STATISTICAL ANALYSIS PLAN

SGN35-022

A MULTI-CENTER, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED, MULTIPLE-ASCENDING-DOSE STUDY OF BRENTUXIMAB VEDOTIN IN ADULTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS.

STUDY PHASE: PHASE 2A

PRODUCT: BRENTUXIMAB VEDOTIN

AUTHOR: [redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - APPROVAL

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Listed below are modifications made to the SAP after the signed approval(s).

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation of safety, pharmacokinetic, pharmacodynamic and efficacy data for Protocol SGN35-022. It describes the data analysis to be conducted after data base lock and unblinding, and is to be signed prior to those milestones.

This statistical analysis plan (SAP) is based on protocol Amendment 2, dated 25 July 2016.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

To evaluate the safety and tolerability of brentuximab vedotin in adults with active systemic lupus erythematosus (SLE).

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are:

- to explore the pharmacokinetics (PK) and pharmacodynamics (PD) of brentuximab vedotin in adults with active SLE; and
- to explore the efficacy of brentuximab vedotin in adults with active SLE.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a multicenter, randomized, placebo-controlled, double-blind, multiple-ascending-dose study to evaluate the safety and tolerability of brentuximab vedotin in subjects with active SLE. Approximately 40 subjects in 4 dosing cohorts (10 subjects per cohort) are planned for study participation at approximately 20 study sites in the US. Subjects who meet inclusion and exclusion criteria will be randomly assigned in a 4:1 ratio within each dosing cohort to receive IV brentuximab vedotin or placebo every 3 weeks (Days 1, 22, 43, and 64) for a total of 4 doses. The following doses are planned for each ascending dose cohort:

• 0.3 mg/kg IV every 3 weeks for 4 doses;

• 0.6 mg/kg IV every 3 weeks for 4 doses;

• 1.2 mg/kg IV every 3 weeks for 4 doses; and

• 1.8 mg/kg IV every 3 weeks for 4 doses.

Individual doses are based on subject weight and will be administered as an IV infusion over approximately 30 minutes. Dose and/or schedule adjustments are not permitted. In-line filters are permitted. However the study drug cannot be mixed with other medications. Further instructions on the dose preparation and administration will be provided in the Pharmacy Manual.

Initiation of enrollment at the next dose level will only commence upon endorsement of the SMC following review of the safety data. Depending on the findings, the SMC may recommend additional enrollment of subjects at specific dose levels to better characterize the safety of a particular dose, or may recommend different dose regimens based on the emerging safety data. When available from each full cohort, the SMC will review all Day 85 safety data and may recommend that an already enrolled succeeding dose cohort be discontinued, or its treatment regimen truncated. Doses are not to exceed 1.8 mg/kg IV every 3 weeks or equivalent. Up to 20 subjects total may be enrolled via additional SMC-recommended cohorts for a total of up to 60 subjects.

3.1.1. SAMPLE SIZE

Since no prior studies in SLE have been conducted with brentuximab vedotin, the primary objective of this study is to evaluate the safety and tolerability of brentuximab vedotin in this patient population. As such, the number of subjects planned has been based on clinical judgment, to provide sufficient experience upon which to design a larger efficacy (Phase 2) study.

3.1.2. BLINDING

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. Brentuximab vedotin and placebo solutions for IV administration will be identical in physical appearance. The treatment each subject will receive during the treatment period will not be disclosed to the Investigator, study site personnel, subject, or the blinded study team.

For more details on blinding refer section 5.6 Blinding of the protocol.

3.2. METHOD OF TREATMENT ASSIGNMENT

The subjects will be randomly assigned to the study treatment by the study site using Interactive Web Response System (IWRS). The IWRS will provide the study drug kit number(s) of the blinded study drug to be dispensed. Randomization will occur on Day 1 prior to the first dose.

3.3. SCHEDULE OF EVENTS

Schedule of events can be found in APPENDIX 2: SCHEDULE OF EVENTS of the protocol.

3.4. CHANGES TO ANALYSIS FROM PROTOCOL

There are no meaningful deviations from the analyses planned in the study protocol.

4. PLANNED ANALYSES

4.1. SAFETY MONITORING COMMITTEE (SMC)

Please refer to the SMC SAP.

4.2. INTERIM ANALYSIS

No formal interim analyses are planned.

4.3. FINAL ANALYSIS

The final analyses will be conducted after the finalization of the SAP, database lock and unblinding.

5. ANALYSIS SETS

5.1. SAFETY ANALYSIS SET

The safety analysis set (SAF) includes all subjects who receive at least one dose of study medication. Subjects in this population is used for all safety, dosing, demographic, disposition and pharmacodynamic summaries. The SAF will be analyzed according to the treatment administered.

5.2. FULL ANALYSIS SET

The full analysis set (FAS) includes all randomized subjects, without regard for treatment administration. The FAS will be analyzed according to the treatment assigned, and used for all efficacy analyses.

5.3. PER-PROTOCOL ANALYSIS SET

The per-protocol analysis set (PPAS) includes all randomized subjects who have received at least 1 dose of study medication, have both the baseline and Day 85 SRI and have no protocol violations. The PPAS will be analyzed according to the actual treatment received, and will be used for the secondary efficacy analysis only.

5.4. PHARMACOKINETIC ANALYSIS SET

The PK analysis set (PKAS) includes all randomized subjects who have received at least 1 dose of brentuximab vedotin, have a post-baseline PK measurement. The PKAS will be analyzed according to the treatment administered.

5.5. PHARMACODYNAMIC ANALYSIS SET

The PD analysis set (PDAS) includes all randomized subjects who have received at least 1 dose of study medication, have a post-baseline PD measurement. The PDAS will be analyzed according to the treatment administered.

6. GENERAL CONSIDERATIONS

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

6.1. SUMMARY STATISTICS

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including N, mean, standard deviation (SD), coefficient of variation (CV%), median, 25th percentile, 75th percentile, minimum, and maximum values. CV will not be presented for change from baseline results. 95% CI will be reported in place of CV for efficacy variables.

In general, data will be summarized for each dose group, with all placebo subjects aggregated into a single group, and scheduled study day/visit. Data for all active-treated subjects combined will also be presented when appropriate. Descriptive statistics for optional tests will be suppressed if the sample size is below 3.

6.2. PRECISION

All variables, including derivations thereof, will be reported to the same precision as the source data.

For the reporting of descriptive statistics, the mean, standard deviation, standard error and confidence intervals will be presented to one digit more precision than the source data. The minimum, median, 25th percentile, 75th percentile and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 1 decimal place. P-values, if any, shall be reported to four decimal places or as <0.0001.

6.3. BASELINE

Baseline, is defined as the last scheduled non-missing measurement taken prior to dosing and will correspond to

Day 1 (predose) for clinical laboratory evaluations, physical examinations, vital signs and ECGs. Baseline for efficacy and pharmacodynamics is defined as the Day 1 assessments. However, if a subject is missing the planned baseline collection, the previous non-missing evaluation if available will become the baseline value.

End of treatment (EOT) is defined as Day 85 for use in the efficacy analyses.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

Unscheduled measurements will not be included in summary statistics, but will contribute to the assessment of clinical outliers. Early termination results will be recorded as such, and included with the summaries.

In the case of a retest of a scheduled assessment, the earliest available measurement for that scheduled time (i.e. the original assessment) will be used for summaries unless flagged as invalid.

Listings will include all scheduled, unscheduled, retest and early discontinuation data.

6.5. COMMON CALCULATIONS

- Change from baseline (CFB) = Observed Value (after baseline) – Baseline Value
- Percent change from baseline (PCFB) = CFB / Baseline Value * 100.
- Change from end of treatment (CFEOT) = Observed Value (after treatment end) – EOT Value
- Percent change from end of treatment (PCFEOT) = CFEOT / EOT Value *100.

6.6. SOFTWARE VERSIONS

All derivations, statistical analyses, summaries and listings will be generated using SAS version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Graphics may be prepared using the same version of SAS.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENT FOR COVARIATES

The baseline value for a dependent variable will be used as a continuous covariate in statistical models when available.

7.2. MULTICENTER STUDIES

Given the small number of subjects per study center/site, no adjustment for site effects will be considered OR sites will be aggregated according to geographic regions: USA (Western, Southern, Central, Northeast), Central America, South America, and Canada.

7.3. MISSING DATA

Missing data will not be imputed. Treatment attribution of adverse events and concomitant medications, in the event of missing dates, will be determined as specified in Appendix 2.

7.4. MULTIPLICITY

Given the lack of primary statistical hypotheses, small sample size, large number of endpoints, and the hypothesis generating nature of this study, no adjustment for multiplicity will be made for this study.

7.5. SUBGROUP ANALYSES

No subgroup analyses will be performed for this study.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP outline the presentations, format and content of the summary tables, figures and listings to be provided by Quintiles Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent, are randomized and received study medication, will be accounted in this study. Subject disposition will be tabulated for each dose group with the number of subjects who are randomly assigned to treatment, complete the study, prematurely discontinue, and the reason for early discontinuation. A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each subject.

Listings of subject consent, screen failures, inclusion/exclusion criteria responses, study eligibility, study drug administration and study visits will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics such as age, sex, race, ethnicity, height, weight, and body mass index (BMI) will be summarized and tabulated by dose group. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percent will be presented for sex, race, and ethnicity. No statistical testing will be carried out for demographic or other baseline characteristics.

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- Age (years) will be calculated as the number of complete years for patients' birth date relative to date of consent.

10.2. LUPUS DIAGNOSIS

Current signs and symptoms for lupus will be listed along with the date and length of lupus diagnosis.

10.3. CHEST X-RAY

The date and overall interpretation of chest x-rays taken in the 3-months prior to Screening will be listed.

11. PROTOCOL DEVIATIONS AND VIOLATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedure requirements. The noncompliance may be either on the part of the subject, the site PI, or the study site staff. Any subject enrolled who does not meet eligibility criteria will be considered an enrollment deviation.

All protocol deviations will be summarized with the number (%) of subjects by category and/or type deviation.

Protocol violations are defined as those meriting exclusion from the PPAS. These will be identified through review of the protocol deviation logs prior to database lock and unblinding. All protocol violations and those meriting exclusion from the PPAS will be listed.

12. MEDICAL HISTORY

Medical History is collected and will be coded using MedDRA Version 18.0. Medical history will be listed and summarized by SOC and preferred term for each treatment group.

13. MEDICATIONS

Medication usage is collected and coded using the WHO Drug Dictionary 01MAR2014.

- 'Prior' medications are medications which started and stopped prior to providing informed consent.
- 'Concomitant' medications are medications which were taken during the treatment period, or specifically:
  - started after providing informed consent or
  - started prior to providing informed consent and ended after providing informed consent or was ongoing

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

A subject listing of all previous and concomitant medications will be presented. The total number and percentage of subjects with concomitant medications will be presented by Anatomical Therapeutic Chemical (ATC) classification and preferred term. This summary will not include previous medication.

Lupus specific medications will be listed separately, based on the specific eCRF panel.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication as the number of doses administered (1, 2, 3 or 4) will be listed for each subject, and summarized.

The percentage of subjects with dose interruptions due to treatment-emergent AEs will be summarized by treatment.

15. EFFICACY OUTCOMES

There is no primary efficacy endpoint defined for this study. Secondary and exploratory efficacy analysis are described below.

15.1. GENERAL METHODOLOGY

If subjects are missing assessments during participation in the trial (prior to completion or withdrawal), these will be assumed to be non-events. The denominator used for percentages or proportions in tabulations will be the number of subjects in the analysis set with available data for the corresponding time point and treatment group.

The time to a pre-defined event will be calculated in days for each subject and response/flare as the date of the first event minus the date of randomization. If the date of the event is not recorded, the date of the study visit will be used. When there are multiple criteria to be met, the first event date is defined as the first date on which all criteria are met concurrently. If no flare/event occurred prior to the end of study participation (including for early termination), the time to flare will be regarded as censored at termination.

15.2. SECONDARY EFFICACY

All secondary efficacy analyses will be performed using both the FAS and the PPAS.

15.2.1. SRI RESPONSE

Systemic Lupus Erythematosus Responder Index (SRI) response will be assessed for Study Days 22, 43, 64, 85, 106, and 127, with Day 85 specified as the secondary endpoint for the study.

15.2.1.1. DERIVATION

The SRI definition of response includes meeting all of the following criteria:

- Reduction from baseline in SLEDAI of at least 4 points;
- no new British Isles Lupus Assessment Group (BILAG) A organ domain scores, relative to baseline
- no more than 1 new BILAG B score, relative to baseline;
- no worsening (increase of < 10% of scale length) in PhGA, relative to baseline.

Assessment for response will be made using data only for the visit of interest and baseline, without regard for changes at prior on-treatment visits.

15.2.1.2. ANALYSIS

The following analyses will be performed for all study days with Day 85 specified as the secondary endpoint, and all other visits falling under exploratory analyses.

The percentage of subjects demonstrating SRI Response will be presented by treatment with 95% CI using Wilson's score method (SAS PROC FREQ syntax: table response/binomial (wilson)). Comparisons between each active treatment group and placebo will be performed using Fisher's exact test (two-sided). The ratio of percentages (relative risk) for active to placebo will be presented for each dose level with corresponding 95% CI, based on the score method [Farrington] (SAS PROC FREQ syntax: table trta*response / relrisk(method=score equal)). Percentages with Wilson 95% CI will be plotted versus study day per treatment, with all treatments overlain.

Logistic regression of the log odds of SRI response on log2 dose level (mg/kg) will be performed. Placebo subjects will be treated as a having dose of 0 mg/kg. Based on this model, the estimate of the slope and odds ratio (OR) for a doubling of dose will be presented with 95% CI (based on the profile likelihood) and two-sided p-value (Wald test).

15.3. EXPLORATORY EFFICACY

All efficacy variables outside SRI are defined as exploratory for this protocol. All exploratory efficacy analyses will be performed using the FAS only. Analyses will be performed for all scheduled on-treatment assessments collected.

15.3.1. BILAG 2004

The BILAG disease activity index is assessed and scored by trained study investigators based the past 4 weeks of patient experience. Scoring is performed for each of the following domains: constitutional, mucocutaneous, central nervous system, musculoskeletal, cardiovascular/respiratory, abdominal, renal, ophthalmic and haematological. A total score will be derived from the nine domains by the investigator, as the maximum severity across the domains. No programmatic derivation is required for the index itself. BILAG scores are graded as follows: Grade A represents very active disease; Grade B represents moderate disease activity; Grade C

indicates mild stable disease; Grade D indicates no disease activity; Grade E indicates no current or previous disease activity.

No numeric scores will be assigned to the grades for any analyses.

15.3.1.1. DERIVATION

BILAG CLINICAL RESPONSE

BILAG Clinical Response is defined as:

- BILAG C scores or better in all organ domains; which includes by definition no new BILAG A or B scores in any organ domain

BILAG PARTIAL CLINICAL RESPONSE

BILAG Partial Clinical Response is defined as:

- at most 1 BILAG A or B score in any organ domain

15.3.1.2. ANALYSIS

BILAG domain scores will be tabulated by treatment group at each visit, plus categories for grade B or worse and grade C grade or better. Shifts from baseline among the grades will be tabulated similarly. Individual grades for each domain will be graphed over time, treating grade as ordinal, with one plot per subject.

The analysis for BILAG clinical response (full and partial) will replicate that performed for SRI.

15.3.2. BICLA RESPONSE

15.3.2.1. DERIVATION

The BILAG-based Combined Lupus Assessment (BICLA) definition of response includes all of the following:

- BILAG-2004 improvement (all A scores at baseline improved to B/C/D, and all B scores improved to C or D);
- no worsening in disease activity (no new BILAG-2004 A scores and ≤ 1 new B score);
- no worsening of total SLEDAI-2K score from baseline (no change or reduction from baseline);
- no significant deterioration (< 10% worsening) in 100 mm visual analogue PhGA;
- no treatment failure (See Section 15.3.15)

Patients' BICLA response will be derived from the above criteria for visits on which all of the component variables are captured.

15.3.2.2. ANALYSIS

The analysis for BICLA response will replicate that performed for SRI.

15.3.3. CLASI

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) consists of measures of cutaneous disease activity and damage over 14 anatomical locations, with the scores ranging from 0-70 and 0-56, respectively, and higher scores indicating greater severity (Klein, 2010). Scores are determined by trained investigators and are recorded on the eCRF.

15.3.3.1. DERIVATIONS

CFB, PCFB, CFEOT and PCFEOT will be calculated for this endpoint.

15.3.3.2. ANALYSIS

Observed and change values will be summarized by treatment group. Means with 95% CI will be plotted for Observed and CFB values over time with treatment groups overlain. Individual values over time will be plotted over time per treatment group.

An analysis of covariance model will be fit for CFB/CFEOT at each scheduled time, with a fixed effect for treatment group and a covariate for the baseline value. Comparisons will be made between each dose level, and all active treated subjects combined versus placebo at the 5% significance level (two-sided). Least-squares treatment means and mean differences will be estimated with 95% CI and two-sided p-values for the test of no treatment difference.

15.3.4. SLEDAI-2K

The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) is numeric index based on 24 outcomes covering 9 organs systems, each with scores ranging from 1 to 8 when the outcome is present (Yee, 2011). The total SLEDAI-2K score is the simple sum of the scores and falls between 0 and 105, with higher scores representing higher disease activity. Scores are determined by trained investigators and are recorded on the eCRF.

15.3.4.1. DERIVATIONS

CFB, PCFB, CFEOT and PCFEOT will be calculated for this endpoint and the organ systems.

A SLEDAI clinical response is defined as an improvement (reduction) of 4 or more points, relative to baseline.

15.3.4.2. ANALYSIS

The analyses for SLEDAI-2K scores will replicate those performed for CLASI.

The analysis for SLEDAI clinical response will replicate those performed for SRI.

Boxplots profiles of SLEDAI-2K through time (study day) for each dose level. Stacked bar graphs will be generated for each subject with all visits included, with stacks comprised of the scoring domains, and dose levels comprising separate pages.

15.3.5. GLOBAL ASSESSMENTS: PTGP, PTGA, PHGA

Physician's Global Assessment of Disease Activity (PhGA), Patient's Global Assessment of Disease Activity (PtGA), Patient's Global Assessment of Pain (PtGP) are assessed as visual analog scale responses ranging from 0 to 100 mm, with higher numbers indicating greater activity/pain.

15.3.5.1. DERIVATIONS

CFB, PCFB, CFEOT and PCFEOT will be calculated for these endpoints. The following reductions in global scores will be derived: 20%, 50% and 70%, labeled as PhGA20/50/70, PtGA20/50/70, PtGP20/50/70.

15.3.5.2. ANALYSIS

The analyses for global assessments will replicate those performed for CLASI. PhGA20/50/70, PtGA20/50/70, and PtGP20/50/70 will be tabulated by treatment.

Grouped subject-level line (spaghetti) plots vs study day will be generated, with one plot per dose level.

15.3.6. SWOLLEN AND TENDER JOINT COUNTS

Swollen and tender joint counts (SJC; TJC) are measured out a total of 66 and 68 joints, respectively.

15.3.6.1. DERIVATIONS

CFB, PCFB, CFEOT and PCFEOT will be calculated for both joint counts. The following reductions in PCFB joint counts from baseline will be derived: 20%, 50% and 70% (SJC20/50/70 and TJC20/50/70).

15.3.6.2. ANALYSIS

The analyses for SJC/TJC will replicate those performed for CLASI. SJC20/50/70 and TJC20/50/70 will be summarized by treatment.

15.3.7. ACR RESPONSE

The American College of Rheumatology (ACR) response criteria are standard criteria used to identify improvement across 7 biometrics by a specified minimum percentages of 20, 50 and 70%.

15.3.7.1. DERIVATIONS

ACR20, ACR50 and ACR70 responses relative to baseline will be assessed on Days 43, 85 and 127 using the standard definition (Felson, 1995), namely a 20/50/70% reduction in both SJC and TJC, plus a 20/50/70% reduction in 3 of the following 5 tests: PtGP, PtGA, PhGA, HAQ-DI and ESR. Response will only be assessed for subjects for whom sufficient variables are available at the given visit, and will otherwise be regarded as a missing value.

15.3.7.2. ANALYSIS

The analysis for ACR response will replicate that performed for SRI.

15.3.8. SELENA SLE FLARES

Occurrence of SELENA SLE flares will be recorded on the eCRF.

A mild/moderate flare is defined to include any of the following:

- increase in SLEDAI ≥ 3 points, relative to baseline
- new/worse skin, stomatitis, serositis, arthritis, or fever
- increased prednisone < 0.5 mg/kg/day
- added NSAID/hydroxychloroquine
- increase in PhGA ≥ 1.0, relative to baseline

A severe flare is defined to include any of the following:

- increase in SLEDAI ≥ 12 points, relative to baseline
- new/worse CNS-SLE, vasculitis, nephritis, myositis, platelet count < 60,000/µL, hemolytic anemia with hemoglobin < 7 mg/dL, requiring doubling > 0.5 mg/kg/day prednisone
- hospitalization for SLE
- prednisone > 0.5 mg/kg/day
- new immunosuppressive increase in PhGA to > 2.5, relative to baseline

15.3.8.1. DERIVATIONS

Time to flare will be calculated for each severity as defined in Section 15.1.

15.3.8.2. ANALYSIS

The analysis for incidence of flares will replicate that performed for SRI, and will be performed for each severity grade (mild/moderate and severe) and overall.

The flare-free survival function will be estimated by treatment group and for all active-treated subjects combined using Kaplan-Meier methodology, with 95% confidence intervals based on Greenwood's formula. These survival curves will be plotted. The KM estimates of quartiles for time to event with the corresponding 95% CIs will be provided for each treatment and for all active-treated subjects, when estimable, using Greenwood's formula.

15.3.9. BILAG SLE FLARES

15.3.9.1. DERIVATION

A moderate flare is defined as ≥ 2 new BILAG B domain scores, relative to baseline. A severe flare is defined as development of any new BILAG A domain score, relative to baseline.

The time to first flare will be derived for each severity above, as detailed in Section 15.1. If a subject experiences both moderated and severe flares during the course of the study, both events will be analysed separately.

The number of domains exhibiting a new A or B score will be determined per subject per study visit.

15.3.9.2. ANALYSIS

The analysis for BILAG SLE flares (moderate, severe, moderate or severe) will replicate that performed for SRI. Flare-free survival will be analyzed as detailed for SELENA flares (Section 15.3.8.2). The number of domains exhibiting a new A or B scores will be tabulated.

15.3.10. RENAL FLARES

Renal flares are defined as in Section 6.2.2 of the study protocol, and occurrences are captured on the eCRF.

15.3.10.1. DERIVATION

The time to first flare will be calculated in days as defined in Section 15.1.

15.3.10.2. ANALYSIS

The analysis for occurrence of renal flares will replicate that performed for SRI. Flare-free survival will be estimated as detailed for SELENA flares (Section 15.3.8.2).

15.3.11. ACTIVE RENAL DISEASE

Active Renal disease is defined as in Section 6.2.2 of the study protocol, and occurrences are captured on the eCRF.

15.3.11.1. DERIVATION

The time to first diagnosis will be calculated in days as defined in Section 15.1.

15.3.11.2. ANALYSIS

The analysis for occurrence of active renal disease will replicate that performed for SRI. Flare-free survival endpoints will be analyzed as detailed for SELENA flares (Section 15.3.8.2).

15.3.12. CONCOMMITANT USE OF ORAL CORTICOSTEROIDS

Use of oral corticosteroids is collected continuously in the concomitant medication panel of the eCRF and will be identified using the WHO anatomical therapeutic class.

15.3.12.1. DERIVATION

Corticosteroid usage will be assessed (present vs absent) for each postdose visit, as the interval starting with the date following the previous visit and ending with the date of the current visit (inclusive).

The time to first usage of oral corticosteroids will be calculated in days as defined in Section 15.1.

15.3.12.2. ANALYSIS

The analysis for corticosteroid usage will replicate that performed for SRI. Corticosteroid -free survival endpoints will be analyzed as detailed for SELENA flares (Section 15.3.8.2).

15.3.13. TREATMENT FAILURE

Treatment failure is defined as meeting at least one of the following criteria, and will be recorded on the eCRF:

- Death
- Premature withdrawal from the study due to adverse events or lack of efficacy
- Addition of new or increased immunosuppressive or antimalarial or increased or parenteral corticosteroids.

15.3.13.1. DERIVATION

The time to treatment failure will be to the first occurrence of the above events, calculated in days as defined in Section 15.1.

15.3.13.2. ANALYSIS

The time to treatment failure will be analyzed as detailed for SELENA flares (Section 15.3.8.2).

15.3.14. HAQ-DI

The Health Assessment Questionnaire (HAQ) Disability Index (DI) assesses patient disability over the past week over 8 daily functions and activities on a scale of 0 to 3, with 0 indicating no difficulty and 3 indicating inability. Version 96.4 is being used for this study. The independent HAQ assessments for pain and health VAS are also collected.

15.3.14.1. DERIVATION

The standard HAQ-DI will be scored according to the instructions for version 96.4 (National Institute of Environmental Health Sciences, 1996), including the handling of missing values. In summary, the maximum severity reported for each function is averaged across all available functions for the assessment. If an aide or device is used or if help is required from another individual, then the minimum score for that function is 2. The HAQ-DI will be calculated to 3 decimal places.

CFB, PCFB, CFEOT and PCFEOT will be calculated. The following reductions in HAQ-DI score from baseline will be derived: 20%, 50% and 70% (HAQ20, HAQ50 and HAQ70).

15.3.14.2. ANALYSIS

The analyses for HAQ-DI will replicate those performed for CLASI. HAQ20/50/70 will be summarized by treatment.

15.3.15. SF-36

The RAND 36-Item Short Form Health Survey (SF-36; Version 1.0) estimates quality of life indices over 8 components ranging from 0 to 100, over the past four weeks, plus subjects' perception of change in health. Scores represent the percentage of total possible score achieved and higher scores indicates a more favorable health state.

15.3.15.1. DERIVATION

Scoring of the SF-36 will comply with the Rand scoring instructions version 1 (Rand Corporation, 2016), including the handling of missing components. Responses are coded to scores ranging from zero to 100, based on Table 1

in the instructions. Groups of scores are then averaged to form the overall score for each component, based on Table 2 of the instructions.

No normalization will be performed on the component scores, in compliance with the version 1 scoring instructions. Summary scores for physical and mental health will be derived from all components of the SF-36 using orthogonal factor scoring coefficients derived from a large sample that allow the components to be correlated, using the 1998 z-scores for the 8 components.

CFB, PCFB, CFEOT and PCFEOT will be calculated for all scores.

15.3.15.2. ANALYSIS

The analyses for SF-36 physical and mental component scores will replicate those performed for CLASI. Summary statistics for the observed scores only will be presented for the 8 SF-36 components.

15.3.16. FACIT-F

Functional Assessment of Chronic Illness Therapy (FACIT) measures subjects' quality of life level (QOL) over the categories of physical, social/family, emotional and functional well-being over 27 questions using on a five-point Likert scale (0 to 4), with higher scores indicating better QOL. A supplementary fatigue score is measured over 13 additional questions using the same scale, for which a score of less than 30 indicates severe fatigue.

15.3.16.1. DERIVATION

The FACIT-F fatigue score, FACIT-F Trial Outcome Index (TOI), Functional Assessment of Cancer Therapy-General (FACT-G), and FACIT-F total score will be calculated from the Likert responses. FACIT-F Scoring Guidelines Version 4 (Cella, 2004) will be used to derive each component score and the following indices:

- FACIT-F fatigue score = weighted sum of available response scores * 13; range 0-52
- FACIT-F Trial Outcome Index (TOI) = weighted sum of available physical, functional, and fatigue scores; range 0-108
- FACT-G total score = weighted sum of available physical, social/family, emotional and functional scores; range 0-108
- FACIT-F total score = weighted sum of available components scores (physical, social/family, emotional, functional, fatigue); range 0-160

CFB, PCFB, CFEOT and PCFEOT will be calculated for all scores.

15.3.16.2. ANALYSIS

The analyses for all FACIT scores will replicate those performed for CLASI. The Likert responses will be listed only.

15.3.17. LUPUSQOL

The LupusQOL measures subjects' quality of life level for the past four weeks over eight domains (physical health, pain, planning, intimate relationship, burden to others, emotional health, body image, fatigue) using 34 questions using on a five-point Likert scale (0 to 4), and yielding scores ranging from 0 to 100, with higher scores indicating better QOL.

15.3.17.1. DERIVATION

Scores for each domain will be calculated as the average of the available Likert responses/4 * 100 (McElhone, 2007). CFB, PCFB, CFEOT and PCFEOT will be calculated for all domains.

15.3.17.2. ANALYSIS

The analyses for all LupusQOL scores will replicate those performed for CLASI.

15.3.18. URINARY CELLULAR CASTS, PYRUIRA AND HEMATURIA

Urinary cellular casts (RBC and WBC only), RBC and WBC in urine are recorded as ordinal categorical results by the clinical labs.

15.3.18.1. DERIVATION

No derivations are required for this analysis.

15.3.18.2. ANALYSIS

Shift tables will be presented, tabulating the number of subjects moving from baseline to the each of the result categories for these laboratory tests. This analysis may be repeated for subjects assessed with active renal disease at any point during the trial, if sufficient sample size is available.

15.3.19. PROTEIN/CREATININE RATIO AND EGFR

Protein/creatinine ratio and eGFR are captured as central laboratory results.

15.3.19.1. DERIVATION

CFB, PCFB, CFEOT and PCFEOT will be calculated for all of these laboratory tests.

15.3.19.2. ANALYSIS

The analyses will replicate those performed for CLASI. This analysis will be repeated for subjects assessed with active renal disease at any point during the trial.

16. PHARMACOKINETIC OUTCOMES

16.1. PHARMACOKINETIC CONCENTRATIONS

Concentrations of brentuximab vedotin (ADC), total antibody (TAb), and monomethyl auristatin E (MMAE) will be assayed for samples collected on Days 1, 2, 3, 8, 15, 22, 43, 64, 85 and 106. Antitherapeutic antibodies are measured prior to each dosing and on Days 1, 85, 106, and 127.

16.2. PHARMACOKINETIC PARAMETERS

Derivation the pharmacokinetic parameters is the responsibility of the sponsor or designee, and outside the scope of this SAP.

16.3. ANALYSES

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided.

Plasma concentrations will be summarized using descriptive statistics for each treatment group/dose level. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Figures of arithmetic mean concentration-time data ±SD will be presented for each treatment on linear and semi-logarithmic scales. The incidence of antitherapeutic antibodies will be tabulated.

A subject listing of all concentration-time data for each treatment will be presented. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales.

Plasma parameters will be summarized using descriptive statistics for each treatment group/dose level. Dose proportionality will be assessed using least-squares regression of the log-transform PK parameters on log dose. Slope and intercept estimates will be presented with 90% CI. AUC and Cmax parameters will be plotted vs dose on the log-log scale, with the regression lines overlain.

17. PHARMACODYNAMIC OUTCOMES

17.1. PHARMACODYNAMIC VARIABLES

The following variables are collected as PD endpoints throughout this study:

- flow cytometry for specific lymphocyte populations
- inflammatory markers, including: ESR, hsCRP, sCD30, and soluble CD153 (sCD153)
- quantitative autoantibody assays including, but not limited to:
  - antinuclear antibodies (ANA), as assessed by indirect immunofluorescence titer: quantified in ratios such as 1:80, 1:160, 1:320.
  - anti-dsDNA;
  - anti-C1q (quantitative);
  - anti-Smith antibodies (anti-Sm), anti-ribonucleoprotein (anti-RNP), anti-Sjögren's Syndrome A antibodies (anti-SSA), and anti-Sjögren's Syndrome B antibodies (anti-SSB);
  - anti-cardiolipin IgA, IgG and IgM, anti-β-2-glycoprotein IgG and IgM, lupus anticoagulant;
  - direct Coombs test (Positive/Negative); and
  - quantitative IgG, IgM, IgA, and IgE
- complement studies: C1q, C3, C4, and CH50
- lymph node or tonsil biopsies (optional): T cell subpopulations, CD4+ and CD4+CD30+, and subpopulations of each, CD8+ and CD8+CD30+; B cell subpopulations, germinal center structure

Note that samples collected for cytokine assessment were planned for possible future testing and therefore outside the scope of this SAP.

17.2. DERIVATIONS

CFB, PCFB, CFEOT and PCFEOT will be calculated for all quantitative PD tests. The following reductions in PCFB from baseline will be derived for ESR only: 20%, 50% and 70% (ESR20/50/70).

17.3. ANALYSES

The analyses for all PD variables scores will replicate those performed for CLASI. ESR20/50/70 will be tabulated by treatment. The incidence of positivity for the following will also be tabulated: ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-SSA, anti-SSB, anti-cardiolipin, anti-β-2-glycoprotein I, lupus anticoagulant, anti-C1q, and direct Coombs test.

Assayed values reported by the labs as below limit of quantitation (BLQ: e.g. <0.3 U/mL) will be treated as that limit for analyses. For summarizing incidence, BLQ values will be treated as Negative.

The following tests will be analyzed on the log 10 scale: anti-SSA, anti-SSB, anti-RNP70.

For ANA values, the denominator will be used for analyses (e.g. 80, 160, 320) and log-transformed for quantitative analyses.

Any results from lymph node or tonsil biopsies will be listed only.

18. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

PK vs PD analyses are outside the scope of this document and may be analyzed separately.

19. SAFETY OUTCOMES

All analyses for safety outcomes will be based on the Safety Analysis Set.

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs, including SAEs; recording of concomitant medications; physical and neurological examination findings; ECG recordings; and measurements of vital signs and protocol-specified laboratory tests. In addition, subjects will be closely monitored for signs and symptoms suggestive of neuropathy or PML.

19.1. ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 18.0.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication.

Pretreatment AEs are defined as AEs occurring prior to dosing. These events will be presented in the listings only and are not included in the tabular summary of AEs.

See Appendix 2 for handling of partial dates for AEs. In the rare case where it is not possible to assess treatment emergence, the AE will be classified as treatment emergent (i.e. the worst case).

Severity

Adverse event severity will be graded using the NCI-CTCAE, version 4.03. TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity grade will be used in the corresponding severity summaries.

Relationship to Study Medication

Relationship to study medication, as indicated by the Investigator, is classified as Related and Unrelated .A ”related” TEAE is defined as a TEAE with a causal relationship between the study drug and the AE, such as:

- an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, or Stevens-Johnson syndrome); or
- an event that is not commonly associated with study drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture).

An unrelated AE to study medication is defined as another cause of the AE is more plausible (eg, due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study drug, or a causal relationship is considered biologically implausible.

TEAEs with a missing relationship to study medication will be regarded as "related" to study medication. If a subject reports the same AE more than once within a particular SOC/ PT, the AE with the highest level of relationship to study medication will be used in the corresponding relationship summaries.

All AE tabulations will be performed by treatment group and active-treated overall, and will include the number and percentage of subjects. All percentages will be based on the number of patients in the Safety Population. Incidence of TEAEs will be tabulated by the following:

- Across all System Organ Class (SOC) and Preferred Term (PT), By Severity Grade, by Relationship, by Leading to Discontinuation, and by Seriousness
- By System Organ Class (SOC) and Preferred Term (PT)
- By System Organ Class (SOC), Preferred Term (PT) and Severity Grade
- By System Organ Class (SOC), Preferred Term (PT) for AEs Related to study medication only

19.1.1. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication or dose interruption will be identified by using the variable pertaining to outcome on the Adverse Events page of the CRF, and listed.

19.1.2. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the CRF, and will be summarized and listed.

Incidence of serious TEAEs will be tabulated by the following:

- By System Organ Class (SOC) and Preferred Term (PT)
- By System Organ Class (SOC), Preferred Term (PT) and Severity Grade
- By System Organ Class (SOC), Preferred Term (PT) and Severity Grade for SAEs Related to study medication only

19.1.3. Adverse Events of Special Interest

AEs of special interest (AEOSI) are defined as those related to peripheral neuropathy (including PML) and infusion site reactions (eg, pain, irritation, itching), and will be identified using the corresponding standardized MedDRA query. AEOSI will be separately listed and summarized by SOC/PT and overall.

19.1.4. DEATHS

If any subjects die during the study, as recorded on the adverse events page of the eCRF, the information will be presented in a data listing.

19.2. LABORATORY EVALUATIONS

Serology screening, results from tuberculosis screening, urine pregnancy tests, will be listed.

Central laboratory results will be included in the reporting of this study. A list of laboratory assessments to be included in the outputs is included in Schedule of events and the protocol, Section 6.3.4. Presentations will use SI Units, as provided by the labs.

Protocol-specified clinical laboratory tests will be summarized using descriptive statistics. Clinical laboratory data collected during study conduct, which were not required per protocol, such as for special testing to evaluate an AE, will be listed separately and not summarized.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements) for all on-treatment and follow-up visits.
- Shift from baseline according to CTCAE severity grading for all on-treatment and follow-up visits.
- Tabulation of categorical/qualitative results
- Listing of lab results outside the normal range/abnormal (high or low)
- Listing of lab results with CTCAE severity grading of 1 or above

19.2.1. LABORATORY REFERENCE RANGES AND CTCAE GRADING

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges by the lab vendors and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

Clinical laboratory reference/normal ranges will be listed.

In addition, safety laboratory assessments will also be categorized for severity in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) criteria, version 4.03.

19.3. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Sitting Systolic and Diastolic Blood Pressure (mmHg) and Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{o}C)
- Weight (kg)
- BMI (kg/m^2)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Tabulation of clinically noteworthy results based on the criteria specified below.

The denominator used for percentages in tabulations will be the number of subjects in the safety analysis set with available data for the corresponding time point and treatment group.

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Heart rate	bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

19.4. ECG EVALUATIONS

The following ECG parameters will be measured using standard 12-lead ECG: HR, PR, QRS, QT, RR, QTcB and QTcF. The following summaries will be provided for ECG parameters:

- Actual and change from baseline by visit
- Tabulation of potentially clinically significant results based on the criteria specified below.

Variable	Unit	Change	High
QTcF	ms	≥ 30 ms increase from baseline	≥ 450 ms

T-wave, U-wave and overall assessment of ECG (Investigator's judgment are recorded as following:

- Normal
- Abnormal, Not Clinically Significant (ANCS)
- Abnormal, Clinically Significant (ACS)

Electrocardiogram evaluations will be tabulated by visit.

19.5. PHYSICAL EXAMINATION

Physical examination results will be listed and abnormal physical examination findings summarized by body system. Any clinically significant abnormalities will be recorded as adverse events.

20. REFERENCES

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McElhone, K. (2007). Development and Validation of a Disease-Specific Health-Related Quality of Life Measure, the LupusQoL, for Adults With Systemic Lupus Erythematosus. *Arthritis & Rheumatism, 57*(6), 972–979. doi:10.1002/art.22881

Yee, C.-S. (2011). The use of Systemic Lupus Erythematosus Disease Activity Index-2000 to define active disease and minimal clinically meaningful change based on data from a large cohort of systemic lupus erythematosus patients. *Rheumatology, 50*(5), 982-988. doi:doi:10.1093

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APPENDIX 1. Programming Conventions for Outputs

OUTPUT CONVENTIONS

Outputs will be presented according to the following Quintiles Global Biostatistics Standard Output Conventions, which is available upon request.

DATES & TIMES

Depending on data available, dates and times will take the format DDMONYYYY; times will take the format HH:MM:SS.

SPELLING FORMAT

English US

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in this order:

Treatment Group	For Tables, Listing and Graphs
Placebo	Placebo
X.X mg/kg IV for each dose level	X.X mg/kg
All active dose levels combined	≥0.3 mg/kg

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template): Subject identifier, date (where available), study day

Partial Date Conventions

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE

START DATE	STOP DATE	ACTION
		If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - AUTHORS

	Name	Signature	Date
Author:	[redacted]	[redacted]	17 Feb 2017
Position:	[redacted]		
Company:	Quintiles		

[redacted]

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - APPROVAL

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	[redacted]	[redacted]	7 Feb 2017
Position:			
Company:	Seattle Genetics		
Approved By:	[redacted]	[redacted]	February 2017
Position:	[redacted]		
Company:	Seattle Genetics		