Protocol Number: IM128035
IND Number: 122,786
Ex-US Non-IND
EUDRACT Number 2016-000101-37
Date: 05-May-2016
Revised Date: 13-Feb-2017

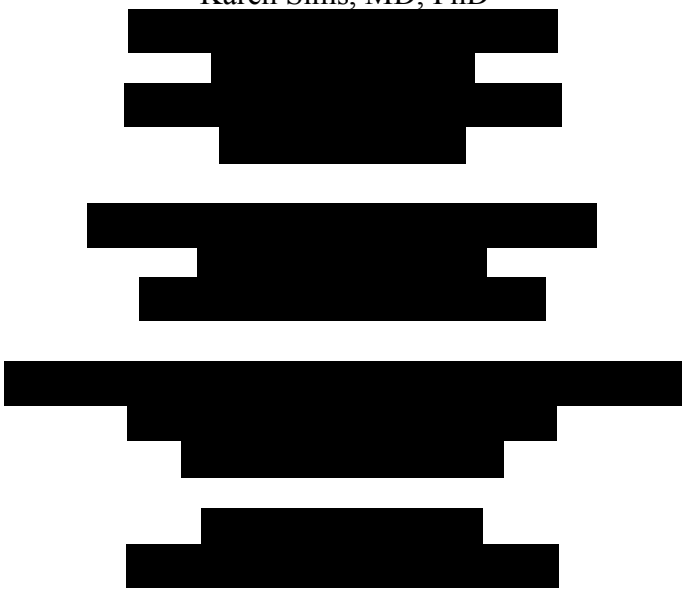
Clinical Protocol IM128035

A Phase II, Randomized, Multi-Center, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of BMS-931699 (lulizumab) or BMS-986142 in Subjects with Moderate to Severe Primary Sjögren's Syndrome

Revised Protocol Number: 02
Incorporates Amendment 02 and Administrative Letter 02

Study Director and Medical Monitor

Karen Sims, MD, PhD



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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.

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SYNOPSIS

Clinical Protocol IM128035

Protocol Title: A Phase II, Randomized, Multi-Center, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of BMS-931699 (lulizumab) or BMS-986142 in Subjects with Moderate to Severe Primary Sjogren's Syndrome

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

BMS-931699 (lulizumab) is an anti-human cluster of differentiation (CD)28 receptor antagonist Vk domain antibody (dAb), formatted with 40 kDa branched polyethylene glycol (PEG). It will be administered subcutaneously (SC) at a dose of 12.5 mg weekly in a double-blind fashion for 12 weeks.

BMS-986142 is a reversible Bruton's tyrosine kinase (BTK) inhibitor that will be administered orally at a dose of 350 mg daily in a double-blind fashion for 12 weeks.

Study Phase: II

Research Hypothesis: Treatment with BMS-931699 (lulizumab) or BMS-986142 for 12 weeks is more effective than placebo in decreasing the ESSDAI score in subjects with moderate to severe primary Sjögren's syndrome (pSS).

Objectives:

Primary: To evaluate the efficacy of treatment with either lulizumab or BMS-986142 versus placebo in subjects with moderate to severe primary Sjögren's syndrome as measured by the change from baseline in ESSDAI at Week 12 between active treatment arms (lulizumab or BMS-986142, respectively) and the placebo arm.

Secondary:

To assess the:

- Change from baseline in ESSPRI score at Week 12
- Proportion of subjects with a ≥ 3 point improvement from baseline in ESSDAI at Week 12
- Proportion of subjects with a ≥ 1 point improvement from baseline in ESSPRI at Week 12
- Proportion of subjects with both ≥ 3 point improvement in ESSDAI and ≥ 1 point improvement in ESSPRI from baseline at Week 12
- Change from baseline in ESSDAI scores at Week 4 and Week 8
- Change from baseline in ESSPRI scores at Week 4 and Week 8
- Change from baseline in ESSPRI components (Dryness, Fatigue, and Pain) at Week 4, 8 and 12
- Change from baseline in unstimulated and stimulated salivary flow rate at Weeks 4, 8, and 12
- Change from baseline in ocular surface staining, Schirmer's test, and tear-break up time test at Weeks 4, 8, and 12
- Safety and tolerability of lulizumab or BMS-986142 in subjects with moderate to severe pSS, as measured by adverse events, laboratory parameters, vital signs, physical exams, and ECGs
- Change from baseline in patient and physician assessments of disease activity:
  - Numeric rating scale (NRS) scores for mouth, eye and vaginal dryness
  - Subject global assessment of disease activity (SubGDA) and physician global assessment of disease activity (phyGDA)
  - PROMIS Fatigue Short Form
  - Short Form-36 acute (SF-36 acute)

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  - Female Sexual Function Index (FSFI)
  - Work participation and activity impairment questionnaire (WPAI)
- Trough concentrations of lulizumab and BMS-986142 in pSS subjects

Study Design:

This is a 12-week randomized, double-blind, placebo-controlled, parallel group study with adaptive design features based on an interim analysis (IA). The study will initially have a 28-day Screening Period followed by up to 12 weeks of double-blind treatment with either lulizumab, BMS-986142, or placebo.

Screening Period: The standard duration of the Screening Period is up to 28 days (4 weeks), with up to two Screening Visits allowed for subjects who require adjustment of oral corticosteroids or who are taking hydroxychloroquine. Subjects who are on oral corticosteroids at a dose higher than 10 mg/day will require a taper at the beginning of the Screening Period to a stable dose of no more than 10 mg/day of prednisone (or equivalent) by at least 14 days prior to dosing (Day -14), and will need to be reevaluated at a second screening visit prior to randomization (Day 1). Subjects who are taking hydroxychloroquine (HCQ, Plaquenil®) at screening who meet the study criteria will be required to return for a second visit during the screening period to collect baseline HCQ PK samples. Should more time be needed, the duration of the Screening Period may be extended up to another week (total of 5 weeks or 35 days) depending on dose stabilization, technical issues, or subject scheduling.

Study Summary: Subjects with moderate to severe primary Sjögren's syndrome will receive lulizumab, BMS-986142, or matching placebos for up to 12 weeks, followed by a 6-week follow-up period.

Upon meeting the Inclusion/Exclusion criteria, approximately 75 subjects will be equally randomized to 1 of the 3 treatment arms as shown in Figure 1 below.

An interim analysis will be conducted after at least 30 subjects reach Week 12 (complete 12 weeks of treatment) and complete the specified assessments for the Week 12 ESSDAI score. The interim analysis will be conducted in a fully blinded manner such that treatment group assignments of study subjects are not known and are not used in any manner in the analysis. A blinded examination of the variance of the primary endpoint will be performed and compared to the assumption used in planning the study. If this comparison suggests the initial assumption was substantially too low, the total study sample size may be increased by up to 45 additional subjects (ie, to a maximum of 120 subjects in total) to maintain adequate statistical power. The blinded IA will not interfere or alter any subject's treatment, that is, subjects who were enrolled before the IA is completed will continue the originally assigned treatment arm if they have received at least 1 treatment and the dose is considered safe.

Ongoing assessment of safety will be performed by an independent Data Monitoring Committee (DMC). The DMC may make recommendations to the Sponsor regarding conduct of the study based on safety observations.

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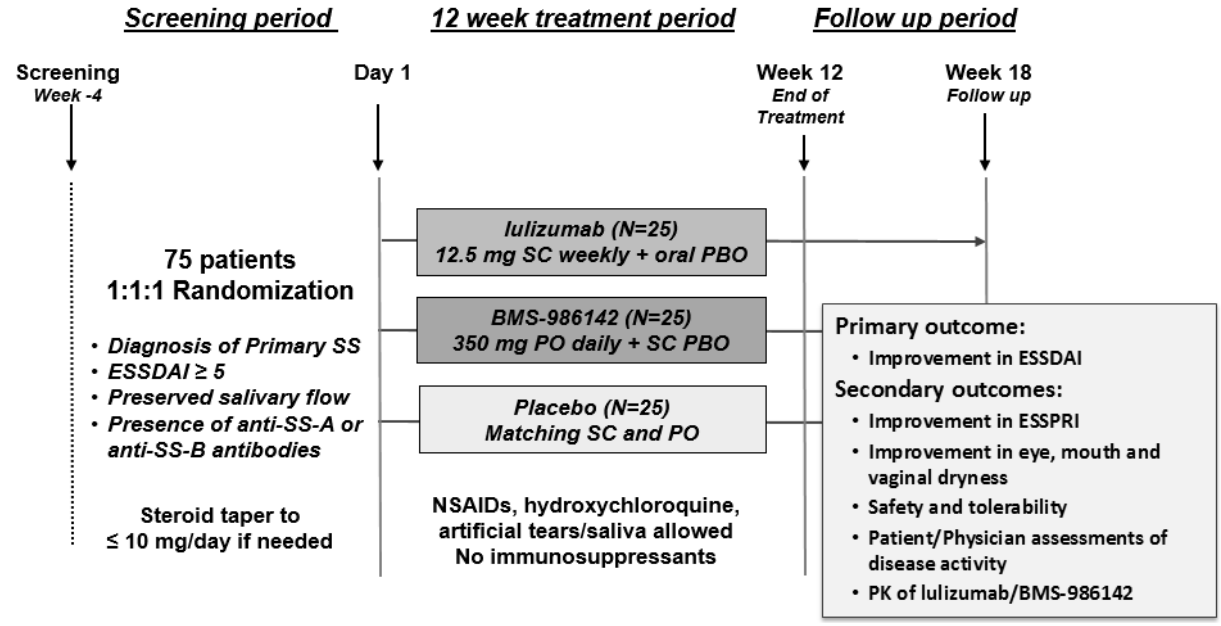
Figure 1: Study Design Schematic



Duration of Study:

The approximate duration of the study is up to a 5-week screening period (35 days), a 12-week double-blind treatment period (84 days), and 6 weeks of follow-up (42 days), for a total of up to 23 weeks (161 days).

Number of Subjects:

Approximately 75 subjects will be randomized across the three arms of this study. The study will utilize an equal randomization scheme (1:1:1) that will result in approximately 25 subjects in each arm. An interim analysis will be conducted in a fully blinded manner to examine the variability of the primary outcome measure and compare that to the assumption used in planning the study. If this comparison suggests the initial assumption was substantially too low, the total study sample size may be increased by up to 45 additional subjects (ie, to a maximum of 120 subjects in total) to maintain adequate study power.

Study Population:

Men or women (not nursing or pregnant) ages 18 to 70 years old (inclusive at time of randomization), diagnosed with primary Sjögren's syndrome by the 2016 ACR-EULAR Classification Criteria, for at least 16 weeks prior to screening. Women of childbearing potential must use an acceptable method of highly effective contraception to avoid pregnancy for the duration of dosing and at least 65 days after the last dose of study medication.

Key Inclusion Criteria:

1. Subjects diagnosed or classified as having moderate to severe primary Sjögren's syndrome based on the 2016 ACR-EULAR Classification Criteria for Sjögren's syndrome, with disease duration from time since diagnosis of at least 16 weeks prior to the Screening Visit
2. ESSDAI ≥ 5; including disease activity (any score > 0) in at least one of the following domains: Glandular, Articular, Hematological, Biological, Lymphadenopathy
3. Positive anti-SS-A/Ro or anti-SS-B/La autoantibody
4. Unstimulated whole saliva secretion > 0.01 mL/min

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

Study Drug for IM128-035		
Medication	**Potency**	**IP/Non-IP**
BMS-931699-01[a] Injection	12.5 mg/mL	IP
BMS-986142-01 Film Coated Tablet	50 mg	IP
Matching Film-Coated placebo for 50 mg BMS-986142-01 tablets	placebo	IP
BMS-986142-01 Film Coated Tablet	150 mg	IP
Matching Film Coated Placebo for 150 mg BMS-986142-01 tablets	placebo	IP

[a] The clinical label will reflect the product name as "BMS-931699-01" to be linked with the product description on the vial.

Study Assessments:

Efficacy will be assessed using the ESSDAI and ESSPRI scores, as well as various other pharmacodynamic (PD), clinical, and patient reported measures of dryness and disease activity as listed under the objectives and endpoints. Safety (through reporting of adverse events, clinical laboratory results, physical examination, which includes vital signs and electrocardiograms [ECGs]), PK, pharmacodynamics, exploratory biomarkers, target engagement, and immunogenicity will also be assessed.

Statistical Considerations:

Sample Size:

The sample size calculation is based on the power to compare change from baseline in ESSDAI at Week 12 between active treatment arms (lulizumab or BMS-986142) and the placebo arm. With a two-sided, two-sample t-test at significance level 0.05, data from 25 treated subjects per arm will provide approximately 90% power to detect a placebo-adjusted 3-point decrease from baseline for each active treatment group, assuming common standard deviations of 3.2. In addition, the Hochberg's step-up procedure will be used to adjust the multiplicity due to the comparison of two active treatment arms (lulizumab or BMS-986142) to the placebo arm.

The primary efficacy analysis will be conducted on all randomized subjects who received at least one dose of study drug.

An interim analysis will be conducted after at least 30 subjects reach Week 12 (complete 12 weeks of treatment) and complete the specified assessments for ESSDAI. The interim analysis will be conducted in a fully blinded manner such that treatment group assignments of study subjects are not known and are not used in any manner in the analysis. A blinded examination of the variance of the primary endpoint will be performed and compared to the assumption used in planning the study. If this comparison suggests the initial assumption was substantially too low, the total study sample size may be increased by up to 45 additional subjects (ie, to a maximum of 120 subjects in total) to maintain the desired study power. Regardless of the outcome from the blinded examination of variability, the study sample size will not be decreased. A maximum study sample size of 120 subjects in total, ie, 40 subjects per arm, can provide each active treatment arm 79% power to detect a placebo-adjusted 3-point decrease from baseline for common standard deviations as large as 4.8, using a two-sided two-sample t-test comparing each active treatment arm to placebo at significant level 0.05.

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Endpoints:

The primary endpoint is to compare the change from baseline in ESSDAI score at Week 12 between active treatment arms (lulizumab or BMS-986142) and the placebo arm.

Secondary Endpoints:

- Change from baseline in ESSPRI score at Week 12
- Proportion of subjects with ≥ 3 points of improvement from baseline in ESSDAI at Week 12
- Proportion of subjects with ≥ 1 point of improvement from baseline in ESSPRI at Week 12
- Proportion of subjects with both ≥ 3 points improvement in ESSDAI and ≥ 1 point of improvement in ESSPRI from baseline at Week 12
- Change from baseline in:
  - ESSDAI scores at Weeks 4 and Week 8
  - ESSPRI scores at Weeks 4 and Week 8
  - ESSPRI individual component (Dryness, Fatigue, and Pain) scores at Weeks 4, 8, and 12
  - Unstimulated and stimulated salivary flow rate at Weeks 4, 8, and 12
  - Ocular surface staining, Schirmer's test and tear break-up time test at Weeks 4, 8, and 12
- Safety and tolerability of lulizumab or BMS-986142 as measured by adverse events, laboratory parameters, vital signs, physical exams, and ECGs
- Change from baseline in patient and physician assessments of disease activity:
  - Numeric rating scale (NRS) for mouth, eye and vaginal dryness
  - Subject global assessment of disease activity (SubGDA) and physician global assessment of disease activity (phyGDA)
  - Short Form-36 (SF-36)
  - Female Sexual Function Index (FSFI)
  - Work participation and activity impairment questionnaire (WPAI)
  - PROMIS Fatigue Short Form
  - Trough concentrations of BMS-931699 and BMS-986142 at protocol-specified time points

Efficacy Analyses:

Primary efficacy analysis:

The mixed effects model with repeated measures (MMRM) will be used to model the change from baseline in ESSDAI score over time for all treatment arms. Details of the model will be given in the statistical analysis plan. The least square means of the differences of Week 12 change in ESSDAI from baseline between each active treatment and the placebo will be estimated and their corresponding two-sided 95% confidence intervals will be provided. In addition, as part of the secondary objective, similar outputs will be provided for the changes in ESSDAI score at Weeks 4 and 8.

The Hochberg's step-up procedure will be used to adjust the multiplicity due to the comparison of two active treatments (lulizumab or BMS-986142) to the placebo arm in the primary endpoint (ie, change from baseline in ESSDAI at Week 12). The corresponding adjusted p-values for the Hochberg procedure will be provided.

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Secondary efficacy analysis:

For all secondary endpoints, no multiplicity adjustment will be applied, and nominal p-values may be provided if applicable. For each of the following categorical secondary endpoints, the estimate and its corresponding two-sided 95% confidence interval will be calculated for the proportion for each treatment arm. In addition, as exploratory analyses, differences of the proportions between each active treatment arm and the placebo arm will be evaluated and their corresponding two-sided 95% confidence intervals will be provided.

- Proportion of subjects with a ≥ 3 point improvement from baseline in ESSDAI at Week 12
- Proportion of subjects with a ≥ 1 point improvement from baseline in ESSPRI at Week 12
- Proportion of subjects with both ≥ 3 point improvement from baseline in ESSDAI and ≥ 1 point improvement from baseline in ESSPRI at Week 12

Similar to the primary endpoint, the following continuous secondary endpoints will be analyzed using the MMRM method:

- Change from baseline in ESSPRI scores at Week 4, 8 and, 12
- Change from baseline in score of each individual ESSPRI components (Dryness, Fatigue, and Pain) at Weeks 4, 8, and 12
- Change from baseline in mouth dryness as measured by unstimulated and stimulated salivary flow rate at Weeks 4, 8, and 12
- Change from baseline in eye dryness as measured by ocular surface staining, Schirmer's test, and tear break-up time test at Weeks 4, 8, and 12

Analyses for other outcomes research assessments will be discussed in Outcome Research Analyses section.

[redacted]

Safety analyses:

All recorded adverse events will be listed and tabulated by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator, and abnormalities, if present, will be listed. Any pre-established Events of Special Interest will be listed and summarized.

[redacted]

Interim analysis:

One interim analysis will be conducted when at least 30 subjects reach Week 12 (complete 12 weeks of treatment) and complete specified assessments for ESSDAI.

The interim analysis will be conducted in a fully blinded manner such that treatment group assignments of study subjects are not known and are not used in any manner in the analysis. Specifically, a blinded examination of the variance of the primary endpoint will be performed and compared to the assumption used in planning the study. If this comparison suggests the initial assumption is substantially too low, the total study sample size may be increased by up to 45 additional subjects (ie, to a maximum of 120 subjects in total) to maintain the desired study power.

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Regardless of the outcome from the blinded examination of variability, the study sample size will not be decreased. Details on the blinded sample size re-estimation will be given in the statistical analysis plan.

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1 INTRODUCTION AND STUDY RATIONALE

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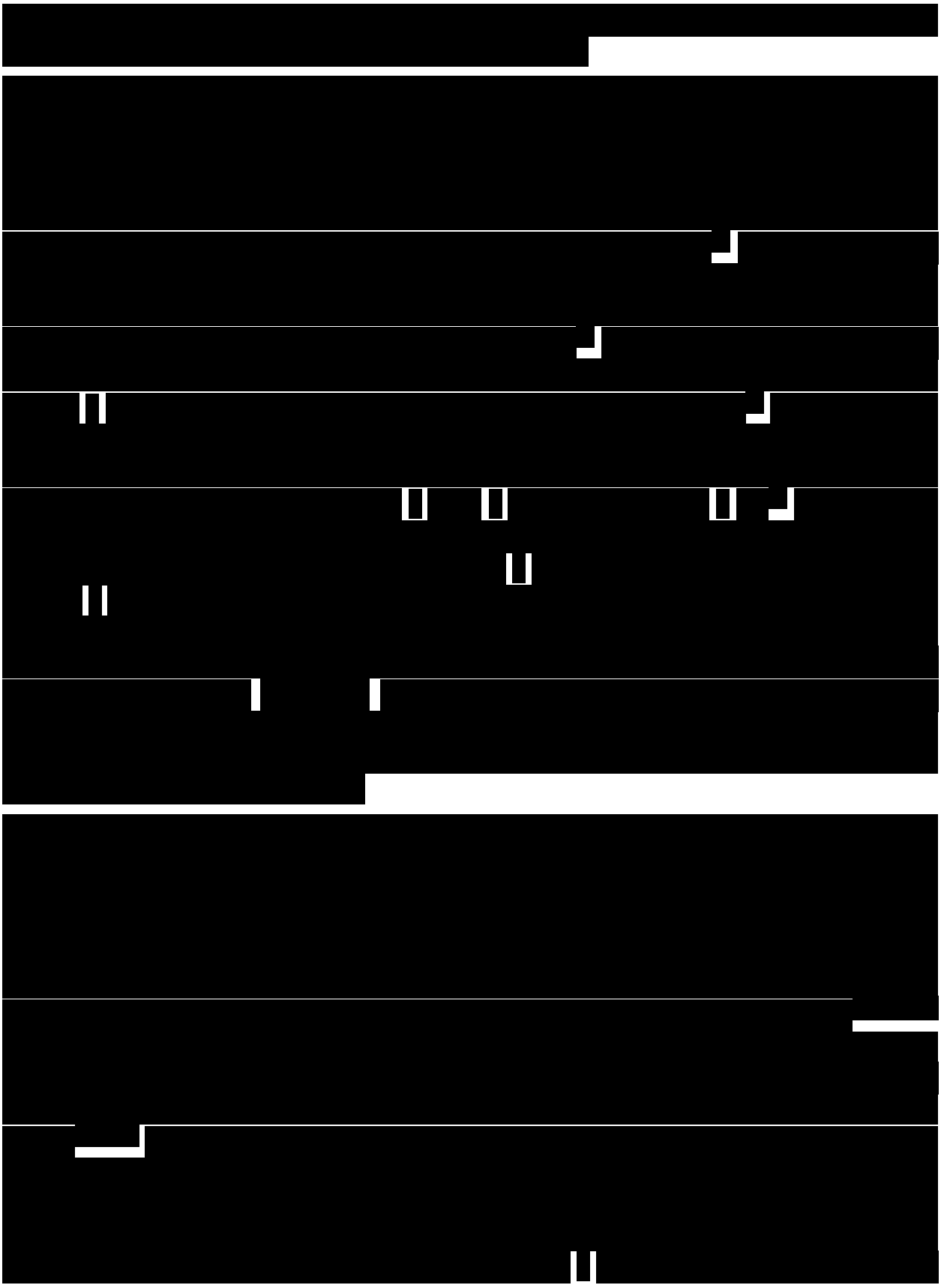

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1.2 Research Hypothesis

Treatment with BMS-931699 (lulizumab) or BMS-986142 for 12 weeks is more effective than placebo in decreasing the ESSDAI score in subjects with moderate to severe pSS.

1.3 Objectives(s)

1.3.1 Primary Objective

To evaluate the efficacy of treatment with either lulizumab or BMS-986142 versus placebo in subjects with moderate to severe pSS as measured by the change from baseline in ESSDAI at Week 12 between active treatment arms (lulizumab or BMS-986142, respectively) and the placebo arm.

1.3.2 Secondary Objectives

To assess the:

- Change from baseline in ESSPRI score at Week 12
- Proportion of subjects with a ≥ 3 point improvement from baseline in ESSDAI at Week 12
- Proportion of subjects with a ≥ 1 point improvement from baseline in ESSPRI at Week 12
- Proportion of subjects with both ≥ 3 points improvement in ESSDAI and ≥ 1 point improvement in ESSPRI from baseline at Week 12
- Change from baseline in ESSDAI scores at Week 4 and Week 8
- Change from baseline in ESSPRI scores at Week 4 and Week 8
- Change from baseline in ESSPRI components (Dryness, Fatigue, and Pain) at Weeks 4, 8, and 12

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- Change from baseline in unstimulated and stimulated salivary flow rate at Weeks 4, 8, and 12
- Change from baseline in ocular surface staining, Schirmer's test, and tear break-up time test at Weeks 4, 8, and 12
- Safety and tolerability of lulizumab or BMS-986142 in subjects with moderate to severe pSS, as measured by adverse events, laboratory parameters, vital signs, physical exams, and ECGs
- Change from baseline in patient and physician assessments of disease activity:
  - Patient Numeric Rating Scale (NRS) scores for mouth, eye and vaginal dryness (see Appendices 7, 8 and 9)
  - Subject global assessment of disease activity (SubGDA, see Appendix 5) and physician global assessment of disease activity (phyGDA, see Appendix 6)
  - Short Form - 36 acute (SF-36 acute, see Appendix 12)
  - Female Sexual Function Index (FSFI, see Appendix 11)
  - Work participation and activity impairment questionnaire (WPAI, see Appendix 13)
  - PROMIS Fatigue Short Form (see Appendix 10)
- [redacted]

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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).

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

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).

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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 IB or product labeling information to be provided to subjects and any updates.

The investigator or BMS 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.

BMS 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

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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 12-week randomized, double-blind, placebo-controlled, parallel group study with adaptive design features based on an interim analysis (IA). The study will initially have a 28-day screening period followed by up to 12 weeks of double-blind treatment with either lulizumab, BMS-986142, or a matching placebo.

Screening period:

The standard duration of the Screening Period is up to 28 days (4 weeks), with up to two Screening Visits allowed for subjects who require adjustment of oral corticosteroids or who are taking HCQ. Subjects who are on oral corticosteroids at a dose higher than 10 mg/day will require a taper at the beginning of the Screening Period to a stable dose of no more than 10 mg/day of prednisone (or equivalent) for least 14 days prior to dosing (Day -14), and will need to be reevaluated prior to randomization (Day 1). Subjects who are taking HCQ at screening who meet the study criteria will be required to return for a second visit during the screening period to collect baseline HCQ PK samples as described in Section 5.5 (these subjects should bring their daily dose of HCQ to the clinical site to be administered at the site). Should more time be needed, the duration of the Screening Period may be extended up to another week (total of 35 days or 5 weeks) depending on dose stabilization, technical issues, or subject scheduling. Study procedures will occur as specified in Table 5.1-1.

Double-blind treatment period:

Upon meeting the Inclusion/Exclusion criteria, approximately 75 subjects with moderate to severe pSS will be equally randomized to 1 of 3 treatment arms (lulizumab, BMS-986142, or matching placebos) for up to 12 weeks of treatment, followed by a 6 week follow-up period after completion of treatment. During this period, the dose of oral corticosteroids, hydroxychloroquine, pilocarpine, cevimeline, cyclosporine eye drops, lifitegrast, autologous serum eye drops, oral and ocular lubricants and/or NSAIDs should remain stable. No additional immunosuppressive medications may be started unless indicated for the treatment of adverse

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events. Analgesics are permitted with certain restrictions (see Section 3.4.1.2). Study procedures will occur as specified in Table 5.1-2, Table 5.5-1, and Table 5.6-1.

If a subject discontinues early from treatment, all procedures scheduled for the End of Week 12/End of treatment visit should be performed at the time of actual discontinuation/end of treatment. At the end of the double blind treatment period, alternate therapies for Sjögren's syndrome should be discussed with subjects.

Interim analysis:

An IA of all accumulated primary endpoint (ESSDAI) data up to Week 12 will be performed after at least 30 subjects reach Week 12 (complete 12 weeks of treatment) and complete the specified assessments for the Week 12 ESSDAI score. The interim analysis will be conducted in a fully blinded manner, such that treatment group assignments of study subjects are not known and are not used in any manner in the analysis. A blinded examination of the variance of the primary endpoint will be performed and compared to the assumption used in planning the study. Based on the results, the study sample size may be increased to maintain adequate statistical power. The blinded IA will not interfere or alter any subject's treatment, that is, subjects who were enrolled before the IA is completed will continue the originally assigned treatment arm if they have received at least 1 treatment and the dose is considered safe.

Follow-Up Period:

After completion of the double-blind treatment period or early discontinuation from the study, all subjects will continued to be followed for an additional 6 week safety follow-up period. There will be two post treatment Follow-Up visits at Week 15 (or 3 weeks after early discontinuation) and Week 18 (or 6 weeks after early discontinuation). Study procedures will occur as specified in Table 5.1-2.

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

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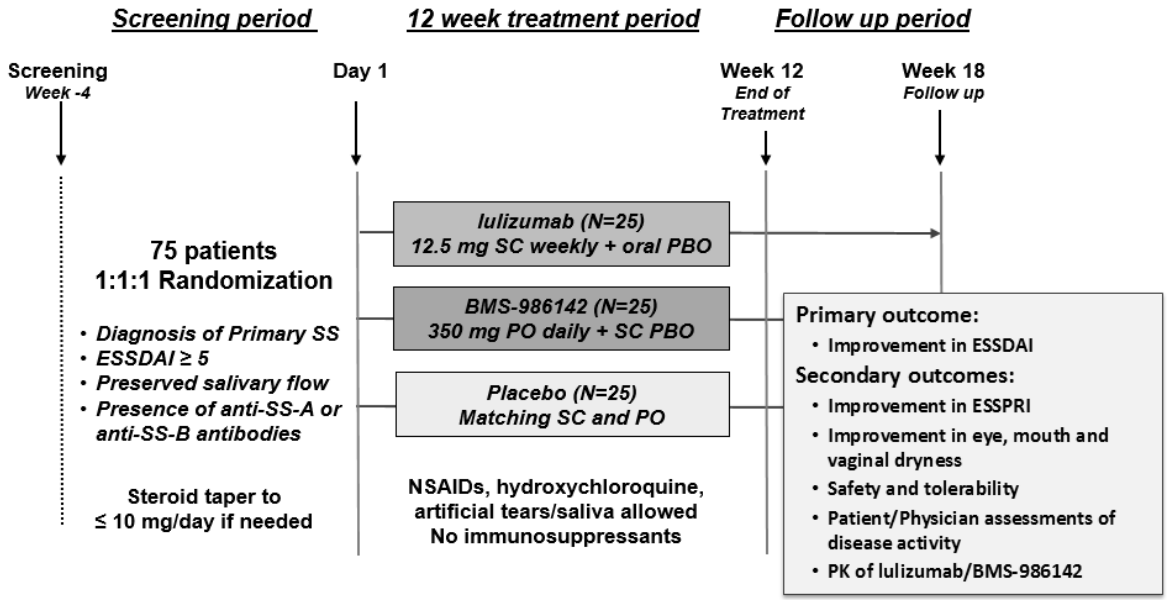
Figure 3.1-1: Study Design Schematic



The approximate duration of the study is up to a 5-week screening period (35 days), a 12-week double-blind treatment period (84 days), and 6 weeks of follow up (42 days), for a total of up to 23 weeks (161 days).

The start of the trial is defined as the date of the first Screening Visit for the first subject screened. The end of the trial is defined as the date of the last visit or scheduled procedure shown in the Time & Events schedule for the last subject. Study completion is defined as the final date when the data from the last safety follow-up visit for the last subject has been received at BMS and the study is considered clinically complete.

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study. Pending appropriate preclinical and clinical data to support further drug development, BMS may authorize a study extension, or another mechanism to provide study drug to subjects who received clinical benefit in this study at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; d) BMS terminates development of the drug; or e) therapeutic alternatives become available in the local market.

3.3 Study Population

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

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3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects from whom signed written consent for participation in this study has been obtained

2. Target Population

a) Subjects diagnosed or classified as having moderate to severe pSS (primary Sjögren's syndrome is defined as Sjögren's syndrome in the absence of another autoimmune disease or rheumatologic condition) based on the 2016 ACR-EULAR Classification Criteria (see Appendix 2) for pSS, with disease duration from time since diagnosis of at least 16 weeks prior to the Screening Visit

b) ESSDAI ≥ 5, including disease activity (any score > 0) in at least one of the following domains: Glandular, Articular, Hematological, Biological, Lymphadenopathy

c) Positive anti-SS-A/Ro or anti-SS-B/La autoantibody

d) Unstimulated whole saliva secretion > 0.01 ml/min

e) Prednisone or other oral corticosteroid use is not required, however, if subject is taking prednisone (or prednisone-equivalent), dose must be tapered to a maximum of 10 mg/day for at least 14 days prior to Day 1 (randomization)

f) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented

3. Age and Reproductive Status

a) Males and Females, ages 18 to 70 years old, inclusive, at the time of randomization

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 pregnant or breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with lulizumab or BMS-986142 plus 5 half-lives of the active treatment with the longest half-life given treatment will be blinded (lulizumab [half-life of 7 days]), plus 30 days (duration of ovulatory cycle) for a total of 65 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 lulizumab or BMS-986142 plus 5 half-lives of the active treatment with the longest half-life given treatment will be blinded (lulizumab [half-life of 7 days]) for a total of 35 days post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time

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

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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 WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception (Refer to Appendix 1 for a list of acceptable methods), which have a failure rate of < 1% when used consistently and correctly.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Secondary Sjögren's syndrome

b) Other systemic autoimmune disease (eg, RA, SLE, multiple sclerosis [MS], vasculitis)

c) Subjects with a condition that, in the opinion of the Investigator, may confound the diagnosis of pSS, including but not limited to: head and neck radiation, graft versus host disease, lymphoma, prior or current diagnosis of sarcoidosis, chronic viral diseases such as HIV, HTLV, or HCV, or IgG4 disease

d) Very severe pSS or severe complications of pSS at the time of the screening visit, including but not limited to:

i) severe or ESSDAI Renal Domain High Activity - renal disease including but not limited to interstitial nephritis, glomerulonephritis, nephrotic syndrome with proteinuria > 3 gm/day and/or serum creatinine ≥ 2.0 mg/dL

ii) severe or ESSDAI CNS or PNS Domain High Activity - neurologic disease including but not limited to central or peripheral neuropathy or CNS vasculitis

iii) severe or ESSDAI Pulmonary Domain High Activity - pulmonary disease including but not limited to interstitial pneumonitis or obstructive bronchiolitis

iv) severe or ESSDAI Cutaneous Domain High Activity - documented vasculitis (mild isolated cutaneous vasculitis is not a contraindication)

v) lymphoma or other lymphoproliferative disease

vi) cryoglobulinemia with neurological, renal or visceral involvement

vii) severe or ESSDAI Muscular Domain High Activity - myositis

viii) any complication requiring corticosteroid therapy ≥ 1 mg/kg during the 30 days preceding the screening visit

e) Subjects with an acutely infected salivary gland within 30 days of the screening visit

2. Medical History and Concurrent Diseases

a) Subjects at risk for tuberculosis (TB). Specifically, subjects with:

i) Current clinical, radiographic or laboratory evidence of active TB

ii) A history of active TB within the last 3 years, even if treated

iii) A history of active TB greater than 3 years ago unless there is documentation that the prior anti-TB treatment was appropriate in duration and type

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iv) Therapy for latent TB which has not been completed as per local country guidelines

v) Positive interferon gamma release assay (IGRA) for TB unless proper treatment is documented as above

b) Subjects with any bacterial infection within the last 60 days prior to screening (enrollment), unless treated and resolved with antibiotics, or any chronic or history of recurrent bacterial infection (such as chronic pyelonephritis, osteomyelitis and bronchiectasis)

c) Subjects who have a history of systemic fungal infections (such as histoplasmosis, blastomycosis, or coccidiodomycosis)

d) 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 visit (enrollment)

e) Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral infection at the time of potential enrollment, including subjects with history or evidence of Human Immunodeficiency Virus (HIV) infection or who have a positive HIV test at screening

f) Any significant concurrent medical condition at the time of screening or baseline visit, including, but not limited to, the following:

i) Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary or active infection/infectious illness) that, in the Investigator's judgment will substantially increase the risk to the subject if he or she participates in the study

ii) Cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell or squamous cell carcinoma that has been treated with no evidence of recurrence). Subjects with a history of lymphoma at any time are excluded

iii) Female subjects with a breast cancer screening suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations

iv) Class III or IV congestive heart failure as defined by the New York Heart Association

v) Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cerebrovascular disease within 24 weeks before screening

vi) Liver cirrhosis or other underlying liver disease (eg, non-alcoholic steatohepatitis, primary sclerosing cholangitis, primary biliary cirrhosis/cholangitis)

vii) Any significant coagulation or platelet function disorders (eg, von Willebrand's disease)

viii) Any gastrointestinal condition that could impact study drug absorption

ix) Any other concomitant medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study

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g) Major surgical intervention or scheduled surgery during the 8 weeks preceding enrollment

h) Subjects currently on hydroxychloroquine who cannot provide documentation of an ophthalmologic evaluation (including evaluation of the retina) or who have evidence of retinopathy within 6 months of screening

i) Donation of blood to a blood bank or in a clinical study (except a screening visit) within 4 weeks of study drug administration (within 2 weeks for plasma only)

j) Blood transfusion within 4 weeks of study drug administration

k) Inability to be venipunctured and/or tolerate venous access

l) Subjects with a history of (within 12 months of signing the consent), or known current problems with drug or alcohol abuse

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

n) Subjects who have received treatment with an investigational drug within 12 weeks or less than 5 terminal half-lives of elimination (whichever is longer) of randomization (Day 1)

o) Live vaccine administration to subjects within 30 days of enrollment, during the screening or study periods, or for 8 weeks after completion of dosing

p) Subjects who are unwilling or have difficulty swallowing oral tablets

3. Physical and Laboratory Test Findings

a) Subjects with positive HBsAg, or subjects with positive anti-HBc antibody with detectable quantitative HBV DNA. Subjects with negative HBsAg but with high risk for latent HBV infection (including subjects with known family history of HBV infection, HBV carrier, personal medical history of hepatitis or blood transfusion history) should be tested for quantitative HBV DNA at the investigator's discretion. Subjects with positive quantitative HBV DNA are excluded from the study

b) Hepatitis C antibody-positive subjects who are also HCV positive by confirmatory testing such as PCR

c) Positive HIV test

d) Have any clinically significant laboratory abnormalities (confirmed by repeat testing) including but not limited to:

i) Hepatic

(1) ALT ≥ 2 x ULN (Upper limit of normal)

(2) AST ≥ 2 x ULN

(3) Total bilirubin ≥ 1.5 x ULN

ii) Hematology

(1) WBC count < $3000/mm^3$ ($3.0 \times 10^9/L$)

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(2) Hemoglobin < 9 g/dL

(3) Absolute neutrophil count < 1000/mm^3 (1.0 x 10^9/L)

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

iii) Creatinine ≥ 2.0 mg/dL

e) Subjects with a positive TB IGRA (such as Quantiferon® TB Gold, Refer to Section 3.3.2 #2a)

f) Any other significant laboratory abnormalities that, in the opinion of the Investigator, might place the subject at unacceptable risk for participation in this study (please discuss with BMS Medical Monitor if there are any questions in regards to inclusion/exclusion criteria)

4. Allergies and Adverse Drug Reaction

a) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity)

5. Prior and Concomitant Medications

a) Oral corticosteroids > 10 mg/day within 14 days of dosing (Day 1), or corticosteroid therapy ≥ 1 mg/kg during the 4 weeks preceding enrollment

b) Intravenous, intramuscular or intra-articular corticosteroids within 4 weeks of enrollment

c) Treatment started or an unstable dose of non-steroidal anti-inflammatory drugs (NSAIDs), pilocarpine, cevimeline (Evoxac®), topical corticosteroid eye preparations, lifitegrast (Xiidra®), autologous serum eye drops, or cyclosporine eye drops (Restasis®) within 14 days of dosing (doses must be held for at least 12 hours prior to any study visit after Screening)

d) Use of methotrexate, cyclophosphamide, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil (MMF) or leflunomide within 12 weeks of enrollment

e) Treatment started or an unstable dose of hydroxychloroquine (Plaquenil®) within 8 weeks of enrollment. Doses higher than 400 mg/day are not permitted. Use of other antimalarials (eg, chloroquine, quinacrine) is not permitted

f) Use of rituximab within 6 months prior to enrollment or lack of recovery of CD19+ B cells to > 10/µl at screening in any subject with prior rituximab use

g) Previous treatment with other biologics either marketed or in development (eg, abatacept, tocilizumab, belimumab, TNF inhibitors) within 6 months prior to enrollment

h) Subjects are not permitted to have new installation of lacrimal punctum plugs within 4 weeks of randomization (Day 1) or during the course of the study. 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)

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

c) Inability to comply with restrictions and prohibited treatments as listed in Section 3.4

d) Adults under guardianship or protection

e) Participation in another interventional therapeutic trial (treatment underway or in study follow-up period)

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

A woman 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 > 40mIU/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. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 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.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Restricted treatment for the different study periods are detailed below:

3.4.1.1 Restricted/Prohibited Treatments Prior to Enrollment/Randomization

- Oral corticosteroids > 10 mg/day within 14 days of dosing (Day 1), or corticosteroid therapy ≥ 1 mg/kg during the 4 weeks preceding enrollment
- Intravenous, intramuscular or intra-articular corticosteroids within 4 weeks of enrollment.

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- Treatment started or an unstable dose of NSAIDs, pilocarpine, cevimeline (Evoxac®), topical corticosteroid eye preparations, lifitegrast (Xiidra®), cyclosporine eye drops (Restasis®) or autologous serum eye drops within 14 days of dosing (dose must be held for at least 12 hours prior to any study visit after Screening)
- Artificial tears and/or saliva are permitted, but must be held on the day of study visit
- Use of methotrexate, cyclophosphamide, cyclosporine, tacrolimus, azathioprine, MMF or leflunomide within 12 weeks of enrollment
- Treatment started or an unstable dose of hydroxychloroquine (Plaquenil®) within 8 weeks of enrollment. Doses higher than 400 mg/day are not permitted. Use of other antimalarials (chloroquine, quinacrine) is not permitted
- Use of rituximab within 6 months prior to enrollment or lack of recovery of CD19+ B cells > 10/μl at screening in any subject with prior rituximab use
- Previous treatment with other biologics either marketed or in development (eg, abatacept, tocilizumab, belimumab, TNF inhibitors) within 6 months prior to enrollment
- Live vaccine administration to subjects within 30 days of enrollment, during the screening or study periods, or for 8 weeks after completion of dosing

3.4.1.2 Restricted/Prohibited Treatments During Double-Blind Treatment Period

All restrictions during the double-blind period only apply to the management of symptoms for pSS.

For concomitant treatments for other conditions, see Section 3.4.1.3. Some of the drugs used for other conditions may result in drug interactions and may be prohibited or restricted. Any medication initiated during the treatment period should be discussed with the BMS Medical Monitor.

Hydroxychloroquine (Plaquenil®)

All subjects who enter the screening period on hydroxychloroquine must remain on a stable dose of no more than 400 mg daily from the time of signing the informed consent for the duration of the study. New initiation of hydroxychloroquine, a daily dose > 400 mg/day, or a change in the dose of hydroxychloroquine is not permitted during the screening or dosing periods. The use of other antimalarials is not permitted.

Steroids

All subjects taking oral prednisone or its equivalent during screening must remain at a dose ≤ 10 mg/day for the entirety of the dosing period. Intra-articular, intramuscular (IM) or intravenous (IV) corticosteroid injections, or initiation of topical corticosteroid eye preparations are not permitted during the screening or dosing periods unless required for treatment of adverse events in consultation with the BMS Medical Monitor.

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Ocular and Oral Lubricants

Subjects who enter the screening period on a stable dose of pilocarpine, cevimeline (Evoxac®), topical corticosteroid eye preparations, cyclosporine eye drops (Restasis®), lifitegrast (Xiidra®), or autologous serum eye drops are permitted to remain on these medications during the screening and dosing period, but must hold the dose(s) for at least 12 hours prior to any study visit until all study assessments are completed. These medications may not be initiated during the screening or dosing period. Artificial tears and saliva are permitted but must be held on the day of a study visit until all study assessments are completed.

Analgesics and NSAIDs

- NSAIDS doses should remain stable with the exception of decreases being permitted due to related adverse events, such as gastric toxicity.
- Analgesics
  - Acetaminophen (paracetamol) maximal dose 2 g/day

    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 2 g/day
  - Narcotic analgesics must not exceed 30 mg/day of morphine or its equivalent
  - Tramadol doses must be stable
  - Acetylsalicylic acid is allowed in low doses (eg, ≤ 100 mg/day) for cardiovascular prophylaxis

Immunosuppressives

The following medications are prohibited during the screening, dosing and follow-up periods:

- methotrexate
- cyclophosphamide
- leflunomide
- azathioprine
- cyclosporine
- tacrolimus
- MMF
- rituximab
- belimumab
- tocilizumab

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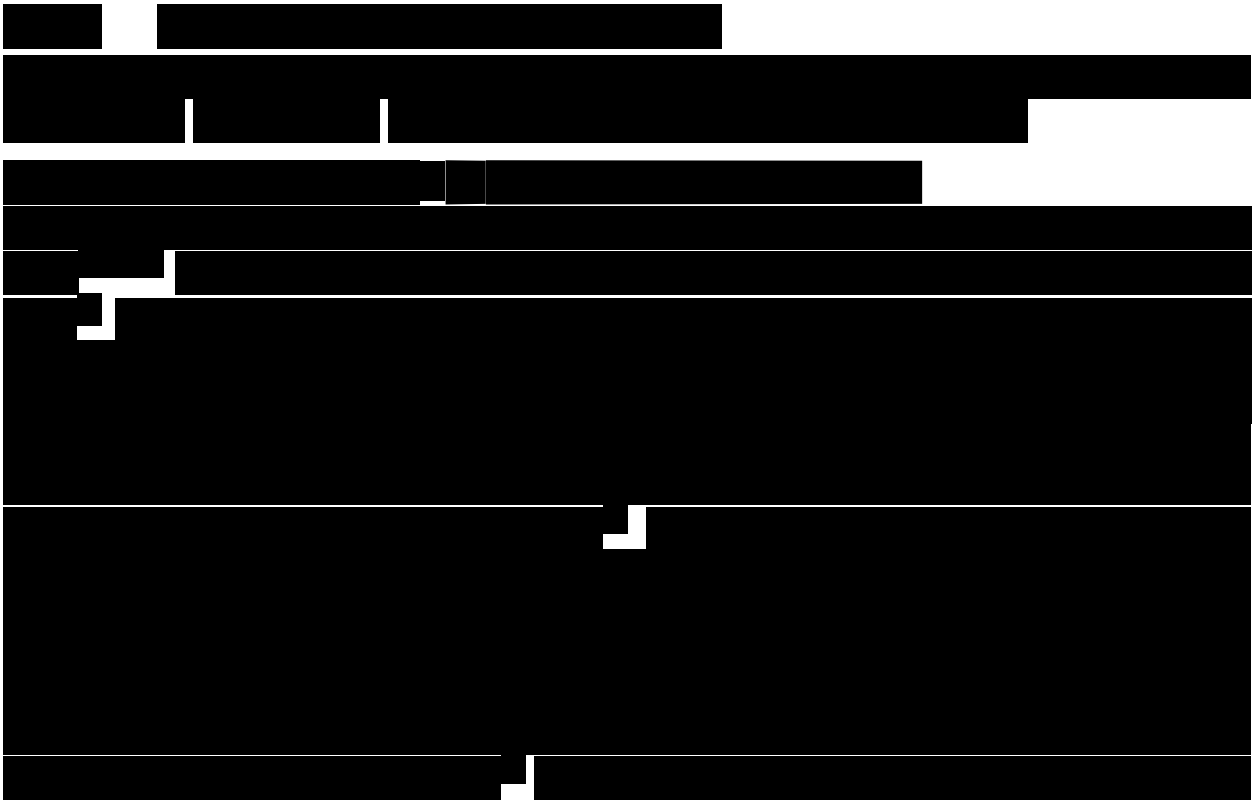
- All investigational and approved biologic therapies (including but not limited to abatacept, etanercept, anakinra, infliximab, etc.)
- Use of any investigational drug other than study medication

Hormonal Contraceptives:

The use of hormonal contraceptives (oral, via implant/depot or via eluting IUD) are prohibited as a method of highly effective contraception due to safety concerns from transient liver function test elevations observed in the drug-drug interactions study (IM006032) with BMS-986142 and a combination oral contraceptive (ethinyl estradiol and the norethindrone acetate). In the study, a total of 10 of 16 subjects that were dosed with the oral contraceptive and BMS-986142 in combination had mild to moderate elevations of transaminases without an associated increase of total bilirubin. The majority of ALT elevations were < 3xULN. The maximum increase occurred in one subject with an ALT 5.8x ULN without accompanying total bilirubin elevation. Most subjects had no symptoms, however, 3 subjects had nausea, 2 subjects had vomiting and 1 had chills. All of the elevated transaminase levels returned to baseline. An evaluation of the cause of the transaminase elevation is ongoing, but no marked changes in the exposures of BMS-986142 or the components of the oral contraceptive were observed in a preliminary assessment of the data (i.e. no pharmacokinetic drug-drug interaction occurred during co-administration).

In addition, the use of oral or implantable estrogen-based hormone replacement therapy is also prohibited until additional drug interaction data becomes available. See Section 3.4.1.3.



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3.4.2.2 Infections

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

3.5 Discontinuation of Subjects Following Treatment with Study Drug

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 or withdrawal of informed consent
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- 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
- Unblinding a subject for any reason (emergency or non-emergency)
- Use of prohibited medication
- Development of new active manifestations of pSS requiring treatment with any non-protocol approved medications during the study
- Inability or subject's failure to comply with the protocol requirements
- Pregnancy
- Male subjects must discontinue treatment if their female partners become pregnant during the trial. After discontinuation, male subjects are required to continue using a highly effective method of contraception for a total of 35 days post-treatment completion
- Severe (eg, ≥ Grade 3), drug-related AEs of infection, bleeding events/coagulopathy, or injection site reactions

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- ANC < 500/mm^3, confirmed by repeat
- Potential drug induced liver injury (see Section 6.6 for definition)

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/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 call the BMS Medical Monitor/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 BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug 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).

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

3.6 Post Study Drug Follow up

In this study, ESSDAI and ESSPRI as well as other efficacy measures at Week 12 are key endpoints of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study subject's participation in the specified follow up period of the study, whichever comes first.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to

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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.

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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:

- All products, active or placebo, being tested or used as a comparator in a clinical trial
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection

Table 4-1: Study Drugs for IM128035

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open-Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-931699-01 Injection[a] The composition of the drug product is 12.5 mg/mL, BMS-931699 (lulizumab) in 20 mM phosphate, pH 5.9, with 5% (w/v) sorbitol	12.5 mg/mL	IP	Open-Label	3 cc vial with 13mm opening, 1-panel / Open-label Appearance clear to slightly opalescent, colorless to pale yellow solution	Store refrigerated 2 – 8 °C Protect from light, Protect from freezing
BMS-986142-01 Film Coated Tablet	50 mg	IP	Blinded Label	Plain, yellow, round film coated tablet HDPE Bottle	Store refrigerated 2 – 8 °C Store in a tightly closed container
Placebo for BMS-986142-01 Film Coated Tablet, 50mg	Placebo	IP	Blinded Label	Plain, yellow, round film coated tablet HDPE Bottle	Store refrigerated 2 – 8 °C Store in a tightly closed container

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Table 4-1: Study Drugs for IM128035

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open-Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986142-01 Film Coated Tablet	150 mg	IP	Blinded Label	Plain, yellow, oval film coated tablet HDPE Bottle	Store refrigerated 2 – 8 °C Store in a tightly closed container
Placebo for BMS-986142-01 Film Coated Tablet, 150mg	Placebo	IP	Blinded Label	Plain, yellow, oval film coated tablet HDPE Bottle	Store refrigerated 2 – 8 °C Store in a tightly closed container

[a] The clinical label will reflect the product name as "BMS-931699-01" to be linked with the product description on the vial

BMS will provide BMS-931699-01, BMS-986142-01 and matching placebo for BMS-986142-01 tablets to all investigating sites. For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the product label (eg, normal saline placebo for BMS-931699)

Pharmacy dosing manual will be provided separately to the sites.

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4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

In this protocol, investigational products (also described in Table 4-1) are:

- BMS-931699/lulizumab injection (12.5mg/vial, 12.5mg/mL) for subcutaneous administration
- BMS-986142 50mg tablet (round) for oral administration
- BMS-986142 150 mg tablet (oval) for oral administration
- Matching Placebo for BMS-986142 50 mg tablet (round) for oral administration
- Matching Placebo for BMS-986142 150 mg tablet (oval) for oral administration

The placebo for BMS-931699/lulizumab injection is normal saline solution. The investigational sites will provide the normal saline for preparation of placebo BMS-931699/lulizumab.

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 (Plaquenil®)
- Prednisone or other oral corticosteroids
- Pilocarpine, cevimeline (Evoxac®), cyclosporine eye drops (Restasis®)
- NSAIDs & analgesics
- Ocular and oral lubricants (artificial tears or saliva)

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

4.3 Storage and Dispensing

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

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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 and Section 4.8 for return and destruction instructions.

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

Please refer to the current versions of the IBs and/or pharmacy reference sheets for complete storage, handling, dispensing information for BMS-931699/lulizumab and BMS-986142.

Lulizumab:

Preparation for Subcutaneous (SC) Use for BMS-931699/lulizumab

For SC dosing, no dilution of drug product solution (12.5 mg/mL) will be required for the 12.5 mg dose. A commercially available appropriately sized sterile needle and appropriate syringe should be used for withdrawal from vial and administration (refer to the pharmacy dosing manual for further details on the subcutaneous preparation and administration for materials and instructions, which is provided separately).

The placebo for lulizumab injection is normal saline injection, which is administered in a similar fashion as described for the lulizumab injection. The normal saline to use as placebo will not be provided by the Sponsor.

Lulizumab injection should be stored at 2 – 8 °C with protection from light and protection from freezing. After withdrawal into an appropriate sized syringe, the product must be administered within 4 hours. If not dosed immediately, filled syringes should be kept at 2 – 8 °C with protection from light and freezing prior to use.

Study personnel will administer the dose to the subject. The primary point of injection should be one of the upper arms; however, other points of injections are acceptable, such as stomach or thighs. The same injection site should not be used for consecutive study drug administration. The subjects should be monitored for at least 1 hour after each injection for potential reactions.

BMS-986142:

BMS-986142 bottles should be stored at 2 – 8 °C and stored in a tightly closed container.

Please refer to the current version of the IB and/or pharmacy dosing manual for complete storage, handling and dispensing information for lulizumab and BMS-986142.

4.4 Method of Assigning Subject Identification

At the time of the screening visit, immediately after written informed consent is obtained and before performing any study-related procedures, the investigator or coordinator will call into the

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Interactive Voice Response System (IVRS or IWRS) designated by BMS for assignment of a 5 digit subject number that will be unique across all sites. Enrolled subjects, including those not dosed, will be assigned unique sequential subject numbers by the IVRS/IWRS system starting with 00001, 00002, 00003, etc. for identification throughout the study. This subject number must not be reused for any other participant in the study.

After completion of all screening evaluations, on Day 1, all eligible subjects will be randomly assigned to 1 of 3 treatment arms (lulizumab, BMS-986142, or placebo) in an equal ratio. To randomize a subject, a phone call will be placed into the randomization option of the IVRS/IWRS in order to obtain a subject's randomized treatment assignment. Randomization will be assigned in the order in which subjects qualify for treatment, not in the order of study enrollment. The IVRS will be available 24 hours a day, 7 days a week, via a toll-free number (or via the internet for IWRS). Randomization will be stratified by hydroxychloroquine (Plaquenil®) and oral corticosteroid use.

Specific instructions (including an enrollment/randomization worksheet) for the central enrollment and randomization procedure using an IVRS/IWRS will be provided to the site.

Randomized schedules will be generated and kept by the Randomization Group within Drug Supply Management of Bristol-Myers Squibb.

At all study visits when study drug is dispensed, each subject will be assigned specific container numbers by the IVRS/IWRS. Container numbers will be assigned non-sequentially and will correspond to the numbers printed on the containers and bottles containing study drug, and will be recorded on the appropriate eCRF.

4.5 Selection and Timing of Dose for Each Subject

All drug dosing should occur after all study-related assessments, including blood draws, are completed. Refer to Section 5.3 for additional information on the order of procedures.

After randomization, study drug will be dispensed according to the assignment by the IVRS/IWRS system. Study drugs are blinded and will be supplied in bottles for BMS-986142 and its matching placebo for home administration. Doses of lulizumab or matching placebo are to be administered subcutaneously in the clinic or by a health care professional (eg, visiting nurse) in the home if approved by local IRB/EC and the investigator. Doses of BMS-986142 at 350 mg or matching placebo are to be administered orally q24h (one time/day) with water and may be taken with or without food. Three tablets, one tablet from Bottle A and two tablets from Bottle B, will be taken all at the same time, once/day every day. Subjects should be instructed to bring their oral study drug (BMS-986142 or placebo) to be taken at the investigational site at every scheduled visit (eg, weekly if home visits are not performed) to avoid confusion about the timing of dose administration, given the frequency of PK assessments and study procedures during the study. On Day 1 and at Weeks 2, 4, 6, 8, and 10, study drug will be administered in the morning at the study site and after blood samples have been collected and questionnaires have been completed. For subjects who are on a stable dose of HCQ, subjects must also bring their HCQ dose to the site on Day 1, Day 8, Week 2 (Day 15), Week 4 (Day 29) and Week 12 (Day 85) of the study as well as the two follow up visits at Week 15 (Day 106) and Week 18

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(Day 127), as the HCQ dose will be administered at the same time as the study drugs in the morning at the study site to enable pre-dose PK samples to be taken. Two post-dose PK samples (2 and 4 hours after dosing) for HCQ and study drugs will also be collected at the Day 8 visit. However, at other visits, drug should be taken at approximately the same time each day.

For BMS-986142 and matching placebo, each subject will be dispensed a set of two (2) bottles every two weeks during treatment. Bottle A contains 17 tablets and Bottle B contains 34 tablets of blinded study drug. The 3 additional tablets in Bottle A and the additional 6 tablets in Bottle B allow for a +/- 3 day window between each visit in the double-blind phase of the study. All study drug bottles (empty or full) that were dispensed to the subject must be brought back to the study site by the subject at Weeks 1, 2, 4, 6, 8, 10, and 12 during the double-blind period for drug reconciliation/compliance assessments.

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 one of the active products. It is highly desirable that the decision to unblind treatment assignment be discussed with the BMS 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 IVRS/IWRS. For information on how to un-blind in an emergency, consult the IVRS/IWRS manual.

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

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

In case of an emergency, the Investigator(s) has unrestricted access to randomization information via the Interactive Voice Response System (IVRS/IWRS) and is capable of breaking the blind through the IVRS/IWRS system without prior approval from sponsor. Following the unblinding, the Investigator should notify the BMS Medical Monitor.

The Bioanalytical Sciences section or its designate will be unblinded to the randomized treatment assignments in order to minimize unnecessary analysis of samples from control group subjects.

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Interim Analysis:

The interim analysis will be conducted in a fully blinded manner such that treatment group assignments of study subjects are not known and are not used in any manner in the analysis.

4.7 Treatment Compliance

The investigator or designated study personnel will maintain a drug accountability log of all study drug(s) received, dispensed, destroyed and the amount returned to the Sponsor or supply depot. The drug supplies will be inventoried and accounted for throughout the study. The drug accountability log will be reviewed by the study monitor during site visits and at the completion of the study.

Study drug lulizumab or placebo will be administered via SC injection in the clinical facility. The treatment compliance in this study for lulizumab will be done at the study site where documentation of injection and compliance will be maintained.

Study drug BMS-986142 or placebo will be administered orally at home by the subjects or on site during clinic visits. The treatment compliance in this study for BMS-986142 will be determined by counts of returned tablets of study drug and information providing by questioning the subject.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS 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.

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- 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.

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5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (IM128035)[a]

Procedure	Screening Visit 1	Screening Visit 2[b]	Notes
Eligibility Assessments			
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Medical History	X		
Enroll subjects (contact Central Randomization System)	X		Contact IVRS/IWRS for subject number after signing consent. If subject does not meet eligibility criteria, contact IVRS/IWRS to screen fail subject.
Concomitant Medication review	X	X	See Section 3.4 Hydroxychloroquine (if used) must be at a stable dose for 8 weeks prior to screening. Corticosteroids (if used) must be ≤ 10 mg/day for at least 14 days prior to dosing; no changes to other medications within 14 days of dosing.
ESSDAI	X		See Section 5.4.1
Unstimulated salivary flow	X		See Section 5.4.2.2
Anti-SSA/Ro and anti-SSB/La autoantibody	X		
Safety Assessments			
Physical Examination	X		
Targeted Physical Examination		X	targeted PE for steroid taper visits only (not HCQ)
Vital Signs	X	X	
Height and weight	X		
ECG	X		
Chest X-Ray	X		Required only if not performed within 6 months of signing informed consent and/or if documentation of previous CXR is not on file. See Section 5.3.3.

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Table 5.1-1: Screening Procedural Outline (IM128035)[a]

Procedure	Screening Visit 1	Screening Visit 2[b]	Notes
Safety Laboratory Tests	X		At least 10 hour fast required prior to collection of sample. Must include complete blood count with differential, chemistries, liver function tests, PT/PTT, amylase/lipase and urinalysis.
TBNK profile	X		For subjects who have been treated with rituximab in the past. Must be reviewed for CD19+ B cell count > 10/µl prior to dosing on Day 1.
TB Screening	X		See Section 5.3.3
HBsAg, HBcAb	X		May also include reflex HBV DNA testing where required locally
HCV antibody	X		If positive, reflex to HCV confirmation test such as PCR
HIV test	X		Performed locally or centrally per local regulations
Pregnancy Test (WOCBP only) or FSH (to confirm menopause)	X		Serum pregnancy test to be performed only if urine test is positive or un-interpretable, or if necessary as per local/institutional requirements.
Hydroxychloroquine PK sampling (subjects on HCQ only)		X	Subjects should bring their HCQ dose to the clinic for screening Visit 2 to be taken in the clinic. Serial PK sampling at 0hr, 2hr, 4hr after HCQ dosing.

[a] Screening window is 28 days (4 weeks), an additional 7 days (1 week) may be added if necessary; see Section 3.1 for information

[b] Required for any subject who requires a taper of oral corticosteroids during the screening period to ≤ 10 mg/day of prednisone (or equivalent) or any subject on HCQ

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Table 5.1-2: Short-term Procedural Outline (IM128035)

Procedure	During Treatment[a]												End of Trt[a,b]	FU #1[a]	FU #2[a]	Notes
	Day 1 (Baseline)	Day 8 (Week 1)	Day 15 (Week 2)	Day 22[c] (Week 3)	Day 29 (Week 4)	Day 36[c] (Week 5)	Day 43 (Week 6)	Day 50[c] (Week 7)	Day 57 (Week 8)	Day 64[c] (Week 9)	Day 71 (Week 10)	Day 78[c] (Week 11)	Day 85 (Week 12)	Day 106 (Week 15)	Day 127 (Week 18)	
Eligibility Assessments																
Inclusion / Exclusion Criteria	X															
Safety Assessments																
Physical Examination	X												X		X	
Targeted Physical Examination		X	X		X		X		X		X			X		See Section **5.3.4**
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X				X								X			
Safety Laboratory Tests	X	X	X		X		X		X		X		X		X	At least 10 hour fast required prior to collection of sample. Must include complete blood count with differential, chemistry, liver function tests, and urinalysis.
Fasting lipid panel	X								X				X		X	At least 10 hour fast required prior to collection of sample.

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Table 5.1-2: Short-term Procedural Outline (IM128035)

Procedure	During Treatment[a]												End of Trt[a,b]	FU #1[a]	FU #2[a]	Notes
	Day 1 (Baseline)	Day 8 (Week 1)	Day 15 (Week 2)	Day 22[c] (Week 3)	Day 29 (Week 4)	Day 36[c] (Week 5)	Day 43 (Week 6)	Day 50[c] (Week 7)	Day 57 (Week 8)	Day 64[c] (Week 9)	Day 71 (Week 10)	Day 78[c] (Week 11)	Day 85 (Week 12)	Day 106 (Week 15)	Day 127 (Week 18)	
Pregnancy Test (WOCBP only)	X				X				X				X		X	Negative pregnancy test must be confirmed within 24 hrs prior to dosing. Serum pregnancy test to be performed only if urine test is positive or un-interpretable or if necessary per local/institutional requirements.
Adverse Event Assessment																
Monitor for Non-Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 42 days post discontinuation of dosing or completion of subject's participation in the study if the last scheduled visit occurs at a later time.

Table 5.1-2: Short-term Procedural Outline (IM128035)

Procedure	During Treatment[a]												End of Trt[a,b]	FU #1[a]	FU #2[a]	Notes
	Day 1 (Baseline)	Day 8 (Week 1)	Day 15 (Week 2)	Day 22[c] (Week 3)	Day 29 (Week 4)	Day 36[c] (Week 5)	Day 43 (Week 6)	Day 50[c] (Week 7)	Day 57 (Week 8)	Day 64[c] (Week 9)	Day 71 (Week 10)	Day 78[c] (Week 11)	Day 85 (Week 12)	Day 106 (Week 15)	Day 127 (Week 18)	
Biomarker Assessments																
Target Engagement / Receptor Occupancy	X				X				X				X			See Section **5.6**
Clinical Biomarkers	X				X				X				X		X	Includes ANA, IgM RF, SSA, SSB, Complement (CH50, C3, C4), Immunoglobulins (IgG, IgA, IgM), B2M, ESR, hsCRP and soluble free light chains See Section **5.6**
Whole Blood RNA	X				X								X			See Section **5.6**
Whole Blood Immuno-phenotyping	X				X								X			See Section **5.6**
Serum Biomarkers	X				X				X				X			See Section **5.6**
Salivary Biomarkers	X				X				X				X			See Section **5.6**
PBMC Collection	X				X				X				X			See Section **5.6**

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Table 5.1-2: Short-term Procedural Outline (IM128035)

Procedure	During Treatment[a]												End of Trt[a,b]	FU #1[a]	FU #2[a]	Notes
	Day 1 (Baseline)	Day 8 (Week 1)	Day 15 (Week 2)	Day 22[c] (Week 3)	Day 29 (Week 4)	Day 36[c] (Week 5)	Day 43 (Week 6)	Day 50[c] (Week 7)	Day 57 (Week 8)	Day 64[c] (Week 9)	Day 71 (Week 10)	Day 78[c] (Week 11)	Day 85 (Week 12)	Day 106 (Week 15)	Day 127 (Week 18)	
Optional Lip or Parotid Salivary Gland Biopsy with Salivary Gland RNA collection[d]	X												X			Lip or parotid salivary gland biopsy may be performed but same type must be performed at each timepoint. See Section **5.4.3**
PK Assessments																
PK sampling for lulizumab/ BMS-986142	X	X	X		X				X				X	X	X	Subjects should bring their BMS-986142 dose to every clinic visit. See Section **5.5**
PK sampling for hydroxychloroquine	X	X	X		X								X	X	X	See Section **5.5**. Subjects should bring their HCQ dose to the clinic on PK sampling days. Serial PK sampling at 0hr, 2hr, 4hr on Day 8.
Immunogenicity	X				X								X	X	X	See Section 5.8.1
Efficacy Assessments																
ESSDAI	X		X		X		X		X		X		X		X	See Section **5.4.1**.
ESSPRI	X		X		X		X		X		X		X		X	See Section 5.7
Schirmer's Test[e]	X				X				X				X			See Section **5.4.2.1**
Ocular Surface	X				X				X				X			See Section **5.4.2.1**

Table 5.1-2: Short-term Procedural Outline (IM128035)

Procedure	During Treatment[a]												End of Trt[a,b]	FU #1[a]	FU #2[a]	Notes
	Day 1 (Baseline)	Day 8 (Week 1)	Day 15 (Week 2)	Day 22[c] (Week 3)	Day 29 (Week 4)	Day 36[c] (Week 5)	Day 43 (Week 6)	Day 50[c] (Week 7)	Day 57 (Week 8)	Day 64[c] (Week 9)	Day 71 (Week 10)	Day 78[c] (Week 11)	Day 85 (Week 12)	Day 106 (Week 15)	Day 127 (Week 18)	
Staining[e]																
Tear Break-up Time Test[e]	X				X				X				X			See Section **5.4.2.1**
Unstimulated and Stimulated Salivary Flow	X				X				X				X			Subjects should refrain from eating/drinking for 90 min prior to tests. Specimens should be retained in separate containers for biomarker analysis. See Section **5.4.2.2**
Sicca symptoms Numeric Rating Scales (NRS)	X		X		X		X		X		X		X		X	Oral, ocular & vaginal dryness scales. See Section 5.7
phyGDA	X		X		X		X		X		X		X		X	See Section 5.7
subGDA	X		X		X		X		X		X		X		X	See Section 5.7
PROMIS Fatigue SF	X				X				X				X		X	See Section 5.7
SF-36 (acute)	X				X				X				X		X	See Section 5.7
Female Sexual Function Index (FSFI)	X				X				X				X		X	See Section 5.7
Work Participation	X				X				X				X		X	See Section 5.7

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Table 5.1-2: Short-term Procedural Outline (IM128035)

Procedure	During Treatment[a]												End of Trt[a,b]	FU #1[a]	FU #2[a]	Notes
	Day 1 (Baseline)	Day 8 (Week 1)	Day 15 (Week 2)	Day 22[c] (Week 3)	Day 29 (Week 4)	Day 36[c] (Week 5)	Day 43 (Week 6)	Day 50[c] (Week 7)	Day 57 (Week 8)	Day 64[c] (Week 9)	Day 71 (Week 10)	Day 78[c] (Week 11)	Day 85 (Week 12)	Day 106 (Week 15)	Day 127 (Week 18)	
and Activity Impairment Questionnaire (WPAI)																
Study Drug																
Randomize through IVRS/IWRS system	X															
Dispense supplies of BMS-986142 or matched placebo for home administration	X		X		X		X		X		X					Daily dosing of BMS-986142 or matched placebo at home or in the clinic. Subject should bring dose to the clinic to be administered at the site on study visit days.
Dosing of subcutaneous lulizumab or matched placebo	X	X	X	X	X	X	X	X	X	X	X	X				Subjects should be observed in the clinic for 2 hours after dosing on Day 1, then 1 hour after dosing for subsequent doses.
Reconciliation of oral Study Medication (BMS-986142 or matched placebo)		X	X		X		X		X		X		X			

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[a] Visit window of ± 3 days

[b] All procedures scheduled for the End of Week 12/End of treatment visit should be performed at the time of actual discontinuation/end of treatment.

[c] May be a home visit conducted by visiting health care professional if approved by IRB and investigator. If visit is a home visit, the subject's signs and symptoms will be assessed.

[d] Biopsy procedure window of ± 5 days (5 days **prior to dosing only** for Day 1/baseline biopsy)

[e] Ophthalmologic procedure window of ± 5 days (5 days **prior to dosing only** for Day 1/baseline assessments), all assessments must be performed at same visit

In the event multiple assessments are required at the same study visit, the assessments should be performed in the following order whenever possible:

1) Disease activity assessments (eg, ESSDAI, ESSPRI, symptom scales)
2) Vital signs, physical exams, ECGs
3) Salivary flow assessments
4) Blood draws for safety labs, pre-dose PK assessments and biomarker assessments
5) Administration of study medication(s) and HCQ (if applicable)
6) Post-dose PK assessments (if applicable)
7) Ophthalmologic assessments (if performed on the same visit day)
8) Optional lip or parotid salivary gland biopsy

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5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in 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 Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the BMS Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests). The site will have available a well-calibrated scale(s) and/or balance(s) for recording body weight and weight of the pre- and post-salivary flow collection tubes and moistened gauze (if using), a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. The site will have urine collection containers, a refrigerated centrifuge, a heating block, a monitored and alarmed refrigerator, and freezer (-20°C or below), as well as containers and dry ice for shipment and storage of blood and urine samples. The site will provide all materials required for accurate source documentation of study activities.

Subjects will be provided with cooler bags and gel packs for transporting BMS-986142/matched placebo as it needs to be kept refrigerated.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), and IBs. Case report forms (electronic or hard copy) will be provided by BMS. Ten centimeter rulers will be provided by BMS for measurement of the Physician and Subject's Global Assessment of disease activity on the Case Report Form.

All Investigator sites within this study will use an Electronic Data Capture (EDC) tool to submit study data to BMS. Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields at Investigator sites, except for fields specific to Pregnancy Forms. Pregnancy Forms will be submitted to BMS using paper CRFs. Subject ESSPRI, Subject Global Assessment of disease activity worksheet, sicca symptoms NRS scales, fatigue, sexual function, and quality of life questionnaires will be completed by the subject and the information will then be entered with the EDC tool by the investigational site staff. ESSDAI and Physician Global Assessment of disease activity worksheet will be completed by the investigator and will then be entered with the EDC tool. Subject completed scales and questionnaires will be retained at the investigational site. Examples of the worksheets, scales and questionnaires that BMS will provide are included in Appendices 3 - 13, however the country specific translations may include slight customizations as per local requirements (eg, removal of the BMS logo). Translation certificates are available upon request.

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Study supplies and documents (eg, electronic Case Reports Forms, patient drug logs, etc.) will be provided to the study center by BMS. Urine pregnancy test kits, laboratory specimen collection kits and instructions for collection will be provided by central laboratory vendor. IVRS/IWRS worksheets and instruction manuals will be provided by the IVRS/IWRS vendor.

5.3 Safety Assessments

All subjects who receive at least one dose of study medication will be evaluated for safety parameters. Additionally, any occurrence of an SAE from the time of consent until 42 days post-discontinuation of study drug dosing will be documented. Any occurrence of non-serious AEs will be collected from first dose of study drug until 42 days post discontinuation of dosing. Safety assessments include the following:

- Adverse Events
- Safety laboratory tests
- Physical examination
- Vital signs
- ECGs

On Day 1, the results of all assessments must be reviewed to assure that eligibility requirements are met before contacting the Central Randomization System for the subject's randomization assignment. All assessments should be performed or administered prior to study drug administration unless otherwise indicated. Furthermore, patient scales, questionnaires and disease activity assessments (ie, ESSPRI, fatigue, quality of life and VAS/NRS scales) must be performed prior to all other assessments. Every effort must be made to ensure the same evaluator will complete the assessments for each subject at all visits.

After completion of patient scales, questionnaires and disease activity assessments, vital signs collection (blood pressure, heart rate, respiration rate, temperature), physical exams (when applicable), ECGs (when applicable), salivary flow assessments (when applicable), safety laboratory assessments, and pre-dose PK and laboratory biomarker assessments will occur before the first dose of study medication is given from the assigned kit. At subsequent visits, this same order of assessments should be followed prior to the administration of the dose of assigned study drug. Subjects will be observed at the site for a minimum of 2 hours after receiving their first dose of study medication (tablet and injections) on Day 1. The observation period should be extended if clinically indicated. At subsequent visits subjects should be observed for 1 hour post-injection.

Subjects who discontinue from the double-blind treatment period should have "End of Treatment Visit" procedures performed and should return to the clinical for the "Follow-Up Visits" approximately 21 and 42 days after the "End of Treatment Visit". All procedures required for these visits should be completed as well as collection of concomitant medication information.

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

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your institutional or medical practice 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 the sponsor.

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The severity of observed adverse events will be graded by National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance.

Ongoing assessment of safety will be performed by an independent Data Monitoring Committee (DMC). The DMC may make recommendations to the Sponsor regarding conduct of the study based on safety observations.

5.3.1 Imaging Assessment for the Study

Not Applicable.

5.3.2 Laboratory Testing

A central/local laboratory will perform the analyses and will provide reference ranges for these tests.

All scheduled, routine safety laboratory testing should be performed after a minimum 10 hour fast. Detailed instructions on the collection, processing, and shipping of all blood and urine samples will be provided to the investigator in a separate manual at or before the time of study initiation.

The following clinical laboratory tests will be performed:

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count TBNK for CD19+ B cell count (screening only, for subjects with prior rituximab use)	
PT/PTT (screening only)	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Uric acid Fasting glucose Lipase (screening only)	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase Amylase (screening only)

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Fasting lipid panel: total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (Day 1, Week 8, Week 12 and Follow-Up Week 18 only) ESR (local test) hsCRP
Urinalysis
Protein Glucose Blood Leukocyte esterase Specific gravity pH Reflex to microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick Spot urine protein/creatinine ratio [UPCR] (screening only, in subjects with clinical suspicion of nephrotic syndrome or clinically significant protein on urinalysis)
Serology
Serum for hepatitis C antibody, hepatitis B surface antigen, hepatitis B core antibody (screening only) HIV testing (screening only, may be performed locally or via central lab per local requirements) Auto-immune serology: ANA, Anti-SSA/Ro, Anti-SSB/La, Rheumatoid Factor Immunoglobulin levels: IgM, IgA, and IgG Complement levels (C3, C4, CH50)
Other Analyses
IGRA/TB Test
Pregnancy test (WOCBP only; urine test, serum test only to be performed if urine test is positive or un-interpretable, or if necessary as per local/institutional requirements).
Follicle stimulating hormone (FSH): (screening only, for post-menopausal women only, see Section 3.3.3)

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.1.1).

5.3.3 Tuberculosis Screening

A chest x-ray (CXR) and physical examination (PE) are considered part of the process to assess a subject's eligibility as outlined in Section 3.3.2.

CXR at the screening visit is required if not already performed within 6 months of obtaining written informed consent or if documentation of the X-ray result is not on file.

In addition to a complete physical examination and medical history to evaluate exposure to tuberculosis, all subjects will have a screening test, an interferon gamma release assay [(IGRA) eg, QuantiFERON TB Gold®], preferably performed centrally. T-Spot® testing (if available)

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may be used as a reflex test in the event of an indeterminate result of the QuantiFERON TB Gold® test. If unable to obtain central lab results (eg, repeated test due to indeterminate result), an IGRA test could be obtained locally, after consultation with the BMS Medical Monitor. Indeterminate tests may be repeated once in an effort to obtain a definitive negative or positive result. If two indeterminate tests are recorded subject should be excluded from study participation.

Subjects with a positive screening test will not be eligible for the study unless they can provide documentation of completion of approved treatment for latent TB prior to dosing of study drug, and the subject has a negative chest X-ray done at screening that reveals no evidence of active TB.

5.3.4 Physical Exams

A complete medical history and physical exam will be obtained at the screening visit.

Complete and/or targeted/interim physical examinations may be performed by a Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physician's Assistant (PA), or Nurse Practitioner (NP). While the targeted/interim physical examination may not be as comprehensive as the initial full examination, key aspects of the targeted/interim examination should evaluate important body systems as clinically indicated. These body systems include at a minimum, the heart, lungs, abdomen, lymph nodes and skin. Evaluation of liver, spleen, breast and other body systems is at the discretion of the examiner. A targeted/interim physical examination may note any changes in the subject's condition (body systems) since the last assessment and does not preclude examination of any of the body systems as clinically indicated.

Every effort should be made to ensure the same evaluator will complete the physical examination for each subject at specified visits throughout the study. Documentation of who performed the examination is to be recorded in source notes.

5.3.5 Electrocardiograms

A standard 12-lead ECG will be recorded at the times noted in the Time and Events Table 5.1-1 and Table 5.1-2.

5.4 Efficacy Assessments

All assessments should be performed prior to dosing.

5.4.1 Primary Efficacy Assessment

The primary efficacy endpoint is change from baseline ESSDAI score at Week 12. The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is a systemic disease activity index that was designed to measure disease activity in subjects with pSS (see Appendix 3).[63] The ESSDAI is now frequently used as a primary endpoint to measure disease activity in clinical studies. BMS will provide the appropriate versions of the assessment scale for use by the site. Sites should only use the versions of the scale provided by BMS for this study. Investigators should assess the ESSDAI parameters as described by Seror et al.[64] The ESSDAI will be completed at the visits noted in the Time and Events Table 5.1-1 and Table 5.1-2. Results from each assessment will be

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recorded in site source records as well as entered into the corresponding eCRF provided by BMS or designee.

5.4.2 Secondary Efficacy Assessments

5.4.2.1 Ophthalmologic Assessments

The following procedures should be performed at baseline/Day 1, Week 4, Week 8, and Week 12 by an ophthalmologist or optometrist experienced in the diagnosis and treatment of Sjögren's syndrome subjects and according to the methods described in Whitcher, et al.[65] A visit window of ± 5 days to perform the ophthalmologic assessments is acceptable (baseline/Day 1 assessment can be performed up to 5 days **prior to dosing** only), but all assessments must be performed during the same visit. The use of alternative ocular dyes may be permitted per local standards and/or regulations, and after consultation with the BMS Medical Monitor.

- Schirmer's test: The test (without anaesthesia) 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 subjects'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 either lissamine green or Rose bengal dye to stain the cornea and conjunctiva, respectively. After instilling the dye, the ocular surface is examined through a slit lamp (biomicroscope) the staining pattern is recorded per the method described in Whitcher, et al[65]

The results from each of the above procedures will be recorded in site source records as well as entered into the corresponding eCRF provided by BMS or designee.

5.4.2.2 Salivary Flow

Whole unstimulated and stimulated salivary flow will be assessed at Screening (unstimulated only), baseline/Day 1, Week 4, Week 8, and Week 12. Subjects should refrain from eating or drinking for at least 90 minutes prior to the test procedures. Any saliva collected should be transferred to the appropriate container containing protease inhibitor cocktail, including notation as to whether it is a stimulated or unstimulated sample, for saliva biomarker assessments on Days 1, 29, 57 and 85 (see Section 5.6). Stimulated and unstimulated samples must not be combined or pooled into a single collection container.

- Unstimulated salivary flow: Subjects should sit quietly, without talking or chewing, and spit any saliva that accumulates in the floor of the mouth during a period of 5 minutes into a pre-weighed tube
- Stimulated whole salivary flow: Subjects should chew on a piece of paraffin ~~(~~wax~~) or~~ (sites accustomed to using pre-weighed, moistened gauze as the stimulant may continue to use this

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method, although it is not preferred due to the potential retention/loss of the saliva sample for biomarker testing within the gauze) for 10 minutes, during which the accumulated saliva is measured by spitting into a pre-weighed tube (and/or by weight of the chewed gauze, if applicable).

The results from each of the above procedures will be recorded in site source records as well as entered into the corresponding eCRF provided by BMS or designee.

5.4.4 Clinical Assessor Requirements

The ESSDAI, and the Physicians Global Assessment of Disease Activity (phyGDA) can be performed by the investigator or sub-investigator. The sub-investigator may be a Doctor of Medicine (MD) or Doctor of Osteopathy (DO), Physician's Assistant (PA) or Nurse Practitioner (NP). The below requirements also pertain to the ophthalmologic procedures (refer to Section 5.4.2).

For each assessment: 1) Every effort should be made to ensure the same assessor is used for a given subject throughout the study, and 2) The clinical assessor cannot be unblinded to study medication assignment or the subject.

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 and all efforts are made to assure consistency between subject evaluations.

5.5 Pharmacokinetic Assessments

Pharmacokinetics of lulizumab and BMS-986142 will be derived from plasma/serum concentration versus time. The pharmacokinetic parameters to be assessed include Ctrough (ng/mL).

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The serum samples from subjects dosed with lulizumab will be analyzed for lulizumab by a validated LC-MS/MS assay. The plasma samples from subjects dosed with BMS-986142 will be analyzed for BMS-986142 by a validated LC-MS/MS assay.

Pharmacokinetic samples collected from a subject who received placebo only for both drugs will not be analyzed. In addition, serum or plasma samples will be archived for potential exposure biomarker response analysis, if the need arises and to the extent possible.

Individual subject PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

Table 5.5-1 lists the sampling schedule to be followed for the assessment of PK for subjects who are not on hydroxychloroquine (HCQ, Plaquenil®). Further details of blood collection and processing will be provided to the site in the procedure manual.

On Day 1 and Day 8, it is important that the SC dose and oral dose are given to the subjects at the same time to make sure the PK samples are taken at the planned hours relative to dosing.

Table 5.5-1: Lulizumab and BMS-986142 Pharmacokinetic(PK) and Immunogenicity(IMG) Sampling Schedule for Subjects NOT on Plaquenil®

Study Day	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	PK Blood Sample	IMG Sample
1	Predose	00:00	X	X
1		2:00	X[a]	
8	Predose	00:00	X	
8		2:00	X[a]	
15	Predose	00:00	X	
29	Predose	00:00	X	X
57	Predose	00:00	X	
85/End of Treatment (EOT)		168:00 for Lulizumab & Predose sample for BMS-986142	X	X
Follow up Day 21 after EOT (Day 106)		672:00 for Lulizumab & 504:00 for BMS-986142	X	X
Follow up Day 42 after EOT (Day 127)		1176:00 for Lulizumab & 1008:00 for BMS-986142	X	X
AE leading to discontinuation[b]			X	X

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[a] Only one tube of plasma sample will be taken. This sample is intended to evaluate BMS-986142 PK.

[b] PK and immunogenicity samples to be drawn for subjects who experience an AE leading to discontinuation of study treatment.

For each PK blood draw, one tube for serum sample and one tube for plasma sample will be taken.

Table 5.5-2 lists the sampling schedule to be followed for the assessment of PK for subjects who are on a stable dose of hydroxychloroquine (HCQ, Plaquenil®). Serial blood PK samples of HCQ will be taken during Screening (subjects taking HCQ who have met all entry criteria must return for Screening Visit #2 for this collection), on Day 8 and Day 29 in addition to lulizumab and BMS-986142 blood PK samples.

For sampling time points that only lulizumab and BMS-986142 PK samples are collected, one tube for serum sample and one tube for plasma sample will be taken.

For sampling time points that both lulizumab/BMS-986142 and HCQ PK samples are collected, one tube for serum sample, one tube for plasma sample and one tube for HCQ whole blood sample will be taken. Except for the 2 and 4 hours samples on Day 8, only one plasma tube sample for BMS-986142 and one whole blood tube for HCQ will be taken.

Trough level HCQ blood PK samples will be taken on Day 1, Day 15, Day 29, Day 85 and at the two follow-up visits on Days 106 and 127 (Table 5.5-2). Subjects should bring their daily dose of HCQ to the clinical site on these days to be administered at the site.

On Day 8, it is important that the dosing of study drug (a SC injection and an oral dose) and the HCQ are given to the subjects at the same time to make sure the PK samples are taken at the planned hours relative to dosing.

Pharmacokinetics of HCQ will be derived from whole blood concentration versus time. The pharmacokinetic parameters to be assessed include Cmax, and AUC (0-4h) at Screening (Visit #2) and Day 8. Ctrough will be assessed on screening day, Day 1, Day 8, Day 15, Day 29, and at the two follow-up visits on Days 106 and 127.

Table 5.5-2: Lulizumab, BMS-986142, and HCQ Pharmacokinetic and Immunogenicity Sampling Schedule for Subjects on Plaquenil®

Study Day	Time (Relative Oral Dosing of HCQ) Hour	Time (Relative to Dosing) Hour: Min	HCQ PK Blood Sample	BMS-986142 and Lulizumab PK Blood Sample	IMG Sample
Screening (Visit #2)	Predose	00:00	X		
Screening (Visit #2)		2:00	X		
Screening		4:00	X		

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Table 5.5-2: Lulizumab, BMS-986142, and HCQ Pharmacokinetic and Immunogenicity Sampling Schedule for Subjects on Plaquenil®

Study Day	Time (Relative Oral Dosing of HCQ) Hour	Time (Relative to Dosing) Hour: Min	HCQ PK Blood Sample	BMS-986142 and Lulizumab PK Blood Sample	IMG Sample
(Visit #2)					
1	Predose	00:00	X	X	X
1		02:00		X[a]	
8	Predose	00:00	X	X	
8		2:00	X	X[a]	
8		4:00	X	X[a]	
15	Predose	00:00	X	X	
29	Predose	00:00	X	X	X
57	Predose	0:00		X	
85/End of Treatment of Lulizumab and BMS-986142 (EOT)	Predose	00:00	X	X	X
Follow up Day 21 after EOT (Day 106)	Predose	00:00	X	X	X
Follow up Day 42 after EOT (Day 127)	Predose	00:00	X	X	X
AE leading to discontinuation[b]			X	X	X

[a] Only one tube of plasma sample will be taken. This sample is intended to evaluate BMS-986142 PK.

[b] PK samples to be drawn for subjects who experience an AE leading to discontinuation of study treatment.

The whole blood samples will be analyzed for HCQ by a validated LC-MS/MS assay. Cmax, AUC (0-4), and Ctrough will be compared within the same subjects among screening, Day 8, and Day 29.

[redacted]

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Table 5.6-1: [redacted]

5.6.1 Additional Research

This protocol will include residual sample storage for additional research (AR).

For All US sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

For non-US Sites:

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health

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authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- Residual samples from biomarker, biopsy and PK sample collections (see Table 5.6.1-1) will also be retained for additional research purposes

Samples kept for future research will be stored at the BMS Biorepository in NJ, USA or an independent, BMS-approved storage vendor.

- The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.
- Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 5.6.1-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
PK	*All*
Whole Blood	*All*
Blood RNA	*All*
PBMCs	*All*
Serum	*All*
Saliva	*All*
Biopsy	*All*
Biopsy RNA	*All*

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5.7 Outcomes Research Assessments

Questionnaires and investigator/subject assessments will be completed, prior to study drug administration, on either paper forms or an electronic tablet (ePRO) and information gathered on this device will serve as the source document where possible. BMS will provide the appropriate versions of the assessment scales for use by the site. Sites should only use the versions of the scales provided by BMS for this study.

The following additional symptom scales and patient reported outcome measures will be collected:

Completed by Investigator (at baseline/Day 1 and Days 15, 29, 43, 57, 71, 85, and Follow-up Day 127):

- Physician global assessment of disease activity (phyGDA, See Appendix 6)

Completed by subject (at baseline/Day 1 and Days 15, 29, 43, 57, 71, 85, and Follow-up Day 127):

- ESSPRI (see Appendix 4)
- Numeric rating scales (see Appendices 7, 8, and 9) for ocular, oral and vaginal dryness (females only)
- Subject global assessment of disease activity (SubGDA, See Appendix 5)

Completed by subject (at baseline/Day 1 and Days 29, 57, 85, and Follow-up Day 127)

- PROMIS Fatigue Short Form (see Appendix 10)
- Female Sexual Function Index (FSFI, see Appendix 11)
- Short Form-36 acute (SF-36 acute, see Appendix 12)
- Work Participation Activity Index (WPAI, see Appendix 13)

[redacted]

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any

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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. Severity of all adverse events will be graded by using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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

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

6.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [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.)

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

Although pregnancy, overdose, cancer, and potential 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 5.6.1 and 5.6.2 in the Investigator Brochures (IBs) 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 from the date of subject's written consent until 42 days post discontinuation of dosing.

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

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

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SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (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 BMS (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).

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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 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 (35 days for lulizumab), the investigator must immediately notify the BMS Medical Monitor (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 BMS Medical Monitor 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.

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 BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. 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).

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6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee (DMC) will monitor overall safety data regularly to ensure that the benefits and risks of study participation remain acceptable. Based on the regular reviews of emerging data, the DMC may recommend to the Sponsor alteration and/or termination of the trial or a treatment group, or cessation of further enrollment into a treatment group.

Data summaries and listings will be provided to the DMC to facilitate their safety assessment at the regularly scheduled times as well as on an ad hoc basis if needed. The DMC will review safety data including SAEs and events of special interest, focusing on early signal detection. Further details on the frequency, content, and methods of data reports to the DMC will be outlined in the Charter of that Committee along with the processes and procedures the committee will follow.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size calculation is based on the power to compare change from baseline in ESSDAI at Week 12 between active treatment arms (lulizumab or BMS-986142) and the placebo arm. With a two-sided two-sample t-test at significance level 0.05, data from 25 treated subjects per arm will provide approximately 90% power to detect a placebo-adjusted 3-point decrease from

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baseline for each active treatment group, assuming common standard deviations of 3.2.[66] In addition, the Hochberg's step-up procedure will be used to adjust the multiplicity due to the comparison of two active treatment arms (lulizumab or BMS-986142) to the placebo arm.

The primary efficacy analysis will be conducted on all randomized subjects who received at least one dose of study drug.

An interim analysis will be conducted after at least 30 subjects reach Week 12 (complete 12 weeks of treatment) and complete the specified assessments for ESSDAI. The interim analysis will be conducted in a fully blinded manner such that treatment group assignments of study subjects are not known and are not used in any manner in the analysis. A blinded examination of the variance of the primary endpoint will be performed and compared to the assumption used in planning the study. If this comparison suggests the initial assumption was substantially too low, the total study sample size may be increased by up to 45 additional subjects (ie, to a maximum of 120 subjects in total) to maintain adequate study power.[67,68,69] Regardless of the outcome from the blinded examination of variability, the study sample size will not be decreased. A maximum study sample size of 120 subjects in total, ie, 40 subjects per arm, can provide each active treatment arm 79% power to detect a placebo-adjusted 3-point decrease from baseline for common standard deviations as large as 4.8, using a two-sided two-sample t-test comparing each active treatment arm to placebo at significant level 0.05.

8.2 Populations for Analyses

- All Enrolled Subjects, defined as all subjects who sign an informed consent
- All Randomized Subjects, defined as all subjects who were randomized to a treatment group
- Modified Intent-to-Treat (MITT) Analysis Population: All randomized subjects who have received at least one dose of the study medication. Subjects will be grouped according to the treatment to which they were randomized by IVRS/IWRS at the start of the study
- As-Treated Analysis Population: All Subjects who have received at least one dose of study medication. Subjects will be grouped according to the treatment that they actually received as opposed to the treatment to which they were randomized. Subjects will be grouped 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 he/she received
- Biomarker Analysis Population, defined as all subjects that receive any study medication and have at least 1 post-treatment biomarker measurement
- Pharmacokinetic Population, defined as all subjects who receive any study medication and have any available concentration-time data
- Immunogenicity Population, defined as all subjects who receive study drug and have at least 1 post treatment immunogenicity measurement

Analyses performed for all randomized subjects will be according to the as randomized groups, that is, subjects are categorized to the group to which they were assigned by the IVRS/IWRS.

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Efficacy and safety analyses will be performed using the MITT Analysis Population and the As Treated Analysis Population respectively.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint is to compare the change from baseline in ESSDAI score at week 12 between active treatment arms (lulizumab or BMS-986142) and the placebo arm.

8.3.2 Secondary Endpoint(s)

- Change from baseline in ESSPRI score at Week 12
- Proportions of subjects with ≥ 3 points of improvement from baseline in ESSDAI at Week 12
- Proportions of subjects with ≥ 1 point of improvement from baseline in ESSPRI at Week 12
- Proportion of subjects with both ≥ 3 points improvement in ESSDAI and ≥ 1 point improvement in ESSPRI from baseline at Week 12
- Change from baseline in:
  - ESSDAI scores at Week 4 and Week 8
  - ESSPRI scores at Week 4 and Week 8
  - ESSPRI individual component (Dryness, Fatigue, and Pain) scores at Weeks 4, 8, and 12
  - Unstimulated and stimulated salivary flow rate at Weeks 4, 8, and 12
  - Ocular surface staining, Schrimer's test, and the tear break-up time test at Weeks 4, 8, and 12
- Safety and tolerability of lulizumab or BMS-986142 in subjects with moderate to severe pSS, as measured by AEs, laboratory parameters, vital signs, physical exams, and ECGs
- Subject and physician assessments of disease activity:
  - Numeric rating scale (NRS) for mouth, eye and vaginal dryness
  - Subject global assessment of disease activity (SubGDA) and physician global assessment of disease activity (phyGDA),
  - Short Form-36 (SF-36)
  - Female Sexual Function Index (FSFI)
  - Work participation and activity impairment questionnaire (WPAI)
  - PROMIS Fatigue Short Form
- Trough concentrations of BMS-931699 and BMS-986142 at time points specified in Section 5.5

[redacted]

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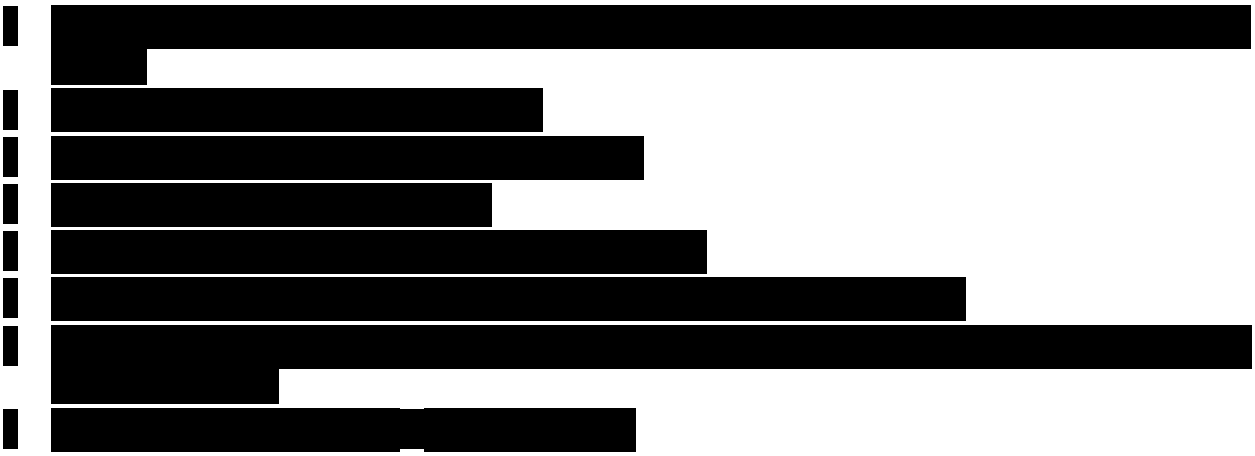

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics of all randomized subjects who received at least one dose of study medication will be summarized. For continuous variables, they will be summarized using means, medians, standard deviations and ranges. The distribution of categorical variables will be summarized by treatment group using frequency and percentage.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Efficacy Analyses

The mixed effects model with repeated measures (MMRM) will be used to model the change from baseline in ESSDAI score over time for all treatment arms. Details of the model will be given in the statistical analysis plan. The least square means of the differences of Week 12 change in ESSDAI from baseline between each active treatment and the placebo will be estimated and their corresponding two-sided 95% confidence intervals will be provided. In addition, as part of the secondary objective, similar outputs will be provided for the changes in ESSDAI score at Weeks 4 and 8.

The Hochberg's step-up procedure will be used to adjust the multiplicity due to the comparison of two active treatments (lulizumab or BMS-986142) to the placebo arm in the primary endpoint (ie, change from baseline in ESSDAI at Week 12). The corresponding adjusted p-values for the Hochberg procedure will be provided.

8.4.2.2 Secondary Efficacy Analyses

For all secondary endpoints, no multiplicity adjustment will be applied, and nominal p-values may be provided if applicable. For each of the following categorical secondary endpoints, the estimate and its corresponding two-sided 95% confidence interval will be calculated for the proportion for each treatment arm. In addition, as exploratory analyses, differences of the proportions between each active treatment arm and the placebo arm will be evaluated and their corresponding two-sided 95% confidence intervals will be provided.

- Proportion of subjects with a ≥ 3 point improvement from baseline in ESSDAI at Week 12

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- Proportion of subjects with a ≥ 1 point improvement from baseline in ESSPRI at Week 12
- Proportion of subjects with both ≥ 3 point improvement from baseline in ESSDAI and ≥ 1 point improvement from baseline in ESSPRI at Week 12

Similar to the primary endpoint, the following continuous secondary endpoints will be analyzed using the MMRM method:

- Change from baseline in ESSPRI scores at Week 4, 8, and, 12
- Change from baseline in score of each individual ESSPRI components (Dryness, Fatigue, and Pain) at Weeks 4, 8, and 12
- Change from baseline in mouth dryness as measured by unstimulated and stimulated salivary flow rate at Weeks 4, 8, and 12
- Change from baseline in eye dryness as measured by ocular surface staining, Schirmer's test, and tear break-up time test at Weeks 4, 8, and 12

Analyses for other outcomes research assessments will be discussed in Outcome Research Analyses section.

Exploratory endpoints may be summarized descriptively for each treatment arm for the absolute value and change (or percent change) from baseline whenever applicable and appropriate. Moreover, if applicable and appropriate, modeling techniques such as the MMRM method may be used for exploratory endpoints (eg, ESSDAI domains) as well.

8.4.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed. Any pre-established Events of Special Interest will be listed and summarized.

[redacted]

[redacted]

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8.4.6 Outcomes Research Analyses

Descriptive summary statistics will be provided for absolute value and change (or percent change) from baseline in primary measures as well as eligible sub-domain scores for all the following outcome research assessments:

- Numeric Rating Scale (NRS) scores for mouth, eye and vaginal dryness
- Subject global assessment of disease activity (SubGDA) and physician global assessment of disease activity (phyGDA)
- Short Form - 36 acute (SF-36 acute)
- Female Sexual Function Index (FSFI)
- Work participation and activity impairment questionnaire (WPAI)
- PROMIS Fatigue Short Form

In addition, the MMRM method or other modelling methods may be applied to changes from baseline in primary measures (eg, total scores) of the above outcome research measures whenever appropriate. Details for those analyses will be provided in the statistical analysis plan.

8.4.7 Other Analyses

After the database lock, exposures predicted from population PK model may be used to conduct exposure-response analysis for improvement of endpoint scores (ESSDAI and ESSPRI), clinical response, clinical remission, safety end points as well as biomarkers to guide dose selection and study designs for future subject studies. Results of population PK analyses and exposure-response will be reported separately.

Cmax and AUC(0-4h) of hydroxychloroquine (Plaquenil®) will be compared for Screening, Day 8 and Day 29.

[redacted]

8.5 Interim Analyses

One interim analysis will be conducted when at least 30 subjects reach Week 12 (complete 12 weeks of treatment) and complete the specified assessments for the Week 12 ESSDAI score.

The interim analysis will be conducted in a fully blinded manner such that treatment group assignments of study subjects are not known and are not used in any manner in the analysis. Specifically, a blinded examination of the variance of the primary endpoint will be performed and compared to the assumption used in planning the study. If this comparison suggests the initial assumption is substantially too low, the total study sample size may be increased by up to 45 additional subjects (ie, to a maximum of 120 subjects in total) to maintain adequate study power.[67,68,69] Regardless of the outcome from the blinded examination of variability, the study

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sample size will not be decreased. Details on the blinded sample size re-estimation will be given in the statistical analysis plan.

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents: This includes the subject's Global Assessment of Disease Activity, the Physician Global Assessment of Disease Activity, the PROMIS fatigue scale, the SF-36, and the WPAI.

In addition, the study may be evaluated by BMS 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.

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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.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

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 and the following non-investigational product(s): not applicable (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.

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If...	Then...
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • 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)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS 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 BMS 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 paper or electronic SAE form and Pregnancy Surveillance form, respectively. If electronic

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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 BMS.

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, including any paper or electronic 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 BMS or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. 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. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing 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.

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10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the subject. 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. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

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11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
ACR	American College of Rheumatology
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure

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Term	Definition
BRt	Total amount recovered in bile
%BRt	Total percent of administered dose recovered in bile
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca++	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
CLD	Dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	Apparent clearance of free drug or clearance of free if (if IV)
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)

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Term	Definition
Ctrough	Trough observed plasma or serum concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DMC	Data Monitoring Committee
DRt	Total amount recovered in dialysate
%DRt	Total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ESR	Erythrocyte Sedimentation Rate
ESR	Expedited Safety Report
ESSDAI	EULAR SS Disease Activity Index
ESSPRI	EULAR SS Patient-Related Index
EULAR	European League Against Rheumatism
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
FRt	total amount recovered in feces
%FRt	total percent of administered dose recovered in feces
FSH	follicle stimulating hormone
FSFI	Female Sexual Function Index
%FE	percent fecal excretion
fu	fraction of unbound drug
g	gram

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Term	Definition
GC	gas chromatography
GCP	Good Clinical Practice
G criteria	adjusted R2 value of terminal elimination phase
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
IA	Interim analysis
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
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K3EDTA	potassium ethylenediaminetetraacetic acid
K+	potassium
kg	kilogram
λz	terminal disposition rate constant
L	liter
LC	liquid chromatography

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Term	Definition
LDH	lactate dehydrogenase
ln	natural logarithm
Lz_Start	The time point starting the log-linear elimination phase defining ther terminal half life
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
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
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	Ratio of metabolite Ctau to parent Ctau, 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
NSAID	nonsteroidal anti-inflammatory drug

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Term	Definition
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PD	pharmacodynamics
phyGDA	Physician global assess of disease activity
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PROMIS Fatigue SF	Patient Reported Outcomes Measurement Information System Fatigue Short Form
pSS	Primary Sjögren's syndrome
PT	prothrombin time
PTT	partial thromboplastin time
Pu	percent of unbound drug
QC	quality control
QD, qd	quaque die, once daily
R2	coefficient of determination
RA	Rheumatoid Arthritis
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form – 36 acute
SLE	Systemic lupus erythematosus
SOP	Standard Operating Procedures
sp.	species
Subj	subject
SubGDA	Subject global assessment of disease activity
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
T-HALFeff_AUC	Effective elimination half life that explains the degree of AUC accumulation observed

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Term	Definition
T-HALFeff_Cmax	Effective elimination half life that explains the degree of Cmax accumulation observed)
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
UPCR	Urine protein/creatinine ratio
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	ultraviolet
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WPAI	Work Participation and Activity Impairment Questionnaire
x g	times gravity

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APPENDIX 1 METHODS OF CONTRACEPTION

At a minimum, subjects must agree to use one highly effective method of contraception (or one highly effective plus one less effective method, as per local country regulations) 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 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**.**

- Non-hormonal intrauterine devices (IUDs) such as ParaGard®
- Bilateral tubal occlusion
- Vasectomised partner with documented azoospermia 90 days after procedure
  - Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of surgical success
- Complete abstinence
  - Complete abstinence is defined as the complete avoidance of heterosexual intercourse. (refer to Glossary of Terms)
  - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment plus 5 half-lives of the investigational drug plus 30 days for women (65 additional days) and 5 half-lives of the investigational drug for men (35 additional days)
  - It is not necessary to use any other method of contraception when complete abstinence is elected
  - Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Table 5.1-1 and Table 5.1-2
  - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence
  - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Male or female condom with or without spermicide*

* A male and a female condom must not be used together.

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UNACCEPTABLE METHODS OF CONTRACEPTION

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

HORMONE-BASED METHODS OF CONTRACEPTION

- Hormone-based contraception for study subjects who are WOCBP is prohibited due to the lack of data available for potential drug-drug interactions between BMS-986142 and hormonal contraceptives
- Female partners of male subjects participating in the study may use hormone-based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug

Approved v4.0 930101424 4.0