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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

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

PROTOCOL(S) IM128-035

VERSION # 1.0

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Schedule of Analyses:

The following analyses will be performed:

- 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 (i.e., to a maximum of 120 subjects in total) to maintain adequate study power..[24,25,26] 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.
- A final analysis will be performed after the last treated subject in the study reaches the end of the study.

2 STUDY DESCRIPTION

2.1 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

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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 hydroxychloroquine (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 protocol 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 protocol 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 events. Analgesics are permitted with certain restrictions (see protocol Section 3.3). Study procedures will occur as specified in protocol 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 interim analysis 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 interim analysis 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.

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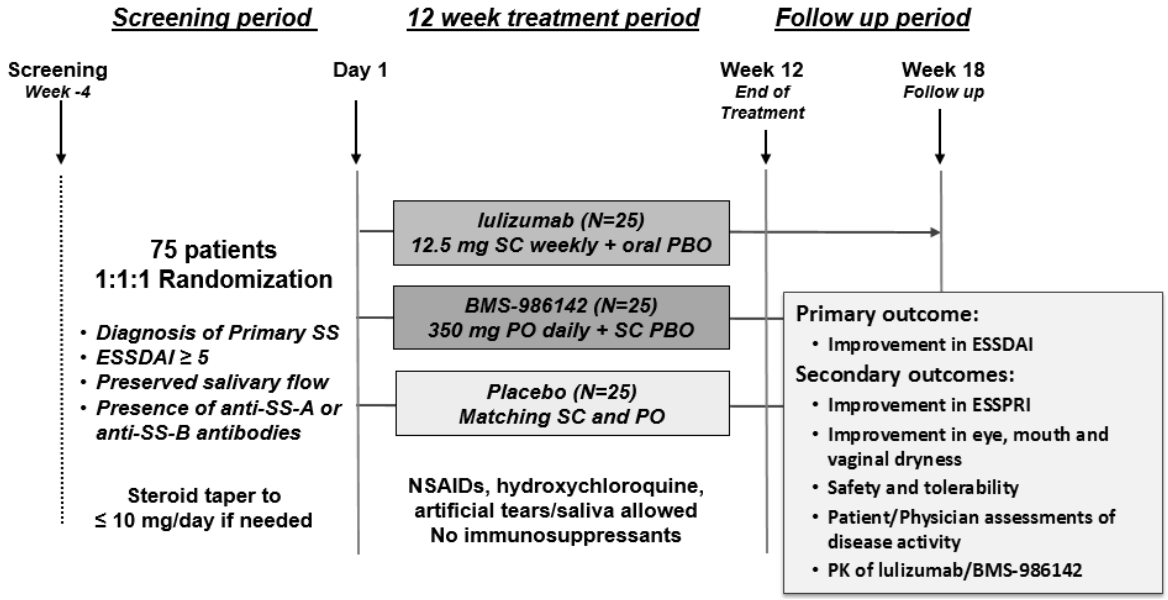
Follow-Up Period:

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 protocol Table 5.1-2.

The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: 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.

2.2 Treatment Assignment

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 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.

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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.

2.3 Blinding and 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, i.e., 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

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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.

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.

2.4 Protocol Amendments

There have been two protocol amendments and two administrative letters in the study protocol, which do not affect the analysis.

2.5 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.

3 OBJECTIVES

3.1 Primary

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.

3.2 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 points improvement in ESSDAI and ≥ 1 point improvement in ESSPRI from baseline at Week 12

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- 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
- 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)
- Trough concentrations of lulizumab and BMS-986142 in pSS subjects

[redacted]

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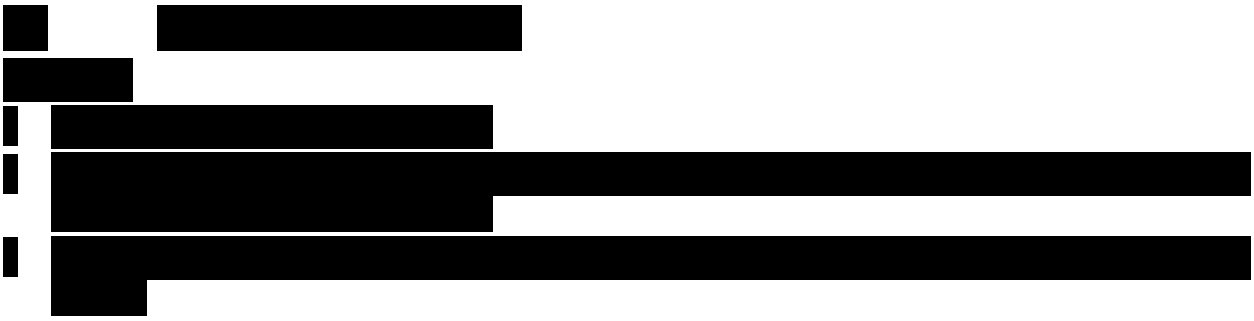
4 ENDPOINTS

4.1 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.

4.2 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, Schirmer'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 protocol Section 5.5



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5 SAMPLE SIZE AND POWER

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.[27] 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 (i.e., to a maximum of 120 subjects in total) to maintain adequate study power.[28,29,30] 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, i.e., 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.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

The following periods are defined in this SAP for the purpose of analyses and reporting.

- **Pre-treatment period**: It covers the time period which starts from the day of enrollment and lasts until the initiation of the randomized double-blind treatment period.

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- **Double-blind treatment and follow-up periods:** It starts at the time of the first dose of blinded treatment and continues up to 42 days post last dose.

6.2 Treatment Regimens

All subjects will receive one of the following treatments:

- BMS-931699/lulizumab injection 12.5mg for subcutaneous administration weekly
- BMS-986142 350mg for oral administration daily
- Matching placebos

For analysis, subjects will appear in the "as randomized" treatment group, which is defined as the treatment group to which a subject was randomized at the start of the double-blind treatment period (even if the treatment they received was different).

The "as treated" treatment group is the same as the "as randomized" treatment group, except in cases where information was available which indicated that a subject received a different treatment for the entire course of their participation in the study (or period). In this case, the "as treated" treatment group is set to the treatment the subject actually received. In cases where a subject never received the treatment as assigned by randomization, then the "as treated" treatment group is the first treatment received.

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

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7 STATISTICAL ANALYSES

7.1 General Methods

7.1.1 Change from Baseline

Change from baseline to any Visit t in double-blind treatment period is defined as follows:

$$C_{Visit\ t} = M_{Visit\ t} - M_{baseline}$$

where:

- $C_{\text{Visit t}}$ is the change from baseline at Visit *t*,
- $M_{\text{Visit t}}$ is the measurement at Visit *t,*
- M_{baseline} is the measurement at baseline.

The "Visit t" and baseline to which a measurement belongs is determined using the conventions described in Section 8.1.

7.1.2 Percent Change from Baseline

Percent change from baseline to any Visit *t* in double-blind treatment period is defined as follows:

$$P_{Visit\ t} = 100 \times (M_{Visit\ t} - M_{baseline}) / M_{baseline}\ .$$

Where

- $P_{\text{Visit t}}$ is the percent change from baseline at Visit *t*,
- $M_{\text{Visit t}}$ is the measurement at Visit *t*,
- M_{baseline} is the measurement at baseline.

The "Visit t" and baseline to which a measurement belongs is determined using the conventions described in Section 8.1.

For analyses of parameters in terms of percent change from baseline to Visit t, values will first be transformed to natural logarithms (Ln) and the results will be expressed as geometric mean percent changes from baseline. Analysis will be performed using the logarithms of the post-baseline to baseline ratios. Subsequently, the estimates from the analysis will be back-transformed to original values for reporting in the tables using the formulae detailed in Table 7.1.2-1.

Table 7.1.2-1: Formulae Used to Transform Back onto the Original Scale the Estimates of Percent Change from Baseline Analyzed as Geometric Mean

Quantity	Computation method

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Table 7.1.2-1: Formulae Used to Transform Back onto the Original Scale the Estimates of Percent Change from Baseline Analyzed as Geometric Mean

Quantity	Computation method
Geometric mean of the Visit *t* to baseline ratio	Exp(mean change from baseline in natural logarithm)
Mean percent change from baseline	100 × [exp(mean change from baseline in natural logarithm*) – 1]
Standard error of mean percent change from baseline	100 × exp(mean change from baseline in natural logarithm) × standard error of mean change from baseline in natural logarithm* – or, equivalently – 100 × Geometric mean of the Visit *t* to baseline ratio × standard error of mean change from baseline in natural logarithm*
Lower confidence limit for mean percent change from baseline	100 × [exp(lower confidence limit for mean change from baseline in natural logarithm*) – 1]
Upper confidence limit for mean percent change from baseline	100 × [exp(upper confidence limit for mean change from baseline in natural logarithm*) – 1]
Adjusted geometric mean of the Visit *t* to baseline ratio	exp(Adjusted mean change from baseline in natural logarithm*)
Adjusted mean percent change from baseline	100 × [exp(Adjusted mean change from baseline in natural logarithm*) – 1]
Standard error of adjusted mean percent change from baseline	100 × exp(Adjusted mean change from baseline in natural logarithm) × standard error of mean change from baseline in natural logarithm* – or, equivalently – 100 × adjusted geometric mean of the Visit *t* to baseline ratio × standard error of mean change from baseline in natural logarithm*
Lower confidence limit for adjusted mean percent change from baseline	100 × [exp(lower confidence limit for adjusted mean change from baseline in natural logarithm*) – 1]
Upper confidence limit for adjusted mean percent change from baseline	100 × [exp(upper confidence limit for adjusted mean change from baseline in natural logarithm*) – 1]
Adjusted geometric mean of the Visit *t* to baseline ratio achieved with each dapagliflozin *treatment arm* relative to that achieved with C*ontrol*, expressed as a percent difference. Please note that for the SAS output, a shorter text will be used: Adjusted GM of Visit *t*/Baseline for each dapagliflozin *treatment arm* relative to *Control*, in % difference.	100 × (((adjusted mean percent change for dapagliflozin *treatment arm* +100)/(adjusted mean percent change for *Control* +100)) – 1) – or, equivalently – 100 × (exp(difference in adjusted mean change from baseline between dapagliflozin *treatment arm* and *Control* in natural logarithm*) – 1)

*Change in natural logarithm refers to a calculated difference between two values after performing a natural logarithmic transformation on each.

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7.1.3 Descriptive Summaries of Continuous Variables

Descriptive summaries of continuous variables in terms of baseline values, change or percent change from baseline values will be provided by treatment group and overall, as applicable. These summaries may include the estimations of means, medians, standard deviations and ranges, as applicable.

7.1.4 Descriptive Summaries of Categorical Variables

Descriptive summaries of categorical variables will consist of frequencies and percentages for each treatment group and overall, as applicable.

7.1.5 Mixed effects Model with Repeated Measures

7.1.5.1 Model Specification

A mixed effect model with repeated measures analysis using 'direct likelihood' will be performed. The SAS procedure PROC MIXED will be used.

The dependent variable will be the change from baseline to each Visit t included in the model for efficacy endpoints examining changes from baseline. For analyses of parameters in terms of percent change from baseline at Visit t, values will first be transformed to logarithms and the results will be expressed as geometric mean percent changes from baseline. The dependent variable will be the natural logarithms (Ln) of the post-baseline to baseline ratios. The model estimates will be back transformed to original values using the formulae detailed in Table 7.1.2-1.

The preferred model will include the fixed categorical effects of treatment, visit, randomization stratification factors (i.e. one term for each combination of the stratification factors of hydroxychloroquine and oral corticosteroid use based on IVRS) and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-visit interaction. For parameters analyzed as percent change from baseline, the natural logarithm of the baseline values will be used in the above model specification. An unstructured matrix for the within-subject error variance-covariance will be used. The denominator degrees of freedom will be calculated according to the Kenward-Roger method.

In case of non-convergence of the preferred model or memory space issues the following back-up models are defined:

1) The first backup model is the same as the preferred model but the Kenward-Roger method will be replaced by Satterthwaite approximation.
2) The second backup model is the same as the preferred model but without the term for baseline measurement-by-visit interaction.

The second back-up model will only be provided if the first back-up model does not converge or has memory issues.

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The model will provide least-squares mean estimates, standard errors and 2-sided 95% confidence intervals for mean change at all time points within and between treatments. Where applicable, for specific visits, the t-statistic corresponding to the Type III sums of squares for the differences in the least squares means will be used to obtain p-values for treatment group comparisons.

7.1.5.2 Model Assumption Assessment

The assumptions underlying the longitudinal repeated measures analysis model will be checked, if specified in Section 7.5. This section also details the steps to follow in case these assumptions would not be satisfied.

Assessment of Treatment-by-Baseline Interaction:

Treatment-by-baseline interaction will be assessed for the Visit 85 estimates. In the model defined in 7.1.5.1, the interaction will be tested by including the treatment-by-baseline interaction.

The following contrast statements will be used of testing for interaction.

- Contrast coefficients for all visits but Visit 85 will be zero.
- Contrast coefficients at Visit 85 are presented in Table 7.1.5.2-2.

Table 7.1.5.2-2: Contrast Coefficients for the treatment-by-baseline interaction for visit 85 estimates

Treatment by baseline interaction	Contrast Coefficients
Lulizumab by baseline value	1
BMS-986142 by baseline value	0
Placebo by baseline value	-1
Lulizumab by baseline value	0
BMS-986142 by baseline value	1
Placebo by baseline value	-1

The test for interaction will be performed at the 0.10 level of significance. If significant, the interaction will be assessed as qualitative or quantitative. Assessment of the interaction type will be based on regression lines plotted for each treatment group. The intercepts and slopes for these regression plots will be obtained from the analysis model including the interaction term. The intercepts will be estimated by the least squares means. The abscissa of the plots will range from the minimum baseline value from all subjects included in the analysis to the maximum baseline value.

If the regression lines do not cross, or the crossing is judged not severe (i.e., the crossing occurs near the boundary or beyond the range of baseline values), then the interaction will be considered quantitative and this does not compromise the validity of the treatment comparisons. In this case, the treatment comparisons will be made using the model without the interaction term.

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Otherwise, the interaction will be considered qualitative and treatment comparisons will not be presented as a result of the complete model. In this case, the impact of the baseline value on treatment effect will be investigated by summarizing the data in subsets defined by baseline categories.

Assessment of Treatment-by-Randomization Stratification Factor Interaction:

Treatment-by-combination of stratification factors interaction for estimates at Visit 85 will be assessed using method described below. In the model defined in 7.1.5.1, the interactions will be tested by including the treatment-by-combination of stratification factor interaction and appropriate contrast statement for testing the interaction in the visit 85 estimates. Contrast coefficients for all visits but Visit 85 will be zero. The tests for interaction will be performed at the 0.10 level of significance.

Outlier Detection:

Specifically, an outlier is defined as an observation with a residual that is more than three times the interquartile range above the 75th percentile or below the 25th percentile. Outliers will be identified based on diagnostics performed for the primary efficacy outcome measure using standardized residuals from the mixed effect model with repeated measurement. These diagnostics will be based on the box plot. If outliers are present, then additional sensitivity analyses will be performed with the outliers excluded, in order to assess their impact on the results.

Adjustments for baseline imbalances:

Adjustments for baseline imbalances between treatment groups in the longitudinal repeated measures model may be performed as a sensitivity analysis: baseline characteristics for which a clinically important imbalance exists between the treatments will be identified. If such imbalances exist, an adjustment will be performed by including the corresponding baseline characteristics as additional covariates in the longitudinal repeated measures model. This will allow the assessment of the importance of these imbalances on the treatment group comparisons.

7.1.6 Kaplan-Meier Curve and Estimates for Time-to-Event Analyses

Kaplan-Meier plots[31] of time to event variables will be displayed by treatment group. Unless otherwise specified, the plot will be presented only when there are at least 5 events in one treatment group. Additionally, a table will accompany the plot and will display the Kaplan-Meier estimates of the cumulative proportion (with 95% CI calculated based on Greenwood's method[32] when applicable) of subjects with event at specific time points by treatment group. If the estimated lower bound of 95% CI is below 0 or the estimated upper bound of 95% CI is over 1, then it will be restricted to 0 or 1 respectively.

7.1.7 Test for Proportion of Subjects with a Characteristic at Visit t

In cases that a comparisons between proportions is needed, the Chi-square test will be used to compare the proportions between each of the active treatment arms and the placebo arm. The

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Chi-square p-value will be provided for each comparison between the active treatment and the placebo arm. In addition, the difference of in proportions between each active treatment and the placebo arm will be estimated and their corresponding 95% confidence interval will be calculated.

The construction of confidence intervals for binary variables will be based on normal approximation if the number of the events in each individual treatment arm is at least 5. Otherwise, confidence interval using an exact method will be provided. The exact confidence intervals for binary variable within treatment group and between treatment groups will be constructed.

7.2 Study Conduct

Relevant protocol deviations, which could have an impact on the primary/key efficacy endpoint, will be identified for all subjects who are randomized and receive study medication during the double-blind period. Details of relevant protocol deviations are provided in APPENDIX 1.

All subjects with relevant protocol deviations that could affect the primary efficacy will be identified prior to database lock and unblinding of treatment assignment. All relevant protocol deviations will be listed and summarized by treatment group. The subjects identified with relevant protocol deviation will not be excluded from any analysis population described in Section 6.3. If at least 10% of total subjects in all treatment arms in the efficacy analysis population demonstrate relevant protocol deviations, a per-protocol analysis may be performed. The per-protocol analysis will exclude data from subjects with relevant protocol deviations as specified in APPENDIX 1.

7.3 Study Population

7.3.1 Subject Disposition

The disposition of subjects will be summarized for the pre-treatment period, double-blind treatment and follow-up periods.

The summary of subject disposition for the pre-treatment period will be based on all enrolled subjects. It will include a summary of the:

- number of subjects enrolled
- number (percentage) of subjects randomized
- number (percentage) of subjects not randomized
- number of subjects randomized and treated by treatment group
- number of subjects randomized but not treated by treatment group
- number (percentage) of subjects per reason for not being randomized.

Percentages will be on all enrolled subjects. The reasons for not being randomized will also be listed, for those subjects that were not randomized.

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The summary of subject disposition for the double-blind treatment period will be based on the MITT analysis population and will summarize by treatment group the:

- number (percentage) of subjects completing the double-blind treatment period
- number (percentage) of subjects not completing the double-blind treatment period (i.e. early discontinued subjects)
- number (percentage) of subjects per reason for not completing the double-blind treatment period (i.e. reasons for early discontinuation)
- number (percentage) of subjects continuing in the study (i.e. entering in the follow-up period)
- number (percentage) of subjects not continuing in the study (i.e. not entering in the follow-up period)
- number (percentage) of subjects per reason for not continuing in the study

Percentages will be on all randomized and treated subjects. The reasons for not completing the double-blind treatment period or for not continuing in the study will also be listed, for those subjects that either did not complete the double-blind treatment period or did not continue in the study.

The summary of subject disposition for the follow-up period will be based on the MITT analysis population for those subjects that have entered the follow-up period (based on information on the status page at the end of double-blind treatment) and will summarize by randomized treatment group the:

- number (percentage) of subjects completing the follow-up period
- number (percentage) of subjects not completing the follow-up period
- number (percentage) of subjects per reason for not completing the follow-up period

Percentages will be on all subjects entering the follow-up period. The reasons for not completing the follow-up period will also be listed, for those subjects that did not complete the follow-up period.

The number of subjects enrolled, randomized, and treated will be summarized by country and study site.

7.3.2 Demography and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by randomized treatment group and overall based on the MITT analysis populations. For continuous variables, they will be summarized using means, standard deviations and ranges, based on non-missing observations (see Section 7.1.3). The distribution of categorical variables will be summarized by treatment group using frequency and percentage (see Section 7.1.4). For categorical variables, percentages will be calculated out of the total number of subjects in the data set, overall and by treatment group (i.e., each denominator includes the number of subjects with missing/unknown values for the characteristic).

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Table 7.3.2-2: Demographic and Baseline Characteristics

Characteristic	Summarized as	Categories
Age (years)	Categorical and Continuous	< 65yrs ≥ 65yrs
Gender	Categorical	Male Female
Female Age	Categorical	≤ 50yrs > 50yrs
Race	Categorical	White Black or African American Asian Other
Ethnicity (to be summarized only for USA subjects)	Categorical	Hispanic/Latino Non Hispanic/Latino
Region	Categorical	North America South America Europe Asia (see APPENDIX 2)
Total Body Weight (kg)	Continuous	
Time from First Diagnosis of Sjogren's syndrome (years)	Continuous	
Randomization stratification factors as recorded on IVRS	Categorical	Hydroxychloroquine use (YES/NO) Oral corticosteroid use (YES/NO) Combinations of both: Hydroxychloroquine use and Oral corticosteroid use Hydroxychloroquine use and No oral corticosteroid use No hydroxychloroquine use and Oral corticosteroid use No hydroxychloroquine use and No oral corticosteroid use
Randomization stratification factors as recorded on eCRF	Categorical	Hydroxychloroquine use (YES/NO) Oral corticosteroid use (YES/NO) Combinations of both: Hydroxychloroquine use and Oral corticosteroid use Hydroxychloroquine use and No oral corticosteroid use No hydroxychloroquine use and Oral corticosteroid use No hydroxychloroquine use and No oral corticosteroid use
Number of 2015 ACR-EULAR Classification Criteria met	Continuous	

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Table 7.3.2-2: Demographic and Baseline Characteristics

Characteristic	Summarized as	Categories
ESSDAI Total Score	Continuous	
ESSDAI Constitutional Domain Score	Continuous	
ESSDAI Lymphadenopathy Domain Score	Continuous	
ESSDAI Glandular Domain Score	Continuous	
ESSDAI Articular Domain Score	Continuous	
ESSDAI Cutaneous Domain Score	Continuous	
ESSDAI Pulmonary Domain Score	Continuous	
ESSDAI Renal Domain Score	Continuous	
ESSDAI Muscular Domain Score	Continuous	
ESSDAI Peripheral Nervous System (PNS) Domain Score	Continuous	
ESSDAI Central Nervous System (CNS) Domain Score	Continuous	
ESSDAI Haematological Domain Score	Continuous	
ESSDAI Biological Domain Score	Continuous	
ESSPRI	Continuous	
Unstimulated whole saliva secretion	Continuous	
Stimulated whole saliva secretion	Continuous	
Schirmer's Test moisture measure for both eyes	Continuous	
Vaginal dryness numeric rating scale	Continuous	
Physician's global assessment of disease activity (MDGA)	Continuous	
Subject's global assessment of disease activity (PGA)	Continuous	

7.3.3 General Medical History

The number (percent) of subjects with general medical history findings before the first study medication will be summarized by treatment group and overall using the MITT analysis population. A corresponding listing of medical history findings will be provided.

7.3.4 Prior (Current) Medication

Prior (current) medications are defined as medications with a start date prior to the first day of double-blind treatment period and without a stop date prior to the consent date, i.e. current

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medication will be any medication with at least 1 dose taken on or after the day of consent date up to the day prior to the first dose of study medication.

Prior medication information before the first study medication will be summarized by drug class and (generic) drug name and by treatment group using relative frequencies. Listings of prior medication will be presented. The results will be based on the MITT analysis population.

Missing and partial date handling of start and stop dates of prior medications, is described in Section 8.5. The World Health Organization (WHO) dictionary is used to code non-study medications.

7.4 Extent of Exposure

7.4.1 Study Therapy

The extent of exposure during the double-blind treatment period will be summarized for the As-treated analysis population in the following ways:

- by the number of days the subject is known to be on study drug, ignoring any dosing interruptions, using the formula below:

  Exposure (in days) = (date of last study medication) - (date of first study medication)

  For Lulizumab or matching placebo, the date of last study medication corresponds to the last date of study medication + 7 days (the offset of 7 days represents the dosing interval of 7 days).
  For BMS-986142 or matching placebo, the date of last study medication corresponds to the last date of study medication +1.

  Because subjects receive either lulizumab or BMS-986142 together with the corresponding matching placebo for each medication

  – the date/time of first study medication will be the earliest of the dates/times of first administration of BMS-986142 or Lulizumab or matching placebo.
  – the date/time of last study medication will be the maximum of last study medication date/time as described above for each medication.

  The frequency will be presented according to the duration ranges (in days) : 1-28, 29-56, 57-84 and >=85.

- by the number of Lulizumab or matching placebo study drug injections. The frequency will be presented using the following ranges in the total number of injections: 1-4, 5-8, 9-12, >12.

- by the number of BMS-986142 or matching placebo doses. The frequency will be presented using the same ranges as for the summary of number of days.

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In addition to the frequencies mentioned above, the mean, standard deviation, median, minimum and maximum values will be summarized for all the above mentioned ways of summarizing extend of exposure.

7.4.2 Discontinuations from Study Therapy

Discontinuation from study therapy is defined as subject's termination of the study medication without resumption prior to study completion. Section 3.5 of the protocol mentions the reasons for which a subject must discontinue treatment.

Discontinuation from study therapy during the double-blind period is capture on the study status case report form (CRF) pages. For the analysis of discontinuations from study therapy refer to section 7.3.1.

7.4.3 Treatment Compliance

The CRF for this study will capture information on injections of the Lulizumab or matching placebo and doses of BMS-986142 or matching placebo.

The number of subjects with missed injections or doses (excluding missed injections or doses due to premature discontinuation from the study) will be summarized by number of missed injections or doses based on the As-treated analysis population for the ST period by treatment groups. The summary will be produced separately for missed injections and missed doses. A corresponding listing for all subjects who skip either any injection or dose will be produced.

[redacted]

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7.4.5 Immunosuppressant Medication

Immunosuppressant medications summaries will be provided to present the medication use of corticosteroids, NSAIDs (non-steroidal anti-inflammatory drugs), and non-biologic DMARDs (non-biologic disease-modifying antirheumatic drugs).

This summary will include both prior and concomitant medications (see sections 7.3.4 and 7.4.4 for definitions, respectively).

The number and percent of subjects receiving corticosteroids, NSAIDs, and DMARDs will be summarized by treatment group for MITT analysis population.

7.4.6 Corticosteroids

The average daily corticosteroid dose (prednisone equivalent) and its change from baseline will be summarized over time by treatment group for the double-blind period using the MITT analysis population.

7.4.7 Narcotic analgesics

A summary of use of narcotic analgesics will be provided. This summary will include both prior and concomitant medications (see sections 7.3.4 and 7.4.4 for definitions, respectively). The number and percent of subjects receiving narcotic analgesics will be summarized by treatment group for MITT analysis population.

7.4.8 Anticoagulants

A summary of use of anticoagulants will be provided. This summary will include only prior medications (see sections 7.3.4 for definition). The number and percent of subjects receiving anticoagulants as prior medication will be summarized by treatment group for MITT analysis population.

7.5 Efficacy

Unless otherwise specified, all efficacy analyses will be produced using the MITT analysis population.

7.5.1 Primary efficacy analysis

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 Protocol Appendix 3).[33] The ESSDAI parameters are assessed by the investigators and the results from each assessment are recorded in site source records as well as entered into the corresponding eCRF. The ESSDAI total score will be calculated as described in section 8.6

The primary efficacy endpoint is change from baseline ESSDAI score at Week 12.

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 are presented in section 7.1.5.1.

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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.

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. The corresponding adjusted p-values for the Hochberg procedure will be provided.

The model assumption assessment will be performed following the methodology described in section 7.1.5.2.

In addition, the same model will be used to provide estimates for the changes in ESSDAI score at each time point of assessment as per protocol.

In case that more than 10% of subjects in any treatment group have a relevant protocol deviation, leading to exclusion of efficacy data, then this analysis will be repeated excluding efficacy data from subjects with relevant protocol deviations, as described in APPENDIX 1.

7.5.2 Secondary and Exploratory Efficacy Analyses

For all secondary endpoints, no multiplicity adjustment will be applied. Nominal p-values will be provided.

7.5.2.1 Categorical Endpoints

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, differences of the proportions between each active treatment arm and the placebo arm will be evaluated and their corresponding two-sided 95% confidence intervals and nominal p-values 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

The subjects that have discontinued the study prematurely or have missing assessments for ESSDAI or ESSPRI at Week 12, they will be counted in these analyses as having no improvement since baseline.

The same analysis will be repeated at each timepoint of assessment of ESSDAI and ESSPRI as per protocol. For these analyses no nominal p-values will be produced.

For the calculation of ESSDAI refer to section 8.6. For the calculation of ESSPRI refer to section 0.

7.5.2.2 Continuous Endpoints

The change from baseline in the following continuous endpoints will be analyzed with mixed effects model with repeated measures (MMRM) as described in section 7.1.5.1. The model will

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include all assessments for each parameters as defined in the protocol. Nominal p-values will be provided for those endpoints that are defined as secondary endpoints in the protocol.

- Change from baseline in ESSDAI scores at each time point of assessment. The change from baseline at Week 4, 8, are defined as secondary endpoints as per protocol. The change from baseline at Week 12 is the primary efficacy endpoint (see section 7.5.1). See Section 8.6 for calculation of ESSDAI.
- Change from baseline in ESSDAI domain scores at each time point of assessment. This is considered as an exploratory efficacy endpoint. The scores for the ESSDAI domains Glandular, Articular, Hematological, Biological, Lymphadenopathy, Pulmonary and Constitutional will be analyzed with mixed effect models. The scores for the ESSDAI domains Central Nervous System (CNS), Cutaneous, Muscular, Peripheral Nervous System (PNS) and Renal will be analyzed with summary statistics. See Section 8.6 for calculation of ESSDAI domain scores.
- Change from baseline in ESSPRI scores at each time point of assessment. The change from baseline at Week 4, 8, and, 12 are defined as secondary endpoints as per protocol. See Section 0 for calculation of ESSPRI.
- Change from baseline in score of each individual ESSPRI components (Dryness, Fatigue, and Pain) at each time point of assessment. The change from baseline at Weeks 4, 8, and 12 are defined as secondary endpoints as per protocol. See Section 0 for calculation of individual ESSPRI components.
- Change from baseline in mouth dryness as measured by unstimulated and stimulated salivary flow rate at Weeks 4, 8, and 12. See Section 8.8 for calculation of salivary flow rate.

  Change from baseline in eye dryness as measured by ocular surface staining (see section 8.11) , Schirmer's test (see section 8.9), and tear break-up (see section 8.10) time test at Weeks 4, 8, and 12. These analysis will be repeated for each eye separately and combining information for the two eyes taking the average of test values on the same visit.

The analyses of secondary endpoints that refer to outcome reported measurements are described in section 7.8. The analysis of Trough concentrations of study drugs are described in section 7.7.

7.6 Safety

The safety analysis endpoints described in this section are considered as secondary endpoints. For their analysis, there will be no statistical testing of group.

Analysis of all safety data will follow the BMS standard safety data conventions[34] [35] and supplements to the standard conventions as defined in this document.

All summaries of safety parameters during the double-blind period will be provided by treatment groups. All safety assessments will be included in the summary tables if the onset date is on or after the first dose date and the event occurs within the double-blind period or within 42 days post last dose date.

Presentations for the double-blind period will be provided by "as treated" treatment group for the as-treated analysis population, unless otherwise specified.

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7.6.1 Adverse Events

All AEs are coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the latest approved version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Listings and summaries will be based on the resulting SOCs and PTs.

AEs will be included in the frequency tabulations if they occur while a subject is on study medication up to and including 42 days after the last dose of study medication of either active medications or matching placebos. These AE summaries will be based on proportions, which represent the number of subjects experiencing the AEs divided by the number of subjects received with at least 1 dose of study medication.

In summaries by SOC and PT, AEs will be sorted by decreasing frequency within each SOC and PT according to the Lulizumab group. In summaries by PT, AEs will be sorted by decreasing frequency within PT according to the Lulizumab group. Counting rules for adverse events are described in section 8.18.

All adverse events listings will indicate the unique subject identifier, age, gender, current treatment, the date of onset, the date of resolution, day of onset relative to the start of treatment, action taken, investigator's assessment of severity and relationship to study drug.

Laboratory AEs are laboratory changes identified by the investigator as AEs and thus reported on the AE pages of the eCRF.

7.6.1.1 Adverse Events

All serious and non-serious adverse events with onset during the double-blind treatment period will be summarized by SOC, PT, and treatment group and overall. These summaries will be produced for:

- all adverse events
- adverse events related to the administration of the study drug, as determined by the investigator
- adverse events leading to discontinuation of study medication, as indicated in the eCRF. This analysis will include events independently of the time distance the last dose date.
- most common adverse events (reported in 10% of subjects or more in any treatment group)
- all serious adverse events, as captured on special CRF pages
- all serious adverse events related to the administration of the study drug, as captured on special CRF pages
- adverse events by intensity, as determined by the investigator

The following adverse events of special interest will be summarized by PT and treatment groups during the double-blind period. A subject listing will also be provided.

- Infections: All reported infections and infestations within the SOC: *Infections and infestations*. The severity of serious infections will be summarized. In addition, a listing of opportunistic infections will be provided.

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- Injection Reactions (Local and Systemic): All reported events defined in pre-specified MedDRA code of local and systemic injection reactions.

Additionally, a subject listing will be provided for the following adverse events of special interest that occurred during the double-blind period:

- Malignancy: All reported events defined in MedDRA Maintenance and Support Services Organization (MSSO) Structured MedDRA Query (SMQ) list.
- Autoimmunity: All reported events defined in pre-specified MedDRA code of autoimmune disorders.
- Transaminases Increased: All reported events defined in MedDRA Maintenance and Support Services Organization (MSSO) Structured MedDRA Query (SMQ) list. of "Drug related hepatic disorders - comprehensive search (SMQ)"

In addition, the number and proportion of subjects who experienced an AE once or multiple times (0 Events, 1 Events, 2-3 Events, >=4 Events) will be summarized by PT and treatment groups for most common AE (at least 5% subject in any treatment group) and events of special interest of infections. This analyses will be performed following the counting rules for unique adverse events as described section 8.18.2.

The following subject listings will be produced for:

- all reported adverse events, displaying all events (including pre-treatment events) that occurred at any time point during the study for subjects that received at least one dose of double-blind medication
- all unique instances of adverse events (see section 8.18.2), displaying all events (including pre-treatment events) that occurred at any time point during the study for subjects that received at least one dose of double-blind medication
- all serious adverse events, which will also be used for the purpose of clinical trial transparence for posting at public websites (e.g., NIH's www.ClinialTrials.gov)
- listing of most common non-serious AEs, for the purpose of clinical trial transparency for posting at public websites (e.g., NIH's www.ClinialTrials.gov)
- adverse events leading to discontinuation of study medication
- all infections
- all malignancies
- all autoimmune disorders
- local injection reactions
- systemic injection reactions

In addition, all SAEs will be described in narratives, regardless of investigator assessment of causality.

7.6.1.2 Deaths

All deaths recorded on the status page, the AE page, or SAE page (with a death date, cause of death, outcome or SAE categorization present) of the CRF will be considered a death in the

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analyses. Any deaths that occur during the study will be described in depth as narrative in the CSR. All Adverse events with the outcome of death reported during the study will be listed.

7.6.2 Laboratory evaluation

Unless otherwise specified, laboratory data obtained after the start of study medication dosing up to and including 42 days after the last double-blind dosing date will be considered as obtained during the double-blind treatment period.

7.6.2.1 Marked Laboratory Abnormalities

Laboratory marked abnormality using pre-defined abnormality criteria will also be descriptively summarized (see APPENDIX 3). The results of all protocol-specified clinical laboratory tests, as well as laboratory results outside of the normal range, will be listed.

The frequency of subjects with any marked laboratory abnormality will be presented by laboratory test during the double-blind treatment period. The results are based on the As-treated analysis population.

The criteria used for classifying laboratory test results as markedly abnormal will be listed.

7.6.2.2 Change from Baseline for Selected Laboratory Parameters Over Time

Scheduled laboratory measurements and corresponding change from baseline values will be summarized by treatment and nominal visit for each laboratory test for the As Treated analysis population using descriptive statistics (see section 7.1.3). Visit windows are provided in Section 8.1 in order to link each laboratory test to a scheduled visit. The following laboratory parameters will be analyzed:

- Hemoglobin
- Hematocrit
- Total leukocyte count
- Basophils Count
- Eosinophils Count
- Lymphocytes Count
- Monocytes Count
- Neutrophils Count
- Platelet count
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- Lactate dehydrogenase (LDH)

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- Creatinine
- Blood Urea Nitrogen (BUN)
- Uric acid
- glucose at fasting state
- Total Protein
- Albumin
- Sodium
- Potassium
- Chloride
- Calcium
- Phosphorus
- Magnesium
- Creatine kinase
- Total cholesterol at fasting state
- HDL-cholesterol at fasting state
- LDL-cholesterol at fasting state
- Triglycerides at fasting state
- ESR (local test)
- hsCRP
- Urine Protein
- Urine Glucose
- Urine Blood
- Urine Specific gravity
- Urine pH

As per protocol all laboratory parameter mentioned above are part of the safety laboratory test panel and are supposed to be assessed with the subject at fasting state. However for analysis purposes all data will be considered for analysis, even if the subject was not in a fasting state, unless if it is mentioned otherwise above. In these cases, only those measurement where the subject was on fasting state will be considered for analysis.

7.6.2.3 Pregnancy Test Results

A by-subject listing of positive pregnancy test results will be provided using the As-treated analysis population.

7.6.3 Electrocardiogram

Summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for each ECG parameters and the corresponding changes from baseline by treatment

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and visit. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed.

The frequency distribution of subjects' maximum recorded post-dose QTcF, PR, QRS and ΔQTcF (see section 8.19) will be tabulated by treatment and summarized within the CSR text for the ranges in Table 7.6.3-2. Individual QTcF, PR, QRS or ΔQTcF values meeting these criteria will be flagged in the data listing.

Table 7.6.3-2: Electrocardiogram Parameter Categorization

Parameter	Categorization
QTcF (msec)	=< 450
	450 < to =< 480
	480 < to =< 500
	> 500
PR (msec)	=< 200
	> 200
QRS (msec)	=< 120
	> 120
Change from baseline in QTcF (msec)	=< 30
	30 < TO =< 60
	> 60

7.6.4 Vital Sign

Vital signs parameters (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and body temperature) will be listed. Summaries of vital sign parameters will be provided for each vital sign parameter at corresponding visits by treatment and respective changes from baseline. Subjects with vital signs outside of a pre-specified range will also be listed.

The following criteria will be used to determine vital sign results that are outside of a pre-specified range, where changes from baseline are based on matched postural positions and are calculated as parameter value - baseline parameter value:

Table 7.6.4-2: Vital signs criteria

Vital sign	Criteria
Heart Rate(bpm)	Value > 100 and change from baseline > 30, or
	Value < 55 and change from baseline < -15
Systolic BP(mmHg)	Value > 140 and change from baseline > 20, or
	Value < 90 and change from baseline < -20
Diastolic BP(mmHg)	Value > 90 and change from baseline > 10, or
	Value < 55 and change from baseline < -10

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Table 7.6.4-2: Vital signs criteria

Vital sign	Criteria
Respiration(breaths/min)	Value > 16 or change from baseline > 10
Temperature (°C)	Value > 38.3°C or change from baseline > 1.6°C

7.6.5 Physical Examination Findings

All physical examination abnormal findings will be listed per subject by visit.

[redacted]

7.8 Outcomes Research Analyses

The outcome research analysis endpoints described in this section are considered as secondary endpoints. For their analysis, no multiplicity adjustment will be applied and no p-values will be provided.

Descriptive summary statistics (see section 7.1.3) will be provided for absolute value and change (or percent change) from baseline to all assessments as described in the protocol for primary measures the following outcome research assessments:

- Numeric Rating Scale (NRS) scores for mouth, eye and vaginal dryness (see section 8.12). Each of these scores will be analyzed separately.
- Subject global assessment of disease activity (SubGDA) and physician global assessment of disease activity (phyGDA) will be analyzed separately (see section 8.13)

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- Short Form - 36 acute (SF-36 acute) (see section 8.14). Both the physical and mental scales as well as the individual sub-scales will be analyzed.
- Female Sexual Function Index (FSFI) (see section 8.15). Both the full scale score and the individual domain scores will be analyzed.
- Work participation and activity impairment questionnaire (WPAI) (see section 8.16). Percent work time missed due to health, percent impairment while working due to health, percent overall work impairment due to health and percent activity impairment due to health will be analyzed.
- PROMIS Fatigue Short Form 8a (see section 8.17).

If deemed necessary after observing results from the analyses described above, the MMRM method or other modelling methods may be applied to changes from baseline in primary measures (e.g., total scores) of the above outcome research measures.

7.9 Biomarker Analyses

[redacted]

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[redacted]

7.9.2 Biopsies

The focus scores of lip or parotic gland biopsies and the corresponding changes from baseline will be summarized by treatment and visit using descriptive statistics (see section 7.1.3). Visit windows are provided in Section 8.1 in order to link each score test to a scheduled visit.

A subject listing of all lip or parotic gland biopsy findings will be provided.

[redacted]

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[redacted]

7.11 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 (i.e., to a maximum of 120 subjects in total) to maintain adequate study power.[28 29 30] Regardless of the outcome from the blinded examination of variability, the study sample size will not be decreased.

The blinded examination of the variance will be based on the following assumptions:

- the placebo adjusted change from baseline at Week 12 for both active treatment arms (lulizumab or BMS-986142) will be 3 ESSDAI points
- the change from baseline at Week 12 will be the same for both active treatment arms.

The calculation of the blinded examination of the variance will include randomized subjects who received at least one dose of study drug with non missing ESSDAI assessment both for baseline and Week 12. Subjects will be considered for analysis if their Week 12 assessment occur while on double-blind study medication.

The estimate of the blinded examination of the variance $S^2_{blinded}$ will be computed using the formula mentioned by Kieser and Friede (2000)[36]:

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$$S^2_{blinded} = S^2_{pooled} - \frac{\frac{n}{3}}{n-1} \cdot \sum_{i=1}^{3} (\mu_i - \bar{\mu})^2$$

where:

- S^2_{pooled} is the variance of change from baseline at Week 12 in ESSDAI as calculated based on all subjects included in the interim analysis
- n is the number of subjects included in the interim analysis (across all treatment groups)
- μ_i is the assumed change from baseline at Week 12 for each of the 3 arms
- $\bar{\mu}$ is the assumed overall mean. For this calculation it is assumed to be average of μ_i across all treatment groups

Since μ_i and $\bar{\mu}$, the $\sum_{i=1}^{3} (\mu_i - \bar{\mu})^2$ will be approximated by the term below:

$$\left(\xi_{Lulizumab} - \frac{\xi_{Lulizumab} + \xi_{BMS-986142} + \xi_{Placebo}}{3} \right)^2 +$$

$$+ \left(\xi_{BMS-986142} - \frac{\xi_{Lulizumab} + \xi_{BMS-986142} + \xi_{Placebo}}{3} \right)^2 +$$

$$+ \left(\xi_{Placebo} - \frac{\xi_{Lulizumab} + \xi_{BMS-986142} + \xi_{Placebo}}{3} \right)^2$$

where

$\xi_{Lulizumab} = \xi_{BMS-986142}$=3 ESSDAI points and $\xi_{Placebo}$ =0.

The common standard deviation will be estimated based on the estimate of the blinded examination of the variance.

The common standard deviation will be compared against the initial study assumptions for sample size estimation (see section 5). Would it be substantially larger than the initially planned, the sample size for the study will be re-estimated taking into consideration the maintenance of adequate power for the study (see section 5).

The final decision on sample size and power for this study will be made by BMS senior management.

8 CONVENTIONS

8.1 Time from first diagnosis of Sjogren's syndrome

The time from first diagnosis of Sjogren's syndrome of T1DM is calculated as the number of years from the diagnosis date to informed consent date:

(1 + consent date - diagnosis date) / 365.25.

If the date of diagnosis is partially missing, the following rules will take effect:

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- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
- Missing day and month, but year is present: the day and month will be imputed as 30 June of the year (provided that the imputed date is less than the consent date).
- Missing year, but day and month are present: No imputations will occur, and the subject will be excluded from all related summaries.
- Missing day, month and year: No imputations will occur, and the subject will be excluded from all related summaries.
- If any such imputed date falls after the consent date, then the diagnosis date will be taken as equal to the consent date.

In cases that these dates are presented in listings, only the portion of the date of diagnosis actually observed, rather than imputed dates, will be displayed in listings.

8.2 Analysis Window for Longitudinal Assessments

8.2.1 Baseline Value

For each subject, the baseline value of a parameter is defined as the last assessment of that parameter on or prior to the date/time of the first dose of the double-blind study medication.

If time is of measurement of a parameter or time of first dose are missing, then the baseline value is defined as the last assessment of that parameter on or prior to the date of the first dose of the double-blind study medication.

8.2.2 Longitudinal Assessments

Day 1 for the double-blind treatment period is the start date of double-blind treatment medication. The observation closest to the target day (and time where applicable) is the measurement used in the analysis for each scheduled visit.

The following visit windows will apply for all measurements in the double-blind treatment and follow-up periods:

Table 8.2.2-1: Visit Windows for Double-Blind Treatment Period

Visit	Target Day	Day Range
Day 8 (Week 1)	8	Post-baseline - 11*
Day 15 (Week 2)	15	12 - 18*
Day 22 (Week 3)	22	19 - 25*
Day 29 (Week 4)	29	26 - 32*
Day 36 (Week 5)	36	33 - 39*
Day 43 (Week 6)	43	40 - 46*
Day 50 (Week 7)	50	47 - 53*
Day 57 (Week 8)	57	54 - 60*

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Table 8.2.2-1: Visit Windows for Double-Blind Treatment Period

Visit	Target Day	Day Range
Day 64 (Week 9)	64	61 - 67*
Day 71 (Week 10)	71	68 - 74*
Day 78 (Week 11)	78	75 - 81*
Day 85 (Week 12)	85	82 - 95*

* see section 8.3 for the definition of double-blind treatment period

Day 1 for the follow-up period is the day after the last day of double-blind treatment period (see section 7.4.1 for definition of last day of double-blind treatment period). The observation closest to the target day (and time where applicable) is the measurement used in the analysis for each scheduled visit. Because of the definition of post double-blind treatment observations that may still fall in the double-blind period (see Section 8.3) the early days during the follow-up period may actually provide data that are still considered as occurring during double-blind period.

Table 8.2.2-2: Visit Windows for the Follow-Up Period

Visit	Target Day in Follow-up Period	Day Range in Follow-up Period
Day 106 (Week 15)	21	Post double-blind treatment - 31
Day 127 (Week 18)	42	32 - latest assessment

The use of post double-blind treatment observations that may still fall in the double-blind period is specified in Section 8.3.

For all parameters, if a subject has more than one measurement included within a window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day, the earlier assessment will be used. In case of ties located on the same side of the target day (i.e. more than one value for the same day but different time), the value with the earlier entry date/time will be used.

8.3 Post-Treatment Efficacy and Safety Observations

While efficacy and safety observations will be listed regardless of whether the subject was taking blinded study drug, observations may not contribute to summaries/analyses if they are measured after the last dose of double-blind study medication as indicated below:

- all efficacy, clinical biomarkers and outcome research will be included in the analyses of double-blind period if measured on or prior to 28th day after the last dose date of lulizumab or matching placebo or on or prior to the 2nd day after the last dose date of BMS-986142 or matching placebo, whichever is latest. These windows are based on the four half-life times of each active medication (7 days for lulizumab, 11 hours for BMS-986142).

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- all vital signs, pharmacokinetic, and immunogenicity assessments will be included in the analyses of double-blind period if measured on or prior to 21th day after the last dose date of lulizumab or matching placebo or on or prior to the 2nd day after the last dose date of BMS-986142 or matching placebo, whichever is latest. These windows are based on the three half-life times of each active medication (7 days for lulizumab, 11 hours for BMS-986142). These windows are different from the rest of the parameters because of the protocol visit schedule at 21 days since the end of the double-blind period.
- all adverse events will be included in the analyses of double-blind period if measured on or prior to 42th day after the last dose date of lulizumab or matching placebo or on or prior to the 3rd day after the last dose date of BMS-986142 or matching placebo, whichever is latest. These windows are based on the six half-life times of each active medication (7 days for lulizumab, 11 hours for BMS-986142).
- all safety laboratory and lipid parameter will be included in the analyses of double-blind period if measured on or prior to 28th day after the last dose date of lulizumab or matching placebo or on or prior to the 2nd day after the last dose date of BMS-986142 or matching placebo, whichever is latest. These windows are based on the four half-life times of each active medication (7 days for lulizumab, 11 hours for BMS-986142). These windows are different from the rest of the safety parameters because of the protocol visit schedule at 42 days since the end of the double-blind period.

8.3.1 Missing and Multiple Measurements

For listings of efficacy, safety, pharmacokinetic, biomarkers, immunogenicity, outcome research measures, missing values will be represented as not reported.

For all analyses and summaries of efficacy, safety, outcome research measures, missing values will not be imputed.

Some laboratory samples may be inadvertently analyzed multiple times for the same test, producing multiple lab results on the same collection date and time for the same subject. The selection of laboratory result for analysis for this subject will follow BMS global standard.

All blood pressure measurements will be included in the summaries/analysis independently of the position they were measured, e.g., sitting, supine, standing.

8.4 Assignment of Doses to Adverse Events and Laboratory Assessments

In case of missing dates and/or times, prior to assigning the treatment that the subject received at the onset of an AE or at the time of a laboratory assessment, imputation rules will be applied as follows:

For AEs, a missing or incomplete onset date will be imputed according to the following conventions:

- If the onset date for an AE is missing or incomplete, an imputed date will be derived to slot the event to an appropriate analysis period. This derived date will not be reported in summary tables or listings. Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

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- If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):
  - First active study medication date
  - Consent date
  - Visit date corresponding to the visit at which the event was reported.
  - If a valid non-missing date is not available for any of these dates, the derived onset date will be set to missing.
- If an onset date is incomplete, the derived onset date will be calculated using the following algorithm:
  - Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence):
    - First active study medication date
    - Consent date
    - Visit date corresponding to the visit at which the event was reported
    - If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing.
  - Based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.
  - If the surrogate date is non-missing then:
    - If the derived date is on or after the surrogate date use the derived date as calculated
    - If the derived date is prior to the surrogate date and the surrogate date is consistent with the partial data provided for the onset date, use the surrogate date as the derived date
    - If the derived date is prior to the surrogate date and the surrogate date is not consistent with the partial data provided for the onset date then set the derived onset date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If a year and month is provided, set the derived date to the last day of that month.
  - If all three dates used to determine the surrogate date are missing, then based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.

A drug treatment file will be created, containing any starting and stopping dose as well as intermediate dose changes within each study period, with dates and times as recorded on the CRF. In this context,

- the date of the first dose of study medication is defined as the earliest start date with number of tablets > 0 or injections > 0 reported on the study medication page.
- the date of the last dose of study medication is defined as the latest start or stop date with number of tablets > 0 or injections > 0 reported on the study medication page.

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- if a dosing time is missing for a starting dose of study drug in a study period or a dose change, then it is defaulted to 9:00.
- if there's a gap in the dosing information, then the dosing time corresponding to the start date of the gap, is defaulted to 00:00.

If a dosing time is missing for a last stop dosing date for the study drug in a study period, then it is defaulted to 23:59.

8.4.1 Treatment at Onset of an Adverse Event

Both onset date and (if requested) onset time of an AE will be compared to the dosing information. Treatment will then be the dose at the last observation for a subject in the dosing file where the AE onset date/time is not earlier than the dose date/time.

8.4.2 Treatment at the Time of a Laboratory Assessment

Laboratory draw date and time will both be compared to the dosing information. Treatment at the time of the laboratory assessment will then be the dose at the last observation for a subject in the dosing file where the laboratory date/time is not earlier than the dose date/time.

8.5 Non-study Medications

Start and stop date of all non-study medications are collected on the CRF. In order to classify medication as prior or concomitant, partial, missing or invalid start and stop dates will be imputed where possible as follows:

- If the reported start date is missing or invalid and the informed consent date is not missing or invalid, then the imputed start date is set equal to the informed consent date. If the consent date is missing or invalid and the birth date is not missing or invalid, then the imputed start date is set equal to the birth date. If the start date, the consent date and the birth date are all invalid or missing, then the imputed start date is set equal to missing.
- If the reported start date is partially entered, then the imputed start date is set equal to the earliest possible reported start date based on the partial entered reported start date.
- If the reported end date is missing, continuing, unknown or invalid, then the imputed end date is set equal to the most recent database extraction date.
- If the reported end date of the medication is partial, then the imputed end date is set equal to the last possible reported end date based on the partial entered reported end date.

Imputed dates will not appear on the listings of non-study medication.

8.6 EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)

The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) total score is calculated as the sum of scores for activity level for each domain.[33] The scores and the domains are presented in Table 8.6-2.

The ESSDAI domain scores will be calculated using the values presented in in Table 8.6-2 for each domain separately.

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Table 8.6-2: The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) scoring algorithm

Domain	Score for activity level
Constitutional	No=0, Low=3, Moderate=6
Lymphadenopathy	No=0, Low=4, Moderate=8, High=12
Glandular	No=0, Low=2, Moderate=4
Articular	No=0, Low=2, Moderate=4, High=6
Cutaneous	No=0, Low=3, Moderate=6, High=9
Pulmonary	No=0, Low=5, Moderate=10, High=15
Renal	No=0, Low=5, Moderate=10, High=15
Muscular	No=0, Low=6, Moderate=12, High=18
Peripheral Nervous System (PNS)	No=0, Low=5, Moderate=10, High=15
Central Nervous System (CNS)	No=0, Moderate=10, High=15
Haematological	No=0, Low=2, Moderate=4, High=6
Biological	No=0, Low=1, Moderate=2

Information extracted from Table 1 in Seror R, Theander E, Brun JG, et al. Ann Rheum Dis, 2015;74:859–866. [33]

[redacted]

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8.18 Counting rules for adverse events

8.18.1 At Subject Level

Where a subject has multiple adverse events within the same system organ class in a single analysis period, the subject will only be counted once at the system organ class level in adverse event frequency tables.

When a subject has the same adverse event, based on preferred terminology, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Relationship to study medication
- Intensity of event
- Onset date and time

When assessing relationship to study medication, relationship as reported by the investigator, events will be reported as related or not to study medication. Related events will take precedence over unrelated events in determining the event to include in summary tables.

More intense events will take precedence over less intense events in determining the event to include in summary tables.

Earlier onset date-time events will take precedence over late onset date-time events in determining the onset to include in summary tables.

When reporting adverse events by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Intensity of event
- Onset date and time

Subjects will only be counted once in the 'Total' at their maximum intensity, regardless of SOC or PT.

8.18.2 At Event Level

At event level, each unique AE record will be counted. Unique AE record can be obtained by collapsing all AE records following a standard algorithm. The CRF data will be processed according to standard BMS algorithms to categorize each line of patient data as a new occurrence or a continuation of an existing event. This determination will be based upon onset and resolution dates. Each line of patient data will represent the maximum severity observed as well as the last known assessed relationship to study medication by the investigator.

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8.19 Conventions of ECG Data

All available non-missing values of ECG parameters should be used in the listings, summarizations, and analyses. However, if QTcF is missing and RR in seconds is available, then QTcF will be calculated as

$$QTcF = \frac{QT}{RR^{1/3}}.$$

If both QTcF and RR in seconds are missing, then QTcF will be calculated as

$$QTcF = \frac{QT}{\left(60/HEART\ RATE\right)^{1/3}}$$

8.20 Percent Compliance Calculation

Percent compliance for the double-blind study medication during the double-blind treatment period is defined for each subject as the number of tablets and injections taken, divided by the number of tablets that should have been taken.

For BMS-986142, the number of tablets that should have been taken is calculated as 1 + the number of days from the first double-blind treatment period dose recorded in the "Record of Study Medication" to the last double-blind treatment dose, times the prescribed daily dose (i.e. 2 tablets per day, one from each bottle). The number of tablets taken is the total number of tablets recorded (sum of bottle 1 and bottle 2) as taken based on the CRF, summed over the days counted when calculating the number of tablets that should have been taken, including the day of the last double-blind treatment dose.

For Lulizumab, the same calculation will be used. The number of injections that should have been administered is calculated as 1 + the number of days from the first double-blind treatment period dose recorded in the "Record of Study Medication" to the last double-blind treatment dose divided by 7. The number of injections administered is the total number of injections recorded as administered based on the CRF, summed over the days counted when calculating the number of injections that should have been administered, including the day of the last double-blind treatment dose.

8.21 Strip Sign for Selected Laboratory Data

For selected laboratory test values that have been received with an operator sign as a part of the result (>, ≥, <, or ≤), a process to strip the operator sign will be applied and the resulting numeric values will be used for data analysis. The raw value with operator will remain as such on the CRF (or in the electronic record) and in the database.

The applicable impacted laboratory tests and applicable operator signs will be identified during the course of the study and study monitoring. For laboratory parameters not included in any statistical analyses, operator signs will not be stripped and the value will counted as missing.

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8.22 United States Conventional Units and Standard International Units for Laboratory Data

Unless otherwise specified, all analyses of laboratory data (independently of being safety or efficacy) will be performed in both United States Conventional Units (US) and Standard International Units (SI). Conversion between US and SI, and vice versa, will be performed using the BMS standard conversion factors.

8.23 Laboratory evaluations

All laboratory evaluations performed by central laboratories and local laboratories that are included in the database will be included in summary tables and in the listings.

9 CONTENT OF REPORTS

The results of the study conducted by Protocol IM128-035 will be presented in a standard BMS CSR appendix. Key results and any unanticipated findings that are unusual for this study will be identified. A meeting for the initial dissemination of study results will be held after database locked. Attendees at this meeting will review all efficacy and safety summaries and listings and will identify key results that should be highlighted in the CSR.

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APPENDIX 1 RELEVANT PROTOCOL DEVIATIONS

Number	Relevant Protocol Deviation Criteria	Exclusion Level
1	Randomized subjects who do not have moderate to severe primary Sjögren's syndrome, defined is defined as Sjögren's syndrome in the absence of another autoimmune disease or rheumatologic condition) based on the 2015 ACR-EULAR Classification Criteria.	Complete exclusion
2	Randomized subjects without ESSDAI ≥ 5, including disease activity (any score > 0) in at least one of the following domains: Glandular, Articular, Hematological, Biological, Lymphadenopathy.	Complete exclusion
3	Randomized subjects without Positive anti-SS-A/Ro or anti-SS-B/La autoantibody.	Complete exclusion
4	Randomized subjects who received more than 10mg/day of prednisone (or prednisone equivalent) for at least 14 days prior to Day 1 (randomization).	Complete exclusion
5	Randomized subjects who did not receive at least 4 consecutive doses of Lulizumab or matching placebo.	Partial exclusion (Efficacy data after the 21th day of the interruption will be excluded)
6	Randomized subjects who did not receive BMS-986142 or matching placebo for at least 14 consecutive days.	Partial exclusion (Efficacy data after the 14th day of the interruption will be excluded)
7	Randomized subjects to placebo receiving active medication dose of Lulizumab for at least 4 doses and BMS-986142 for at least 14 doses.	Partial exclusion (Efficacy data from the first dose date of active medication will be excluded)
8	Randomized subjects receiving initiating or increasing the baseline dose (if already in such a medication) in any of the protocol specified list of restricted and prohibited treatments during double-blind treatment period.	Partial exclusion (Efficacy data from the first dose date of restricted or protocol medication will be excluded)
9	Randomized subjects less than 80% or more than 120% compliant with any of the double-blind treatment regimens.	Complete exclusion

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APPENDIX 2 GEOGRAPHIC REGIONS

Geographic Region	Countries
North America	United States Puerto Rico Mexico
South America	Chile Colombia Peru
Europe	France Germany Netherlands Russia Greece Romania Hungary Italy Poland South Africa
Oceania	Australia

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APPENDIX 3 MARKED LABORATORY ABNORMALITIES CRITERIA

Laboratory parameter	Code	Low Criterion		High Criterion	
		US units	SI units	US units	SI units
Hemoglobin	HB	< BASELINE - 0.3 g/dL	< BASELINE -3 g/L		
		< 7 G/DL	< 70 G/L		
Hematocrit	HCT	< 0.75*BASELINE			
Erythrocytes	RBC	< 0.75*BASELINE			
Platelet Count	PLAT	< 0.5*BASELINE AND <100 x10*9 c/L IF BASELINE < LLN		>1.5*ULN IF LLN <= BASELINE <= ULN	
		<0.67*LLN IF LLN <= BASELINE <= ULN			
		<50 x10*9 c/L			
Leukocytes	WBC	<0.75*LLN IF LLN <= BASELINE <= ULN		> 1.25*ULN IF LLN <= BASELINE <= ULN	
		<0.8*BASELINE IF BASELINE < LLN		>ULN IF BASELINE < LLN	
		< LLN IF BASELINE > ULN		> 1.2*BASELINE IF BASELINE > ULN	
		<2.0 x10*3 c/uL	<2.0 x10*9 c/L		
Neutrophils + Bands (absolute)	PMNBA	<1.000 x10*3 c/uL	<1.000 x10*9 c/L		
Eosinophils (absolute)	EOSA			> 0.750 x10*3 c/uL	> 0.750 x10*9 c/L
Basophils (absolute)	BASOA			>0.400 x10*3 c/uL	>0.400 x10*9 c/L
Monocytes (absolute)	MONOA			> 2.000 x10*3 c/uL	> 2.000 x10*9 c/L
Lymphocytes (absolute)	LYMPA	< 0.750 x10*3 c/uL	< 0.750 x10*9 c/L	> 7.500 x10*3 c/uL	> 7.500 x10*9 c/L
		<0.5 x10*3 c/uL	<0.5 x10*9 c/L		
Blasts (relative)	BLAST			>0 %	>0
PT Ratio	PTR			> 1.33*BASELINE	
aPTT Ratio	APTTR			> 1.33*BASELINE	
Intl Normalized Ratio	INR			> 1.33*BASELINE	
Alkaline Phosphatase	ALP			> 2*ULN IF LLN <= BASELINE <= ULN	
				> 3*BASELINE IF BASELINE > ULN	

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Laboratory parameter	Code	Low Criterion		High Criterion	
		US units	SI units	US units	SI units
				>5.0 xULN	
Aspartate Aminotransferase	AST			> 3*ULN IF LLN <= BASELINE <= ULN	
				> 4*BASELINE IF BASELINE > ULN	
				>5.0 xULN	
Alanine Aminotransferase	ALT			> 3*ULN IF LLN <= BASELINE <= ULN	
				> 4*BASELINE IF BASELINE > ULN	
				>5.0 xULN	
G-Glutamyl Transferase	GGT			> 2*ULN IF LLN <= BASELINE <= ULN	
				> 3*BASELINE IF BASELINE > ULN	
Bilirubin, Total	TBILI			> 2*ULN IF LLN <= BASELINE <= ULN	
				> 4*BASELINE IF BASELINE > ULN >3.0 xULN	
Bilirubin, Direct	DBILI			> 1.5*ULN IF LLN <= BASELINE <= ULN	
				> 2*BASELINE IF BASELINE > ULN	
Blood Urea Nitrogen	BUN			> 2*BASELINE	
Creatinine	CREAT			> 1.5*BASELINE	
				>3.0 xULN	
Protein/Creatinine Ratio	PRCRR			> 4 mg/mg	> 4519.8 mg/mmol
Creatinine Clearance	CRCL	< 0.67*BASELINE			
Sodium, Serum	NA	< 0.95*LLN IF LLN <= BASELINE <= ULN		> 1.05*ULN IF LLN <= BASELINE <= ULN	
		< 0.95*BASELINE IF BASELINE < LLN		> ULN IF BASELINE < LLN	
		< LLN IF BASELINE > ULN		> 1.05*BASELINE IF BASELINE > ULN	
		< 130 mEq/L	< 130 mmol/L	> 155 mEq/L	> 155 mmol/L

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Laboratory parameter	Code	Low Criterion		High Criterion	
		US units	SI units	US units	SI units
Potassium, Serum	K	< 0.9*LLN IF LLN <= BASELINE <= ULN		> 1.1*ULN IF LLN <= BASELINE <= ULN	
		< 0.9*BASELINE IF BASELINE < LLN		> ULN IF BASELINE < LLN	
		< LLN IF BASELINE > ULN		> 1.1*BASELINE IF BASELINE > ULN	
		< 2.5 mEq/L	< 2.5 mmol/L	> 6.0 mEq/L	> 6.0 mmol/L
Chloride, Serum	CL	< 0.9*LLN IF LLN <= BASELINE <= ULN		> 1.1*ULN IF LLN <= BASELINE <= ULN	
		< 0.9*BASELINE IF BASELINE < LLN		> ULN IF BASELINE < LLN	
		< LLN IF BASELINE > ULN		> 1.1*BASELINE IF BASELINE > ULN	
Carbon Dioxide, Total	CO2	< 0.75*LLN IF LLN <= BASELINE <= ULN		> 1.25*ULN IF LLN <= BASELINE <= ULN	
		< 0.75*BASELINE IF BASELINE < LLN		> ULN IF BASELINE < LLN	
		< LLN IF BASELINE > ULN		> 1.25*BASELINE IF BASELINE > ULN	
Bicarbonate	HCO3	< 0.75*LLN IF LLN <= BASELINE <= ULN		> 1.25*ULN IF LLN <= BASELINE <= ULN	
		< 0.75*BASELINE IF BASELINE < LLN		>ULN IF BASELINE < LLN	
		<LLN IF BASELINE > ULN		> 1.25*BASELINE IF BASELINE > ULN	
Calcium	CA	< 0.8*LLN IF LLN <= BASELINE <= ULN		> 1.2*ULN IF LLN <= BASELINE <= ULN	
		< 0.75*BASELINE IF BASELINE < LLN		>ULN IF BASELINE < LLN	
		<LLN IF BASELINE > ULN		> 1.25*BASELINE IF BASELINE > ULN	
		< 7 mg/dL	< 1.75 mmol/L	> 12.5 mg/dL	> 3.13 mmol/L
Phosphorus, Inorganic	PHOS	< 0.75*LLN IF LLN <= BASELINE <= ULN		> 1.25*ULN IF LLN <= BASELINE <= ULN	
		< 0.67*BASELINE IF BASELINE < LLN		>ULN IF BASELINE < LLN	
		< LLN IF BASELINE > ULN		> 1.33*BASELINE IF BASELINE > ULN	
		< 2.0 mg/dL	< 0.65 mmol/L		
Magnesium,	MG	< 0.6*LLN IF LLN <= BASELINE <=		> 2.0*ULN IF LLN <= BASELINE	

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Laboratory parameter	Code	Low Criterion		High Criterion	
		US units	SI units	US units	SI units
Serum		ULN		<= ULN	
		< 0.67*BASELINE IF BASELINE < LLN		>ULN IF BASELINE < LLN	
		<LLN IF BASELINE > ULN		> 2.0*BASELINE IF BASELINE > ULN	
Glucose, Serum	GLUC	< 65 mg/dL	< 3.6 mmol/L	> 220 mg/dL	> 12.2 mmol/L
Glucose, Fasting Serum	GLUCF	< 0.8*LLN IF LLN <= BASELINE <= ULN		> 1.5*ULN IF LLN <= BASELINE <= ULN	
		< 0.8*BASELINE IF BASELINE < LLN		>ULN IF BASELINE < LLN	
		< LLN IF BASELINE > ULN		> 2.0*BASELINE IF BASELINE > ULN	
Protein, Total	TPRO	< 0.9*LLN IF LLN <= BASELINE <= ULN		> 1.1*ULN IF LLN <= BASELINE <= ULN	
		< 0.9*BASELINE IF BASELINE < LLN		>ULN IF BASELINE < LLN	
		<LLN IF BASELINE > ULN		> 1.1*BASELINE IF BASELINE > ULN	
Albumin	ALB	< 0.9*LLN IF LLN <= BASELINE <= ULN			
		< 0.75*BASELINE IF BASELINE < LLN			
		< 2 g/dL	< 20 g/L		
Cholesterol, Total	CHOL			> 2*BASELINE	
Triglycerides, Fasting	TRIGF			>= 2.0*ULN IF LLN <= BASELINE <= ULN	
				> 2.0*BASELINE IF BASELINE > ULN	
Amylase, Total	AMYL			> 3*ULN IF LLN <= BASELINE <= ULN	
				> 4*BASELINE IF BASELINE > ULN	
Creatinine Phosphokinase	CK			> 4*BASELINE	
Uric Acid	URIC			> 1.5*ULN IF LLN <= BASELINE <= ULN	
				> 2*BASELINE IF BASELINE > ULN	
Lactate Dehydrogenase	LD			> 1.5*ULN IF LLN <= BASELINE <= ULN	

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Laboratory parameter	Code	Low Criterion		High Criterion	
		US units	SI units	US units	SI units
				> 3*BASELINE IF BASELINE > ULN	
Protein, Urine	UPRO			>= 2 IF MISSING BASELINE VA >= 4	
				>= 2 IF 0=< BASELINE =<0.5	
				>= 3 IF BASELINE = 1	
				>= 4 IF 2=< BASELINE =<3	
Glucose, Urine	UGLU			>= 2 IF MISSING BASELINE VA >= 4	
				>= 2 IF 0=< BASELINE =<0.5	
				>= 3 IF BASELINE = 1	
				>= 4 IF 2=< BASELINE =<3	
Ketones, Urine	UKET			>= 2 IF MISSING BASELINE	
				>= 4	
				>= 2 IF 0=< BASELINE =<0.5	
				>= 3 IF BASELINE = 1	
				>= 4 IF 2=< BASELINE =<3	
Blood, Urine	UBLD			>= 2 IF MISSING BASELINE	
				>= 4	
				>= 2 IF 0=< BASELINE =<0.5	
				>= 3 IF BASELINE = 1	
				>= 4 IF 2=< BASELINE =<3	
Leukocyte Esterase, Urine	ULEUK			>= 2 IF MISSING BASELINE	
				>= 4	
				>= 2 IF 0=< BASELINE =<0.5	
				>= 3 IF BASELINE = 1	
				>= 4 IF 2=< BASELINE =<3	
RBC, Urine	URBC			>= 2 hpf IF MISSING BASELINE	
				>= 4 hpf	
				>= 2 hpf IF 0=< BASELINE =<0.5 hpf	
				>= 3 hpf IF BASELINE = 1 hpf	
				>= 4 hpf IF 2 hpf =< BASELINE =<3 hpf	
WBC, Urine	UWBC			>= 2 hpf IF MISSING BASELINE	

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Laboratory parameter	Code	Low Criterion		High Criterion	
		US units	SI units	US units	SI units
				>= 4 hpf	
				>= 2 hpf IF 0=< BASELINE =<0.5 hpf	
				>= 3 hpf IF BASELINE = 1 hpf	
				>= 4 hpf IF 2 hpf =< BASELINE =<3 hpf	

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APPENDIX 4 DOCUMENT HISTORY

Version	Statistician	Date	Notes/Revisions
1.0	Alexandros-Georgios Chalamandaris	30 October 2016	Original version

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