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Study SC1401

Title: A Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of 1.5 mg/kg per Day of Sarecycline Compared to Placebo in the Treatment of Acne Vulgaris.

Protocol Date: December 16, 2015

Statistical Analysis Plan (SAP) Date: March 3, 2017

1.0 TITLE PAGE

Study SC1401

A Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of 1.5 mg/kg per Day of Sarecycline Compared to Placebo in the Treatment of Acne Vulgaris

STATISTICAL ANALYSIS PLAN – Amendment 1

Final: 20 Feb 2017
Revised: 03 Mar 2017 (Amendment 1 Date)

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
CFB	change from baseline
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
ECG	electrocardiogram, electrocardiographic
IGA	Investigator's Global Assessment
IRT	Interactive Response Technology
ITT	intent to treat
LOCF	last observation carried forward
MI	multiple imputation
MMRM	mixed model repeated measures
OC	observed cases
PCS	potentially clinically significant
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SI	*Le Système International d'Unités* (International System of Units)
SID	subject identification number
TEAE	treatment-emergent adverse event

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the final protocol of Study SC1401 (15 Aug 2014) and the most recent amendment (Version 3 dated 16 Dec 2015). [redacted]
Specifications of tables, figures, and data listings are contained in a separate document. The SAP for pharmacokinetic/pharmacodynamic data will be prepared separately.

Study SC1401 is a phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate efficacy and safety of an approximate 1.5 mg/kg/day dose of oral sarecycline compared to placebo in the treatment of moderate to severe facial acne vulgaris. The study will include approximately 1000 males and females 9 to 45 years of age with moderate to severe facial acne vulgaris and no disorders that would preclude the use of tetracycline-class antibiotics at approximately 50 sites.

The study includes a screening period of up to 35 days to establish eligibility and baseline conditions followed by a 12-week treatment period. Eligible subjects will be randomized in a 1:1 ratio to receive daily oral doses of either 1.5 mg/kg sarecycline tablets or placebo tablets. Subjects will return to the clinic on an outpatient basis following 3, 6, 9 and 12 weeks of treatment. At each clinic visit, facial acne will be evaluated through lesion counts and Investigator's Global Assessment (IGA) scores by visual inspection; non-facial inflammatory acne will also be evaluated by IGA of the neck, chest and back. The co-primary efficacy endpoints of the study are the absolute change from baseline in the facial inflammatory lesion count at Week 12 and a dichotomized IGA (dichotomized to reflect either 'success' or 'failure' with 'success' defined as at least a 2-point decrease from baseline in the IGA assessment and a score of clear [0] or almost clear [1] on the IGA assessment) at Week 12. Safety evaluations (adverse events, vital signs, clinical laboratory evaluations, electrocardiograms (ECG) and physical examinations) will be conducted at specific treatment period visits and at study termination.

The study drug, referred to as investigational product in this statistical analysis plan, quantity and dispensing schedule for this study are as follows:

Visit	Quantity Dispensed
Screen Visit (SV) 2	30
1	30
2	30
3	30

The schedule of evaluations for Study SC1401 is presented in Table 4-1.

Table 4–1. Study Schedule of Events: Study SC1401

	Screening Period		Treatment Period					
	SV1	**SV2 (Baseline Assessment)**	**Telephone Contact Week 1 ± 3 d**	**Visit 1 Week 3 ± 3 d**	**Visit 2 Week 6 ± 3 d**	**Visit 3 Week 9 ± 3 d**	**Visit 4 Week 12 /ET ± 3 d**	**Visit 5[d] Week 13 /ET ± 3 d**
Informed Consent	X							
Assign Subject Number using the IRT	X							
Inclusion/ Exclusion	X	X						
Demographic Data	X							
Medical/ Surgical History	X							
Physical Examination	X	X[a]					X	**X**
Height & Weight	X	Weight only					Weight only	**Weight** only
Vital Signs	X	X		X	X	X	X	**X**
Hematology, Serum Chemistry, Urinalysis and Lipids	X	X[b]		X			X	
TSH, Free T4 and T3	X						X	
Urine pregnancy test	X	X		X	X	X	X	**X**
ECG	X						X	
Facial Investigator's Global Assessment		X		X	X	X	X	
Facial Lesion Counts		X		X	X	X	X	
Facial Photographs		X		X	X	X	X	
Non-facial Investigator's Global Assessment		X		X	X	X	X	

Table 4–1. Study Schedule of Events: Study SC1401

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	SV1	**SV2 (Baseline Assessment)**	**Telephone Contact Week 1 ± 3 d**	**Visit 1 Week 3 ± 3 d**	**Visit 2 Week 6 ± 3 d**	**Visit 3 Week 9 ± 3 d**	**Visit 4 Week 12 /ET ± 3 d**	**Visit 5[d] Week 13 /ET ± 3 d**
Skindex Questionnaire		X					X	
Dispense Diary for Subjects Participating in PK Sampling		X				X		
PK Blood Sample Collection for PK 1, PK 2, **and PK 3** [C]				X			X	
Review and Collect Diaries				X			X	
Randomization		X						
Dispense Study drug		X		X	X	X	**X[d]**	
Study drug Accountability /Compliance			X	X	X	X	X	
Concomitant Medication Use	X	X		X	X	X	X	**X**
Adverse Events	X	X	X	X	X	X	X	**X**

ECG= electrocardiogram; ET= End of treatment; X[a]: Only for subjects requiring medication/therapy washout; X[b]: Re-draw blood and urine samples for clinical laboratory evaluations only if washout duration exceeded 5 weeks. [C] PK Schedule 1**,** PK Schedule 2**, or PK Schedule 3** should be performed at selected sites based on what the subject chose in the ICF, [d]**For subjects participating in PK Schedule 3 only**.

5.0 OBJECTIVES

The primary objective is to evaluate the efficacy of oral sarecycline 1.5 mg/kg/day compared to placebo in treating inflammatory acne lesions in subjects with moderate to severe facial acne vulgaris based on Investigator's Global Assessment score and inflammatory lesion counts.

The secondary objectives are to evaluate the safety of oral sarecycline 1.5 mg/kg/day based on adverse events, vital signs, electrocardiograms, physical examinations and clinical laboratory tests.

6.0 ANALYSIS POPULATIONS AND DATASETS

6.1 SCREENED POPULATION

The Screened Population will consist of all subjects who underwent a Screening Visit 1 and received a subject identification number (SID).

6.2 SAFETY POPULATION

The Safety Population will consist of all subjects who received at least one dose of investigational product. All summaries of this population will be based on the treatment group each subject actually received.

6.3 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) Population will consist of all randomized subjects. All summaries of this population will be based on the treatment group each subject was randomized to receive.

6.4 PER-PROTOCOL POPULATION

Per-protocol (PP) population will consist of all subjects in ITT population, as defined below. All summaries of this population will be based on the treatment group each subject was randomized to receive.

Subjects with the following conditions will be excluded from the PP population:

1. Did not meet inclusion/exclusion criteria
2. Have taken any interfering concomitant medications
3. Duration of treatment less than 68 days, or did not complete study based on subject exit status, or overall study drug compliance less than 80%
4. Received treatment different from the assigned treatment

A list of subjects with conditions 1, 2, and 3 above prior to unblinding will be created. This list will be reviewed by a Clinical Representative to determine which subjects are to be excluded from the PP population. These subjects will then be documented in a signed memo prior to unblinding. The subjects who received treatment different from the assigned treatment (condition 4) will be identified after unblinding and will be documented in a separate signed memo.

Three "visit types" will be defined for the purposes of analysis and summaries:

- Observed Cases (OC) – includes assessments collected at each scheduled visit. All applicable efficacy and safety variables will be summarized for OC visits.

- Multiple Imputation Data – for the primary and secondary efficacy endpoints, missing data will be imputed using multiple imputation procedures further described in Section 16.2.
- LOCF – defined as the last post-baseline data recorded for each efficacy variable. This visit will be denoted as Week 12 (LOCF) and will only be used to summarize efficacy data. The LOCF visit provides missing value imputation for subjects who do not provide data for the Week 12 visit.

7.0 SUBJECT DISPOSITION

The number and percentage of subjects in 3 of the study populations (Safety, ITT and PP) will be summarized by treatment group and study center; the Screened Population will be summarized overall only by study center.

Screen-failure subjects (ie, subjects screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for the Screened Population. The number and percentage of subjects who complete the treatment period and of subjects who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the ITT Population. The reasons for premature discontinuation from the treatment period as recorded on the termination pages of the electronic case report forms (eCRF) will be summarized (number and percentage) by treatment group for the ITT Population. All subjects who prematurely discontinue during the treatment period will be listed by discontinuation reason for the ITT Population.

All subjects who are in ITT Population but not in PP Population will be listed with reasons provided.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; age group (≥ 9 years and < 18 years vs. ≥ 18 years); age group (≥ 9 years and < 12 years, ≥ 12 years and < 18 years, and ≥ 18 years); race; sex; weight; weight group (33 to 54 kg, 55 to 84 kg, and 85 to 136 kg), height; body mass index (BMI), calculated as weight [kg]/(height [m])^2; BMI group (< 25 kg/m^2 vs. ≥ 25 kg/m^2); and hormonal contraceptive use in females) and other baseline characteristics (inflammatory lesion counts, IGA score, and IGA scores for neck, chest, and back sites) will be summarized descriptively by treatment group for the Safety, ITT, and PP populations. Weight rounding for weight group is in the following way: 54.4 to 54, 54.5 to 55. Continuous variables will be summarized by number of subjects and mean, median, SD, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects.

Comparability between treatment groups for efficacy variables will be tested using a 2-way analysis-of-variance model with treatment group and study center as the factors for continuous variables (inflammatory lesion counts and IGA score) and the CMH test, controlling for study center, for the categorical variable of IGA score. Because of their clinical importance, IGA score of the baseline characteristics will be treated as both a continuous and categorical variable.

Abnormalities in subjects' medical and surgical histories will be coded using the *Medical Dictionary for Regulatory Activities,* version 18.0 or newer. The number and percentage of subjects with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by treatment group and overall for the Safety Population.

Prior medications including acne medications are those medications with an end date before the date of the first dose of investigational product. Concomitant medications including acne medications are those medications with either 1) a start date that is after the first dose of investigational product, 2) a start date prior to the first dose of investigational product with end date on or after the date of first dose of investigational product, or 3) a start date prior to the first dose of investigational product and its use is ongoing. Any concomitant medications taken after the date of the last visit will not be presented in the summary tables but will be included in the subject data listings.

Both prior and concomitant medications will be coded by drug preferred name and therapeutic class. The use of prior and concomitant medications and the use of prior and concomitant acne medications will be summarized by the number and percentage of subjects in each treatment group and overall for the Safety Population. If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject would be counted only once for the coded drug preferred name or therapeutic class.

The World Health Organization (WHO) Drug Dictionary, version March 2015 or newer, will be used to classify prior and concomitant medications by WHO Drug Anatomical/Therapeutic/Chemical category and WHO Drug preferred name.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Exposure to the investigational product for the Safety Population during the double-blind treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of the investigational product to the date of the last dose of the double-blind investigational product, inclusive. Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) will be presented by treatment group. Additionally, these summaries will present the number and percentage of subjects for each interval (1 week multiples) of total exposure in each treatment. The denominators for calculating the percentages will be based on the number of subjects with exposure for each treatment.

Subjects in the PK Schedule 3 group who receive one active dose of study drug after study assessments at Week 12 will also be listed (separately) for this single-dose exposure.

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for a specified period is defined as the number of tablets actually taken by a subject during that period divided by the expected number of tablets taken for the same period multiplied by 100. This information will be obtained from the drug accountability of the subject's eCRF. The total number of tablets actually taken will consist of subtracting both the total numbers of tablets returned and the total numbers of tablets lost from the total number of tablets dispensed. The number of tablets expected to be taken for a specific treatment period will be calculated based on the number of days in that period. Descriptive statistics for dosing compliance will be presented by treatment group for the whole double-blind treatment period for the Safety Population.

10.0 EFFICACY ANALYSES

The efficacy analyses will be based on the ITT Population. All summaries on this population will be based on the investigational product each subject was randomized to receive. The multiple imputation (MI) approach will be used to impute missing values for co-primary and secondary efficacy analyses and details are further described in Section 16.2. Sensitivity analyses for efficacy parameters will be performed using alternative approaches to handle missing data, as well as an observed cases (OC) approach using the PP population. *Baseline* for efficacy is defined as the last non-missing efficacy assessment before the first dose of the investigational product. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

The descriptive statistics for all the continuous variables will include the mean, median, 25th percentile, 75th percentile, standard deviation (SD), standard error of mean (SEM), minimum, maximum, and number of subjects. Descriptive summaries will be provided for raw, change from baseline (CFB), and %CFB values for continuous efficacy endpoints. Frequency distributions for all the categorical variables will be presented as counts and percentages. Summaries will be provided by visit and treatment, as appropriate.

While every effort will be made to randomize a sufficient number of subjects at each study site, in the event that this is not possible, study sites may be pooled for statistical inference testing. Study sites (centers) will be pooled by geographical location based on region definitions from the US Census Bureau (Northeast, Midwest, South, and West; US Census Bureau, 2013) for analysis purposes so that in each pooled site the number of subjects is reasonably large and consistent in size between pooled sites. Sites within a geographic location will be pooled starting with the sites that have the lowest number of randomized subjects pooled together such that the pooled site has a minimum of 12 randomized subjects after pooling.

The sites to be pooled for each geographic location will be documented in a signed memo prior to unblinding of the treatment code. A list of sites and the corresponding pooled sites will be presented.

10.1 CO-PRIMARY EFFICACY PARAMETERS

There will be two co-primary efficacy parameters (endpoints) for this study. The first co-primary efficacy endpoint will be the absolute CFB in inflammatory lesion counts at Week 12. This variable will be considered a continuous variable. The second co-primary efficacy endpoint will be IGA success at Week 12. IGA success will be a dichotomous variable defined as at least 2-point decrease from baseline on the IGA assessment as well as a score of clear (0) or almost clear (1) on the IGA assessment.

10.1.1 CFB in Inflammatory Lesion Counts

The co-primary endpoint, absolute CFB in inflammatory lesion counts at Week 12, will be analyzed using an analysis of covariance (ANCOVA) model with the baseline value as a covariate and additional terms included to represent effects of treatment and (pooled) site. The primary efficacy analysis will be based on the ITT population. Missing data will be imputed using an MI approach further described in Section 16.2. The adjusted means with associated 95% confidence intervals (CIs) from the ANCOVA model will also be presented for each treatment and for the difference between the treatments. Statistical significance between the treatments, sarecycline compared to placebo, will be declared if the p-value of the hypothesis test from the ANCOVA model is less than or equal to 0.05. The ANCOVA model will be performed using SAS® PROC MIXED with the methodology of Littell et al. (2006).

Let X_{ijk} and Y_{ijk} be the baseline and endpoint values for the *k*th subject in the *j*th site and the *i*th treatment, where $k=1,\ldots, n_j$, j=1, …, c (the number of sites after pooling, if applicable) and *i*=sarecycline, placebo. Then

$$Y_{ijk} - X_{ijk} = \mu + \tau_i + \gamma_j + \beta X_{ijk} + \varepsilon_{ijk}$$

where μ is the overall mean, τ is the fixed effect of the *i*th treatment, γ is the fixed effect of the *j*th site, β is a regression coefficient for baseline and ε_{ijk} is the $NID(0,\sigma^2)$ random error component. Hypothesis tests for the active treatment effect of sarecycline compared to placebo will be conducted using differences of adjusted means.

As site is included in the primary ANCOVA model, a treatment-by-site interaction will be investigated as an exploratory analysis to assess the homogeneity of treatment effects across site. This effect will be investigated analytically prior to any pooling of sites by adding the interaction term to the ANCOVA model and testing for significance. Because interactions are not powered in this study, testing for significance will be at the 0.10 level. However, any significant interaction findings at the 0.10 level will also take into account the potential for spurious results. Further exploration may be done graphically with interaction plots to determine the nature of the interaction and to identify any "outlier" sites with attention focused on qualitative differences in treatment effects. If large differences in treatment effects are seen in any "extreme" sites, then sensitivity analyses will be performed that exclude sites with the highest extreme treatment effect values from the analysis. Any such sites may be further investigated for explanation involving study conduct, subject demographics, current medications, etc.

In addition, the following sensitivity analyses will be performed:

- Inflammatory lesion count data will be analyzed for CFB at Week 12 according to an ANCOVA model with the baseline value as a covariate and effects of treatment and (pooled) site using the PP population with OC data.

- LOCF will be used as an imputation method for cases where the Week 12 CFB in inflammatory lesion counts value is missing. The endpoint will then be analyzed according to an ANCOVA model with the baseline value as a covariate and effects of treatment and (pooled) site.

- Baseline observation carried forward will be used as an imputation method for cases where the Week 12 CFB in inflammatory lesion counts value is missing. The endpoint will then be analyzed according to an ANCOVA model with the baseline value as a covariate and effects of treatment and (pooled) site.

- Mixed model repeated measures (MMRM) analysis will be used to explore the sensitivity of data handling for CFB in inflammatory lesion counts for subjects who withdraw from the study. The model will include the fixed effects of treatment, pooled site, and visit, the baseline value as a covariate, and the treatment-by-visit interaction term. An unstructured covariance matrix will be used initially in the model for the correlation pattern among the repeated measures. If this does not converge, then the Toeplitz covariance structure (TYPE=TOEP in SAS MIXED procedure) will be used instead. If the results from the MMRM analyses differ qualitatively with the results from the primary efficacy analysis, further analyses will be performed to investigate the causes of the difference. However, the results from the primary efficacy analysis will be considered the primary efficacy results.

- A rank transformation will be applied to each of the multiple datasets created from the MI approach and the analysis will proceed for Week 12 using an ANCOVA model on the ranks with the baseline value as a covariate and effects of treatment and (pooled) site. Tied values will receive the mean value (midranks) of the corresponding ranks.

10.1.2 IGA Success

The co-primary efficacy endpoint, percentage of subjects with IGA success at Week 12, will be analyzed for the ITT population using the CMH test with adjustment for (pooled) site. Missing data will be imputed using an MI approach further described in Section 16.2. The rate difference and the 95% CIs for the rate difference and the relative rate and the 95% CIs for the relative rate will be presented as well. The CI for the treatment rate difference will be based on two-sided 95% Wald type CIs with CMH weights (Kim & Won, 2013, Yan & Su, 2010).

The homogeneity of treatment effects across (pooled) site will be investigated as an exploratory analysis using the Breslow-Day test. If the Breslow-Day test indicates large heterogeneity in the odds ratios across (pooled) site, then further exploration may be done graphically or with further investigation for explanation involving study conduct, subject demographics, current medications, etc.

In addition, the following sensitivity analyses will be performed:

- IGA success at Week 12 will be analyzed using a CMH test with adjustment for (pooled) site on the PP population with OC data.

- For IGA success, subjects who discontinue from the study early will be coded as failures for the Week 12 analysis. A sensitivity analysis of IGA success using this data handling convention will be performed using a CMH test with adjustment for (pooled) site.

- For IGA success, subjects who discontinue from the study early will be coded as failures for subjects on sarecycline and successes for subjects on placebo. A sensitivity analysis of IGA success using this data handling convention will be performed using a CMH test with adjustment for (pooled) site.

10.2 SECONDARY EFFICACY PARAMETERS

There will be 8 sets of secondary efficacy endpoints for this study: percent CFB in inflammatory lesion counts at Week 12, absolute and percent CFB in inflammatory lesion counts at Weeks 9, 6, and 3, and absolute and percent CFB in noninflammatory lesion counts at Weeks 12, 9, 6, and 3. These variables will be considered continuous variables.

A hierarchical testing approach will be used for the secondary efficacy endpoints, such that statistical testing will only be performed if both co-primary efficacy endpoints are statistically superior to placebo at α=0.05. In addition, statistical testing of the secondary endpoints will be conducted in the following order, with all tests proceeding at the 0.05 level if and only if the previous tests were all significant at the 0.05 level:

1. Percent CFB for inflammatory lesion counts at Week 12

2. Absolute and percent CFB for inflammatory lesion counts at Week 9 (both endpoints must be significant at the 0.05 level to proceed to the next analyses)

3. Absolute and percent CFB for inflammatory lesion counts at Week 6 (both endpoints must be significant at the 0.05 level to proceed to the next analyses)

4. Absolute and percent CFB for inflammatory lesion counts at Week 3 (both endpoints must meet the 0.05 level for Week 3 to meet statistical significance)

5. Absolute and percent CFB for noninflammatory lesion counts at Week 12 (both endpoints must be significant at the 0.05 level to proceed to the next analyses)

6. Absolute and percent CFB for noninflammatory lesion counts at Week 9 (both endpoints must be significant at the 0.05 level to proceed to the next analyses)

7. Absolute and percent CFB for noninflammatory lesion counts at Week 6 (both endpoints must be significant at the 0.05 level to proceed to the next analyses)

8. Absolute and percent CFB for noninflammatory lesion counts at Week 3 (both endpoints must meet the 0.05 level for Week 3 to meet statistical significance)

These endpoints will be analyzed for each visit using an analysis of covariance (ANCOVA) model with terms included to represent effects of treatment and (pooled) site and the baseline values as a covariate for the ITT population. Missing data will be imputed using an MI approach, as described in Appendix 16.2. The adjusted means with associated 95% CIs for the ANCOVA model will also be presented for each treatment and for the difference between the treatments. Statistical significance between the treatments, sarecycline compared to placebo, will be declared if the p-value of the hypothesis test from the ANCOVA model is less than or equal to 0.05.

For the Week 12 percent CFB analysis, as site is included in the ANCOVA model, a treatment-by-site interaction will be investigated as an exploratory analysis to assess the homogeneity of treatment effects across site. This effect will be investigated analytically by adding the interaction term to the ANCOVA model and testing for significance. Because interactions are not powered in this study, testing for significance will be at the 0.10 level. However, any significant interaction findings at the 0.10 level will also take into account the potential for spurious results with attention focused on qualitative differences in treatment effects. If large differences in treatment effects are seen in any "extreme" sites, then sensitivity analyses will be performed that exclude sites with the highest extreme treatment effect values from the analysis. Further exploration may be done graphically with interaction plots to determine the nature of the interaction and to identify any "outlier" sites. Any such sites may be further investigated for explanation involving study conduct, subject demographics, current medications, etc.

An additional exploratory analysis will be done for the percent CFB analysis by visit. A rank transformation will be applied to each of the multiple datasets created from the MI approach and the analysis will proceed using an ANCOVA model on the ranks with the baseline value as a covariate and effects of treatment and (pooled) site. Tied values will receive the mean value (midranks) of the corresponding ranks.

10.3 ADDITIONAL EFFICACY PARAMETER

[redacted]

[redacted]

10.4 SUBGROUP ANALYSES

Primary and secondary efficacy variable summaries will be repeated for the following subgroups by study visit using OC data:

- Gender: male and female
- Age groups: >= 9 and < 18 years; ≥ 18 years
- Race: white, African-American/Black, other
- Body mass index: < 25 kg/m^2 and ≥ 25 kg/m^2
- Baseline acne severity (IGA score): moderate and severe
- Hormonal contraceptive use in females: female subjects who use hormonal contraceptives versus female subjects who do not
- Weight groups: 33 to 54 kg, 55 to 84 kg, and 85 to 136 kg

10.5 OTHER EFFICACY PARAMETERS

10.5.1 IGA for Non-facial Sites

[redacted]

10.5.2 Skindex Questionnaire

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

10.6 ADDITIONAL EFFICACY ANALYSES

[redacted]

11.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs) and clinical laboratory, vital sign, ECG, and noninflammatory lesion counts parameters. For each safety parameter of the clinical laboratory, vital sign, ECG parameters, and noninflammatory lesion counts parameters, the last nonmissing safety assessment on or before the date of the first dose of the investigational product will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of subjects and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects.

11.1 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities,* version 18.0 or newer.

Adverse events with onset on or after the first dose date of the study drug will be considered as "treatment-emergent adverse event (TEAE)". An AE that occurs more than 30 days after the date of the last dose of the investigational product will not be counted as a TEAE.Adverse events summaries will present the number and percentage of subjects reporting an adverse event by treatment and overall as well as the number of events reported. The denominators for calculating the percentages by treatment will be based on the number of subjects exposed in the Safety population to each treatment and overall. The treatment will be based on the double-blind treatment received. For subjects who are in PK schedule 3, the TEAE summary described will comprise data prior to the active dose taken at the Week 12 visit. Further adverse events experienced after this Week 12 dose will be listed separately for these subjects.

The number and percentage of subjects reporting TEAEs in each treatment group and overall will be tabulated by system organ class and preferred term and further categorized by severity and relationship to study treatment. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and relationship.

The incidence of common ($\geq$ 2% of subjects in any treatment group) TEAEs will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for sarecycline treatment group.

The total number of TEAEs by severity and relationship to study treatment will be summarized by treatment group.

A serious adverse event (SAE) that occurred between the date of the first dose of the investigational product and 30 days after the date of the last dose of the investigational product, inclusive, will be considered an on double-blind therapy SAE. However, for any subject in the PK schedule 3 group, SAEs that occur after the Week 12 active dose will not be included. These events will be listed separately. The number and percentage of subjects who have on-therapy SAEs will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for sarecycline treatment group. In addition, the incidence of on-therapy SAEs that led to death will be summarized separately by preferred term for each treatment group.

The number and percentage of subjects in the Safety Population who have AEs leading to premature discontinuation of the investigational product will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for sarecycline treatment group.

Gastrointestinal AEs of special interest will be pre-specified prior to database lock. The number and percentage of subjects in the Safety Population who have gastrointestinal TEAEs of special interest will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for sarecycline treatment group. In addition, these TEAEs will be further categorized by relationship to study treatment.

For the Screened Population, separate tabular displays will be presented for subjects who died, subjects with SAEs, and subjects with AEs leading to premature discontinuation.

11.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by double-blind treatment group for the following laboratory analytes:

Hematology: Hemoglobin, hematocrit, red blood cell count, mean cell volume, white blood cell count, white blood cell count differential, and platelet count

Chemistry: albumin, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, gamma glutamyl transferase, glucose, lactate, dehydrogenase, total bilirubin, creatine phosphokinase, total protein, serum creatinine, sodium potassium, calcium, chloride, bicarbonate, and phosphorus

Urinalysis: color, specific gravity, potential for hydrogen (pH), leukocytes, ketones, protein, glucose, blood, and bilirubin

Lipid Profile: total cholesterol and triglycerides

Thyroid Function: thyroid stimulating hormone and free T4 and T3

Other	Urine pregnancy test

Continuous clinical laboratory analytes will be summarized by double-blind treatment, analyte, and visit using descriptive statistics. Categorical laboratory analytes, classified as normal or abnormal (low or high), will be summarized by double-blind treatment group,

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit criteria provided by the [redacted] (Appendix 1). The number and percentage of subjects who have PCS postbaseline clinical laboratory values will be tabulated by double-blind treatment group for the treatment period. The percentages will be calculated relative to the number of subjects with available non-PCS baseline values and at least 1 postbaseline assessment for the treatment period. The numerator will be the total number of subjects with available non-PCS baseline values and at least 1 PCS postbaseline value for the treatment period. A supportive tabular display of subjects with PCS postbaseline values will be provided, including SID, study center number, and baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in subjects who had PCS postbaseline clinical laboratory values will be provided.

Shift tables from baseline to end of the double-blind study period for clinical laboratory parameters will be presented by treatment group for the following categories: low, normal, and high.

Subjects with potential drug induced liver injury (elevated AST or ALT 3 times upper limit of normal (ULN) or greater and elevated bilirubin greater than 2 times ULN) will be listed. In addition, a tabular display showing all AEs that occurred in subjects with potential drug induced liver injury will be provided.

11.3 VITAL SIGNS

Descriptive statistics for vital signs (systolic and diastolic blood pressures, heart rate, and weight) and changes from baseline values at each visit and at the end of the double-blind study period will be presented by treatment group.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 11.3–1. The number and percentage of subjects with PCS postbaseline values will be tabulated by treatment group for the double-blind treatment period. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 postbaseline assessment for the treatment period. The numerator will be the total number of subjects with available baseline values and at least 1 PCS postbaseline value for the treatment period. A supportive tabular display of subjects with PCS postbaseline values will be provided, including SID, study center number, and baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in subjects who had PCS postbaseline vital sign values will be provided.

Shift tables from baseline to end of the double-blind study period for vital signs (systolic and diastolic blood pressures, pulse rate) will be presented by treatment group for the following categories: low, normal, and high

Table 11.3–1. Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	*Age*	*Gender*	*Flag*	*Criterion Value*
Systolic blood pressure, mm Hg	9 to 45	Female or Male	High	> 140
Diastolic blood pressure, mm Hg	9 to 45	Female of Male	High	≥ 90
Heart rate, beats per minute	9 to 12	Female	High	> 121
			Low	< 50
	9 to 12	Male	High	> 112
			Low	< 49
	13 to 16	Female	High	> 118
			Low	< 48
	13 to 16	Male	High	> 110
			Low	< 42
	17 to 45	Female or Male	High	> 110
	17 to 45	Female or Male	Low	< 44

11.4 ELECTROCARDIOGRAM

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, and QTc) and changes from baseline values at each assessment time point to the end of the double-blind study period will be presented by treatment group. The QTc will be calculated using both the Bazett and Fridericia corrections.

Electrocardiographic parameter values are considered PCS if they meet or exceed the higher-limit PCS criteria listed in Table 11.4–1. The number and percentage of subjects with PCS postbaseline ECG values will be tabulated by treatment group for the double-blind treatment period. The percentages will be calculated relative to the number of subjects with available non-PCS baseline values and at least 1 postbaseline assessment for the treatment period. The numerator is the total number of subjects with available non-PCS baseline values and at least 1 PCS postbaseline value for the treatment period. A supportive tabular display of subjects with PCS postbaseline values will be provided, including SID, study center number, baseline, all postbaseline (including non-PCS) values, and change from baseline.

In addition, a tabular display showing all AEs that occurred in subjects who had postbaseline PCS ECG values will be provided.

A shift table from baseline to the end of the double-blind study in the Investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display showing subjects with postbaseline clinically significant ECG abnormalities according to the Investigator's overall interpretation will be provided.

Table 11.4–1. Criteria for Potentially Clinically Significant Electrocardiograms

Parameter	*Unit*	*Higher Limit*
QRS duration	msec	≥ 120
PR interval	msec	> 220 or < 110
QTc (QTcB or QTcF) interval	msec	> 500

QTc = QT interval corrected for heart rate.

11.5 OTHER SAFETY PARAMETERS

11.5.1 Noninflammatory Lesion Counts

Noninflammatory lesions (open and closed comedones) will be counted and recorded in the eCRF and will be analyzed for CFB using an ANCOVA model effects of treatment, (pooled) site, and the baseline value as a covariate using OC data. Note that non-inflammatory lesion counts serve as both a safety and efficacy parameter in this study, reflecting a dual role of assessing efficacy while also evaluating patient safety.

12.0 HEALTH OUTCOMES ANALYSES

No health outcome analyses are planned for this study.

13.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

14.0 DETERMINATION OF SAMPLE SIZE

The sample size was selected to provide an adequate number of subjects to compare the efficacy of sarecycline treatment to placebo and to provide an adequate number of subjects needed for a safety database.

Sample size estimates were calculated for each of the co-primary efficacy endpoints, absolute CFB in facial inflammatory lesion counts and facial IGA success (based on at least 2-point decrease from baseline in IGA score), and the first secondary efficacy endpoint, percent CFB in facial inflammatory lesion counts at Week 12 last observation carried forward (LOCF). The results from a recent study (Study PR-10411) of sarecycline compared to placebo treatment were used to estimate the sample size needed to show a significant difference between the treatments at α=0.05 and 90% power using two-sided tests and a 1:1 randomization. It should be noted that one outlier in the data for Study PR-10411 was removed from the estimate for absolute CFB in inflammatory lesion counts in order to provide more accurate estimates for the sample size determination. Results of the calculations and the estimates used in the calculations are provided below:

Continuous Endpoints[a]	*Sarecycline CFB or %CFB*	*Placebo CFB or %CFB*	*Common SD*	*Sample per Treatment*	*Total Sample Size*
Absolute CFB in inflammatory lesion counts (co-primary)	16	13	12	338	676
Percent CFB in inflammatory lesion counts (secondary)	52%	39%	41%	210	420

a Sample size was based on a two sample t-test of no difference between the treatments

Dichotomous Endpoints[a]	*Sarecycline Rate*	*Placebo Rate*	*Difference in Rates*	*Sample per Treatment*	*Total Sample Size*
IGA Success (2-point decrease in IGA score from baseline and a score of clear/almost clear; co-primary)	23%	10%	13%	170	340

a Sample size was based on a χ^2 test of no difference between the proportions

While the IGA scale proposed for the Phase 2 study is slightly different than the IGA scale in the Phase 2, the number of subjects to be enrolled (500 per treatment; 1000 total) should provide more than sufficient power for the efficacy evaluations. Additionally, a larger sample is needed in order to provide sufficient numbers of subjects on sarecycline treatment for a safety database.

15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.3 (or newer) of SAS on a LINUX operating system.

16.0 DATA HANDLING CONVENTIONS

16.1 VISIT TIME WINDOWS

Table 16.1–1 presents the visits assigned for efficacy and safety analyses and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 16.1–1. Visit Time Windows

Derived Visit	*Scheduled Visit Day*[a]	*Window*
Baseline	Day 1	Days ≤ 1
Week 3	Day 22	Days [2, 32]
Week 6	Day 43	Days [33, 53]
Week 9	Day 64	Days [54, 74]
Week 12	Day 85	Days ≥ 75
End of study[b]	Final or Termination Visit during the treatment period	

a Relative to the date of the first dose of the investigational product or date of randomization if patient did not receive any dose. Day 1 = the date of the first dose of the investigational product (or date of randomization if patient did not receive a dose). There is no Day 0.

b Presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs.

If the assessment date (if the assessment date is unavailable, using visit date instead) is on or after the date of the first dose of the investigational product, the study day is calculated by assessment date – date of the first dose of the investigational product + 1. If the assessment date is before the date of the first dose of the investigational product, the study day is calculated by assessment date – date of the first dose of the investigational product. Therefore, a negative day indicates a day before the start of the investigational product.

If a subject has 2 or more visits within the same window, the last visit with a nonmissing value will be used for analysis.

16.2 MISSING DATA HANDLING FOR PRIMARY AND SECONDARY EFFICACY ENDPOINTS

For the co-primary and secondary efficacy analyses, the primary missing data imputation method is multiple imputation, as outlined in the following procedures:

- The SAS PROC MI procedure with a fully conditional specifications (FCS) method will be used to create 20 imputations. The FCS is proposed as it allows for accommodation of categorical variables and it has the versatility to handle arbitrary missing data patterns. Based on these 20 imputations, the relative efficiency will be 0.995 for 10% of missing data and 0.990 for 20% of missing data (Rubin, 1976, 1987, 1996) .

- For inflammatory lesion counts, if any of the subtypes (papules, pustules, and nodules/cysts) is missing, the inflammatory lesion count is missing. The variables included in the imputations are age, gender, and the measurements of the corresponding endpoint count) at baseline, Week 3, Week 6, Week 9, and Week 12.
- For IGA, the raw scores will be used for the imputation. The variables included in the imputations are age, gender, and the measurements of the endpoint at baseline, Week 3, Week 6, Week 9, and Week 12.
- All imputations will be performed by treatment group based on the randomized study medication and based on the randomized gender strata. The number of imputation is set at 20 with number of 50 burn-in iterations. The seed used for imputation for all endpoints is [redacted]. The logistic regression model for gender is based on the probability of female. For age, IGA raw scores and lesion counts, regression with predictive mean matching method will be used. The imputed values will be rounded to the nearest integer for IGA and lesion counts.
- The following are the SAS programs used to impute IGA at week 12:

The following SAS program will be used to impute inflammatory and non-inflammatory lesion counts at week 12.

[redacted]

- An analysis of covariance (ANCOVA) model for inflammatory lesion counts and a CMH analysis for the IGA success as stated in Sections 10.1.1 and 10.1.2, respectively, will be performed for each of the imputed dataset.
- An analysis of covariance (ANCOVA) model for inflammatory and non-inflammatory lesion counts as stated in Section 10.2 will be performed for the imputed dataset for the secondary endpoints.
- The SAS PROC MIANALYZE procedure will be used to produce final parameter estimates, including the point estimates and standard errors, adjusted treatment differences, confidence intervals and p-values for the primary and secondary variables.
- For the CMH test, the Wilson-Hilferty transformation (Wilson & Hilferty, 1931, O'Kelly & Ratitch, 2014) will be used. Under the null hypothesis, the transformed statistic is approximately normally distributed:

  $$wh\_CMH^{(m)} = \sqrt[3]{\frac{cmh^{(m)}}{k}} \sim normal(1 - \frac{2}{9k}, \frac{2}{9k})$$

  Where $cmh^{(m)}$ is the chi-square statistics each with k degrees of freedom from $m = 1, \ldots, M$ imputed datasets. In this case, $k=1$. This statistic will be passed to PROC MIANALYZE to obtain the combined p-value for CMH test.

  The same method will be used to obtained the p-values from the Breslow-Day test.

16.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a subject has repeated assessments before the start of investigational product, the results from the final nonmissing assessment made before the start of the investigational product will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

16.4 MISSING DATE OF THE LAST DOSE OF INVESTIGATIONAL PRODUCT

When the date of the last dose of the investigational product is missing for a subject in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

16.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of the investigational product, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of the investigational product, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.6 MISSING RELATIONSHIP TO INVESTIGATIONAL PRODUCT FOR ADVERSE EVENTS

If the relationship to study treatment is missing for an AE that started on or after the date of the first dose of the investigational product, a relationship of related will be assigned. The imputed values for relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of the investigational product, the month and day of the first dose of the investigational product will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of the investigational product, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of the investigational product, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of the investigational product, the day of the first dose of the investigational product will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of the investigational product or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of the investigational product, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of the investigational product or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of the investigational product, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of the investigational product, the date of the first dose of the investigational product will be assigned to the missing start date

- If the stop date is before the date of the first dose of the investigational product, the stop date will be assigned to the missing start date

16.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a subject, the start date will be imputed first.

16.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of the investigational product, the month and day of the first dose of the investigational product will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of the investigational product, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of the investigational product, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of the investigational product, the day of the first dose of the investigational product will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of the investigational product or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of the investigational product, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of the investigational product or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of the investigational product, the first day of the month will be assigned to the missing day

16.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of the investigational product is missing, replace it with the last visit date in the imputations described below. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of the investigational product, the month and day of the last dose of the investigational product will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of the investigational product, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of the investigational product, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of the investigational product, the day of the last dose of the investigational product will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of the investigational product or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of the investigational product, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of the investigational product or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of the investigational product, the first day of the month will be assigned to the missing day

16.9 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Table 16.9–1 shows examples of how some possible laboratory results should be coded for the analysis.

Table 16.9–1. Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test, SI Unit	*Possible Laboratory Results*	*Coded Value for Analysis*
CHEMISTRY		
ALT, U/L	< 5	0
AST, U/L	< 5	0
Bilirubin, total, µmol/L	< 2	0
URINALYSIS		
Glucose, mmol/L	= OR > 55, ≥ 55, > 0	Positive
	≤ 0, negative	Negative
pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Protein	= OR > 3.0, ≥ 3.0, > 0	Positive
	≤ 0	Negative

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

17.0 CHANGES IN AMENDMENT 1 OF THE STATISTICAL ANALYSIS PLAN

Rationale: This SAP, Amendment 1 is being updated prior to database lock to allow for the non-inflammatory lesion count assessment to be considered as a secondary efficacy endpoint. It will be included in the hierarchy of testing of the secondary endpoints to maintain type 1 error control at 0.05. Since this change is occurring after the completion of all patients in the study, and given that there is no impact on patient safety or study conduct, the protocol will not be amended to reflect this change.

Summary of changes: Sections 10.2, 11.5.1, and 16.2 have been updated to add non-inflammatory lesion count changes from baseline as a secondary efficacy endpoint and to reflect the dual nature of this parameter as being evaluated both for efficacy and for safety.

18.0 REFERENCES

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19.0 APPENDICES

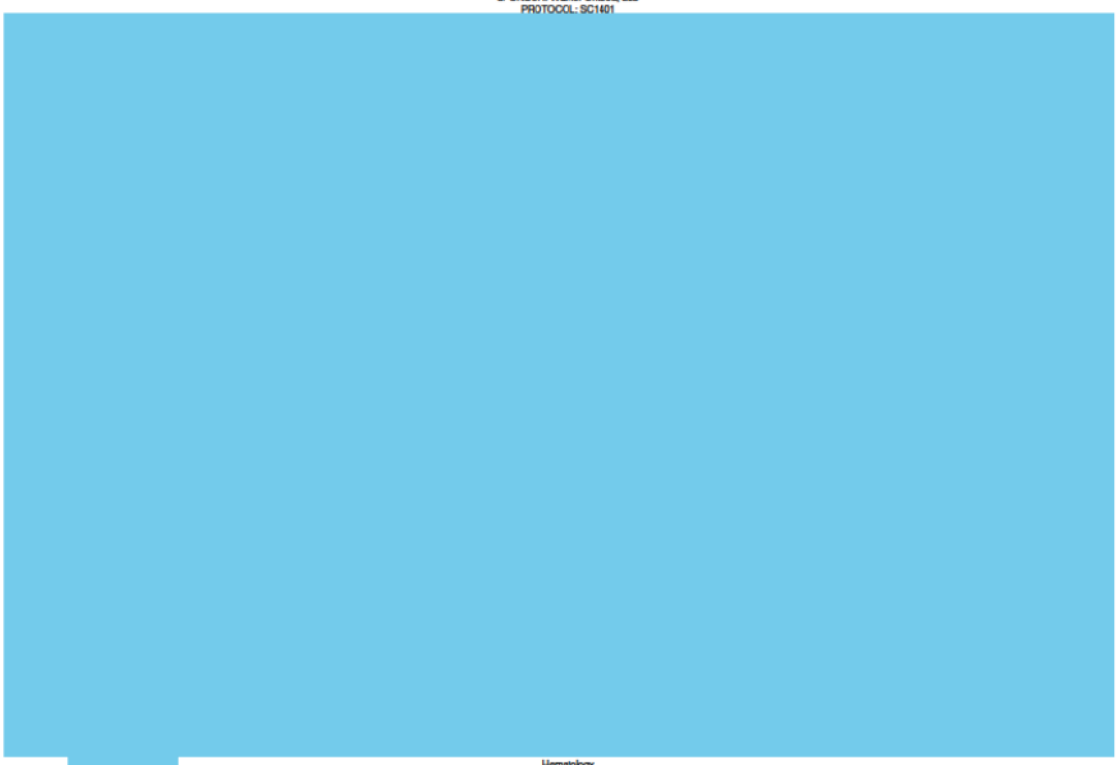
APPENDIX 1 CONVENTIONAL US REPORTING OF REFERENCE RANGES FOR CLINICAL LABORATORY EVALUATIONS

[redacted]

[redacted]

[redacted]

[redacted]



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ALLERGAN

16.1.9 Analysis Plan Prior to Database Lock Study SC1401

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
03-Mar-2017 13:31 GMT-080	[redacted]	Biostatistics Approval
03-Mar-2017 13:45 GMT-080	[redacted]	Clinical Development Approval
03-Mar-2017 14:18 GMT-080	[redacted]	Biostatistics Approval
03-Mar-2017 15:00 GMT-080	[redacted]	Biostatistics Approval

Pre-Specified Preferred Terms Used for Gastrointestinal Standardised MedDRA Queries

SMQ	Sub-SMQ	Scope	Preferrerd Term Name
Gastrointestinal nonspecific inflammation and dysfunctional conditions (SMQ)	Gastrointestinal nonspecific dysfunction (SMQ)	Narrow	Acid peptic disease
		Narrow	Duodenogastric reflux
		Narrow	Dyspepsia
		Narrow	Gastrooesophageal reflux disease
		Narrow	Gastrooesophageal sphincter insufficiency
	Gastrointestinal nonspecific inflammation (SMQ)	Narrow	Colitis
		Narrow	Duodenitis
		Narrow	Enteritis
		Narrow	Erosive duodenitis
		Narrow	Erosive oesophagitis
		Narrow	Feline oesophagus
		Narrow	Functional gastrointestinal disorder
		Narrow	Gastric mucosa erythema
		Narrow	Gastritis
		Narrow	Gastritis erosive
		Narrow	Gastroduodenitis
		Narrow	Gastrointestinal erosion
		Narrow	Gastrointestinal mucosa hyperaemia
		Narrow	Gastrointestinal mucosal exfoliation
		Narrow	Haemorrhagic erosive gastritis
		Narrow	Intestinal angioedema
		Narrow	Oesophageal mucosa erythema
		Narrow	Oesophagitis
		Narrow	Reactive gastropathy
		Narrow	Reflux gastritis
		Narrow	Remnant gastritis
		Narrow	Ulcerative gastritis
		Broad	Gastrointestinal inflammation
		Broad	Oesophageal irritation
	Gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ)	Narrow	Abdominal discomfort
		Narrow	Abdominal distension
		Narrow	Abdominal pain
		Narrow	Abdominal pain lower
		Narrow	Abdominal pain upper
		Narrow	Abdominal symptom
		Narrow	Abdominal tenderness
		Narrow	Abnormal faeces
		Narrow	Aerophagia
		Narrow	Anorectal discomfort

SMQ	Sub-SMQ	Scope	Preferrerd Term Name
		Narrow	Bowel movement irregularity
		Narrow	Change of bowel habit
		Narrow	Constipation
		Narrow	Defaecation urgency
		Narrow	Diarrhoea
		Narrow	Epigastric discomfort
		Narrow	Eructation
		Narrow	Faecal volume decreased
		Narrow	Faecal volume increased
		Narrow	Faeces hard
		Narrow	Faeces soft
		Narrow	Flatulence
		Narrow	Frequent bowel movements
		Narrow	Gastrointestinal pain
		Narrow	Gastrointestinal sounds abnormal
		Narrow	Gastrointestinal toxicity
		Narrow	Infrequent bowel movements
		Narrow	Nausea
		Narrow	Non-cardiac chest pain
		Narrow	Oesophageal discomfort
		Narrow	Oesophageal pain
		Narrow	Vomiting
		Broad	Dysphagia
		Broad	Gastrointestinal tract irritation
		Broad	Regurgitation
		Broad	Retching
		Broad	Steatorrhoea
		Broad	Vomiting projectile
Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ)	Gastrointestinal haemorrhage (SMQ)	Narrow	Anal haemorrhage
		Narrow	Anal ulcer haemorrhage
		Narrow	Anastomotic haemorrhage
		Narrow	Anastomotic ulcer haemorrhage
		Narrow	Anorectal varices haemorrhage
		Narrow	Chronic gastrointestinal bleeding
		Narrow	Colonic haematoma
		Narrow	Diarrhoea haemorrhagic
		Narrow	Diverticulitis intestinal haemorrhagic
		Narrow	Diverticulum intestinal haemorrhagic
		Narrow	Duodenal operation

Pre-Specified Preferred Terms Used for Gastrointestinal Standardised MedDRA Queries

SMQ	Sub-SMQ	Scope	Preferrerd Term Name
		Narrow	Duodenal ulcer haemorrhage
		Narrow	Duodenal vascular ectasia
		Narrow	Duodenitis haemorrhagic
		Narrow	Enterocolitis haemorrhagic
		Narrow	Gastric antral vascular ectasia
		Narrow	Gastric haemangioma
		Narrow	Gastric haemorrhage
		Narrow	Gastric occult blood positive
		Narrow	Gastric ulcer haemorrhage
		Narrow	Gastric ulcer haemorrhage, obstructive
		Narrow	Gastric varices haemorrhage
		Narrow	Gastritis alcoholic haemorrhagic
		Narrow	Gastritis haemorrhagic
		Narrow	Gastroduodenal haemorrhage
		Narrow	Gastroduodenitis haemorrhagic
		Narrow	Gastrointestinal anastomotic leak
		Narrow	Gastrointestinal angiectasia
		Narrow	Gastrointestinal angiodysplasia haemorrhag
		Narrow	Gastrointestinal haemorrhage
		Narrow	Gastrointestinal polyp haemorrhage
		Narrow	Gastrointestinal ulcer haemorrhage
		Narrow	Haematemesis
		Narrow	Haematochezia
		Narrow	Haemorrhagic erosive gastritis
		Narrow	Haemorrhoidal haemorrhage
		Narrow	Intestinal haematoma
		Narrow	Intestinal haemorrhage
		Narrow	Intestinal varices haemorrhage
		Narrow	Large intestinal haemorrhage
		Narrow	Large intestinal ulcer haemorrhage
		Narrow	Lower gastrointestinal haemorrhage
		Narrow	Mallory-Weiss syndrome
		Narrow	Melaena
		Narrow	Melaena neonatal
		Narrow	Neonatal gastrointestinal haemorrhage
		Narrow	Occult blood positive
		Narrow	Oesophageal haemorrhage
		Narrow	Oesophageal intramural haematoma
		Narrow	Oesophageal ulcer haemorrhage

SMQ	Sub-SMQ	Scope	Preferrerd Term Name
		Narrow	Oesophageal varices haemorrhage
		Narrow	Oesophagitis haemorrhagic
		Narrow	Peptic ulcer haemorrhage
		Narrow	Proctitis haemorrhagic
		Narrow	Rectal haemorrhage
		Narrow	Rectal ulcer haemorrhage
		Narrow	Small intestinal haemorrhage
		Narrow	Small intestinal ulcer haemorrhage
		Narrow	Ulcer haemorrhage
		Narrow	Upper gastrointestinal haemorrhage
		Narrow	White nipple sign
	Gastrointestinal obstruction (SMQ)	Narrow	Anal dilation procedure
		Narrow	Anal stenosis
		Narrow	Anastomotic stenosis
		Narrow	Anastomotic ulcer, obstructive
		Narrow	Anorectal stenosis
		Narrow	Appendicolith
		Narrow	Barium impaction
		Narrow	Distal intestinal obstruction syndrome
		Narrow	Duodenal obstruction
		Narrow	Duodenal stenosis
		Narrow	Duodenal ulcer perforation, obstructive
		Narrow	Duodenal ulcer, obstructive
		Narrow	Fibrosing colonopathy
		Narrow	Fixed bowel loop
		Narrow	Gallstone ileus
		Narrow	Gastric ileus
		Narrow	Gastric stenosis
		Narrow	Gastric stent insertion
		Narrow	Gastric ulcer haemorrhage, obstructive
		Narrow	Gastric ulcer perforation, obstructive
		Narrow	Gastric ulcer, obstructive
		Narrow	Gastric volvulus
		Narrow	Gastrointestinal anastomotic leak
		Narrow	Gastrointestinal dilation procedure
		Narrow	Gastrointestinal motility disorder
		Narrow	Gastrointestinal obstruction
		Narrow	Gastrointestinal stenosis
		Narrow	Ileal stenosis

SMQ	Sub-SMQ	Scope	Preferrerd Term Name
		Narrow	Ileus
		Narrow	Ileus paralytic
		Narrow	Ileus spastic
		Narrow	Impaired gastric emptying
		Narrow	Intestinal fibrosis
		Narrow	Intestinal malrotation repair
		Narrow	Intestinal obstruction
		Narrow	Intestinal scarring
		Narrow	Intestinal stenosis
		Narrow	Intussusception
		Narrow	Jejunal stenosis
		Narrow	Large intestinal obstruction
		Narrow	Large intestinal obstruction reduction
		Narrow	Large intestinal stenosis
		Narrow	Malignant bowel obstruction
		Narrow	Mechanical ileus
		Narrow	Necrotising colitis
		Narrow	Necrotising gastritis
		Narrow	Necrotising oesophagitis
		Narrow	Neonatal intestinal obstruction
		Narrow	Obstruction gastric
		Narrow	Obstructive defaecation
		Narrow	Oesophageal compression
		Narrow	Oesophageal dilation procedure
		Narrow	Oesophageal obstruction
		Narrow	Oesophageal stenosis
		Narrow	Peptic ulcer perforation, obstructive
		Narrow	Peptic ulcer, obstructive
		Narrow	Postoperative ileus
		Narrow	Prepyloric stenosis
		Narrow	Pylorus dilation procedure
		Narrow	Rectal obstruction
		Narrow	Rectal stenosis
		Narrow	Small intestinal obstruction
		Narrow	Small intestinal obstruction reduction
		Narrow	Small intestinal stenosis
		Narrow	Stomach dilation procedure
		Narrow	Stricturoplasty
		Narrow	Subileus

SMQ	Sub-SMQ	Scope	Preferrerd Term Name
		Narrow	Volvulus
		Narrow	Volvulus repair
	Gastrointestinal perforation (SMQ)	Narrow	Abdominal abscess
		Narrow	Abdominal hernia perforation
		Narrow	Abdominal wall abscess
		Narrow	Abscess intestinal
		Narrow	Acquired tracheo-oesophageal fistula
		Narrow	Anal abscess
		Narrow	Anal fistula
		Narrow	Anal fistula excision
		Narrow	Anal fistula infection
		Narrow	Anastomotic ulcer perforation
		Narrow	Anovulvar fistula
		Narrow	Aorto-duodenal fistula
		Narrow	Aorto-oesophageal fistula
		Narrow	Appendiceal abscess
		Narrow	Appendicitis perforated
		Narrow	Arterioenteric fistula
		Narrow	Atrio-oesophageal fistula
		Narrow	Chemical peritonitis
		Narrow	Colon fistula repair
		Narrow	Colonic abscess
		Narrow	Colonic fistula
		Narrow	Diverticular fistula
		Narrow	Diverticular perforation
		Narrow	Douglas' abscess
		Narrow	Duodenal perforation
		Narrow	Duodenal ulcer perforation
		Narrow	Duodenal ulcer perforation, obstructive
		Narrow	Duodenal ulcer repair
		Narrow	Enterocolonic fistula
		Narrow	Enterocutaneous fistula
		Narrow	Enterovesical fistula
		Narrow	Fistula of small intestine
		Narrow	Gastric fistula
		Narrow	Gastric fistula repair
		Narrow	Gastric perforation
		Narrow	Gastric ulcer perforation
		Narrow	Gastric ulcer perforation, obstructive

SMQ	Sub-SMQ	Scope	Preferrerd Term Name
		Narrow	Gastrointestinal anastomotic leak
		Narrow	Gastrointestinal fistula
		Narrow	Gastrointestinal fistula repair
		Narrow	Gastrointestinal perforation
		Narrow	Gastrointestinal ulcer perforation
		Narrow	Gastropleural fistula
		Narrow	Gastrosplenic fistula
		Narrow	Ileal perforation
		Narrow	Ileal ulcer perforation
		Narrow	Inguinal hernia perforation
		Narrow	Intestinal fistula
		Narrow	Intestinal fistula infection
		Narrow	Intestinal fistula repair
		Narrow	Intestinal perforation
		Narrow	Intestinal ulcer perforation
		Narrow	Jejunal perforation
		Narrow	Jejunal ulcer perforation
		Narrow	Large intestinal ulcer perforation
		Narrow	Large intestine perforation
		Narrow	Lower gastrointestinal perforation
		Narrow	Mesenteric abscess
		Narrow	Neonatal intestinal perforation
		Narrow	Oesophageal fistula
		Narrow	Oesophageal fistula repair
		Narrow	Oesophageal perforation
		Narrow	Oesophageal rupture
		Narrow	Oesophageal ulcer perforation
		Narrow	Oesophagobronchial fistula
		Narrow	Oesophagopleural fistula
		Narrow	Paraoesophageal abscess
		Narrow	Peptic ulcer perforation
		Narrow	Peptic ulcer perforation, obstructive
		Narrow	Perforated peptic ulcer oversewing
		Narrow	Perforated ulcer
		Narrow	Perineal abscess
		Narrow	Perirectal abscess
		Narrow	Peritoneal abscess
		Narrow	Peritonitis
		Narrow	Peritonitis bacterial

Pre-Specified Preferred Terms Used for Gastrointestinal Standardised MedDRA Queries

SMQ	Sub-SMQ	Scope	Preferrerd Term Name
		Narrow	Procedural intestinal perforation
		Narrow	Rectal abscess
		Narrow	Rectal fistula repair
		Narrow	Rectal perforation
		Narrow	Rectoprostatic fistula
		Narrow	Rectourethral fistula
		Narrow	Retroperitoneal abscess
		Narrow	Small intestinal perforation
		Narrow	Small intestinal ulcer perforation
		Narrow	Umbilical hernia perforation
		Narrow	Upper gastrointestinal perforation
	Gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures (SMQ)	Narrow	Bloody peritoneal effluent
		Narrow	Corrosive gastritis
		Narrow	Fixed bowel loop
		Narrow	Gastric atony
		Narrow	Gastric hypomotility
		Narrow	Gastrointestinal hypomotility
		Narrow	Haemorrhagic ascites
		Narrow	Intra-abdominal haematoma
		Narrow	Intra-abdominal haemorrhage
		Narrow	Megacolon
		Narrow	Mesenteric haematoma
		Narrow	Mesenteric haemorrhage
		Narrow	Mucosal erosion
		Narrow	Mucosal haemorrhage
		Narrow	Mucosal ulceration
		Narrow	Narcotic bowel syndrome
		Narrow	Oesophageal achalasia
		Narrow	Oesophageal atony
		Narrow	Oesophageal hypomotility
		Narrow	Peritoneal haematoma
		Narrow	Peritoneal haemorrhage
		Narrow	Retroperitoneal haematoma
		Narrow	Retroperitoneal haemorrhage
		Narrow	Toxic dilatation of intestine
	Gastrointestinal ulceration (SMQ)	Narrow	Acute haemorrhagic ulcerative colitis
		Narrow	Anal erosion
		Narrow	Anal ulcer
		Narrow	Anal ulcer haemorrhage

SMQ	Sub-SMQ	Scope	Preferrerd Term Name
		Narrow	Anastomotic ulcer
		Narrow	Anastomotic ulcer haemorrhage
		Narrow	Anastomotic ulcer perforation
		Narrow	Anorectal ulcer
		Narrow	Colitis erosive
		Narrow	Colitis ulcerative
		Narrow	Cytomegalovirus gastrointestinal ulcer
		Narrow	Duodenal ulcer
		Narrow	Duodenal ulcer haemorrhage
		Narrow	Duodenal ulcer perforation
		Narrow	Duodenal ulcer repair
		Narrow	Duodenal ulcer, obstructive
		Narrow	Erosive duodenitis
		Narrow	Erosive oesophagitis
		Narrow	Gastric ulcer
		Narrow	Gastric ulcer haemorrhage
		Narrow	Gastric ulcer haemorrhage, obstructive
		Narrow	Gastric ulcer helicobacter
		Narrow	Gastric ulcer perforation
		Narrow	Gastric ulcer perforation, obstructive
		Narrow	Gastric ulcer surgery
		Narrow	Gastritis erosive
		Narrow	Gastritis haemorrhagic
		Narrow	Gastritis hypertrophic
		Narrow	Gastroduodenal ulcer
		Narrow	Gastrointestinal anastomotic leak
		Narrow	Gastrointestinal erosion
		Narrow	Gastrointestinal ulcer
		Narrow	Gastrointestinal ulcer haemorrhage
		Narrow	Gastrointestinal ulcer management
		Narrow	Gastrointestinal ulcer perforation
		Narrow	Haemorrhagic erosive gastritis
		Narrow	Ileal ulcer
		Narrow	Ileal ulcer perforation
		Narrow	Intestinal scarring
		Narrow	Intestinal ulcer
		Narrow	Intestinal ulcer perforation
		Narrow	Ischaemic ulcer
		Narrow	Jejunal ulcer

Pre-Specified Preferred Terms Used for Gastrointestinal Standardised MedDRA Queries

SMQ	Sub-SMQ	Scope	Preferrerd Term Name
		Narrow	Jejunal ulcer perforation
		Narrow	Large intestinal ulcer
		Narrow	Large intestinal ulcer haemorrhage
		Narrow	Large intestinal ulcer perforation
		Narrow	Large intestine erosion
		Narrow	Lip erosion
		Narrow	Necrotising colitis
		Narrow	Necrotising gastritis
		Narrow	Necrotising oesophagitis
		Narrow	Oesophageal ulcer
		Narrow	Oesophageal ulcer haemorrhage
		Narrow	Oesophageal ulcer perforation
		Narrow	Oesophagitis ulcerative
		Narrow	Peptic ulcer
		Narrow	Peptic ulcer haemorrhage
		Narrow	Peptic ulcer helicobacter
		Narrow	Peptic ulcer perforation
		Narrow	Peptic ulcer perforation, obstructive
		Narrow	Peptic ulcer, obstructive
		Narrow	Perforated peptic ulcer oversewing
		Narrow	Perforated ulcer
		Narrow	Proctitis ulcerative
		Narrow	Prophylaxis against gastrointestinal ulcer
		Narrow	Rectal ulcer
		Narrow	Rectal ulcer haemorrhage
		Narrow	Small intestinal ulcer haemorrhage
		Narrow	Small intestinal ulcer perforation
		Narrow	Small intestine ulcer
		Narrow	Stress ulcer
		Narrow	Ulcer
		Narrow	Ulcer haemorrhage
		Narrow	Ulcerative gastritis