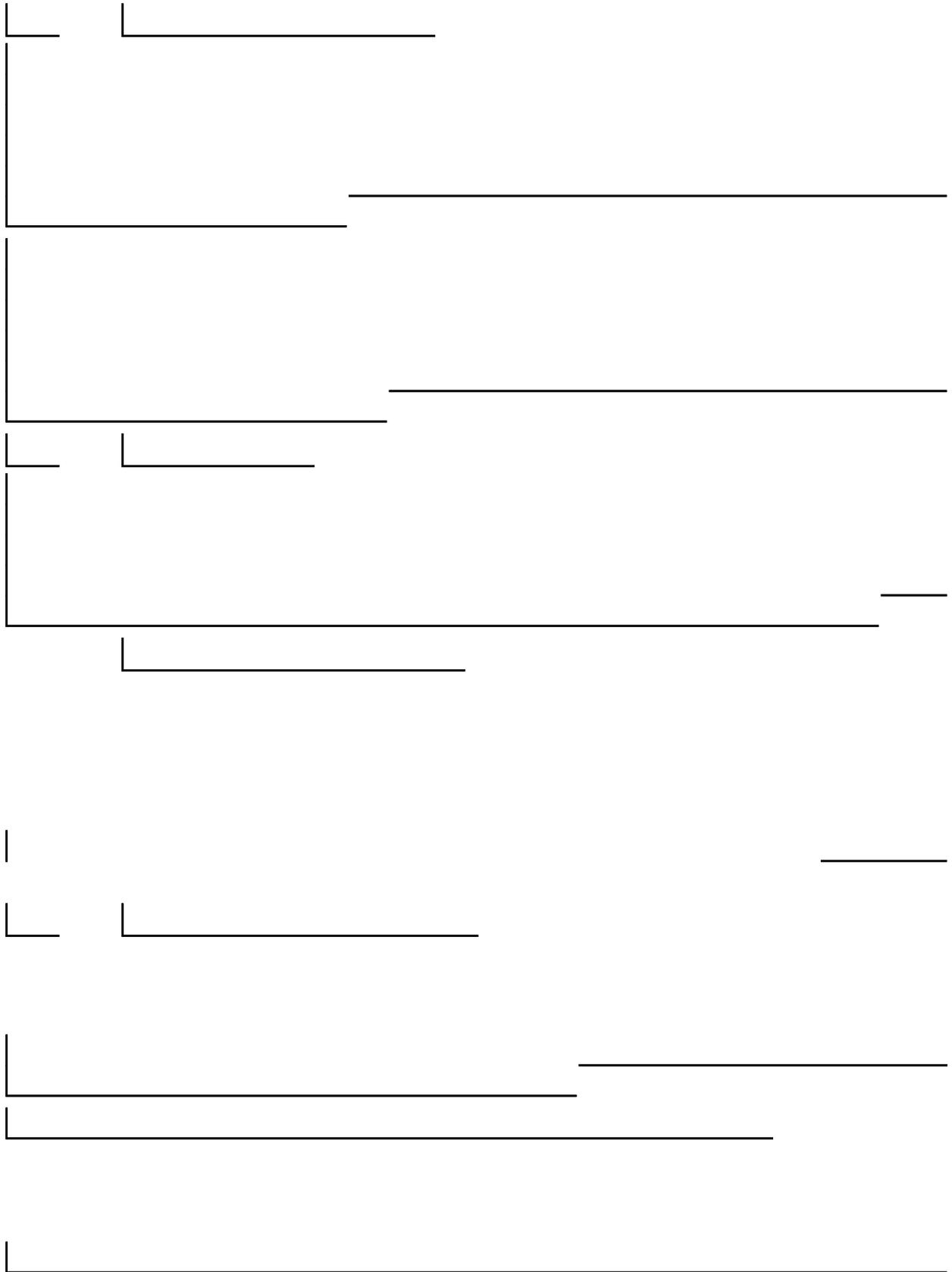
^b Only for subjects discontinuing use of abatacept (off study).

^c These samples will only be evaluated to determine serum abatacept concentration in the event there is a corresponding positive immunogenicity result.

^d These samples should be collected 28 and 84 days after the last dose of study medication. If study medication is discontinued during the Double-Blind Treatment Period and the subject continues to be followed for the scheduled Double-Blind Treatment Period visits these additional samples may not be required.

The capture of precise PK sampling times relative to the actual dosing time is integral to the PK analysis and must be accurately recorded on the central laboratory requisition form. The date and time of sample collection must be recorded so that compliance with the sampling schedule can be confirmed.





performed satisfactorily for evaluation of patients' symptoms in primary SS, and has the advantage that it is easy to use.³³

NRS for mouth dryness

Numeric rating scale for mouth dryness to assess the subject's perception of change in this specific symptom.

NRS for eye dryness

Numeric rating scale for eye dryness to assess the subject's perception of change in this specific symptom.

Subject assessment of disease activity

Visual Analog Scale (VAS) scale to assess patient overall assessment of disease.

PROMIS fatigue assessment

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.

SF-36- assessment of function

SF-36 is a widely used assessment tool that is recognized as a validated instrument to measure quality of life in diseases such as RA. The 36-item Short Form Health Survey (SF-36) has also been used to assess quality of life in patients with pSS.³⁴

Female Sexual Function Index (FSFI)

Women with pSS frequently experience vaginal dryness and dyspareunia. The FSFI is a 19-item index that measures sexual function in six subdomains: desire, arousal, orgasm, lubrication, satisfaction and pain. Higher scores indicate better sexual function. The total score is calculated as the sum of the six domain scores and has a range of 2-36. A cut-off score of < 26.55 has been proposed to indicate sexual dysfunction.³⁵

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

5.8.1.1 Immunogenicity: Blood Collection

Blood samples for determination of antibodies to abatacept, and time-matched PK samples will be collected at times noted in [Section 5.5.1](#). Samples MUST be collected prior to the administration of study medication (SC injections) based on the collection schedule except during the Follow-up Period. Samples will be assayed for the presence of abatacept-specific antibodies.

5.8.1.2 Immunogenicity: Blood Sample Processing, Labeling, and Shipping

Detailed instructions on processing, labeling, handling, storage, and shipping of immunogenicity specimen for analysis will be supplied to Investigators in a separate manual at or before the time of study initiation.

5.8.1.3 Immunogenicity: Sample Analysis

A validated, sensitive, electrochemiluminescence assay (ECL) method will be used to analyze the presence of anti-abatacept antibodies in serum. Samples that are confirmed positive for antibodies specific to the CTLA4 region of abatacept and have abatacept serum concentrations of $\leq 1 \mu\text{g/mL}$ will be further analyzed with a validated, in vitro, cell-based bioassay to determine whether the sera contained abatacept neutralizing activity.

5.9 Labial Salivary Gland or Parotid Gland Biopsy (Substudy)

Sites with experience in this procedure will be asked to participate in this substudy. Optional biopsies should be obtained at baseline/Day 1 (a window of 28 days prior to the start of dosing to accommodate scheduling is acceptable) and at Day 169. Subjects who complete treatment with study drug up to Day 141 of the Double-blind Treatment Period should have the biopsy obtained within 28 days of Day 169.

Briefly, subjects who sign consent to participate in the biopsy substudy will have a 1.5-2 cm incision in the mucosa of the lower lip through the epithelium only. Blunt dissection and removal of the labial salivary glands will be performed and the incision will be sutured. Parotid gland biopsies are also acceptable if performed at sites experienced with this procedure. Salivary/parotid glands will be placed in container containing formalin for further processing by the central labs. Biopsy specimen will be read centrally for histology and examined for RNA expression.

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 *Serious 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 [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See [Section 6.6](#) for the definition of potential DILI.)

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

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 (eg, 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 (eg, 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

Sections 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 and within 84 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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 drug, and pregnancies must be reported to Sponsor or designee within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

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 (eg, 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, or 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.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Data Monitoring Committee (DMC) will be instituted to perform safety monitoring oversight.

Details will be contained in the DMC Charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

A hierarchical testing procedure will be applied for the primary endpoint (change from baseline in ESSDAI at Day 169) and the 2 key secondary endpoints (change from baseline in ESSPRI at Day 169 and change from baseline in the stimulated whole salivary flow at Day 169) to ensure the preservation of the overall type I error of 5%. The first key secondary endpoint will only be tested (at a significance level of 5%) if the test for the primary endpoint is statistically significant at a significance level of 5%. If both the test for the primary endpoint and the first key secondary endpoint are statistically significant (both at a significance level of 5%), then the second key secondary endpoint will be tested (at a significance level of 5%).

A sample size of 172 patients (86 per arm) will achieve 98% power to detect a treatment difference of 3 in changes from baseline in ESSDAI at Day 169 between the abatacept and placebo group using a two-sided t-test with a significance level (alpha) of 0.05 and assuming a common SD of 4.8. The sample size of 86 patients per arm will achieve 90% power to detect a treatment difference of 1 in change from baseline in ESSPRI at Day 169 assuming a common SD of 2. Taking into account the hierarchical procedure, a sample size of 86 patients per arm will achieve an overall power of at least 88.2% (98% multiplied by 90%) to detect both a treatment difference of 3 in mean change from baseline in ESSDAI and a difference of 1 in change from baseline in ESSPRI at Week 24 (Day 169).

The treatment differences of 3 for ESSDAI and 1 for ESSPRI correspond to the minimal clinically important improvement (MCII) for ESSDAI and ESSPRI³⁶, the key endpoints that address the major signs and symptoms of this disease. Estimates of the SD of mean change from baseline in ESSDAI derived from published results³⁷, range from 3.6 to 6.3. Estimates of the SD of mean change from baseline in ESSPRI derived from published results range from 1.7 to 2.2.³⁸

In addition, the power to detect a treatment difference in mean change from baseline of 0.165 mL/min in salivary flow (approximately similar to median reported increase/min with abatacept by Adler et al⁴) in subjects with stimulated whole salivary flow at baseline of at least 0.1 mL/min is 91%, assuming a SD of 0.275 and for a sample size of 62 subjects per arm with a residual salivary flow of at least 0.1 mL/min at screening and baseline.⁴ Taking into account the hierarchical procedure, a sample size of 86 patients per arm will achieve an overall power of at least 80.3 % (98% multiplied by 90% multiplied by 91%) to detect a treatment difference of 3 in mean change from baseline in ESSDAI, a difference of 1 in mean change from baseline in ESSPRI and a treatment difference of 0.165 mL/min in mean change from baseline in salivary flow(in subjects with stimulated whole salivary flow at screening and at baseline of at least 0.1 mL/min) at Week 24 (Day 169).

8.2 Populations for Analyses

- Intent-to-treat (ITT) analysis population: all randomized subjects who receive at least one dose of study medication. Analyses using the ITT analysis population will group the subjects according to the treatment group to which they are randomized.
- Per-protocol (PP) analysis population: all randomized subjects who receive at least one dose of study medication, excluding the subjects with relevant protocol deviations. Analyses using the PP analysis population will group the subjects according to the treatment group to which they are randomized.
- As-treated analysis population: all subjects who receive at least one dose of study medication. Analyses using the as treated analysis population will group the subjects on an as-randomized basis unless the subject received the incorrect medication for the entire period of treatment. In that case, the subject will be analyzed in the treatment group associated with the incorrect medication they received (“as-treated”).
- Cumulative abatacept population: all randomized subject who receive at least one dose of abatacept during the double-blind and/or the open-label period. All subjects of the ‘As-treated population’ will be included, except placebo subjects who never entered the open-label period.
- Immunogenicity analysis population: all subjects who receive at least one dose of study medication and who had at least 1 immunogenicity result reported after start of study medication.
- Full PK analysis population: all subjects who received at least one dose of abatacept study medication and who had at least 1 PK result reported after start of this study medication.
- Evaluable PK analysis population: this population is a subset of the PK analysis population and consists of the evaluable subjects for PK analysis. For all PK summaries and plots, a subject is evaluable for PK analysis at a specific day if the predose PK measurements were collected in the 4 to 10 days window after the previous SC abatacept dose and prior to the dose of the specific day.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The mean change from baseline (Day 1) in ESSDAI at Day 169.

8.3.2 Secondary Endpoint(s)

Key Secondary Endpoints

- The mean change from baseline in ESSPRI at Day 169.
- The mean change from baseline in the stimulated whole salivary flow at Day 169 among subjects with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline.

Other Secondary Endpoints

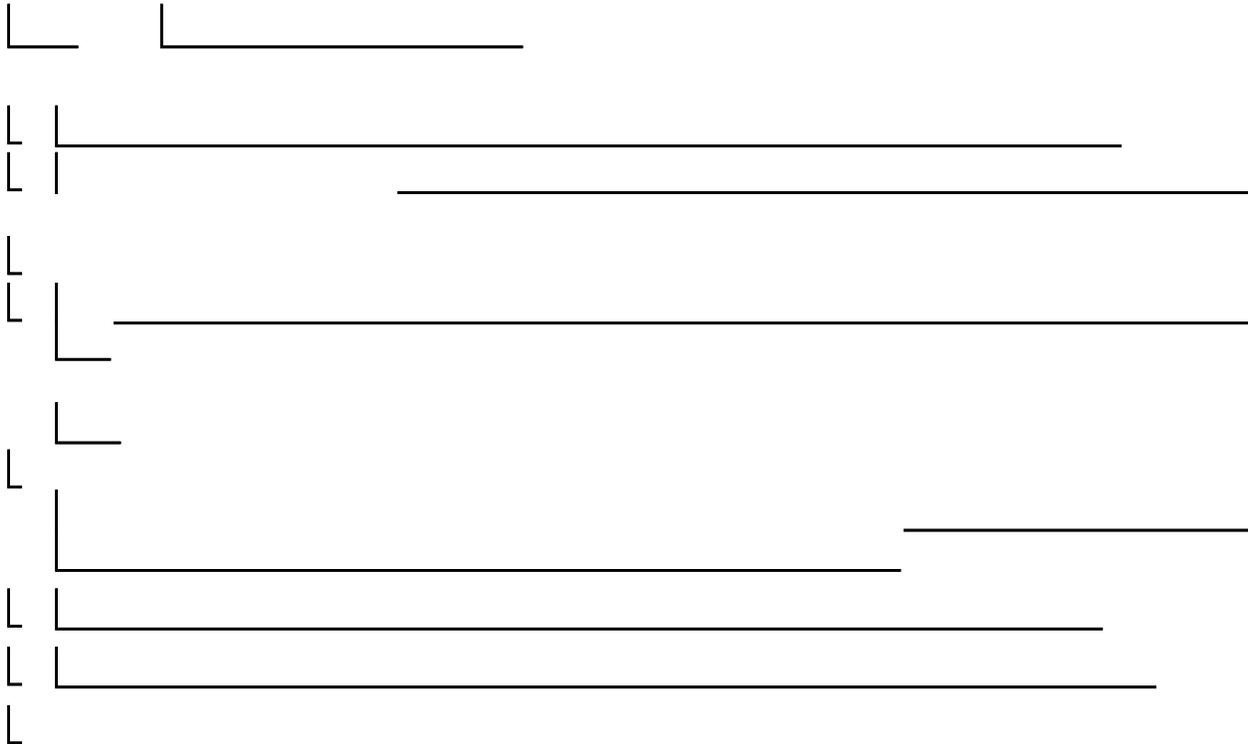
- The mean change from baseline at all measured time points up to Day 169 in the DAS28-CRP among those with a tender plus swollen joint count ≥ 3 at baseline, among those with a tender plus swollen joint count < 3 at baseline and in the full population.
- The mean change from baseline at all measured time points up to Day 169 in the individual components of DAS28-CRP among those with a tender plus swollen joint count ≥ 3 at baseline, among those with a tender plus swollen joint count < 3 at baseline and in the full population.
- Proportion of subjects who achieve a minimally clinically important change (of at least 3 points) in the ESSDAI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- Proportion of subjects who achieve a minimally clinically important change (of at least 5 points) in the ESSDAI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- Proportion of subjects who achieve a minimally clinically important change (of at least 1 point) in the ESSPRI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline at all measured time points up to Day 169 in the ESSDAI in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline at all measured time points up to Day 169 in the ESSPRI in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline in the individual components of the ESSDAI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline in the individual components of the ESSPRI at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary

flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.

- The mean change from baseline in Schirmer's test at all measured time points up to Day 169.
- The mean change from baseline in ocular staining score at all measured time points up to Day 169.
- The mean change from baseline in tear break-up time at all measured time points up to Day 169.
- The mean change from baseline in unstimulated whole salivary flow at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline in stimulated whole salivary flow at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening or baseline.
- The mean change from baseline in patient symptoms using the Numeric Rating Scale (NRS) for mouth dryness at all measured time points up to Day 169 in the full population, among those with stimulated whole salivary flow of at least 0.1 mL/min at both screening and baseline, and among those with stimulated whole salivary flow of less than 0.1 mL/min at screening and baseline.
- The mean change from baseline in patient symptoms using the Numeric Rating Scale (NRS) for eye dryness at all measured time points up to Day 169.
- The mean change from baseline in subject assessment of disease activity at all measured time points up to Day 169.
- The mean change from baseline in the physician global assessment of disease activity at all measured time points up to Day 169.
- The mean change from baseline in patient fatigue using PROMIS Fatigue assessment at all measured time points up to Day 169.
- The mean change from baseline in female sexual function using the FSFI at all measured time points up to Day 169.
- The mean change from baseline in patient function using SF-36 at all measured time points up to Day 169.
- Geometric mean of trough concentration (C_{min}) of abatacept at all measured time points.
- Proportion of subjects with at least one positive immunogenicity response up to Day 169 and during 3 months follow up (for subjects who discontinue during the 6-months double-blind)

and during the cumulative abatacept period and 3 months follow-up (for the cumulative abatacept population).

- Safety (proportion of subjects with adverse events, deaths, SAEs, and AEs leading to discontinuation and proportion of laboratory marked abnormalities) up to Day 169 and during the cumulative abatacept period and follow-up period.



8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demography and baseline disease characteristics will be presented by randomized treatment group and overall for the ITT population. Continuous variables such as age and weight will be summarized using means, standard deviations, median and ranges. Categorical variables such as gender, race and region will be summarized using frequencies.



The table consists of four rows and two columns. The first row has a horizontal line in the right column. The second row has a horizontal line in the right column. The third row has a horizontal line in the right column. The fourth row has a horizontal line in the right column. The rest of the table is empty.

8.4.3 Safety Analyses

The proportion (%) of subjects with adverse events, deaths, SAEs, and AEs leading to discontinuation and subjects with laboratory marked abnormalities up to start of open label for subjects continuing in the OL or up to last dosing date +56 days for subjects discontinuing during double blind will be provided per treatment group using the as-treated population. These safety endpoints will also be summarized during the cumulative abatacept period (from the first day of abatacept treatment in the study up to 56 days after the last abatacept treatment in the study) for the cumulative abatacept population. For the cumulative abatacept population all subjects will be combined in one group.

The proportion (%) of subjects with at least one positive immunogenicity response (relative to baseline) up to Day 169 and 3 months follow up (for subjects who discontinue in the Day 169 short-term period) and during the cumulative abatacept period and 3 months follow-up (for the cumulative abatacept population) will be summarized using the immunogenicity population.

8.4.6 Outcomes Research Analyses

The mean change from baseline for outcome research endpoints (e.g., patient function using SF-36 and patient fatigue using PROMIS Fatigue) will be analyzed using the same approach as done for the mean change from baseline for efficacy endpoints.

8.4.7 Other Analyses

Not applicable.

A detailed description of the analyses in [section 8.4](#) (including sensitivity analyses for efficacy endpoints and additional analyses for efficacy and safety) will be provided in the statistical analysis plan (SAP).

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.

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 (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, 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):	<p>Records or logs must comply with applicable regulations and guidelines and should include:</p> <ul style="list-style-type: none"> • 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 • nonstudy disposition (eg, 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, or a specialty pharmacy)	<p>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.</p> <p>These records should include:</p>

If...	Then...
	<ul style="list-style-type: none"> • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates 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 or 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 subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators 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 (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, 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 (eg, 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
ABA	abatacept
ACA	Anti-centromere antibody
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANA	Anti-nuclear antibody
Anti-CCP2	anti-cyclic citrullinated peptide
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
β2M	β-2-microglobulins
β-HCG	beta-human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca ⁺⁺	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
Cl ⁻	chloride
cm	centimeter
C _{max} , C _{MAX}	maximum observed concentration
C _{min} , C _{MIN}	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
C _t	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours,

Term	Definition
	concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
DILI	Drug induced liver injury
dL	deciliter
DMARD	disease-modifying anti-rheumatic drug
DO	Doctor of Osteopathy
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
EIA	enzyme immunoassay
ESR	Erythrocyte Sedimentation Rate
ESR	Expedited Safety Report
F	bioavailability
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EULAR SS	European League Against Rheumatism Sjögren's Syndrome
FDA	Food and Drug Administration
FLC	Free Light Chain
FS	Focus Score
FSFI	Female sexual function index
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Term	Definition
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO ₃ ⁻	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
ITT	Intent to treat
IU	International Unit
IV	intravenous
IVIG	Intravenous immunoglobulin
K	slope of the terminal phase of the log concentration-time curve
K ₃ EDTA	potassium ethylenediaminetetraacetic acid
K ⁺	potassium
kg	kilogram
L	liter
LDH	lactate dehydrogenase
ln	natural logarithm
LN	Lupus Nephritis
Lz_Start	The time point starting the log-linear elimination phase defining the terminal half life

Term	Definition
Lz_End	The time point ending the log-linear elimination phase defining the terminal half life
Lz_N	Number of time points in the log-linear elimination phase defining the terminal half life
MAR	Missing at random
MCII	Minimally clinically important improvement
MD	Medical Doctor
mg	milligram
Mg ⁺⁺	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MRT	mean residence time
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na ⁺	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NP	Nurse Practitioner
NRS	Numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OSS	Ocular Surface Staining
PBMC	Peripheral Blood Mononuclear Cell
PD	pharmacodynamics
PK	pharmacokinetics
PNS	Peripheral nervous system

Term	Definition
PO	per os (by mouth route of administration)
PROMIS Fatigue	Patient Reported Outcomes Measurement Information System Fatigue
pSS	Primary Sjögren's syndrome
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
QD, qd	quaque die, once daily
R2	coefficient of determination
RA	rheumatoid arthritis
RBC	red blood cell
RF	rheumatoid factor
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-36	Short Form 36
SLE	systemic lupus erythematosus
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TB	Tuberculosis
T-HALF	Half life
T-HALF _{eff} _AUC	Effective elimination half life that explains the degree of AUC accumulation observed
T-HALF _{eff} _C _{max}	Effective elimination half life that explains the degree of C _{max} accumulation observed)
TID, tid	ter in die, three times a day
T _{max} , T _{MAX}	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio

Term	Definition
TR_Cmax	Cmax treatment ratio
UV	ultraviolet
UWS	Unstimulated Whole Salivary Flow
W	washout
WBC	white blood cell
WHO	World Health Organization
Wk	Week
WOCBP	women of childbearing potential
x g	times gravity

APPENDIX 1 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 Mirena®
- 3) Nonhormonal IUDs, such as ParaGard®
- 4) Bilateral tubal occlusion
- 5) Vasectomised partner with documented azoospermia 90 days after procedure
 - a) 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
 - a) Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
 - b) 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).
 - c) It is not necessary to use any other method of contraception when complete abstinence is elected.
 - d) Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in [Section 6.4](#).
 - e) Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
 - f) 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)

