Master Statistical Analysis Plan

for

Rifaximin Delayed Release Studies in Subjects with Active Moderate Crohn's Disease including

RECD3125 and RECD3126

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Table 1. A List of Applicable Studies Covered by This SAP

Protocol Number	Treatment groups	Indication	Phase	Protocol Title
RECD3125	Rifaximin DR Tablets 800 mg BID Vs Placebo BID	Crohn's Disease	3	A Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Multiregional, One Year Study to Assess the Efficacy and Safety of Twice Daily Oral Rifaximin Delayed Release Tablets for Induction of Clinical Remission with Endoscopic Response at 16 Weeks followed by Clinical and Endoscopic Remission at 52 Weeks in Subjects with Active Moderate Crohn's Disease
RECD3126	Rifaximin DR Tablets 800 mg BID Vs Placebo BID	Crohn's Disease	3	A Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Multiregional, One Year Study to Assess the Efficacy and Safety of Twice Daily Oral Rifaximin Delayed Release Tablets for Induction of Clinical Remission with Endoscopic Response at 16 Weeks followed by Clinical and Endoscopic Remission at 52 Weeks in Subjects with Active Moderate Crohn's Disease

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1 TABLE OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BID	Two Times a Day
BSFS	Bristol Stool Form Scale
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRP	C-Reactive Protein
DNA	Deoxyribonucleic Acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th. Edition
DR	Delayed Release
ECG	Electrocardiogram
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GI	Gastrointestinal
HbA1c	Hemoglobin A1c

HIV	Human Immunodeficiency Virus
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IL	Interleukins
IND	Investigational New Drug
ITT	Intent-to-Treat
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NASH	Non-alcoholic Steatohepatitis
NF-kB	Nuclear Factor kappa-light-chain-enhancer of activated B Cells
PCR	Polymerase Chain Reaction
PK	Pharmacokinetic(s)
PP	Per Protocol
PSAP	Pharmacokinetics Statistical Analysis Plan
PXR	Pregnane X Receptor
rCRT	Clinical Remission Rate Treatment
rCRP	Clinical Remission Rate Placebo

RNA	Ribonucleic Acid
ROC	Receiver Operating Characteristics
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SES-CD	Simple Endoscopic Score for Crohn's Disease
SD	Standard Deviation
ULN	Upper Limit of Normal
US	United States
WPAI:CD	Work Productivity and Activity Impairment Questionnaire - Crohn's Disease
WHO	World Health Organization

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocols of Rifaximin delayed release studies including *RECD3125 and RECD3126*. The scope of this plan includes the final analysis. Any changes to the methods described in this SAP will be documented in each clinical study report (CSR).

3 OBJECTIVES

3.1 Primary Objective

- To determine the efficacy of Rifaximin DR 800 mg BID vs. placebo on the induction of clinical remission and endoscopic response following 16 weeks of treatment in subjects presenting with active moderate Crohn's disease.

3.2 Secondary Objective

A key secondary objective is to evaluate clinical and endoscopic remission following an additional 36-week Long Term Treatment Phase of Rifaximin DR 800 mg BID vs. placebo. The secondary objectives of this study are the following:

- Assess the safety of Rifaximin DR following a 16-week induction, and an additional 36-week Long Term Treatment Phase (i.e., up to 52 weeks of treatment for eligible subjects).
- Assess the population pharmacokinetics of Rifaximin DR.
- Characterize the gastrointestinal microbiota from stool samples, and antibiotic resistance from bacteria cultured from stool samples before and after treatment with Rifaximin DR.
- Evaluate the effects of Rifaximin DR treatment on indices of health outcomes.
- Assess the effects of Rifaximin DR treatment on biological (inflammatory) markers of disease.

This applies to both RECD3125 and RECD3126.

4 ENDPOINTS

4.1 Primary Efficacy Endpoint

There will be two co-primary measures of efficacy for Induction of Clinical Remission and Endoscopic Response:

- Clinical symptom remission defined by (1) the total number of liquid/very soft stools for the 7 days prior to the Week 16 visit being ≤ 10 (from CDAI Item 1); AND (2) an abdominal pain rating of ≤ 1(from CDAI Item 2) on each day for the 7 days prior to the Week 16 visit.
- Endoscopic response defined as a ≥ 3-point decrease in the SES-CD from baseline to the SES-CD score obtained between Week 16 and Week 17. SES-CD scores will be calculated from centrally-read digital video of ileocolonoscopies performed at baseline and between Week 16 and Week 17.

For the daily stool data, the number of daily liquid/very soft stools with a consistency of a Bristol Stool Form Scale [BSFS] score of Type 6 or Type 7 will be assessed using the information recorded by the subject via an electronic diary system. The number of liquid/very soft stools in a given week will be calculated as follows:

> (Number of liquid/very soft stools during that week ÷ Number of days with non-missing assessments during that week) × 7

4.2 Key Secondary Endpoints

The key secondary endpoint is clinical and endoscopic remission. Two key co-secondary endpoints of efficacy will assess this endpoint during the Long-Term Treatment Phase.

- Clinical symptom remission defined by (1) the total number of liquid/very soft stools for the 7 days prior to the Week 52 visit being ≤ 10 (from CDAI Item 1); AND (2) an abdominal pain rating of ≤ 1(from CDAI Item 2) on each day for the 7 days prior to the Week 52 visit.
- Endoscopic remission defined as a SES-CD score of ≤ 2 at Week 52. SES-CD scores will be calculated from centrally-read digital video of ileocolonoscopies performed at Week 52.

4.3 Secondary Efficacy Endpoints

- Induction of clinical remission defined as a CDAI Score of less than 150 points at Week 16.
- Clinical symptom remission over time: The total number of liquid/very soft stools for the 7 days prior to each clinic visit being ≤ 10; AND (2) an abdominal pain rating of ≤ 1 on each day for the last 7 days prior to each clinic visit in ≥ 80% of the study visits during the 52-Week Treatment Period, including Week 52.
- Time until durable response (see Section 7.2) to the liquid/very soft stool component of the co-primary endpoint during the 52-Week Treatment Period.
- Time until durable response (See Section 7.2) to the abdominal pain component of the co-primary endpoint during the 52-Week Treatment Period.
- Proportion of subjects with response to the abdominal pain component of the co-primary endpoint at post-baseline time points.
- Proportion of subjects with response to the liquid/very soft stool component of the co-primary endpoint at post-baseline time points.
- Change from baseline in SES-CD score at Week 16 and Week 52.
- Proportion of subjects with SES-CD score of 0 at Week 52.
- Proportion of subjects who achieve clinical remission by the CDAI endpoint at post-baseline time points.
- Time to loss of CDAI response defined by a CDAI score of 150 points during the Long Term Treatment Phase.
- Percentage of subjects who achieve clinical response at post-baseline time points. Clinical response is defined as a reduction of at least 100 points from the baseline CDAI score.
- Time to clinical remission based on abdominal pain and liquid stool components of the co-primary endpoints.
- Time to clinical remission based on CDAI < 150.

- Change from baseline in indices of health outcomes (Inflammatory Bowel Disease Questionnaire [IBDQ], Work Productivity and Activity Impairment Questionnaire for Crohn's Disease [WPAI-CD]) at post-baseline time points.
- Change from baseline in markers of inflammation (e.g. CRP, interleukins, cytokines, fecal calprotectin) at post-baseline time points.

4.4 Safety Endpoints

- Incidence, intensity, and types of adverse events (AEs).
- Changes from baseline in the laboratory parameters (hematology, clinical chemistry, urinalysis).
- Change from baseline in vital sign measurements.

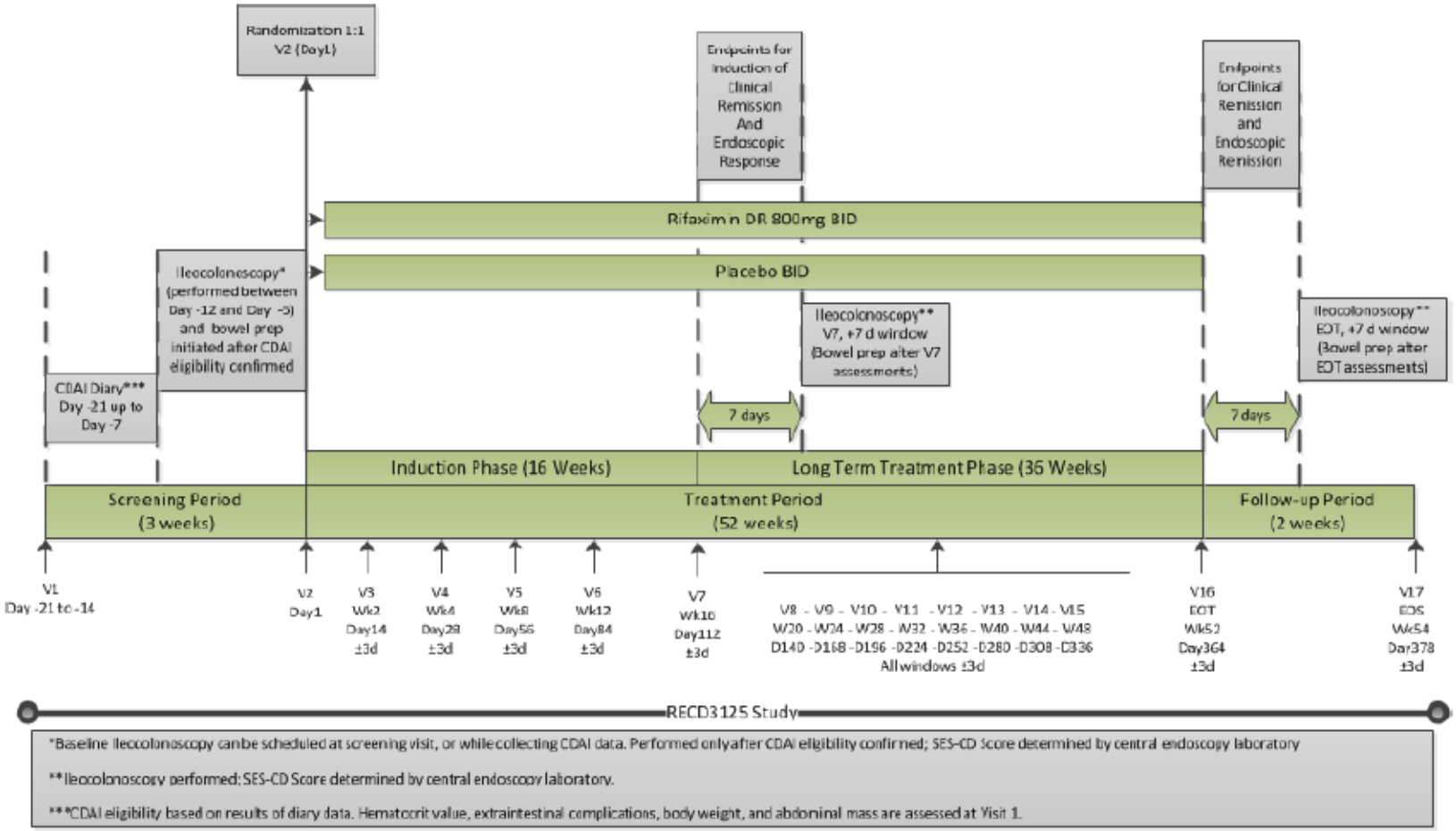
5 STUDY OVERVIEW

5.1 Study Design

RECD3125 and RECD3126 a double-blind, placebo-controlled, parallel-group, multicenter, multiregional, 52-week studies to assess the efficacy and safety of Rifaximin DR tablets for the induction of clinical remission and endoscopic response at 16 weeks followed by clinical and endoscopic remission after 52 weeks of continuous therapy in subjects with active moderate Crohn's disease. Subjects with active, moderate disease defined by a CDAI score of ≥ 220 and ≤ 450 points at screening, and evidence of active ileocolonic Crohn's disease defined by a minimum SES-CD of 7 determined during baseline ileocolonoscopy will be eligible for the study. Eligible subjects will complete a 2- to 3-week Screening Period, a 52-week Treatment Period consisting of a 16-week Induction Phase and 36-Week Long Term Treatment Phase, and a 2-week Follow-up Period. Subjects who successfully complete the 2- to 3-week Screening Period and qualify based on CDAI and SES-CD scores will enter the 52-week Treatment Period of the trial and will be randomized in a 1:1 allocation to Rifaximin DR 800 mg BID or placebo. Randomized subjects will have subsequent ileocolonoscopies conducted at the end of the Induction Phase (between Weeks 16 and 17), and following completion of the 36-week Long Term Treatment Phase (Week 52) to assess the effects of treatment on the degree of mucosal healing. Assessments of efficacy and safety will be performed during clinic visits at Weeks 0

(baseline), 2, 4, 8, 12, and 16; then every four weeks through Week 52. All subjects will complete a 2-week (study drug free) Follow-up Period following completion of the 52-week Treatment Period and will return to the clinic for final assessments (End-of-Study [EOS] visit; Week 54). See Figure 1.

Figure 1 Design Schematic



6 TREATMENT DESCRIPTION

There are two treatment groups as listed below. All treatments will be administered twice daily at morning and evening. The duration of the treatment is 52 weeks.

- Treatment A: Rifaximin DR Tablets 800 mg BID
- Treatment B: Placebo BID

7 STATISTICAL ANALYSIS METHODS

7.1 General Considerations

All data for enrolled subjects will be presented in data listings by subject number.

Continuous data will be described using descriptive statistics: number of observations (n), mean, standard deviation (STD), median, minimum, and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. When categorical data are presented, the percent will be suppressed when the count is zero. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the specified analysis population.

For those summary tables in which baseline and change from baseline measurements will be presented, the baseline is defined subject to each specific analysis.

Safety data will be analyzed using the observed data. Missing values will not be imputed unless otherwise stated.

If additional analyses are required to supplement the planned analyses described in this SAP after database lock, they may be performed and will be identified in the CSR.

Statistical analyses and summaries will be performed using SAS® Version 9.3 or greater or other validated statistical software as required.

7.2 Randomization and Unblinding

Subjects who successfully complete the Screening Period will enter the Treatment Period and will be randomized in a 1:1 allocation to one of two treatment groups for the duration of the study as assigned by the means of centralized electronic randomization system. Randomization will be stratified by study center within a country.

Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of the subject, will the investigator be allowed to unblind a subject's treatment assignment. If the investigator breaks the blind for an individual subject, the reason must be recorded on the CRF and the subject will be removed from the study.

7.3 Sample Size

For sample size justification, reference corresponding study protocols.

Originally planned sample sizes per arm for each of the studies are listed below:

Study	Treatment A: Rifaximin DR Tablets 800 mg BID	Treatment B: Placebo BID
RECD3125	330	330
RECD3126	330	330

Both studies will be terminated early therefore the actual sample size may vary.

7.4 Interim Analyses and Data Monitoring

No interim analyses are planned for this study.

7.5 Analysis Population

The Intent to Treat (ITT) population will include all randomized subjects who take at least one dose of study drug.

The analyses of baseline characteristics, efficacy and safety will be performed for the ITT Population.

7.6 Demographics and Study Summary

7.6.1 Subject Disposition

Subject disposition will be summarized by treatment and study phase and will include the number of subjects entered in the study; number and percentage of subjects who completed or prematurely discontinued (classified by reasons for premature discontinuation); the number of subjects entered in the study at each study site; and the number and percentage of subjects who completed or discontinued at each study site.

7.6.2 Demographics and Baseline Disease Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group. Baseline will be defined as the last assessments prior to initiating the Treatment Period. The following demographic and baseline disease characteristics will be summarized:

7.6.2.1 Demographics

- Age (years) = (date of informed consent signed – date of birth)/365.25;
- Age group (<65, >=65);
- Sex (male/female);
- Ethnicity (Hispanic or Latino/not Hispanic or Latino);
- Race (American Indian or Alaskan Native, Asian, Black or African-American, Native Hawaiian or Other Pacific Islander, White, and Other); subjects who identify more than one race will be categorized as "Other";
- Height (cm);
- Weight (kg);
- Body mass index (kg/m2) = (Weight in kg)/ (Height in m)2;
- Region (US/Rest Of World).

7.6.2.2 Baseline Disease Characteristics

Baseline disease characteristics listed below will be summarized descriptively by treatment group and overall using the ITT population.

- Demographic data (outlined above)
- Baseline CDAI and SES-CD scores
- Duration of the disease (years)
- Location of disease
- Previous steroid use (dose, duration)
- Previous surgery for CD
- Smoking history (nonsmoker/exsmoker/smoker)

7.6.3 Protocol Deviations

All protocol deviations will be listed by subject.

7.6.4 Medical History

All current medical condition and/or other significant medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0, listed by treatment, reported term, System Organ Class, and Preferred Term in a subject data listing.

7.7 Efficacy Analysis

The phrases 'statistical analysis' or 'analysis' will be used to mean inferential analysis (such as performing tests of significance, reporting p-values and confidence intervals). When no inferential analysis will be performed, the phrases 'descriptive analysis' or 'descriptive statistics' will be used (for instance, producing summary tables of means, standard deviations, percentages of responders). All efficacy analyses will be conducted on ITT population. All efficacy analyses will adjust for country.

7.7.1 Primary Efficacy Analysis

7.7.1.1 Induction Phase

There will be two co-primary measures of efficacy assessed during the Induction Phase. The first co-primary endpoint is:

- Clinical symptom remission defined by (1) the total number of liquid/very soft stools for the 7 days prior to the Week 16 visit being ≤ 10 (from CDAI Item 1); AND (2) an

abdominal pain rating of ≤ 1(from CDAI Item 2) on each day for the 7 days prior to the Week 16 visit.

The second co-primary endpoint is:

- Endoscopic response defined as a ≥3-point decrease in the SES-CD from baseline to the SES-CD score obtained between Week 16 and Week 17. SES-CD scores will be calculated from centrally-read digital video of ileocolonoscopies performed at baseline and between Week 16 and Week 17.

For each endpoint, the null hypothesis H0: $\pi R-\pi P=0$ versus the alternative HA: $\pi R-\pi P=0$ is of interest, where πR is the binomial parameter for induction of remission/response for the Rifaximin DR group, and πP is the binomial parameter for induction of remission/response for the placebo group. Subjects who require the initiation of rescue medication and/or surgery for CD will be considered treatment failures from the date of the introduction of the rescue medication and/or surgery, regardless of their actual response data. The Cochran-Mantel-Haenszel (CMH) test, stratified by country, will be used to test the hypothesis. Each null hypothesis of no difference will be rejected if the resulting p-value for the respective statistical test is less than 0.05. Significance for the induction claim will only be declared if both null hypotheses are rejected. As such, the overall Type I error rate will be maintained at the 5% level without adjustment for multiple comparisons.

7.7.1.2 Long Term Treatment Phase

There will be two key co-secondary endpoints of efficacy assessed during the Long Term Treatment Phase. The first is:

- Clinical symptom remission defined by (1) the total number of liquid/very soft stools for the 7 days prior to the Week 52 visit being ≤ 10 (from CDAI Item 1); AND (2) an abdominal pain rating of ≤ 1 (from CDAI Item 2) on each day for the 7 days prior to the Week 52 visit.

The second is:

- Endoscopic remission defined as a SES-CD score of ≤ 2 at Week 52. SES-CD scores will be calculated from centrally-read digital video of ileocolonoscopies performed at Week 52.

For each endpoint, the number and proportion of subjects with clinical and endoscopic remission will be summarized by treatment group.

For each endpoint, the null hypothesis H0: $\pi R-\pi P=0$ versus the alternative HA: $\pi R-\pi P\neq 0$ is of interest, where πR is the binomial parameter for remission for the Rifaximin DR group, and πP is the binomial parameter for remission for the placebo group. Subjects who require the initiation of rescue medication and/or surgery for CD will be considered treatment failures from the date of the introduction of the rescue medication and/or surgery, regardless of their actual response data. The Cochran-Mantel-Haenszel (CMH) test, stratified by country, will be used to test the hypothesis. Each null hypothesis of no difference will be rejected if the resulting p-value for the respective statistical test is less than 0.05. Significance for clinical and endoscopic remission will only be declared if both null hypotheses are rejected. As such, the overall Type I error rate will be maintained at the 5% level without adjustment for multiple comparisons.

If it is evident that the response variable is confounded with some of the background variables, then logistic regression will be performed using the background variables as covariates. The differences between this adjusted analysis and the previous unadjusted analysis will be noted, and the impact of such differences will be discussed.

7.7.2 Secondary Efficacy Analysis

7.7.2.1 Binary outcomes

Analysis of binary endpoints will be based on the methods outlined above for the primary efficacy analysis. It includes:

- Induction of clinical remission defined as a CDAI Score of less than 150 points at Week 16.
- Clinical symptom remission over time: The total number of liquid/very soft stools for the 7 days prior to each clinic visit being ≤ 10; AND (2) an abdominal pain rating of ≤ 1 on each day for the last 7 days prior to each clinic visit in $\geq 80\%$ of the study visits during the 52-Week Treatment Period, including Week 52.
- Proportion of subjects with response to the abdominal pain component of the co-primary endpoint at post-baseline time points.

- Proportion of subjects with response to the liquid/very soft stool component of the co-primary endpoint at post-baseline time points.
- Proportion of subjects with SES-CD score of 0 at Week 52.
- Proportion of subjects who achieve clinical remission by the CDAI endpoint at post-baseline time points.
- Percentage of subjects who achieve clinical response at post-baseline time points. Clinical response is defined as a reduction of at least 100 points from the baseline CDAI score.

7.7.2.2 Time to durable response

Time until durable response endpoints include:

- Time until durable response to the liquid/very soft stool component of the co-primary endpoint during the 52-Week Treatment Period.
- Time until durable response to the abdominal pain component of the co-primary endpoint during the 52-Week Treatment Period.

For time until durable response to the liquid/very soft stool component of the co-primary endpoint during the 52-Week Treatment Phase, a response will be considered durable if it started at Week 4 and lasted through Week 52. A response is defined as total number of liquid/very soft stools for the 7 days prior to the visit being ≤ 10 (from CDAI Item 1). The endpoint is then the time when the durable response began, or the first week of response that began the string of consecutive visits with response through Week 52. It is worth remarking that this endpoint would not be defined for a subject who does not have a durable response, so we consider instead the time of the last visit at which response was achieved. For example, if a subject is categorized as a responder at Week 52, then a durable response was not achieved.

If a subject is categorized as a responder at Week 20, then a durable response started on Week 24.

Time until durable response will be analyzed by the Kolmogorov-Smirnov test. Time until durable response to the abdominal pain component of the co-primary endpoint during the 52-

Week Treatment Phase is analyzed similarly. A response is defined as abdominal pain rating of ≤ 1(from CDAI Item 2) on each day for the 7 days prior to the visit.

7.7.2.3 Continuous outcomes

Change form baseline for the continues outcomes include:

- Change from baseline in SES-CD score at Week 16 and Week 52.
- Change from baseline in indices of health outcomes (Inflammatory Bowel Disease Questionnaire [IBDQ], Work Productivity and Activity Impairment Questionnaire for Crohn's Disease [WPAI-CD]) at post-baseline time points.
- Change from baseline in markers of inflammation (e.g. CRP, interleukins, cytokines, fecal calprotectin) at post-baseline time points.

Change from baseline in continuous outcomes will be analyzed by fitting fixed effects linear models to the data. An initial model with terms for treatment, country, baseline, and baseline by treatment interaction will be fitted. The interaction term will be tested at a 0.10 level. A non-significant interaction will result in dropping the term from the model in subsequent analyses. If the final model involves heterogeneous slopes, then the analysis will include overall plots of baseline versus change from baseline by treatment groups, and plots of the estimated regression lines.

Treatment differences will be estimated and tested at 25th, 50th and 75th percentiles of the baseline value.

The Work Productivity and Activity Impairment Questionnaire: Crohn's disease (WPAI: CD) is an instrument with 6 questions that will be used to assess the effect of CD on subjects' work habits.

WPAI: CD outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes. The four WPAI: CD outcome scores are computed as follows:

- % work time missed due to CD = 100*Q2/(Q2+Q4)
- % impairment while working due to CD = 100*Q5/10
- % overall work impairment= 100*[Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4)]*(Q5/10)]

- % activity impairment due to CD = 100*Q6/10

The IBDQ Global Score is the sum of 32 responses, each ranging from 1 to 7, thus the Global Score ranges from 32 to 224; a higher score indicating a better quality of life.

7.7.2.4 Time to event

Time to event related endpoints include:

- Time to clinical remission based on abdominal pain and liquid stool components of the co-primary endpoints.
- Time to clinical remission based on CDAI < 150.
- Time to loss of CDAI response defined by a CDAI score of 150 points during the Long Term Treatment Phase.

Time to event data (for example, time to clinical remission) will be analyzed by Kaplan-Meier analysis (PROC LIEFTTEST in SAS/STAT) stratified by country.

If the primary efficacy endpoints are not statistically significant, descriptive analysis will be performed for all secondary efficacy endpoints.

7.8 Safety Analyses

7.8.1 Extent of Exposure

The number of subjects administered study drug and the duration of exposure to study drug will be summarized descriptively by treatment group (n, mean, median, SD, minimum, and maximum values). Extent of exposure is defined as last dose of study drug – first dose of study drug +1.

7.8.2 Treatment Compliance and Modifications

Treatment compliance for the rifaximin use will be calculated using the following algorithm:

Percent overall compliance for the rifaximin use will be calculated as: 100*(total number of tablets dispensed – total number of tablets returned)/(4 x total extent of exposure [as defined in Section 7.8.1. above]).

Compliance will be defined for a subject as the receipt of at least 80% and no more than 120% of the expected tablets.

Calculated overall compliance and compliance will be summarized descriptively by treatment group (n, mean, median, SD, minimum, and maximum values). The number and percent of compliant and noncompliant subjects based on the calculated overall compliance will be summarized by treatment group.

7.8.3 Adverse Evets

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Treatment-emergent AEs will be defined as any event with a start date occurring on or after Visit 2 (Day 1) or, if pre-existing, worsening after Visit 2 (Day 1).

7.8.3.1 Treatment-Emergent Adverse Events

A non-fatal AE is considered as a treatment emergent adverse event (TEAE), if the start date of the AE is within the period of first dose date of study medication and last dose date of study medication plus five days. A fatal AE is considered TEAE if the start date of the AE is within the period of first dose date of study medication and last dose of study medication plus 30 days.

The incidence of treatment-emergent AEs will be summarized by body system and MedDRA preferred term. If a subject reports the same AE more than once, then that subject will only be counted once for the summary of that AE, using the most severe intensity.

In case of incomplete or missing AE dates, the standard Salix estimation rule for AEs will be followed in order to determine whether an AE should be considered treatment-emergent. If the AE category still can't be determined, the AE will be considered as TEAE. The onset dates reported in the CRF will be presented in the listings.

Treatment-emergent AEs will be summarized as follows:

- All treatment-emergent AEs;
- All treatment-emergent AEs by intensity;
- All treatment-emergent AEs related to study drug;
- All treatment-emergent SAEs; and

- All treatment-emergent AEs that led to premature discontinuation of study drug.

7.8.3.2 Treatment-Emergent Adverse Events by Intensity

Adverse events are categorized for severity by the investigator as "Mild", "Moderate" or "Severe". The frequency of TEAEs by intensity will be summarized by body system, and preferred term, overall and by treatment group. TEAEs with missing intensity will be considered 'Severe' in the tabular summaries but data listings will show severity listed as missing. In case of multiple TEAEs for the same body system and preferred term for the same subject, only the TEAE with the maximum intensity will be counted in the table.

7.8.3.3 Treatment-Emergent Adverse Events Related to Study Drug

Related AEs are the AEs with "related" for causality. TEAEs with missing relationship to study drug will be considered "related" in the tabular summaries but data listings will show relationship as missing.

7.8.3.4 All Treatment-Emergent Serious Adverse Events by Intensity

Any AE reported as serious in CRF will be reported as a SAE. The clinical database will be reconciled with the serious adverse event database (from the Salix Safety department) before database lock.

All treatment-emergent SAEs will be summarized by body system and preferred term, overall and by treatment group.

7.8.3.5 Treatment-Emergent Adverse Events Leading to Study Premature Discontinuation

All TEAEs that led to subject discontinuation from the study will be summarized and listed separately.

7.8.4 Clinical Laboratory Evaluations

Laboratory values will be summarized at baseline and at each time point. In addition, changes from baseline to last visit will be summarized.

All potentially clinically significant values for clinical laboratory tests will be assessed by the investigator. Out of range laboratory values that may be potentially clinically significant will be flagged for review.

7.8.5 Prior and Concomitant Medications

Prior medications are defined as medications that stop prior to the first dose of study drug. Concomitant medications are defined as medications that (1) start before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) start on or after the date of the first dose of study drug.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Enhanced Dictionary (March 2018 Version) and listed by reported term and Anatomical Therapeutic Class (ATC) classification. Medications will be listed by subject including the start and end dates, or whether it is ongoing, dose, unit, and indication.

7.8.6 Vital Sign Measurements

Vital sign measurements will be summarized at baseline and at each time point. For each summary the number, mean, median, standard deviation, minimum, and maximum values will be presented by treatment and study phase.

7.8.7 Physical Exam

Physical examination data will be listed.

7.8.8 Electrocardiogram (ECG)

ECG parameters will be summarized by treatment group using descriptive statistics. In order to assess the QT interval data, corrected QT (QTc) values will be calculated based on the following methods.

1) Fridericia's correction: QTc=QT/RR0.33,

2) Bazett's Correction: QTc=QT/RR0.5,

QTc interval data at post-baseline visits will then be summarized descriptively by central tendency techniques. In addition, the frequency counts and percentages by treatment group for the following categories will be provided:

>450 with Baseline <=450,

>480 with Baseline <=480,

>500 with Baseline <=500,

Increases from baseline > 30 and

Increases from baseline > 60.

7.9 Clinical biology

Only a portion of clinical biology data will be available at the time of database lock. Final clinical biology analysis/summary outputs will be generated when all clinical biology data are available.

7.10 Statistical and analytical issues

7.10.1 Handling of Dropouts or Missing Data

Missing data will be handled using the Worst-Case analysis method for the primary and key secondary endpoints. In the Worst-Case analysis, subjects with fewer than 4 days of diary data in a given week will be considered non-responders for that week. Additionally, subjects with missing SES-CD data will be classified non-responder for that measure in that week.

The following three sensitivity analyses will be conducted to address the impact of missing data on the primary and key secondary endpoints:

7.10.2 Last Observation Carried Forward (LOCF) Analysis

In the first analysis, missing values will be replaced with the last previous non-missing value. The baseline values will not be carried forward.

7.10.3 Imputation Rules for Partial or Missing Dates

Imputation of partial dates will be made for AE onset and stop dates, start and end dates of concomitant medication, start date of subsequent anticancer therapy, date of initial diagnosis and death date. If dates are completely missing, no imputation will be made. For any partial date with missing year, no imputation will be made.

The general rule for imputation is:

- If only day is missing, then the 15th of the month will be used.
- If only year is present, then June 30th will be used.

If such imputation date for initial diagnosis is on or after date of first dose, then date of first dose – 1 will be used. If such imputed date for subsequent anticancer therapies is before date of last dose, then date of last dose + 1 will be used. If the imputed date is for an AE start date and is in the same year and month as but before the first dose date, then the first dose date will be used, or if the imputed AE start date is after the AE end date, then the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as but after the last dose date + 30 days, then the last dose date + 30 days will be used.

If the imputed date is for an AE end date and is after the death date, then the death date will be used, or if the imputed AE end date is before the AE start date, then the AE start date will be used.

Every effort will be made to obtain complete dates for deaths. If both month and day are missing for death date or a death date is totally missing, do not impute and censor the subject survival time. If death year and month are available but day is missing, the following algorithm will be used:

- If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.

7.11 Multiplicity

The study has a single primary endpoint as the primary hypothesis, therefore no multiplicity adjustment is needed to the overall significance level of 0.05. Additionally, the clinical trial will be providing data for two separate indications (induction and long term treatment) with each indication having its own separate endpoint. On that basis, no multiplicity adjustment is needed to the overall significance level of 0.05 per indication because conclusions will be reached independently for induction and separately for long term treatment.

8 CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Because both studies will be terminated early and for the purpose of abbreviated CSR originally planned evaluations that will not be performed include:

Additional analysis of Secondary Efficacy Endpoints:

- Longitudinal analysis using a mixed model of the change from baseline in continuous outcomes measured at multiple post-baseline time points.
- Determination whether the declaration of response based on the co-primary endpoints for induction parallels the pattern of CDAI scores
- Comparison of changes in the CDAI scores between responders and non-responders to the co-primary endpoints via Wilcoxon rank-sum test

Analysis Exploratory Endpoints:

- Characterization of stool microbiota at baseline and after 16 and 52 weeks of treatment.
    - Baseline and post-treatment bacterial DNA isolated from stool for 16S rRNA gene amplification.
    - Descriptive characterization of bacteria in stool by:
        - Isolation and identification of selected Gramnegative and Gram-positive bacteria.
        - Resistance to selected antibiotics, including rifaximin and rifampin.
- Genomic profiling of pregnane X receptor (PXR) in blood.
- Population pharmacokinetics of rifaximin.

Clinical Laboratory Assessments:

- A summary of shifts from baseline to final evaluation for each treatment group for each parameter.

Electrocardiogram

- QT correction based on linear regression techniques

These changes will be documented in the Clinical Study Report