NCT#: NCT02240108

CLINICAL RESEARCH PROTOCOL

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

Protocol ID:	RECD3126
IND Number:	115,638 **EudraCT Number:** 2014-001645-24
Clinical Phase:	3
Treatment Regimen:	Rifaximin Delayed Release (DR) Tablets 800 mg BID or Placebo BID
Indication:	Moderate Crohn's Disease
Sponsor:	Salix Pharmaceuticals, Inc. 8510 Colonnade Center Drive Raleigh, North Carolina, USA 27615
Study Director:	[redacted] Salix Pharmaceuticals, Inc. [redacted]
Medical Monitor:	[redacted] Salix Pharmaceuticals, Inc. [redacted]
Principal Investigator:	Multicenter
Protocol Date:	14Jul2014

SIGNATURE PAGE

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

This study protocol has been reviewed and approved by the undersigned persons. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version and the applicable legal and regulatory requirements.

Study Director: [redacted]

)Jg1rjy

Date

Salix Pharmaceuticals, Inc.

[redacted]

[redacted]

Date

Salix Pharmaceuticals, Inc.

RECD3126 Investigator Protocol Agreement

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the Sponsor, Salix Pharmaceuticals, Inc. (Salix).
- Not to implement any deviations from or changes to the protocol without agreement from the Sponsor and prior review and written approval from the Institutional Review Board/Institutional Ethics Committee (IRB/IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational drug(s), as described in this protocol and any other information provided by the Sponsor including, but not limited to the following: the current investigator's brochure or equivalent document provided by Salix and approved product label, if applicable.
- That I am aware of, and will comply with, "good clinical practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the investigational drug(s) and of their study-related duties and functions as described in the protocol.
- To periodic on-site monitoring of the case report forms (CRFs) and source documents by Salix or designee and to on-site inspection of CRFs and source documents by appropriate regulatory authorities, including but not limited to the United States (US) Food and Drug Administration (FDA), local governing regulatory bodies, and IRB/IEC inspectors.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply details about the investigator's ownership interest in the Sponsor or study drug, and more generally about his/her financial ties with the Sponsor. Salix will use and disclose the information solely for the purpose of complying with regulatory requirements.

  Hence I:
  - Agree to supply Salix with any information regarding ownership interest and financial ties (including those of my spouse and dependent children);
  - Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and
  - Agree that Salix may disclose this information about such ownership interests and financial ties to regulatory authorities.

Investigator Name [Print]	Investigator Signature	Date

SYNOPSIS

PROTOCOL TITLE:	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
PROTOCOL NUMBER:	RECD3126
SPONSOR:	Salix Pharmaceuticals, Inc.
TREATMENT:	Treatment A: Rifaximin Delayed Release (DR) Oral Tablets 800 mg BID administered continuously without dose-adjustment for 52 weeks Treatment B: Matching placebo BID administered continuously without dose-adjustment for 52 weeks
PRIMARY OBJECTIVE:	To determine the efficacy of Rifaximin DR 800 mg BID vs. placebo for the induction of clinical remission and endoscopic response following 16 weeks of treatment in subjects presenting with active moderate Crohn's disease.
KEY 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.
STUDY DESIGN:	RECD3126 is a double-blind, placebo-controlled, parallel-group, multicenter, multiregional, 52-week study 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 will be eligible if they have active, moderate disease defined by a Crohn's disease Activity Index (CDAI) score of ≥ 220 and ≤ 450 points at screening, and evidence of active ileocolonic Crohn's disease defined by a Simple Endoscopic Score for Crohn's disease (SES-CD) of ≥ 7 on baseline ileocolonoscopy as assessed by blinded central reading. 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 will be randomized in a 1:1 allocation to Rifaximin DR 800 mg BID or placebo at the beginning of the treatment period and will maintain

	treatment assignment throughout the duration of the study. Ileocolonoscopy will be performed on all subjects at baseline (between Visits 1 and 2), between Weeks 16 and 17 (end of the Induction Phase), 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. Subjects will be assessed during clinic visits which are scheduled at Weeks 0 (baseline), 2, 4, 8, 12, and 16; then every four weeks through Week 52. All subjects will be required to complete a daily diary. 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.
STUDY DURATION:	Per Subject: 2- to 3-week Screening Period, 52-week Treatment Period, and a 2-week Follow-up Period. The maximum duration of subject participation will be 57 weeks.
SUBJECT POPULATION:	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 SES-CD score of ≥ 7 as determined from baseline ileocolonoscopy.
NUMBER OF SUBJECTS:	Approximately 660 total: 330 to Treatment A (800 mg Rifaximin DR BID) and 330 to Treatment B (Placebo BID)
NUMBER OF CENTERS:	Approximately 200
LOCATION:	United States, Canada, Russia, Israel and countries in Europe
CO-PRIMARY EFFICACY ENDPOINT:	There will be two co-primary measures of efficacy assessed during the Induction of Clinical Remission and Endoscopic Response 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.
KEY CO-SECONDARY ENDPOINT:	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
SECONDARY ENDPOINTS:	The following secondary endpoints will be assessed: • Induction of clinical remission defined as a CDAI score of less than 150 points at Week 16. • Proportion of subjects with SES-CD score of 0 at Week 52. • Clinical remission defined as a CDAI score of less than 150 points at post-baseline visits. • Change from baseline in SES-CD score at Week 16 and Week 52. • Clinical symptom remission over time: The total number of liquid/very soft stools for the 7 days prior to each clinic visit being ≤ 10 (from CDAI Item 1); AND (2) an abdominal pain rating of ≤ 1(from CDAI Item 2) on each day for the last 7 days prior to each clinic visit in ≥ 80% of the study visits during the 52-Week Treatment Phase, including Week 52. • Time to loss of CDAI response defined by a CDAI score of ≥ 150 points during the Long Term Treatment Phase. • Time until durable response to the liquid/very soft stool component of the co-primary endpoint during the 52-Week Treatment Phase.

	• Time until durable response to the abdominal pain component of the co-primary endpoint during the 52-Week Treatment Phase. • 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 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. • Time to clinical response based on Week 16 co-primary endpoints.
SAFETY ENDPOINTS:	• Incidence, intensity, and types of adverse events (AEs). • Changes from baseline in the laboratory parameters (hematology, clinical chemistry, urinalysis). • Changes from baseline in vital sign measurements.
OTHER ENDPOINTS:	Exploratory assessments will include: • 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 Gram-negative 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.

SAMPLE SIZE:	The information below provides the background information for sample size determination for the induction of clinical remission with endoscopic response at 16 weeks followed by clinical and endoscopic remission at 52 weeks. For placebo, the expected rates are based on data from a Phase 2 study (RETIC 03/06) conducted in subjects with active moderate Crohn's disease. The rates for Rifaximin DR are based on the assumption that Rifaximin DR will provide a somewhat higher induction of remission rate. Expected rates for induction of clinical remission with endoscopic response at Week 16 are 40% for placebo and 55% for Rifaximin DR. Based on a significance level of 5% (alpha 0.05), a sample size of approximately 240 subjects per treatment group will have at least 90% power to test the hypothesis that Rifaximin DR is superior to placebo for each co-primary endpoint considered individually. Approximately 80% power is available to detect significant differences between Rifaximin DR and placebo for each of the co-primary endpoints. For the long term treatment phase, a 15% treatment effect is expected for both clinical symptom and endoscopic remission at Week 52. Based on this assumption and testing at a significance level of 5% (alpha 0.05), a sample size of approximately 210 subjects per treatment group will have at least 90% power to test the key secondary efficacy hypothesis that Rifaximin DR is superior to placebo when each key co-secondary endpoint is considered individually. In addition, approximately 80% power is available to detect significant differences between Rifaximin DR and placebo for each of the key co-secondary endpoints. An additional consideration for sample size determination is the application of an inflation factor of 20% to account for drop-out rates during the Induction and Long Term Treatment Phases of the study. This consideration suggested that 330 subjects per treatment group would be required at study entry.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-Aminosalicylic Acid
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration-time Curve
BID	Two Times a Day
BSFS	Bristol Stool Form Scale
C. difficile	*Clostridium difficile*
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CLSI	Clinical Laboratory Standards Institute
Cmax	Maximum Observed Plasma Concentration
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
E. Coli	*Escherichia coli*
EDC	Electronic Data Capture
EIA	Enzyme Immunoassay
EIR	Extended Intestinal Release
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	Gastrointestinal
HbA1c	Hemoglobin A1c

Abbreviation	Definition
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IBDQ	Inflammatory Bowel Disease Questionnaire
IBS	Irritable Bowel Syndrome
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IL	Interleukins
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
LFT	Liver Function Test
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMP-9	Matrix Metalloproteinase-9
NASH	Non-alcoholic Steatohepatitis
NC	North Carolina
NF-kB	Nuclear Factor kappa-light-chain-enhancer of activated B Cells
PCR	Polymerase Chain Reaction
PHI	Protected Health Information
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

Abbreviation	Definition
SES-CD	Simple Endoscopic Score for Crohn's Disease
SD	Standard Deviation
tcdB	*C. difficile* Toxin B
Tmax	Time of Maximum Observed Plasma Concentration
TNBS	Trinitrobenzene Sulfonic Acid
TNFα	Tumor Necrosis Factor alpha
ULN	Upper Limit of Normal
US	United States
WPAI:CD	Work Productivity and Activity Impairment Questionnaire - Crohn's Disease
WHO	World Health Organization

1.0 INTRODUCTION

1.1 Disease Background and Scientific Rationale for the Use of Rifaximin DR in Crohn's Disease

Crohn's disease (CD) is a chronic, relapsing, remitting, systemic disease which may result in transmural inflammation of the gastrointestinal tract. The incidence and prevalence rates for CD in Caucasian people in Northern Europe and North America are noted in Table 1.

Table 1: Epidemiology of Crohn's Disease

Factor	Crohn's disease
Incidence per 100,000	1-6
Prevalence per 100,000	10-100
Racial Incidence	High in Caucasians
Ethnic Incidence	High in Jewish people
Gender	Slight female preponderance
Age of Onset	15-25 (peak) 55-65 (2nd smaller peak)

Reference (1)

Crohn's disease may affect any part of the alimentary tract, but mainly affects the ileum (30-40%), ileocolonic region (40-55%) or colon (15-25%). Gastrointestinal symptoms are determined by the anatomical location and the severity of the disease and include:

- General manifestations: fatigue, loss of appetite, fever.
- Bowel specific symptoms: irregular bowel movements, mucus and /or blood in stools, chronic recurrent diarrhea, recurrent abdominal pain, abdominal tenderness, nausea, weight loss, perianal diseases.
- Strictures and fistulae, which may lead to obstructions, abscesses and malabsorption.
- Extraintestinal manifestations: present in up to 30% of CD patients and include arthropathies, bone demineralization, skin lesions, ocular manifestations, hepatic diseases.

Severity of disease generally is assessed by both non-invasive and invasive measures. The Crohn's disease Activity Index (CDAI) score is a weighted, composite index of eight items (stool frequency, severity of abdominal pain, degree of general well-being, presence or absence of extraintestinal manifestations including fistula, use or nonuse of antidiarrheal agents, presence or absence of abdominal mass, hematocrit and body weight). Scores range from 0 to approximately 600 with higher scores indicating greater disease severity. Clinical (asymptomatic) remission is defined as a score of ≤ 150 points. Mild-to-moderate disease and severe disease are defined by scores of > 150 to ≤ 450, and > 450 points, respectively. (See Appendix 2: Crohn's Disease Activity Index).

The Simple Endoscopic Score for Crohn's disease (SES-CD) is a validated instrument reflecting an endoscopist's global appraisal of mucosal lesions in Crohn's disease. The SES-CD grades lesions by location (ileum, right colon, transverse colon, left colon and rectum) using ulcer size, extent of ulcerated surface, extent of affected surface, and presence/type of narrowing. (See Appendix 4: Simple Endoscopic Score for Crohn's Disease (SES-CD) Definitions of SES-CD Variables).

The disease course is variable with some patients experiencing a very mild disease with infrequent flare-ups while others may suffer from more severe disease with frequent hospitalizations. Epidemiological studies show that over 1 year from diagnosis, 10-30% of patients have at least one exacerbation; 67-73% of patients have a chronic intermittent course; and 27% and 29% of patients develop strictures or penetrating disease, respectively (2-6). For refractory CD or CD complicated by perforation, intestinal obstruction, stenosis or fistulae, patients frequently require bowel surgery (3;6-8).

Considerable clinical and experimental evidence exists to demonstrate that an altered immune response to commensal enteric bacteria in a genetically susceptible host plays a key role both in the development and persistence of the intestinal inflammation present in CD (9-11). Recent evidence indicates the presence of characteristic changes in the biostructure of the fecal microbiota in CD patients (12). Additionally, fecal microbiota of CD patients is unstable over time as compared with healthy subjects (13), with increased Enterobacteria and decreased density of beneficial bacteria such as *Firmicutes* (in particular *F. prausnitzii*), *Bifidobacteria*, and *Lactobacilli* (13-16). Furthermore, the correlation between the quantification of *E. coli* in ileal biopsies and the extent of disease activity in CD patients, coupled with the ability of CD-associated *E. coli* to demonstrate pathogen-like adherent and invasive behaviors in cultured cells, support the role of *E. coli* in the inflammatory process (17;18).

Rifaximin is an oral, minimally absorbed, non-systemic, antibacterial agent that exerts its activity in the intestinal lumen. By decreasing the triggers of immune activation as well as enteric inflammatory response, rifaximin may reduce the uncontrolled immune response to enteric bacteria, without the safety concerns associated with systemic broad spectrum antibiotics, including metronidazole and ciprofloxacin.

The use of rifaximin in the treatment of CD is supported by recent microbiologic and pharmacodynamic evidence which suggests both antibacterial and anti-inflammatory effects as mechanisms of action as outlined below:

Antibacterial effect and impact on intestinal microbiota:

- Rifaximin is active against the bacteria that have been investigated as possible pathogenic agents for CD.
- Rifaximin induces in enteroaggregative and enterotoxigenic E. coli a loss of virulence factors such as enterotoxins, surface adhesion factors and matrix metalloproteinase-9 (MMP-9), and changes in epithelial cell physiology associated with changes in bacterial attachment/internalization (19;20).
- Rifaximin did not alter the overall structure of human colonic microbiota, but caused an increase in concentrations of Bifidobacterium, Atopobium and F. prausnitzii, all beneficial bacteria, as shown by a supportive in vitro study using a continuous culture colonic model system to analyze the impact of rifaximin administration on the fecal microbiota of patients affected by colonic active CD (21).

Host effects of Rifaximin:

- Rifaximin affects bacterial translocation to mesenteric lymph nodes (22).
- Rifaximin induced a down-regulation of pro-inflammatory cytokines in both in vitro (20;21) experiments and animal models [trinitrobenzene sulfonic acid (TNBS)-induced colitis]. Rifaximin-induced inhibition of cytokine production protected animals against the development of colitis (23).
- Data indicate that the anti-inflammatory activity of rifaximin is due to its gut-specific human pregnane-X-receptor (PXR) activation (23). Rifaximin activation of PXR induces the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) mediated expression of pro-inflammatory factors (24;25). The down-regulation of NF-κB target genes is coupled with an improvement in clinical symptoms of colitis (26).

1.2 Current Therapy for Crohn's Disease

There is currently no cure for CD. The choice of therapy depends on the anatomical location of the disease, disease severity, and goals of therapy which include induction and maintenance of clinical remission, treatment of infectious and other complications associated with the disease, and avoiding hospitalizations and surgeries. Current treatments for CD include 5-aminosalicylate (5-ASA) compounds, glucocorticoids, immune modulators (6-mercaptopurine, methotrexate, azathioprine), biologic response modulators (Tumor Necrosis Factor alpha (TNFα) inhibitors), and antibiotics. For mild to moderate CD, two approaches to therapy are used in the outpatient setting. Step-up therapy is a graded therapy that initially uses less potent medications (with fewer adverse effects) such as the 5-ASA drugs. If response is inadequate, more potent medications such as the immunomodulators and biologics

are added. Top-down therapy begins with more potent therapies earlier in the course of the disease. Induction of remission for patients in an acute flare is typically achieved using 5-ASA drugs, antibiotics (see below), and/or a glucocorticoid. Patients with severe or fulminant disease are treated aggressively with available pharmacologic agents, bowel rest, parenteral nutrition, and intravenous glucocorticoids.

Antibiotics, primarily metronidazole and ciprofloxacin, are used to treat complications of CD such as perianal disease, small intestinal bacterial overgrowth, postoperative infections, toxic colitis, and secondary infections such as *Clostridium difficile* (*C. difficile*). Given the association between enteric bacteria and CD as noted above, antibiotics have been evaluated as primary therapy for active CD. Metronidazole, a broad spectrum antibiotic with activity against enteric anaerobes, and ciprofloxacin, a broad spectrum antibiotic with activity against aerobic bacteria, have been investigated in several randomized, controlled trials. Results from these trials show that metronidazole given alone or with ciprofloxacin for 12 to 16 weeks is better than placebo, and comparable to methylprednisolone and sulfasalazine at reducing the CDAI score in patients with mild to moderate CD; however, it has been less effective than methylprednisolone at inducing clinical remission (26-29). Ciprofloxacin administered alone for up to 6 weeks has shown similar efficacy to mesalazine at inducing clinical remission (56% and 55%) in patients with mild to moderate disease. Early clinical evidence indicates that metronidazole may be more effective in patients with colonic disease (27;30-32). Metronidazole was more effective than steroids at reducing symptoms of CD including abdominal pain, diarrhea, fever, and general well-being (22). A retrospective review of patients with CD receiving rifaximin 600 mg/day for a median duration of 16.6 weeks demonstrated clinical improvements in CDAI score (33). While the efficacy of antibiotics supports the hypothesis that colonic flora contribute to the etiology of CD, both metronidazole and ciprofloxacin are potent broad spectrum antibiotics with significant side effect profiles and high systemic exposures.

1.3 Rifaximin DR Background

Rifaximin Delayed Release (Rifaximin DR) tablets contain a new pharmaceutical formulation that has been designed to release the active drug following passage through the stomach, and to achieve a homogeneous distribution of rifaximin in the intestinal tract. The intent of the formulation is to provide uniform coverage of the active drug in the intestinal lumen, and to maximize contact with the intestinal mucosa.

1.4 Clinical Experience with Rifaximin

A summary of the clinical studies conducted with rifaximin are provided in the Investigator's Brochure.

Rifaximin DR tablets were described as Extended Intestinal Release (Rifaximin EIR) tablets in previously conducted studies. The release descriptor was changed to 'delayed release' to reflect conventional standard dosage form terminology and the release rate of the drug product from the formulation.

Three pharmacokinetic studies with Rifaximin EIR 400 mg tablets (RETIC/01/06, RETIC/02/06 and RETIC-PK/004/2009) and one supportive study with an 800 mg sachet formulation (CCRU-01514) have been completed to assess bioavailability.

RETIC/01/06 was an open label, randomized cross-over study that assessed the effect of a high-fat breakfast on the bioavailability of a single 1200 mg dose of Rifaximin EIR (tablet formulation), compared to the fasted state in healthy volunteers. Eighteen subjects (9 males and 9 females) were randomized. All subjects received the treatment both in fasting situation and after food. The wash-out period between the two treatments was 8 days. Administration in the fasted and fed state produced similar results in terms of mean C_{max} (standard deviation [SD]) [5.1 (3.8) and 4.4 (2.9) ng/mL, respectively], mean AUC_t [11.3 (8.8) and 10.2 (6.0) ng·h/mL, respectively] and median T_{max} (1 and 1.5 hours, respectively). In addition, the administration of Rifaximin EIR with food did not affect the urinary excretion, which represented < 0.02% of the dose in both conditions. The low systemic absorption was confirmed by a study in healthy subjects (N=9) administered Rifaximin EIR 800 mg (sachet) as a single dose (CCRU-01514).

The very low absorption of rifaximin was also observed in patients with active CD (RETIC/02/06). Eighteen patients with active CD (Harvey Bradshaw index of ≤ 7) and no concomitant treatment with other antibiotics (from the week before screening), or oral and rectal steroids (less than 30 days prior to screening) received a single oral dose of 1200 mg (3 x 400 mg) Rifaximin EIR tablets. Rifaximin peak concentration in plasma was reached on average at 1.8 hours. The C_{max} (SD) averaged 11.8 (10.3) ng/mL and mean AUC_{0-t} (SD) was 47.8 (30.9) ng·h/mL.

An open-label study was performed to assess the bioavailability of a repeat dose of 1200 mg (3 x 400 mg) Rifaximin EIR tablets administered twice daily (total daily dose 2400 mg) for 7 days in 12 (10 evaluable) active CD patients (RETIC-PK/004/2009). On Days 1 and 7, only the morning dose was administered. Systemic exposure to rifaximin was low after both single [C_{max} (SD) = 7.8 (3.5) ng/mL; AUC_{0-t} (SD) =34.6 (19.4) ng.h/mL] and repeat dosing [C_{max} (SD) = 6.1 (2.4) ng/mL; AUC_{0-t} (SD) =41.4 (17.4) ng.h/mL). Steady-state was reached by Day 3 of multiple dosing with a minimal extent of accumulation (RC = 1.42). The amount of rifaximin excreted in urine (cumulative urinary excretion ranging from 0.008 to 0.0136% of the administered dose) confirmed the low absorption.

Two Phase 2 pilot/proof of concept studies (GRACE 01 and GRACE 02), and a Phase 2 dose-range finding study (RETIC/03/06) have been completed; a sachet dosage form of Rifaximin

EIR was used in GRACE 01 and 02, and the present formulation was used in RETIC/03/06. GRACE 01 was a placebo controlled study in 83 mild to moderate CD patients that evaluated Rifaximin EIR 800 mg QD and BID versus placebo; GRACE 02 was an uncontrolled study that evaluated Rifaximin EIR 800 mg QD and BID. Efficacy was evaluated primarily by the rate of clinical remission defined as CDAI score < 150 points after 12 weeks of therapy. Given the small number of patients in both studies, and the uncontrolled design of GRACE 02, neither study met the primary endpoint; data did support potential efficacy in the 800 mg BID regimen.

The current tablet formulation of Rifaximin EIR was evaluated in a Phase II dose range finding study in 402 patients with an acute flare of CD (RETIC/03/06). Patients with a CDAI between 220 and 400 points were randomized to 4 treatment groups: Rifaximin EIR 400 mg twice a day, Rifaximin EIR 800 mg BID, Rifaximin EIR 1200 mg BID or placebo BID for 12 weeks. Patients who achieved clinical remission at the end of the treatment period, defined as CDAI score <150 points, were admitted to a 3-month follow-up phase. Patients were allowed to continue stable doses of oral 5-ASA, mercaptopurine, azathioprine, and/or methotrexate as concomitant therapies throughout the study (up to 12 weeks), while the use of antibiotics and oral, intravenous, and rectal steroids was not permitted.

As add-on therapy (83% of enrolled patients were treated with stable doses of 5-ASA and/or methotrexate, azathioprine and mercaptopurine), Rifaximin EIR 800 mg twice a day was statistically superior to placebo in inducing clinical remission (CDAI < 150 points) after 12 weeks of therapy ($p = 0.007$) and maintaining remission for three months after Rifaximin EIR was stopped ($p = 0.02$).

Headache (6% of patients), CD symptoms (6% of patients), nausea (4% of patients), flatulence (2% of patients), nasopharyngitis (2% of patients), and fever (2% of patients) were the most commonly reported drug-related AEs. One case of *C. difficile* infection was diagnosed 20 days after the end of the treatment period in a patient who received Rifaximin EIR 800 mg twice daily. A sudden death during the follow-up period, caused by acute massive bilateral pulmonary edema, was reported in a patient with preexisting concomitant arrhythmia. The death was assessed as unlikely related to the study drug. No clinically significant changes in the results of safety laboratory tests were observed in any study group.

In addition to the studies noted above for Rifaximin EIR, rifaximin has been studied in approximately 5000 subjects in multiple clinical studies in irritable bowel disease (IBS) (N = 1103); and in other therapeutic areas including treatment of travelers' diarrhea (N = 593), travelers' diarrhea prophylaxis (N = 820), acute hepatic encephalopathy (N = 152), and recurrence of hepatic encephalopathy (N = 348). In addition, there is over 20 years of post-marketing experience with the drug.

1.5 Study Rationale

Crohn's disease is a chronic, relapsing, remitting, systemic disease which may result in transmural inflammation of the gastrointestinal tract. Bacteria might be involved in the development and persistence of inflammation in patients with CD. Rifaximin has been shown to induce in enteroaggregative and enterotoxigenic *E. coli* a loss of virulence factors such as enterotoxins, surface adhesion factors and MMP-9, and changes in epithelial cell physiology associated with changes in bacterial attachment/internalization. Rifaximin DR is an oral, minimally absorbed, non-systemic, antimicrobial agent that exerts its effects on bacteria in the intestinal lumen. By decreasing the triggers of immune activation as well as enteric inflammatory response, rifaximin may reduce the uncontrolled immune response to enteric bacteria, without the safety concerns associated with systemic broad spectrum antibiotics. In a large Phase 2 dose-ranging study, a Rifaximin EIR regimen of 800 mg twice daily for 12 weeks induced remission in patients with mild to moderate CD, and was generally well tolerated. Given the need for safe and effective alternatives to immunomodulator and biologic therapy for CD in patients with mild to moderate disease, this Phase 3 trial will be conducted to assess the viability of Rifaximin DR for the treatment of CD.

Rifaximin is a semisynthetic antibiotic of the rifamycin class. Rifaximin is, however, unique in this class due to its gut-targeted activity and minimal systemic absorption. In vitro, rifaximin binds to the beta subunit of the bacterial DNA-dependent RNA polymerase to inhibit bacterial RNA synthesis, resulting in its classification as a broad spectrum antibiotic. However, in vivo, rifaximin does not appear to affect to a clinically significant extent the numbers or diversity of the endogenous enteric bacteria at therapeutic doses that have been tested.

The clinical experience with rifaximin is extensive, having been commercially available since 1987 following its initial approval in Italy. Today rifaximin is approved and in use in over 35 countries for a number of gastrointestinal (GI) indications which are responsive to its gut-targeted effects. There are more than 800 publications involving rifaximin in the scientific literature, including approximately 100 preclinical and approximately 200 clinical study reports. Rifaximin has also been extensively studied in controlled clinical studies with a total of approximately 5,000 subjects enrolled. Two clinical development programs have resulted in approvals in many of the markets in North America and Europe and include treatment of travelers' diarrhea and the prevention of overt hepatic encephalopathy recurrence. Additionally, there is positive data from prophylaxis of travelers' diarrhea (PRO3 study, Salix data on file) and *C. difficile* infection studies (Study RFCL3001, Salix data on file). Rifaximin possesses a strong safety record and adverse events are well-characterized, generally mild, and similar to placebo.

Crohn's disease is the fourth major development program that has been undertaken with rifaximin. Rifaximin DR has been developed in order to provide a formulation of rifaximin

that exerts its targeted effects on bacteria throughout the small and large intestinal lumens. By decreasing the triggers of immune activation as well as enteric inflammatory response, rifaximin may reduce the uncontrolled immune response to enteric bacteria, without the safety concerns associated with systemic broad spectrum antibiotics. The rationale for Rifaximin DR in the treatment of CD is based on its three plausible mechanisms of action. Rifaximin affects gut bacteria and reduces bacterial products that negatively affect the host. It may also up-regulate gut detoxification mechanisms and decrease the inflammatory response mechanisms of the host to bacterial products. Bacteria have been purported to be involved in the development and persistence of inflammation in patients with CD. Finally, rifaximin impacts both the bacterial and host response and the bacteria host interface. It has been shown to induce in enteroaggregative and enterotoxigenic *E. coli* a loss of virulence factors such as enterotoxins, surface adhesion factors and MMP-9, and changes in epithelial cell physiology associated with changes in bacterial attachment/internalization.

Rifaximin DR presents a unique paradigm in the treatment of mild to moderate CD. The proposed dosing for Rifaximin DR will remain constant from the induction phase through the long term treatment phase with no reduction in dose required. Unlike biologic or corticosteroid therapy, there is no known suppression of the host immune system associated with the use of Rifaximin DR. In a large Phase 2 dose-ranging study, the delayed release formulation of rifaximin (also called Rifaximin EIR) 800 mg, taken twice daily for 12 weeks induced remission in patients with mild to moderate CD, and was generally well tolerated.

1.6 Primary Endpoint Development for the United States

The primary endpoint for this study was developed in collaboration with the United States (US) Food and Drug Administration (FDA). In discussions with Salix, the FDA has indicated that use of the CDAI as the primary endpoint in CD trials will no longer be acceptable. It is now recommended that a co-primary endpoint for CD studies, as defined during the Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT II) meeting, be used to assess clinically meaningful outcomes for both symptoms and changes in the appearance of the inflamed ileocolonic mucosa.

After further discussions with the FDA and several key opinion leaders regarding the best way to meet these recommendations, Salix developed responder criteria based on the validated Short CDAI (34) and data from a previous CD study conducted with rifaximin (Phase 2 dose-range finding study RETIC/03/06). Symptoms included in the short CDAI were “abdominal pain” and “diarrhea frequency”.

Assuming that a CDAI score of < 150 points always reflects the true disease activity of clinical remission in Crohn’s disease, Salix developed a symptom index for Crohn’s disease to assess a clinically significant “symptomatic response.” The following points were used to assess symptomatic activity in Crohn’s disease when a CDAI score of < 150 points is considered the “gold standard”:

- Sensitivity evaluates how well a test is at detecting a positive response, i.e., symptom remission.
- Specificity estimates how likely subjects without clinical remission (i.e., CDAI score of ≥ 150 points) can be correctly ruled out based on the test.
- Accuracy measures how correct a diagnostic test identifies and excludes a given condition (e.g., CDAI < 150 points).

Using the points outlined above, the level of the symptom measures (liquid/very soft stools and abdominal pain) were determined to be sufficient to define symptomatic remission.

An analysis of the data from the Phase 2 CD study conducted with rifaximin was performed in order to determine liquid/very soft stool counts for subjects who had clinical remission and subjects who did not achieve clinical remission based on a CDAI score of < 150 points. The receiver operating characteristics (ROC) curve analysis for the diagnosis of clinical remission by liquid/very soft stool counts showed an area under the ROC curve value of 0.79. The area under the ROC curve value indicated that liquid/very soft stool count had good accuracy in predicting clinical remission based on a CDAI score of < 150 points. Subsequently, the number of liquid/very soft stools was used to identify the cut-points that resulted in the optimal balance of sensitivity, specificity and accuracy for predicting a CDAI score of < 150 points. The data indicated a cutpoint of 10 as optimal. Thus, for liquid/very soft stools, subjects with a weekly total of 10 or less will be classified as responders.

Additional analysis produced a responder definition for abdominal pain. A responder for abdominal pain is based on a daily rating (score) of ≤1.

A responder, based on the Salix endpoint, will meet the criteria for liquid/very soft stools AND abdominal pain in a given week.

The Simple Endoscopic Score for Crohn's Disease (SES-CD) was chosen as the validated measurement of endoscopic appearance because it correlated well with the more complex Crohn's Disease Endoscopic Index of Severity (CDEIS). While the CDEIS has been used for endoscopic scoring of CD lesions for 20 years, it is not commonly used in clinical practice because it is complicated and time-consuming (35). Salix has determined that a decrease in the SES-CD score of at least 3 points is clinically meaningful based on the analysis of the SONIC trial data in Crohn's disease (36). Their analysis included an evaluation of endoscopic response in patients with baseline SES-CD scores of ≥ 7 , and concluded that endoscopic response (defined as a decrease from baseline in SES-CD score of at least 50% after 26 weeks of treatment) could predict patients most likely to achieve corticosteroid-free clinical remission after 50 weeks of treatment. The proposed 3-point change in SES-CD in this study is consistent with the results of the SONIC analysis in predicting corticosteroid-free clinical remission and reflects an approximate 50% reduction in the minimum SES-CD

baseline score at study entry of 7. Whereas endoscopic response, defined as a reduction in the SES-CD score of at least 3 points, reflects a clinically significant improvement in ileocolonic inflammation, there may still be inflammation present. Endoscopic remission has been defined as an absence or near absence of endoscopically evident inflammation as reflected in SES-CD score of 0 to 2 (37).

In order to fully assess for the presence of ileocolonic Crohn's disease and calculate an accurate SES-CD score, the endoscopist must attempt to intubate and visualize the terminal ileum in order to determine presence and extent of disease during each ileocolonoscopy. To reduce the potential for bias or variability in endoscopy scoring, blinded central reading will be utilized to determine the SES-CD scores for all ileocolonoscopies obtained during the study. As such, every effort must be made at each procedure to fully visualize each segment of the terminal ileum and colon to facilitate central reading of the recorded procedures. The rate of withdrawal of the colonoscope during the procedure should also be sufficiently slow as to allow for adequate visualization and scoring of each segment in the video recording by a central reader. Strictures that do not permit further passage of the colonoscope should be annotated as such.

The co-primary efficacy endpoints for induction of clinical remission with endoscopic response are defined by

- 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.

Similarly, there will be two key co-secondary endpoints of efficacy assessed 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.

In the Phase 3 studies Salix is conducting, these endpoints will be evaluated for responsiveness (i.e., demonstrate the ability to detect clinically meaningful change in disease activity indexes of CD, for example full CDAI) and validity (i.e., demonstrate correlations

with other measures of disease activity indexes of CD). These attributes are consistent with recommendations in the published FDA Guidance for Industry on the use of patient-reported outcomes (2009) (38).

2.0 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 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.

2.1.2 Secondary Objectives

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.

2.2 Endpoints

2.2.1 Primary Efficacy Endpoints

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

2.2.2 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. 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.

2.2.3 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 8.6.2) to the liquid/very soft stool component of the co-primary endpoint during the 52-Week Treatment Period.
- Time until durable response (See Section 8.6.2) 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.

2.2.4 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.

2.2.5 Exploratory Assessments

Exploratory assessments will include:

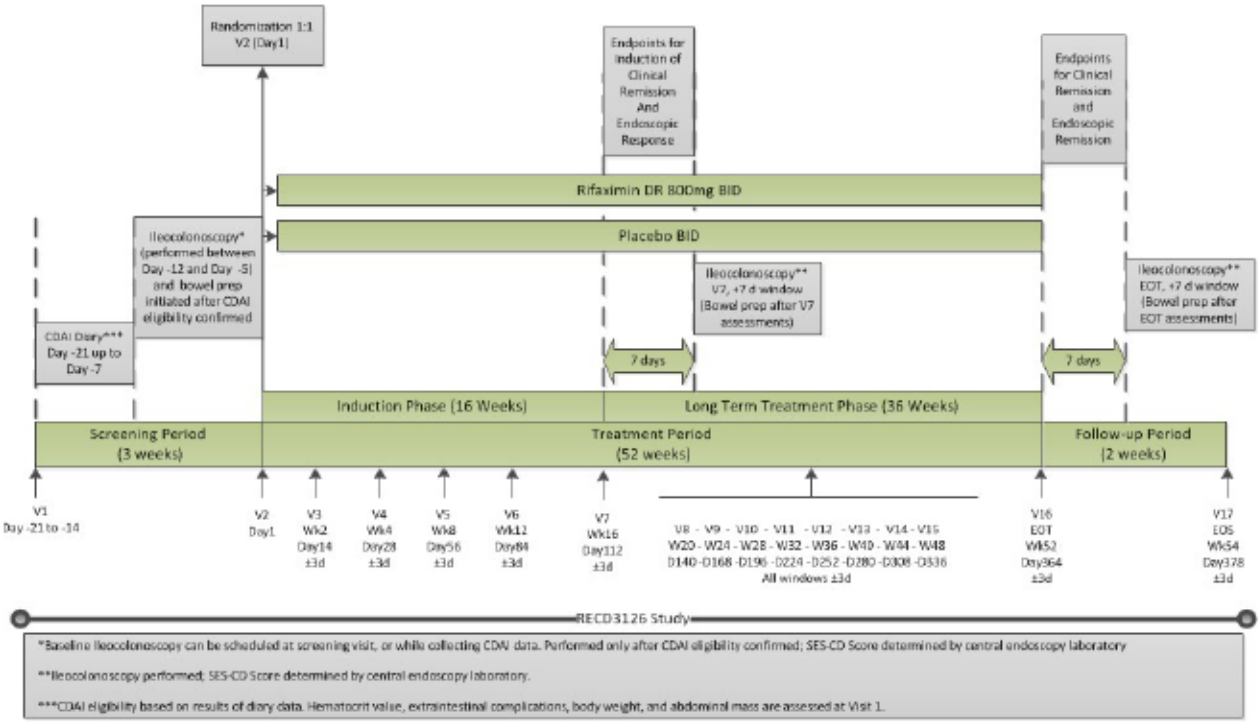
- Characterization of stool microbiota at baseline and after 16 and 52 weeks of treatment.
    - Baseline and post-treatment bacterial DNA isolated from stool for 16S rRNA gene amplification.
    - Descriptive characterization of bacteria in stool by:
        - Isolation and identification of selected Gram-negative 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.

3.0 INVESTIGATIONAL PLAN

3.1 Overview of Study Design

RECD3126 is a double-blind, placebo-controlled, parallel-group, multicenter, multiregional, 52-week study 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



3.2 Rationale for Proposed Study Design

The design of Study RECD3126 including the 52-week Treatment Period assessing both induction of clinical remission with endoscopic response at Week 16 and clinical remission with endoscopic remission at Week 52, the co-primary endpoints selected for induction and the co-measures of efficacy for the Long Term Treatment phase are consistent with regulatory guidance (FDA meeting advice/minutes with Salix/Alfa Wassermann), and the clinical management of patients with Crohn's disease.

Endpoint development is provided in Section 1.6.

3.3 Treatment Assignment/Randomization

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. Treatment groups are as follows:

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

3.4 Procedures for Breaking the Blind

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. To discuss breaking of the blind or to break the blind, please contact the study manager at Salix Pharmaceuticals, Inc. by using the following contact information:

Clinical Project Manager
Rifaximin DR RECD3126 Study
Salix Pharmaceuticals, Inc.
8510 Colonnade Center Drive
Raleigh, NC 27615
[redacted]

For sites outside the USA and Canada:
See your Study Reference Manual for your country specific information.

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.

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

A subject will be eligible for inclusion in this study if he/she meets all of the following criteria:

1. Subject is ≥ 18 years of age at Screening.
2. Subject is male or female.

   Females of childbearing (reproductive) potential must have a negative serum pregnancy test at screening and agree to use an acceptable method of contraception throughout their participation in the study. Acceptable methods of contraception include double barrier methods (condom with spermicidal jelly or a diaphragm with spermicide), hormonal methods (e.g., oral contraceptives, patches or medroxyprogesterone acetate), or an intrauterine device (IUD) with a documented failure rate of less than 1% per year. Abstinence or partner(s) with a vasectomy may be considered an acceptable method of contraception at the discretion of the investigator.

   NOTE: Females who have been surgically sterilized (e.g., hysterectomy) or who are postmenopausal (total cessation of menses for > 1 year) will not be considered "females of childbearing potential".
3. Subject has moderate, non-fistulizing Crohn's disease in the ileum and/or colon as defined by a CDAI score of ≥ 220 and ≤ 450 points prior to randomization; and a SES-CD score of ≥7. The SES-CD score will be calculated using the baseline ileocolonoscopy performed during the Screening Period.

   NOTE: Endoscopists from the Central Endoscopy Laboratory will determine whether the subject meets the SES-CD inclusion criterion. Endoscopists performing the procedures should ensure that all areas of the colon, including the terminal ileum, are adequately visualized as to ensure that a central reader can make a determination of the SES-CD score based on the video recording of the procedure. Strictures that do not permit further passage of the colonoscope should be annotated as such.
4. During the Screening Period, the subject has the following average daily scores for abdominal pain and average number of liquid/very soft stools :
   - An average daily score of > 1.5 for abdominal pain (from CDAI Item 2); and
   - An average daily count of > 1.5 for liquid/very soft stools (from CDAI Item 1). Liquid/very soft stool will be defined as a consistency of Type 6 or Type 7 on the BSFS.
5. Subject is capable of understanding the requirements of the study, is willing to comply with all study procedures, and demonstrates ability to comply with the study electronic

systems (including access to Wi-Fi) required to record Crohn's disease symptoms and CDAI components.

6. Subject understands the language of the informed consent form (ICF), and is capable and willing to sign the informed consent form.

4.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if he/she meets any of the following criteria:

1. Subject has a diagnosis of ulcerative or indeterminate colitis.
2. Subject has a diagnosis of Celiac Disease.
3. Subject has had bowel surgery within 12 weeks prior to screening and/or has surgery planned or deemed likely for Crohn's disease during the study period.
4. Subject has had more than one segmental colonic resection (i.e. more than one of the following: right hemicolectomy, left hemicolectomy, transverse colectomy, ileocecal resection, sigmoid colectomy).
5. Subject has presence of an ileostomy or colostomy.
6. Subject has known fixed symptomatic stenosis/stricture of the small or large bowel.
7. Subject has had more than 3 small bowel resections, or symptoms associated with short bowel syndrome.
8. Subject has current evidence of peritonitis.
9. Subject had history or evidence of colonic mucosal dysplasia.
10. Subject had history or evidence of adenomatous colonic polyps that have not been removed. NOTE: Subjects cannot be enrolled if any adenomatous polyp(s) removed during the screening ileocolonoscopy has evidence of dysplasia or malignancy.
11. Subject has evidence of hepatic dysfunction, viral hepatitis, or current or chronic history of liver disease including non-alcoholic steatohepatitis (NASH) as well as liver function tests (LFTs) with values ≥ 1.5 times the upper limit of normal (ULN) for any of the following LFTs: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or bilirubin (except isolated elevation of unconjugated bilirubin due to Gilbert's Syndrome) at Screening.

    NOTE: Laboratory tests needed for eligibility as related to Inclusion and Exclusion criteria can be repeated once before considering a subject a Screening failure.
12. Subject has diabetes (Type 1 or Type 2) that is poorly controlled in the opinion of the investigator, or has had an HbA1c > 12% within 3 months prior to Screening or at the Screening Visit.

13. Subject has history of the following conditions per Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5):
    - a major psychiatric disorder (including major depression or psychosis)
    - alcohol or substance abuse within 24 months prior to signing the informed consent
14. Subject has a history of seizure disorders.
15. Subject has renal disease manifested by elevations in serum creatinine and/or blood urea nitrogen concentrations of ≥1.5 times the ULN.
16. Subject has unstable cardiovascular or pulmonary disease, categorized by a worsening in the disease condition that requires a change in treatment or medical care within 30 days prior to randomization.
17. Subject has an active malignancy within the last 5 years (exceptions: basal cell carcinomas of the skin, or if female, in situ cervical carcinoma that has been surgically excised).
18. Subject has donated blood or blood products within the past 4 weeks prior to randomization.
19. Subject has known varicella, herpes zoster, or other severe viral infection within 6 weeks of randomization.
20. Subject has known human immunodeficiency virus (HIV) infection.
21. Subject has a positive stool test for *Yersinia enterocolitica*, *Campylobacter jejuni*, *Salmonella*, *Shige*lla, ovum and parasites, and/or *Clostridium difficile*. NOTE: Results of stool tests must be confirmed as negative prior to randomization.
22. Subject has a history of tuberculosis infection and/or has received treatment for a tuberculosis infection. If subject has had a previous positive test for tuberculosis antigen then they must have a current negative chest X-ray to be eligible.
23. Subject used any biologic (e.g., TNFα inhibitor, natalizumab, or similar drugs) within 12 weeks prior to randomization.
24. Subject is unwilling to be tapered off corticosteroids by Week 8 of the Treatment Period or the subject is known by the Investigator to be steroid dependent. NOTE: Use of oral corticosteroids for the treatment of active Crohn's disease is permitted at study entry. Permitted medications are: prednisone if the dose is ≤ 20 mg (or equivalent) per day or budesonide if the dose is ≤ 9 mg/day. The subject must be tapered off the corticosteroids as noted above.
25. Subject used cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, or similar drugs within 8 weeks prior to randomization.
26. Subject used any oral or intravenous antibiotic including rifaximin, rifampin or any drugs in the rifamycin group, within 4 weeks prior to the screening visit.

27. Subject had rectal administration of 5-ASA or corticosteroid enemas/foams/suppositories within 2 weeks prior to screening visit.
28. Subjects used tube or enteral feeding, an elemental diet, or parenteral alimentation within 2 weeks prior to Screening Visit. Note: dietary supplements (e.g. Boost, Ensure) are allowed.
29. Subjects who are planning to begin taking probiotics or similar supplements at or after the Screening Visit, or subjects who began using these supplements within 2 weeks prior to the Screening Visit. NOTE: These supplements are allowed if the subject has been on a stable dose for 2 weeks or more prior to the Screening Visit and the subject plans to remain on that dose throughout the study. The subject should not introduce any new probiotics or similar supplements for the duration of the study. Prior and current use of probiotics or similar supplements will be recorded in the subject's source documents and eCRF.
30. Subject is currently receiving warfarin or other 4-hydroxycoumarins at the Screening Visit, or has plans to initiate the medication at any time during the study.
31. Subject, if female, is currently pregnant or has plans to become pregnant at any time during the study, has a positive pregnancy test at screening or is breast-feeding.
32. Subject has a history of sensitivity to rifaximin, rifampin, rifamycin antimicrobial agents, or any of the components of Rifaximin DR.
33. Subject has used any investigational product within 30 days prior to randomization, or during the study.
34. Subject has any concurrent illness, disability or circumstance that may affect the interpretation of clinical data, could cause noncompliance with treatment or visits or otherwise contraindicates participation in this study in the opinion of the investigator.

4.3 Concomitant Therapies

4.3.1 Permitted Therapy

Subjects will be allowed to continue on the following Crohn's disease-related concomitant medications during the study.

- Oral 5-ASA drugs, if on a stable dose for at least 2 weeks prior to the screening visit (same dosage to be maintained throughout the trial).
- Antidiarrheals (e.g., loperamide) will be assessed at each visit.
- Mercaptopurine, azathioprine, methotrexate, if stable dose for at least 8 weeks prior to the screening visit (same dosage to be maintained throughout the trial).

- Oral steroids (first 8 weeks of Treatment Period only): Prednisolone or prednisone at doses of ≤ 20 mg (or equivalent) per day, or a budesonide dose of ≤ 9 mg per day are permitted. Subjects must be able to be tapered off steroids by Week 8 of the Treatment Period.

4.3.2 Prohibited Therapy

Use of the following medications is prohibited within the inclusion/exclusion specified pre-study time-frames and throughout the study unless otherwise noted:

- Corticosteroids: Parenteral and rectal steroids are prohibited from the screening visit through the end of the study.
- Any oral or intravenous antibiotic. NOTE: A short course of antibiotic to treat acute conditions (e.g., sinusitis, urinary tract infection) is permitted.
- Use of any drug from the rifamycin class at any time during study participation, including rifaximin, rifampin, rifapentine, and rifabutin. Current international trade names of rifaximin include: Alfa Normix, Colidimin, Faxinorm, Flonorm, Lormyx, Normix, Refero, Rifacol, Rifax-Aw, Rifaxan-Aw, Spiraxin, Targaxan, Tixtar, Tixteller, Xifaxan, Xifaxanta, and Zaxine.
- Any biologicals (e.g., TNFα inhibitor, natalizumab, or similar drugs)
- Cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, or similar drugs
- Rectal administration of 5-ASA or corticosteroid enemas/foams/suppositories.
- Use of tube or enteral feeding, elemental diet, or parenteral alimentation.
- Introduction of any new probiotics or similar supplements during the study.
- The introduction of any new medication for the treatment of Crohn's disease is prohibited, unless the medication is required in the Investigator's opinion as rescue medication. Subjects receiving rescue medication will be considered treatment failures but should remain in the study.

All concomitant medications, including those taken 30 days prior to screening visit, will be documented (drug name, start and stop dates, and indication) in the concomitant medication section of the CRF.

4.4 Females of Reproductive Potential

If a female subject becomes pregnant while participating in this study, the study drug will be immediately discontinued and the subject will be followed until the outcome of the pregnancy is known. The pregnancy will be reported to Salix using the guidelines provided in Section 7.7 and Section 7.8.

4.5 Premature Subject Discontinuation

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time. Subjects withdrawn from the study will not be replaced.

A subject may be discontinued from study drug treatment and/or the study for the following reasons:

- Occurrence of an AE and/or SAE, which suggests an unacceptable risk to the subject, in the judgment of the investigator, including worsening of the disease under study.
- Pregnancy (see Section 7.7 for further details).
- Subject request to withdraw.
- Sponsor decision to terminate the study.

For all cases of premature withdrawal from the study listed above or any other, the investigator must provide the reason for discontinuation on the appropriate CRF page. ***The investigator should make every attempt to obtain End of Treatment and End of Study assessments, including ileocolonoscopy.***

If treatment with investigational study drug has been prematurely discontinued, the End of Treatment assessments will be completed, and an attempt should be made to have the subject followed for 14 days after last administration of study drug to perform the End of Study assessments.

If a subject prematurely discontinues treatment with investigational drug at any time due to an AE or SAE, the End of Treatment assessments will be completed, and an attempt should be made to have the subject followed at least 14 days to perform the End of Study assessments, or until resolution or stabilization of the condition resulting in withdrawal has been confirmed.

The Investigator may discontinue individual subjects from the study at any time during the study. The investigator must provide the reason for discontinuation on the appropriate CRF page.

4.6 Study Contact Information

The investigator may deem it necessary to perform special tests, to hospitalize the subject, or to prescribe new drugs. In the event the investigator needs to consult with a Salix representative, please contact:

Clinical Project Manager
Rifaximin DR RECD3126 Study
Salix Pharmaceuticals, Inc.
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[redacted]

For sites outside the USA and Canada:
See your Study Reference Manual for your country specific information.

5.0 TREATMENT OF SUBJECTS

5.1 Formulation and Supply

Study drug will be supplied by Salix as tablets containing 400 mg Rifaximin DR or matching placebo.

Rifaximin DR will be supplied as pink, coated, oval, biconvex tablets. Each Rifaximin DR tablet will contain 400 mg Rifaximin and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, disodium edetate, hypromellose, magnesium stearate, methacrylic acid and ethylacrylate copolymer, microcrystalline cellulose, propylene glycol, red iron oxide E172, talc, and titanium dioxide.

Matching placebo will be supplied as tablets that are identical in appearance to Rifaximin DR tablets with inactive ingredients. The components used in the manufacturing of the matching placebo tables are: calcium phosphate, colloidal silicon dioxide, corn starch, disodium edetate, hypromellose, magnesium stearate, microcrystalline cellulose, propylene glycol, red iron oxide E172, and titanium dioxide.

Additional details are provided in the Rifaximin IB (39).

5.2 Packaging

Salix will supply double-blind study drug in high density polyethylene (HDPE) bottles. Each bottle will contain study drug for 32 days of therapy.

5.3 Labeling

The contents of the label will be in accordance with all applicable regulatory requirements and in the official language for each country. Each label may include, but is not limited to, the following information.

- Federal law statement: Caution New Drug-Limited by United States Law to Investigational Use (US only)
- Study number: RECD3126
- Quantity
- Dosing instructions: Take 2 tablets by mouth 2 times a day, approximately every 12 hours.
- Storage information: Store tablets at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).
- Name, address, and telephone number of the sponsor, contract research organization or investigator
- Study drug, lot number, and expiration or re-test date

- Space for recording visit number, date dispensed, and date returned
- Space for recording subject number and subject initials
- Space for recording investigator name
- "For clinical trial use only" or similar wording
- "Keep out of reach of children"

5.4 Storage and Handling

All study medication will be kept in a secure storage area with limited access. The secure storage area will be maintained under controlled temperature conditions at 20-25°C (68-77°F); excursions are permitted to 15 to 30°C (59 to 86°F).

5.5 Dosing and Dosing Schedule

Study medication will be dosed orally as two tablets twice a day (morning and evening, approximately 12 hours apart) with or without food for 52 weeks.

5.6 Rationale for Dose Selection

The current tablet formulation of Rifaximin EIR was evaluated in a Phase II dose range finding study in 402 subjects with an acute flare of CD (RETIC/03/06). Patients with a CDAI between 220 and 400 points were randomized to 4 treatment groups: Rifaximin EIR 400 mg twice a day, Rifaximin RIR 800 mg BID, Rifaximin EIR 1200 mg BID or placebo BID for 12 weeks. Subjects who achieved clinical remission at the end of the treatment period, defined as CDAI score < 150 points, were admitted to a 3-month follow-up phase. Subjects were allowed to continue stable doses of oral 5-ASA, mercaptopurine, azathioprine, and/or methotrexate as concomitant therapies throughout the study (up to 12 weeks), while the use of antibiotics and oral, intravenous, and rectal steroids were not permitted. As add-on therapy (83% of enrolled subjects were treated with stable doses of 5-ASA and/or methotrexate, azathioprine and mercaptopurine), Rifaximin EIR 800 mg twice a day was statistically superior to placebo in inducing clinical remission (CDAI < 150 points) after 12 weeks of therapy ($p = 0.007$), and maintaining remission for three months after Rifaximin EIR was stopped ($p = 0.02$). In addition, the safety and tolerability of the Rifaximin EIR 800 mg BID regimen in this study was acceptable to warrant further investigation. Based on these data, a dose of 800 mg twice a day was selected for further development.

5.7 Study Drug Accountability

Only authorized site personnel may dispense study drug. Documentation of investigational drug orders, records of study drug receipt, dispensing, and ongoing study drug inventory will be examined and reconciled throughout the study. Only subjects enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements.

Study drug reconciliation will be conducted during monitoring visits to ensure appropriate receipt, storage, dispensing, and documentation of returned study drug. Upon completion of the study, this material will be subjected to final inspection and reconciliation.

The following information will be documented regarding study drug:

- Subject number.
- Subject initials.
- Dispensing date and quantity of tablets.
- Initials of study staff dispensing drug.
- Return date and quantity of drug returned by subject.
- Compliance (%) in taking the study drug at each visit.
- Start and stop dates of study drug.

5.8 Assessment of Compliance

After study drug is dispensed, the investigator or his/her representative will count the unused study drug tablets that were returned by the subject at each visit to assess compliance. Study drug compliance will be recorded in the subject's source documentation and CRF. If the subject forgets to return unused study drug at a visit, then compliance will be confirmed after direct questioning of the subject. The investigator's judgment of compliance will be accepted. Attempts to obtain unused study drug should be made at subsequent visits or by the conclusion of the subject's participation in the trial.

6.0 STUDY PROCEDURES AND ASSESSMENTS

A schedule of assessments to be performed during the study is provided in Appendix 1: Overall Time and Events Schedule. For this study, Day 1 shall be defined as the day of randomization/baseline.

Subjects will be provided bowel prep for use prior to the ileocolonoscopies. The bowel prep will be dispensed by study staff at Visits 1, 7, and 16.

6.1 Study Schedule by Treatment Visit

6.1.1 Visit 1: Screening (Day –21 to Day -14)

Screening evaluations must begin no less than 14 days prior to the Baseline Visit (Visit 2). The following procedures will occur during this visit:

- Informed consent signed by the subject prior to performing any study evaluations or procedures.
- Assign subject identification.
- Medical history and demographic information should be recorded. Approximate date of initial diagnosis and onset of symptoms of Crohn's disease should be documented.
- Adverse events and concomitant medications.
- Inclusion/Exclusion criteria review to ensure subject qualifies for the study.
- Full physical examination including disease specific examination (including assessments for abdominal mass and extraintestinal manifestations of Crohn's disease based on CDAI– see Appendix 2).
- Vital signs (to include measurement of height and weight).
- Electrocardiogram.
- Safety laboratory tests including serum pregnancy test (hematology, blood chemistry, and urinalysis).
- Stool collection and processing NOTE: This sample is collected in part to address Exclusion Criterion 21. Microbiology results required for entry must be received before randomization. If the subject cannot produce a sample during the visit, the subject will be issued a collection kit and asked to collect a specimen at home, refrigerate it immediately and return it to the clinic a minimum of 7 days prior to visit 2.
- Provide subject instruction for daily diary completion.
- Schedule eligibility/baseline ileocolonoscopy and provide bowel prep.

- Subjects who achieve the qualifying CDAI score should have the baseline ileocolonoscopy (for eligibility SES-CD score) performed no later than Day -5.
- Schedule Visit 2

6.1.2 Visit 2: Baseline/Randomization, Week 0/Day 1

The Baseline/Randomization Visit will be performed on Day 1. There is no Day 0 in this protocol. The following assessments are to be completed at Visit 2:

Prior to dosing:

- Adverse events and concomitant medications
- Inclusion/Exclusion review to ensure subject continues to qualify for the study
- Vital signs and weight
- Disease and symptom driven physical examination (including assessments for abdominal mass and extraintestinal manifestations of Crohn's disease based on CDAI – see Appendix 2)
- Safety laboratory tests (hematology, blood chemistry, urinalysis)
- Urine pregnancy test
- Blood draw prior to first dose administration for inflammatory markers, PXR and PK
- Stool and blood collections for long-term storage
- IBDQ and WPAI-CD
- Diary Compliance Check
- Randomization

After first dose assessments:

- Study drug dispensing - first dose to be taken at the clinic under observation. The exact time of dose administration should be recorded.
- Schedule Visit 3

6.1.3 Visits 3, 4, 5, 6: Weeks 2, 4, 8, 12 /Days 14, 28, 56, 84 (± 3 days)

The following assessments are to be completed:

- Adverse events and concomitant medications
- Vital signs and weight

- Disease and symptom driven physical examination (including assessments for abdominal mass and extraintestinal manifestations of Crohn's disease based on CDAI – see Appendix 2)
- Study drug collection and dispensing. NOTE: At Visit 3 no study drug is collected or dispensed.
- Record time and date of most recent dose of study drug. This information must be obtained from the subject and should be his/her best recollection of when they took their most recent dose.
- Safety laboratory tests (hematology, blood chemistry, urinalysis)
- Blood draw for PK (Visit 6 only for PK)
- CDAI assessment (CDAI score will be calculated by EDC system)
- Review dosing and diary compliance
- Schedule the next study visit

6.1.4 Visit 7: Week 16/Day 112 (± 3 days)

The following assessments are to be completed at Visit 7:

- Adverse events and concomitant medications
- Vital signs and weight
- Electrocardiogram
- Full physical examination including disease specific examination (including assessments for abdominal mass and extraintestinal manifestations of Crohn's disease based on CDAI – see Appendix 2).
- Safety laboratory tests (hematology, blood chemistry, urinalysis)
- Urine pregnancy test
- Blood for inflammatory markers
- Stool collection and processing. NOTE: If the subject cannot produce a sample during the visit, the subject will be issued a collection kit and asked to collect a specimen at home, refrigerate it immediately, and bring it to the clinic as soon as possible.
- Stool and Blood collections for Long-term Storage
- CDAI assessment (CDAI score will be calculated by EDC system)
- IBDQ and WPAI-CD
- Review dosing and diary compliance
- Study drug collection and dispensing

- Schedule ileocolonoscopy and dispense bowel prep for ileocolonoscopy
    - Ileocolonoscopy to be performed within 7 days after Visit 7.
    - All Visit 7 procedures to be completed prior to beginning bowel prep.
- Schedule Visit 8

6.1.5 Visits 8, 9, 10, 11, 12, 13, 14, 15: Weeks 20, 24, 28, 32, 36, 40, 44, 48 /Days 140, 168, 196, 224, 252, 280, 308, 336 (± 3 days)

The following assessments are to be completed:

- Adverse events and concomitant medications
- Vital signs and weight
- Disease and symptom driven physical examination (including assessments for abdominal mass and extraintestinal manifestations of Crohn's disease based on CDAI – see Appendix 2)
- Safety laboratory tests (hematology, blood chemistry, urinalysis) with urine pregnancy test at Visit 10 (Week 28) and Visit 13 (Week 40) only; blood draw for PK at Visit 15 only
- At Visit 15 only: Record time and date of most recent dose of study drug. This information must be obtained from the subject and should be his/her best recollection of when they took their most recent dose.
- CDAI assessment (CDAI score will be calculated by EDC system)
- IBDQ and WPAI-CD at Visit 10 (Week 28) and Visit13 (Week 40) only
- Review dosing and diary compliance
- Study drug collection and dispensing
- Schedule the next study visit (Visit 15 should occur in the morning)

6.1.6 Visit 16: End of Treatment (EOT) Visit, Week 52/Day 364 (± 3 days)

The subject's final dose of study drug will be the evening before Visit 16. The following assessments are to be completed at this visit:

- Adverse events and concomitant medications
- Vital signs and weight
- Electrocardiogram
- Full physical examination including disease specific examination (including assessments for abdominal mass and extraintestinal manifestations of Crohn's disease based on CDAI – see Appendix 2).

- Safety laboratory tests (hematology, blood chemistry, urinalysis) including blood for serum pregnancy test and inflammatory markers
- Stool collection and processing. NOTE: If the subject cannot produce a sample during the visit, the subject will be issued a collection kit and asked to collect a specimen at home, refrigerate it immediately, and bring it to the clinic as soon as possible.
- Stool and Blood collections for Long-term Storage
- CDAI assessment (CDAI score will be calculated by EDC system)
- IBDQ and WPAI-CD
- Review dosing and diary compliance
- Collect unused study drug
- Schedule ileocolonoscopy and dispense bowel prep for ileocolonoscopy
    - Ileocolonoscopy to be conducted within 7 days after Visit 16.
    - All Visit 16 procedures to be completed prior to beginning bowel prep.
- Schedule Visit 17, EOS

6.1.7 Visit 17: End of Study (EOS) Visit, Week 54/Day 378 (± 3 days)

The following assessments are to be completed:

- Adverse events and concomitant medications
- Vital signs and weight
- Electrocardiogram
- Safety laboratory tests (hematology, blood chemistry, urinalysis)

6.1.8 Unscheduled Visit

The investigator may perform an unscheduled visit at any time during the study at his/her discretion. Assessments performed at an unscheduled visit should be symptom directed. At a minimum the following assessments should be performed:

- Adverse events and concomitant medications
- Vital signs and weight
- Symptom driven physical examination
- Safety laboratory tests as appropriate (hematology, blood chemistry, urinalysis)

6.1.9 Daily Diary (and/or other subject-collected data)

Electronic system diaries will be utilized to collect subject's responses to the CDAI questions (Appendix 2: Crohn's Disease Activity Index). Each subject will be instructed on the use of the Electronic diary system. Subjects will be provided secure access instructions to the Electronic diary system during the Screening Visit.

6.2 Assessment of Efficacy

Efficacy endpoints are presented in Section 2.2. Analyses of efficacy endpoints are described in Section 8.6.1.

6.2.1 Crohn's Disease Activity Index (CDAI) Score

The CDAI score is a weighted, composite index of eight items (stool frequency, severity of abdominal pain, degree of general well-being, presence or absence of extraintestinal manifestations including fistula, use or non-use of antidiarrheal agents, presence or absence of abdominal mass, hematocrit and body weight). Scores range from 0 to approximately 600 with higher scores indicating greater disease severity. Clinical (asymptomatic) remission is defined as a score of ≤ 150 points. Mild-to-moderate disease and severe disease are defined by scores of > 150 to ≤ 450, and > 450 points, respectively. The CDAI scoring system can be found in Appendix 2: Crohn's Disease Activity Index. CDAI will be evaluated at all clinic visits for the study. CDAI score will be calculated by EDC system.

6.2.2 Simple Endoscopic Score for Crohn's Disease (SES-CD)

The SES-CD is a validated instrument reflecting an endoscopist's global appraisal of mucosal lesions in Crohn's disease. The SES-CD grades lesions by location (ileum, right colon, transverse colon, left colon and rectum) using ulcer size, extent of ulcerated surface, extent of affected surface, and presence/type of narrowing. The SES-CD can be found in Appendix 4. Video recordings of ileocolonoscopies will be reviewed, and SES-CD scores will be calculated by blinded central laboratory endoscopists for the study. The independent central endoscopy readers and the central endoscopy laboratory will not be associated with any institution conducting the study.

In order to fully assess for the presence of ileocolonic Crohn's disease and calculate an accurate SES-CD score, the endoscopist must attempt to intubate and visualize the terminal ileum in order to determine presence and extent of disease during each ileocolonoscopy. To reduce the potential for bias or variability in endoscopy scoring, blinded central reading will be utilized to determine the SES-CD scores for all ileocolonoscopies obtained during the study. As such, every effort must be made at each procedure to fully visualize each segment of the terminal ileum and colon to facilitate central reading of the recorded procedures. The rate of withdrawal of the colonoscope during the procedure should also be sufficiently slow as to allow for adequate visualization and scoring of each segment in the video recording by a

central reader. Strictures that do not permit further passage of the colonoscope should be annotated as such.

6.2.3 Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is a validated 32-item questionnaire with 4 dimensions that assess bowel function, emotional status, systemic symptoms, and social function. The IBDQ can be self-administered. The total score on the index ranges from 32-224, with higher scores indicating better quality of life. A relatively good correlation exists between the IBDQ and the CDAI ($r = -0.67$; $P < 0.001$). Studies have been performed in patients with inflammatory Crohn's disease, but there is no published data on IBDQ scores of patients with primarily fistulizing Crohn's disease. See Appendix 5: Inflammatory Bowel Disease Questionnaire.

6.2.4 Work Productivity and Activity Impairment Questionnaire for Crohn's Disease (WPAI-CD)

The WPAI-CD is a questionnaire that assesses the effect of Crohn's disease on a patient's ability to work and perform regular activities. The WPAI-CD has discriminative validity and reproducibility in Crohn's disease. In addition, evaluative validity and responsiveness to clinically meaningful changes in the WPAI-CD scores have been established for Crohn's disease. WPAI-CD outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (i.e. worse outcomes). Domains evaluated are current employment, work hours missed due to Crohn's disease, work hours missed for other reasons, hours actually worked, degree that Crohn's disease affected productivity while working, and degree that Crohn's disease affected regular activities. See Appendix 6: Work Productivity and Activity Impairment Questionnaire: Crohn's Disease.

6.3 Assessment of Safety

Safety endpoints are presented in Section 2.2.4. Safety assessments will include the following:

- AEs, both reported and observed
- Vital sign measurements (seated blood pressure, pulse and oral temperature)
- Routine hematology and blood chemistry tests and urinalysis
- Electrocardiograms

6.3.1 Clinical Laboratory Tests

The following clinical laboratory tests are to be performed during the study and will be analyzed by a central, licensed clinical laboratory (except for the urine pregnancy tests). At the investigator's discretion, additional blood may be collected for clinical laboratory tests

(i.e., hematology, blood chemistry, and urinalysis) based on patient reported signs and symptoms or previous clinical laboratory test results.

Results from laboratory specimens collected during the Screening Visit must be received by the site prior to Visit 2 (Baseline/Randomization).

The clinical laboratory parameters to be evaluated are as follows:

- **Hematology**: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count.
- **Blood chemistry**: Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin (except in isolated elevation of unconjugated bilirubin), blood urea nitrogen, creatinine, uric acid, electrolytes, lactate dehydrogenase, calcium, albumin, glucose, cholesterol, and triglycerides.
- **Urinalysis**: Routine urine analysis (including but not limited to white blood cell count, red blood cell count, and protein). If there are any positive findings, microscopic examination should be performed to quantify the results.
- **Stool**: Stool testing will be performed during the screening period to identify the presence of enteric infections (e.g. Yersinia enterocolitica, Campylobacter jejuni, Salmonella, Shigella, ovum and parasite and/or Clostridium difficile) and a negative test must be confirmed for subjects prior to randomization.

6.3.2 Assessment of Inflammation Markers

Blood samples for determination of inflammatory markers will be collected at Visit 2 (Baseline/Randomization), Visit 7, and Visit 16 (EOT). Blood samples will be collected in serum-separating tubes to collect serum for inflammatory markers. After allowing blood to clot for approximately 30 minutes, the samples will be centrifuged at 1300g to separate the blood cells from serum. Serum samples will be shipped ambient (CRP) or frozen (other inflammatory markers) to the central laboratory for inflammatory marker testing. The presence of inflammatory markers (which may include CRP, IL-1β, IL-2, IL-6, IL-12, IL-13, TNF-α and endotoxin) will be analyzed using a particle based Cytometric Bead Array immunoassay at the central laboratory.

Blood samples for determination of Pregnane X Receptor (PXR) genotyping will be collected at Visit 2.

- **Blood, Blood Plasma, and Serum for Storage**: Blood, blood plasma, and serum samples will be collected at Visit 2 (Baseline/Randomization), Visit 7, and Visit 16 (EOT). Samples will be stored at ≤ -20° C at the clinical site and shipped on dry ice and stored long-term at ≤ -70°C. These samples may be used for exploratory analyses (potentially including additional inflammatory markers or PXR genotyping) to be

detailed in subsequent site-specific amendments or sub-studies. Subjects will be advised of and must consent to blood and blood plasma collection for storage.

6.3.3 Stool Sample Collection and Testing

Stool sample collection should be performed for the following visits: Screening, Visit 7, and Visit 16 (EOT). Fresh stool samples will be collected at each of the above visits whenever possible. If the subject cannot produce a sample during the visit, the subject will be issued a collection kit and asked to collect a specimen at home, refrigerate it immediately, and bring it to the clinic as soon as possible. Stool samples will be aliquoted into 2-mL polypropylene cryovials, stored at ≤ -20° C at the clinical site, shipped on dry ice and stored long term at ≤ -70°C. Stool samples will be used for the following:

- **Safety Testing for *C. difficile***: A stool sample for analysis of C. difficile for Toxins A & B will be collected at Screening, Visit 7, and Visit 16. Testing will be performed by enzyme immunoassay (EIA).
    - Stool samples testing positive for C. difficile Toxin B will be cultured and tested for resistance to select antibiotics.
- **Fecal Calprotectin Immunoassay**: A stool sample for assay of fecal calprotectin will be collected at Screening, Visit 7, and Visit 16. Stool samples will be collected in sterile specimen cups and stored immediately at ≤ -20° C. Samples will be shipped frozen on dry ice to the central laboratory for testing. Testing will be performed by immunoassay.
- **Microbiota Characterization**: Susceptibility Testing: In a subset of the study population (approximately 10%), the susceptibility of the stool microbiota to rifaximin, rifampin, and other selected antibiotics of clinical interest will be characterized. Stool samples will be inoculated onto various media to identify organisms. Stool cultures will identify and isolate yeast as well as selected bacteria, chosen to incorporate the most prevalent species of intestinal bacteria. Bacteria will be identified and characterized by morphology and physical tests, with identity confirmed with molecular identification systems. Yeast will be identified if present in stool, but will not be tested further. Bacterial sensitivity testing will be performed by broth microdilution (per Clinical Laboratory Standards Institute (CLSI) document M7-A8) for aerobic bacteria and by agar dilution for anaerobic bacteria using clinically relevant antibiotics. Duplicate samples of all isolates and stool aliquots will be stored to allow for potential future analysis.
- **Microbiota Characterization**: Composition, Diversity, DNA Sequencing: In a subset of the study population (approximately 10%), the intestinal microbiota from stool samples will be characterized in terms of composition and diversity, as well as sequencing for specific organisms of interest. Bacterial DNA will be isolated from fecal samples, and the hyper-variable regions of the 16S rRNA gene will be amplified using two-step PCR sequencing technology. All stool samples and DNA isolates will be stored to allow for potential future analysis.

- **Long-term storage for future exploratory analysis.** Subjects must be advised of and provide consent to this stool collection for storage. Additional substudies may be defined in the future.

6.3.4 Urine and Serum Pregnancy Tests

Serum pregnancy tests will be performed for all females of childbearing potential and those who have had a tubal ligation at Visit 1 (Screening) and Visit 16 (EOT). Urine pregnancy tests will be performed for all females of childbearing potential and those who have had a tubal ligation at Visit 2 (Baseline/Randomization) prior to randomization and at Visit 7, Visit 10, and Visit 13. The Visits 1 and 2 pregnancy tests must be confirmed as negative before the administration of study drug.

6.3.5 Safety Monitoring for *C. difficile*

Stool samples must be collected and tested for C. difficile Toxin B gene (tcdB) using real-time polymerase chain reaction (PCR) method for any subject who has worsening, acute diarrhea and abdominal pain during the study, defined by:

- Subject had at least 3 unformed (loose or watery) stools in the last 24 hours.

AND

- Subject has at least 1 other sign of enteric infection present, such as fever, nausea/loss of appetite, vomiting, severe abdominal pain or discomfort.
    - Stool samples testing positive for *C. difficile* Toxin B, will be cultured and tested for resistance to select antibiotics.

All positive test results will be recorded as an adverse event.

6.3.6 Adverse Events

The investigator is responsible for the detection and documentation of events that meet the definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol (Section 7.0). Assessments of occurrences of AEs or SAEs should be conducted during each study visit or as reported by the subject outside of scheduled visits. In order to fulfill international safety reporting obligations, the investigator should include in his or her assessment any AEs resulting from study participation regardless of relation to study drug (e.g., complications resulting from the taking of a blood sample).

6.3.7 Physical Examination

A full physical examination will be performed during Visit 1, Visit 7, and Visit 16 (EOT). A symptom-directed physical examination will be performed at other visits. All physical exams will include the assessments required for CDAI calculation.

6.3.8 Vital Sign Assessments

Vital sign assessments (sitting blood pressure, pulse, and temperature) will be performed at each clinic visit. Vital signs will be measured after the subject has been seated for 5 minutes. Weight will be measured at each clinic visit. Height will only be collected at Visit 1.

6.3.9 Electrocardiogram (ECG)

A standard 12 lead ECG (at rest) will be performed on all subjects at Visits 1, 7, 16 and 17. The baseline ECG obtained at Visit 1 will be performed in triplicate (i.e., three 12-lead ECGs obtained 3 minutes apart). A print out of the ECG reports must be available in the source documentation. The investigator will evaluate if the patient should enter the study based on any findings on ECG.

6.4 Other Assessments

6.4.1 Medical History

Each subject's relevant medical history is to be recorded in source documents and the appropriate CRF pages. Medical history (including past enteric infections) will include a detailed history of the subjects CD (e.g., date of onset, surgical history, location of disease, etc.).

6.5 Pharmacokinetics

Samples will be collected at Visit 2, at Visit 6, and at Visit 15. Collection and recording of the date and time of the last dose administered prior to the visit is required at each visit in order to most accurately estimate rifaximin exposure. Steady-state rifaximin concentrations are anticipated for collections at Visits 6 and 15.

Statistical analysis (including exploratory data analysis and population modeling) will be described in detail in the Pharmacokinetics Statistical Analysis Plan (PSAP) document. The PSAP will be finalized prior to the pharmacokinetic analysis.

7.0 SAFETY REPORTING

Salix maintains a robust pharmacovigilance system comprised of a governance framework and standard operating procedures supporting a systematic process for review, evaluation, and management of accumulating safety data from clinical trials and other sources to:

- Identify a potential new safety signal;
- Ensure that an investigational product's risks are adequately assessed and communicated to investigators, IRBs/IECs, and regulatory bodies during clinical development.
- For this study, safety monitoring activities will include but are not limited to:
- Review and evaluation of single SAE occurrences in real-time as reported through the SAE reporting process as outlined in this section of the protocol;
- Review and evaluation, in real-time, of one or more occurrences of an uncommon SAE that is not commonly associated with product exposure;
- Findings and/or safety data obtained during this study will provide information for the overall review of safety that is conducted by Salix on a routine basis. Salix will report expeditiously any findings from clinical trials (ongoing or completed), epidemiological studies, pooled analysis of multiple studies, and findings from animal or in vitro testing that suggest a significant risk in humans exposed to the study product.

Safety data collection for this study begins at the time of the subject's signing of the informed consent according to the operating definitions defined in this section of the protocol. The investigator is responsible for the detection and documentation of events that meet the definition of an unanticipated problem (refer to the protocol Section 10.1), AE or SAE.

7.1 Operating Definitions for Assessing Safety

7.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a study product and which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, without any judgment about causality (i.e., whether or not considered related to the study product).

An AE **does** include the following:

- Exacerbation or worsening of a pre-existing illness. NOTE: if the pre-existing illness is the disease under study, then "exacerbation" refers to an unexpected worsening from the condition at baseline.
- Increase in frequency or intensity of a pre-existing episodic event or condition.
- Condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study.
- Symptom associated with disease not previously reported by the subject.

An AE **does not** include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) as event terms; the condition that led to the procedure is the AE if it meets the definition of an AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery; and social and/or convenience admissions).
- Overdose of either study product or concurrent medication without any signs or symptoms.
- Symptoms associated with disease, which are consistent with the subject's usual clinical course; unless the subject experiences worsening of their symptom(s) or the symptom(s) meet the criteria for an SAE.

7.1.2 Serious Adverse Event

A SAE is any AE, occurring at any dose, which results in any of the following outcomes ("Occurring at any dose" does not imply that the subject received study product):

- Results in death
- Is life threatening

  NOTE: Life-threatening means that the subject was, in the view of the investigator or sponsor, at immediate risk of death at the time of the event. This definition does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE. "In-patient" hospitalization means the subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a casualty or emergency room.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- A congenital anomaly or birth defect in the offspring of a subject who received study product.
- Important medical events that do not result in death, are not life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

  NOTE: Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Additionally, an adverse event meeting any of the serious outcomes previously defined above that is assessed by the investigator as resulting from study participation (regardless of relationship to study drug) should be treated as a SAE for this protocol (e.g., complications resulting from the taking of a blood sample or performance of a protocol required procedure).

Medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in case of events that do not meet the serious criteria above.

7.2 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., abnormal findings during examinations or ECG monitoring) that are judged by the investigator as **clinically significant** must be recorded as AEs or SAEs if they meet the definition of an AE or SAE. The investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment (including ECG monitoring) is clinically significant.

7.3 Method, Frequency, and Time Period for Detecting AEs and SAEs

At each visit, after the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the following standard questions:

1. "Have you had any (other) medical problems since your last visit/assessment?"
2. "Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?"

7.3.1 The Time Period for Detecting and Reporting of AEs and SAEs

The Time Period for Detecting and Reporting of AEs and SAEs is from the time of informed consent through study completion/withdrawal, including the follow-up period.

7.3.2 Post-Study SAEs

Investigators are not obligated to actively seek SAE information in former study participants, but investigators are encouraged to notify Salix of any SAEs occurring at any time after a subject has discontinued or terminated study participation that they judge may reasonably be related to study treatment or study participation.

7.4 Documenting AEs and SAEs

All AEs that occur after the subject has signed the ICF and during the course of the study, regardless of causality or seriousness, will be assessed and recorded in the subject's medical records and in the CRF. In addition, SAEs must be documented on the paper SAE Report Form.

A separate paper SAE Report Form should be used for each SAE. However, if at the time of initial reporting, multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same SAE Report Form.

The investigator should attempt to establish a diagnosis for the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and SAE and not the individual signs/symptoms.

For clinically significant abnormal laboratory findings or other abnormal assessments meeting the definition of an AE or SAE, a diagnosis, if known (or clinical signs and symptoms if diagnosis is unknown), should be recorded by the investigator. If a diagnosis is unknown and clinical signs and symptoms are not present, then the abnormal finding should be recorded. When documenting as an SAE on the SAE Report Form, relevant laboratory data should either be recorded in the 'Details of Relevant Assessments' section of the SAE Report Form (including the reference range and units) or copies of the laboratory report (with reference ranges and units) should be sent with the SAE Report Form.

The SAE Report Form should be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to Salix Product Safety or Designee. It is **very important** that the investigator provide his/her assessment of causality to study product at the time of initial SAE reporting.

7.5 Follow-up of AEs and SAEs

All AEs, regardless of seriousness, must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, relevant hospital records (i.e. discharge summary), or consultation with other health care professionals.

Salix may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, Salix should be provided with a copy of any postmortem findings, including histopathology.

For SAEs, new or updated information should be recorded on the originally completed paper SAE Report Form and all changes signed and dated by the Investigator or designee. By signing the SAE Report Form, the investigator or designee attests to the accuracy and completeness of the data and that he/she has reviewed and approved the report being submitted. The investigational sites IRB/IEC must be notified about SAEs in accordance with the requirements of the governing IRB/IEC.

7.6 Prompt Reporting of SAEs to Salix Pharmaceuticals

SAEs must be reported promptly to Salix Product Safety or Designee once the investigator determines that the event meets the protocol definition of a SAE.

Prompt reporting of a SAE requires:

- Completion and transmission of the SAE Report Form to Salix Product Safety or Designee via fax within 24 hours of the investigator's knowledge of the event. In parallel, a corresponding AE with the SAE details should be entered into the AE CRF.
- Prompt reporting of additional information for previously reported SAEs should follow the same reporting timeframe as initial reports. In addition, the corresponding AE in the AE CRF (as applicable) should be updated to ensure all data points documented in the AE CRF are aligned with the matching data points on the paper SAE Report Form.

7.7 Pregnancy Reporting

Pregnancies detected in subjects assigned to study treatment should be promptly reported to Salix Product Safety or Designee via fax as soon as the investigator is notified using the Salix Pregnancy Notification Form. If a female subject becomes pregnant following assignment to study treatment, the study product will be immediately discontinued and the subject will be

followed until the outcome of the pregnancy is known. (Refer to the 'Females of Reproductive Potential' Section 4.4).

Salix Product Safety or Designee should be notified via fax of any updates on the status of the pregnancy as soon as the information becomes available by update and/or amendment of the initial pregnancy notification form.

Although pregnancy occurring in a clinical study is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy, for medical reasons, will be recorded as an AE or SAE and followed as such.

7.8 Transmission of SAE Report Forms and Pregnancy Notification Forms

Completed SAE Report Forms and completed Pregnancy Notification Forms should be transmitted via the country specific fax numbers listed in the SAE Form Completion Guidelines which are provided in the Study Reference Manual.

For questions regarding SAE and/or Pregnancy reports, country specific phone numbers are listed in the SAE Form Completion Guidelines which are provided in the Study Reference Manual.

7.9 Regulatory Reporting Requirements for SAEs

The investigator, or responsible person per local requirements, must comply with the applicable local regulatory requirements related to the reporting of SAEs and expedited safety reports to regulatory authorities and their IRB/IEC.

8.0 STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan will be prepared for this study. The plan will contain a discussion of the statistical methods, a description of the computational algorithms and data handling conventions, and specifications for the data summaries and listings. It will be finalized before database lock.

8.1 Randomization

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. Treatment groups are as follows:

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

8.2 Determination of Sample Size

The information below provides the background information for sample size determination for the induction of clinical remission with endoscopic response at 16 weeks followed by clinical and endoscopic remission at 52 weeks. For placebo, the expected rates are based on data from a Phase 2 study (RETIC 03/06) conducted in subjects with active moderate Crohn's disease. The rates for Rifaximin DR are based on the assumption that Rifaximin DR will provide a somewhat higher induction of remission rate.

Expected rates for induction of clinical remission with endoscopic response at Week 16 are 40% for placebo and 55% for Rifaximin DR.

Based on a significance level of 5% (alpha 0.05), a sample size of approximately 240 subjects per treatment group will have at least 90% power to test the hypothesis that Rifaximin DR is superior to placebo for each co-primary endpoint considered individually. Approximately 80% power is available to detect significant differences between Rifaximin DR and placebo for both co-primary endpoints.

For the Long Term Treatment Phase, a 15% treatment effect is expected for both clinical symptom and endoscopic remission at Week 52. Based on this assumption and testing at a significance level of 5% (alpha 0.05), a sample size of approximately 210 subjects per treatment group will have at least 90% power to test the key secondary efficacy hypothesis that Rifaximin DR is superior to placebo when each key co-secondary endpoint is considered individually. In addition, approximately 80% power is available to detect significant differences between Rifaximin DR and placebo for each of the key co-secondary endpoints.

An additional consideration for sample size determination is the application of an inflation factor of 20% to account for drop-out rates during the Induction and Long Term Treatment Phases of the study. This consideration suggested that 330 subjects per treatment group would be required at study entry.

8.3 Analysis Populations

Intent-to-Treat (ITT) Population

The ITT population will include all randomized subjects who take at least one dose of study drug.

Per Protocol (PP) Population will include all subjects in the ITT Population with the exception of those who failed to meet Inclusion Criteria 3 and 4; or met Exclusion Criteria 1, 2, 13 or 14.

The analyses of baseline characteristics and efficacy will be performed for the ITT Population. The primary efficacy analysis also will be performed on the PP Population as a sensitivity analysis. All safety analyses will be performed on the ITT Population.

8.4 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.

8.5 Demographic and Baseline 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:

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).

Baseline characteristics:

All baseline subject characteristics including 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/ex-smoker/smoker), baseline CRP and fecal calprotectin values will be summarized by treatment arm. Baseline comparability will be assessed via descriptive measures, e.g., by comparing means, 95% confidence intervals and proportions.

8.6 Analysis Methods

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 and PP populations. All efficacy analyses will adjust for country.

8.6.1 Primary Efficacy Analysis

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 $\geq$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: $\pi R - \pi P \neq 0$ 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.

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.

The primary efficacy analysis will be repeated on the PP population to assess the robustness of the results of the primary outcome.

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 the ITT Population.

For each endpoint, the null hypothesis H0: πR-πP=0 versus the alternative HA: πR-πP ≠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.

8.6.2 Secondary Efficacy Analyses

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

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.

Change from baseline in continuous outcomes (for example, the change from baseline in the SES-CD at Week 16) 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.

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. Additionally, the change from baseline in continuous outcomes measured at multiple post-baseline time points will be analyzed longitudinally using a mixed model. Models will include fixed effects for baseline

value, country, treatment, week and the treatment by week interaction and allow for random subject effects. Treatment and week will each be fit as categorical variables. Models will be fit using SAS Proc Mixed assuming a compound symmetric correlation structure allowing for heterogeneous variances by week. The Kenward-Rogers approach for computing denominator degrees of freedom will be used to account appropriately for pooling of within- and between-subject variance estimates. Least squares means with 95% confidence intervals will be presented for each treatment*week cross-classification. The basic SAS code will follow the structure below:

```
proc mixed;
class treatment country week subjectID;
model Y = baseline country treatment week treatment*week/ddfm=KenwardRoger solution;
random int/ subject=subjectID type =VC;
lsmeans treatment*week/stderr;
run;
```

Estimate and contrast statements will be included to compare the mean change from baseline averaged over all weeks for the treatment comparison.

To determine whether the declaration of response based on the co-primary endpoints for induction parallels the pattern of CDAI scores, Spearman correlation analyses will be applied to CDAI scores with the occurrence or non-occurrence of response based on the co-primary endpoints (Yes or No). Wilcoxon rank-sum test will be conducted to compare changes in the CDAI scores between responders and non-responders to the co-primary endpoints.

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. A copy of the WPAI: CD questionnaire is provided in Appendix 6.

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. A copy of the IBDQ questionnaire is provided in Appendix 5.

Changes from baseline in the four WPAI: CD and IBDQ Global Score outcomes will be analyzed by the methods outlined above for continuous outcomes.

8.6.3 Safety Analyses

Safety evaluations will be based on the incidence, intensity and types of AEs, and changes in vital signs, clinical laboratory results, physical exam and electrocardiograms. Concomitant medication, exposure to study medication and treatment compliance will be summarized descriptively.

8.6.4 Extent of Exposure and Treatment Compliance

The number of subjects administered study drug, the duration of exposure to study drug, and compliance data will be summarized descriptively.

8.6.5 Adverse Events

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).

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.

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.

8.6.6 Clinical Laboratory Assessments

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

A summary of shifts from baseline to final evaluation will be given for each treatment group for each parameter. The normal range for each parameter will be used to create categories of low, normal, or high. Any result higher than ULN or lower than the lower limit of normal (LLN) will be categorized as high or low respectively, and any result within the lower and

upper limits of normal will be categorized as normal. The number and percentage of subjects in each treatment group in each shift category from baseline to final evaluation will be shown for each parameter.

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.

8.6.7 Vital Signs

Vital sign measurements will be summarized at baseline and at each time point. In addition, changes from baseline to last visit in vital sign measurements will be summarized. For each summary the number, mean, median, standard deviation, minimum, and maximum values will be presented by treatment and study phase.

8.6.8 Concomitant Medications

Concomitant medications taken from screening and during the study will be categorized by World Health Organization (WHO) classification for therapeutic class and drug name and summarized by number and percentage of subjects.

8.6.9 Physical Examinations

Physical examination data will be presented in a data listing.

8.6.10 Electrocardiogram

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 three methods.

1) Fridericia's correction: $QTc=QT/RR^{0.33}$,

2) Bazett's Correction: $QTc=QT/RR^{0.5}$,

And

3) Correction based on linear regression techniques: Based on the data from baseline study population, the intercept(a) and slope (b) will be estimated separately for males and females using the equation $QT=a+b(1-RR)$. Those estimates will be used to calculate the corrected QT values at post baseline time points.

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.

8.7 Statistical and Analytical Issues

8.7.1 Adjustment for Covariates

Efficacy analyses will be adjusted for country and baseline values.

8.7.2 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:

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.

Multiple Imputation Analysis: In the second analysis, missing values will be filled in by the multiple imputation method which involves the following distinct phases:

- The missing data will be filled in to generate complete data sets using SAS/STAT procedure PROC MI;
- The complete data sets will be analyzed using PROC LOGISTIC in SAS/STAT;
- The above two steps will be repeated 5 times;
- The results from the complete data sets will be combined for statistical inference using SAS/STAT procedure PROC MIANALYZE.

Observed Case Analysis: In the third analysis, subjects are excluded from the analysis if the subject has insufficient data to be determined as a responder or non-responder in a given 4-week assessment period. This analysis is not based on the ITT population and, therefore, interpretation of results from this analysis requires substantial caution. This is because the subjects who responded in the respective treatment groups may have different distributions for background characteristics. Thus, additional analysis may be undertaken by the use of statistical methods which provide adjustment for background characteristics.

8.7.3 Interim Analyses and Data Monitoring

No interim analyses are planned for this study.

8.7.4 Multicenter Studies

Centers will be pooled within countries for the assessment of country effects.

8.7.5 Multiple Comparisons/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.

The complete evaluation of clinical efficacy in this study requires the study of multiple key secondary efficacy variables collected at numerous time points. It is therefore necessary to properly and sensitively control the probability of making erroneous conclusions based solely upon compounding the likelihood of a type I error. The issue of multiplicity of secondary measurements will be handled by statistical testing of these outcomes in a hierarchical fashion. The order of secondary endpoints for the Induction and Long Term Treatment Phases are described in Sections 2.2.2 and 2.2.3. Significance tests will be conducted until a non-significant p-value is found ($p > 0.05$). Once a non-significant p-value occurred, all subsequent significance tests will be considered exploratory in nature.

8.7.6 Use of an Efficacy Subset of Subjects

The primary efficacy endpoint will be analyzed using the ITT Population.

8.7.7 Exploration of the Effects of Various Prognostic Factors on Efficacy

This study is not formally intended to obtain data on the influence of demographic and baseline disease characteristics (e.g., gender, race, age, and region (US/ROW)) on efficacy outcomes by the explicit design or randomization. However, the potential influence of these

factors in efficacy outcomes will be investigated by pooled analysis across the two identical studies (RECD3125 and RECD3126, reference: FDA ISE guidance document).

8.7.8 Criteria for Stopping the Study

It is expected that the study will be terminated when the enrollment goals are reached. It is not anticipated that the study will be stopped early for any reason.

9.0 STUDY ADMINISTRATION

9.1 Investigator Information and Training

The investigators and essential support staff will be trained by Salix (or designee) in regards to Good Clinical Practices (GCPs) and all aspects of protocol execution. It is the responsibility of the investigator to train ancillary study staff.

9.2 Monitoring

This study will be monitored by Salix (or designee), in accordance with GCPs and applicable regulations. By signing this protocol, the investigator agrees to periodic, on-site monitoring of all appropriate study documentation.

The progress of the study will be monitored by periodic on-site visits and frequent communications between the Salix (or designee) and the investigator (either by phone, fax, email, or post).

During these contacts, the monitor will:

- Check and assess the progress of the study.
- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.

The objectives of monitoring procedures are to verify that data are authentic, accurate, and complete; that the safety and rights of subjects are being protected; and that the study is conducted in accordance with the currently approved protocol (and any amendments), GCPs, and all applicable regulatory requirements.

9.3 Audits

At its discretion, Salix (or designee) may conduct a quality assurance audit of this study. If such an audit occurs, the investigator agrees to allow the auditor direct access to all relevant documents and to schedule his/her time and the time of his/her staff to permit meetings with the auditor to discuss findings and any relevant issues.

In addition, regulatory agencies may conduct a regulatory inspection of this study. If such an inspection occurs, the investigator agrees to allow the inspector direct access to all relevant documents and to schedule his/her time and the time of his/her staff to permit meetings with the inspector to discuss findings and any relevant issues. The investigator will notify Salix immediately when a Regulatory Agency notifies the site of an inspection.

10.0 ETHICAL AND LEGAL ASPECTS

The investigator and the study staff are responsible for conducting this study in accordance with the applicable principles which have their origins in the Declaration of Helsinki, ICH, GCPs, and all other applicable laws and regulations.

10.1 Institutional Review Board/ Independent Ethics Committee (IRB/IEC) Approval

This protocol, the informed consent form, relevant supporting information, and all types of subject recruitment or advertisement information must be approved by the appropriate IRB/IEC before the study is initiated. Any amendments to the protocol must also be approved, where necessary, by the IRB/IEC prior to implementing changes in the study. Documentation of these approvals must be provided to the sponsor prior to the initiation of the amendment.

The investigator's responsibilities regarding the IRB/IEC are as follows:

- Obtain IRB/IEC approval of the protocol, informed consent form, and any advertisements for subject recruitment prior to their use.
- Obtain IRB/IEC approval for any protocol amendments and revisions to the informed consent document before implementing the changes.
- Provide the IRB/IEC with any required information before or during the study.
- Submit progress reports to the IRB/IEC, as required, during the conduct of the study; request re-review and approval of the study, as needed; provide copies of all IRB/IEC re-approvals and relevant communication to the sponsor.
- Notify the IRB/IEC within 10 days (unless required sooner by IRB/IEC) of all serious and unexpected AEs related to the study medications that are reported to you by the sponsor. The investigator is responsible for updating the IRB/IEC on the progress of the study and of any changes made to the protocol at least once a year or at regular intervals as deemed appropriate. The investigator must also keep the IRB/IEC informed of any AEs, according to the IRB/IEC policy.

  Notifying Salix within 24 hours of awareness and the IRB/IEC within in 10 days (unless required sooner by IRB/IEC) of all unanticipated problems involving risk to subjects or others. **For the purposes of this study, an Unanticipated Problem is defined as any incident, experience, or outcome that meets all of the following criteria**:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

10.2 Subject Information and Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation in layman's terms regarding the nature of the study, along with the aims, methods, objectives, and any potential risks. The informed consent form must be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining the consent (if required by the IRB/IEC) prior to conducting/obtaining any study-related assessments including the discontinuation of any medications prohibited for the study.

If the informed consent form is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended informed consent form by the IRB/IEC and use of the amended document (including for ongoing subjects).

The informed consent form shall also contain the subject's authorization for the use and disclosure of his/her protected health information (PHI) in connection with the study. The authorization shall include at a minimum a clear description of the following: the duration of the authorization, the subject's right of access to the PHI (or any suspension thereof during the course of the study), type of information to be used/disclosed in the study, the names or classes of parties that may use or disclose the PHI, the purpose of the use/disclosure of PHI, the extent of the subject's right to revoke the authorization, the extent to which participation in the study is conditioned on signing the authorization, and the potential for re-disclosure of PHI.

The original and any amended signed and dated informed consent forms must be retained at the study site; and a copy must be given to the subject or subject's legally authorized representative(s).

10.3 Study and Site Closure or Discontinuation

Upon completion of the study, the following activities, when applicable, must be conducted by the monitor in conjunction with the investigator, as appropriate:

- Return of all study data to Salix (or designee).
- Data clarifications and/or resolutions.
- Accounting, reconciliation, and final disposition of used and unused study drug and placebo.
- Review of site study records for completeness.

In addition, Salix reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time and for any reason. If such action is taken, Salix will discuss this with the investigator (including the reasons for taking such action) at that time. Salix will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

10.3.1 Study Discontinuation

Should the investigator, Salix, the FDA or local regulatory authorities become aware of conditions arising during the conduct of this study that may warrant the cessation of the study, such action may be taken. Prior to such action, consultation between Salix, the investigator, and, as appropriate, the FDA and/or local regulatory authorities will take place. Conditions that may result in the termination of the study or parts thereof include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of Salix to alter, suspend, or discontinue the development of the investigational product

10.3.2 Study Site Discontinuation

The study site can be discontinued at the request of Salix, the investigator, or by the FDA or local regulatory authorities.

Conditions that may warrant discontinuation of the study site include, but are not limited to, any of the following:

- Failure of the investigator to accrue subjects into the study at an acceptable rate.
- Failure of the investigator to comply with GCPs and/or applicable current regulations.
- Submission of knowingly false information from the research facility to the sponsor, FDA, or other regulatory authorities.
- Insufficient adherence to protocol requirements and procedures.

If the study is prematurely discontinued, all study data must be returned to Salix or designee. In addition, the site must conduct final disposition of all used and unused study drugs in accordance with Salix procedures for the study. Study termination and follow-up will be performed in compliance with GCP and applicable regulations.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and Salix.

10.4 Handling and Record Keeping

10.4.1 Case Report Forms and Database Processing

Subject data will be collected in an electronic CRF using Electronic Data Capture (EDC). The EDC system will be Part 11 compliant and will have a documented audit trail for all changes made to the electronic CRF.

The Investigator or designee must enter all required subject data using the specified data collection method defined by Salix. The Investigator must sign and date a declaration on the electronic CRF attesting to his/her responsibility for the quality of all data entered and that the data represents a complete and accurate record of each subject's participation in the study. Electronic case report form data will be provided to the Investigator at the end of the study and will need to be retained by the Investigator.

10.4.2 Source Documents

Source documents consist of, but are not limited to, in-patient hospital charts, clinic notes, out-patient records, original test results, laboratory data, worksheets, drug accountability records, informed consent forms, etc. Source documents must be available for review and inspection during on-site monitoring of the study by Salix, their designees, IRB/IEC, and/or appropriate regulatory authorities.

10.4.3 Subject Tracking

A drug accountability log, subject identification log (to be retained by the investigator only), and subject screening/enrollment log will be used to track subject participation in the study.

10.4.4 Study Files

The investigational center will maintain a special study file. This file is subject to review and inspection as described under Section 9.2 and Section 9.3 of this protocol.

10.4.5 Data Management

Data management will be performed in accordance with the standard operating procedures of Salix or its designee.

10.5 Confidentiality

Anonymity of subjects participating in this study will be maintained. Only subject initials and subject number will be on any study documents submitted to the sponsor. Every effort will be

made to maintain the confidentiality of documents that identify the subject by name (e.g., signed informed consent document, laboratory reports, clinic charts), except to the extent necessary to allow auditing by the FDA, or other regulatory authorities. Should the name and/or address of a subject participating in this trial be on a document submitted to the FDA, or other regulatory authorities (e.g., laboratory report), the name and/or address will be completely blocked out and replaced with the subject initials and number.

The investigator and other study site personnel will keep confidential any information provided by Salix (including this protocol) related to this study and all data and records generated in the course of conducting the study, and will not use the information, data, or records for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or study site personnel; (2) information which it is necessary to disclose in confidence to an IRB/IEC solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject, or (4) study results which may be published as described in Section 10.8. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

10.6 Record Retention

Essential documents as described above should be retained for one of the following time periods:

- At least 2 years after approval of the last marketing application,

  OR

- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents should be retained for a longer period however if required by applicable regulatory requirements (i.e., local or country-specific regulations) or by an agreement with the sponsor. It is the responsibility of Salix to inform the investigator/institution as to when these documents no longer need to be retained. It is the investigator responsibility to notify Salix if they move or retire so that document storage can be addressed.

10.7 Financing and Insurance

10.7.1 Finance

The study is supported by Salix.

10.7.2 Insurance and Indemnification

Documentation of product liability insurance is on file at Salix and is available upon request.

10.8 Publication Policy

An Institution and/or the investigator shall have the right, consistent with academic standards, to publish or present the results of the study, provided such publication or presentation does not disclose confidential information or other proprietary trade secrets of Salix. Salix will work with the protocol development team to identify a lead author for manuscript development. The manuscript authors will be determined by the amount of effort and participation each investigator contributes towards the study design, the conduct of the study and the analysis of the study data. Prior to any publication, presentation or other disclosure, the institution and/or investigator will submit the manuscript of any proposed publication (including abstracts, or presentation to a journal, editor, meeting, seminar, or other third party) to Salix at least sixty (60) days before publication, and Salix shall have the right to review and comment upon the proposed publication. Upon sponsor's request, publication will be delayed up to ninety (90) additional days to enable Salix to secure adequate intellectual property protection of property of Salix that could be affected by said publication. Salix shall have the right to require the deletion of any trade secret, or proprietary or confidential information of sponsor. Any publication or disclosure by the Institution and/or Investigator shall give appropriate credit to Sponsor. Where title is not retained by the publisher, title to and the right to determine the disposition of any copyrightable material, first produced or composed in the performance of the study, shall remain with the Institution and/or investigator. With respect to such materials, the Institution and/or investigator hereby grants to Salix an irrevocable, royalty-free, nonexclusive right to reproduce, translate, and use any such copyrighted material for its own research and commercial purposes. Investigator acknowledges and agrees that the study data and results may be disclosed by Salix to other clinical investigators, the FDA, and other regulatory authorities.

10.9 Ownership

All data and records provided by Salix or generated during the study (other than a subject’s medical records) and all inventions discovered during the course of conducting the study are the property of Salix. If a written agreement is executed by the parties for the conduct of the study, which includes ownership provisions inconsistent with this statement, the ownership provisions contained in the written agreement between the parties shall control.

11.0 REFERENCES

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APPENDIX 1: OVERALL TIME AND EVENTS SCHEDULE

STUDY ASSESSMENTS	Screening Period	Treatment Period					Follow-Up Period	Unscheduled Visit
Study Visit	**Visit 1**	**Visit 2**	**Visit 3, 4, 5, 6**	**Visit 7**	**Visit 8, 9, 10, 11,12, 13, 14, 15,**	**Visit 16 (EOT)**	**Visit 17 (EOS)**	
Study Week		**0**	**2, 4, 8 and 12**	**16**	**20, 24, 28, 32, 36, 40, 44, 48**	**52**	**54**	
Study Day	**-21 to –14**	**1**	**14, 28, 56, 84 (±3d)**	**112 (±3d)**	**140, 168, 196, 224, 252, 280, 308, 336 (±3d)**	**364 (±3d)**	**378 (±3d)**	
Informed Consent	X							
Assign Subject Identification	X							
Medical History and Demographics	X							
Adverse Events and Concomitant Medications	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X						
Vital Signs, Weight, and Physical Examination[a]	X(include height)	X	X	X	X	X	X(Vital Signs and Weight Only)	X
Electrocardiogram	X(triplicate)			X		X	X	
Pregnancy Test	X(serum)	X(urine)		X(urine)	X(urine) (V10 and V13 only)	X(serum)		
Safety Laboratory Tests[b]	X	X	X	X	X	X	X	X
Blood Sample for Inflammatory Markers and PXR (V2 only)		X		X		X		
Pharmacokinetic Blood Sample		X	X (V6 only)		X (V15 only)			
Stool Collection and Processing	X			X		X		
Stool/Blood for Long-term Storage		X		X		X		
CDAI assessment calculated by EDC	X		X	X	X	X		
Ileocolonoscopy (SES-CD)[c]	X			X		X		
IBDQ and WPAI-CD		X		X	X (V10 and V13 only)	X		
Electronic Daily Diary Instructions/Completion	X	X	X	X	X	X		
Randomization		X						
Dispense Study Drug		X(1st dose at clinic)	X (except V3)	X	X			
Study Drug Collection/Compliance			X	X	X	X		

a. Perform a full physical examination at Screening (Visit 1), prior to the Long Term Treatment Phase (Visit 7), and at End of Treatment (Visit 16); perform disease and symptom driven physical examination (including assessments for abdominal mass and extraintestinal manifestations of Crohn's disease based on CDAI – see Appendix 2) at other visits.
b. Including *C. Difficile* safety testing as described in Section 6.3.5
c. The baseline ileocolonoscopy will be performed between Day -12 and Day -5; it will provide the baseline SES-CD, and will be used to assess Inclusion Criterion #3. Bowel prep will be dispensed at Visit 1. Ileocolonoscopy to be completed within 7 days after Visit 7 and Visit 16. Bowel prep will be dispensed at Visit 7 and Visit 16, cleansing regimen to begin after Visit 7 and Visit 16 assessments.

APPENDIX 2: CROHN'S DISEASE ACTIVITY INDEX (CDAI)

	DAY -7	-6	-5	-4	-3	-2	-1	7 day Total		
1. Number of liquid or very soft stools*									X 2 =	
2. Abdominal pain									X 5 =	
	0 = none, 1 = mild, 2= moderate, 3 = severe									
3. General well being									X 7 =	
	0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible									

4. Extraintestinal manifestations subject has now (check ALL that apply)

Arthritis/arthralgia ☐

Iritis/uveitis ☐

Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis ☐

Anal fissure, fistula or abscess ☐

Other fistula ☐

Fever over 37.8°C (100°F) during past week ☐

Total checked boxes ____ X 20 = ____

5. Antidiarrheal drugs in the last 7 days — No = 0, Yes = 1 ____ X 30 = ____

6. Abdominal Mass — None = 0, Questionable = 2, Definite = 5 ____ X10 = ____

7. Hematocrit *(%, rounded to whole number)*

Male 47 - _____ = ____ X 6 = ____

or Female 42 - _____ = ____ X 6 = ____

If negative, enter 0

8. Body Weight Calculation**

Ideal Weight _____ kg

minus Actual Weight _____ kg

= _____ ÷ Ideal Weight = _____ X 100 = ____

*(rounded to whole number***)*

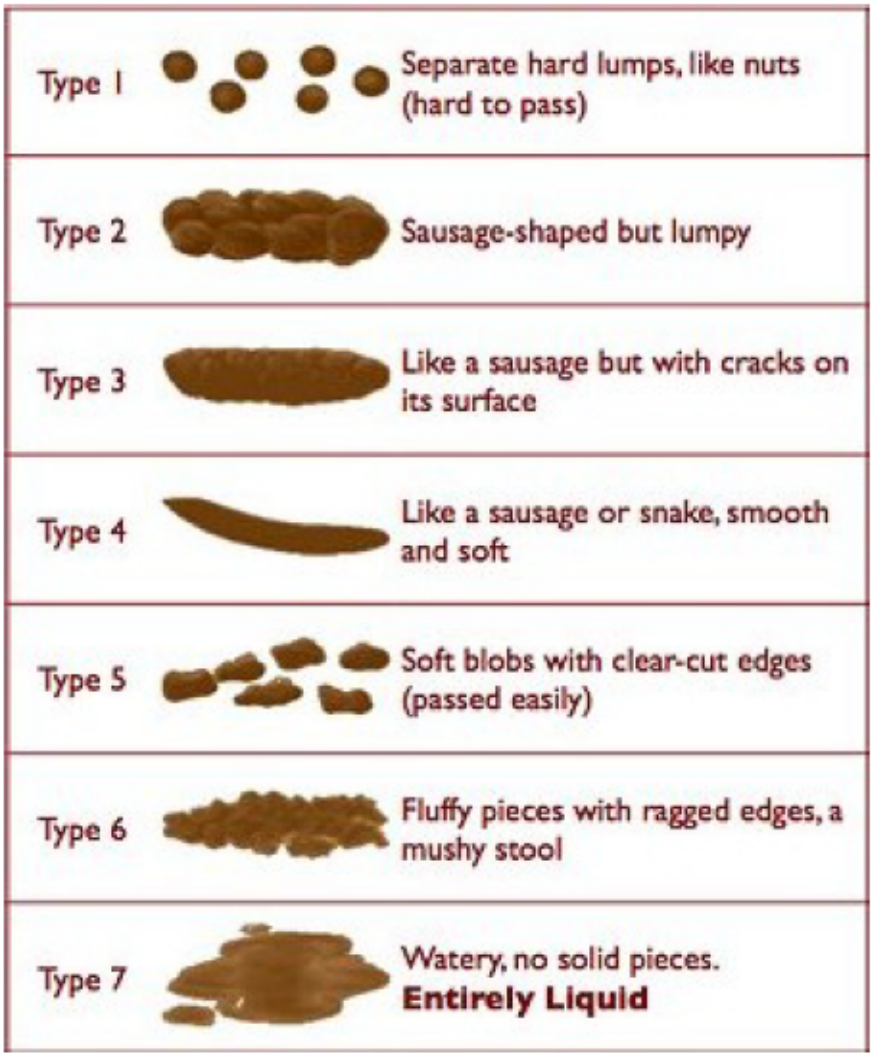
TOTAL CDAI = ____

*Graded using the Bristol Stool Form Scale (Appendix 3)

** See Appendix 8 for calculations of Ideal Body Weight

*** If calculated value >-10, record –10 (maximum lower limit)

APPENDIX 3: BRISTOL STOOL FORM SCALE (BSFS)



APPENDIX 4: SIMPLE ENDOSCOPIC SCORE FOR CROHN'S DISEASE (SES-CD) DEFINITIONS OF SES-CD VARIABLES

Variable	SES-CD values			
	0	*1*	*2*	*3*
Size of ulcers	None	Aphthous ulcers (∅ 0.1 to 0.5 cm)	Large ulcers (∅ 0.5 to 2 cm)	Very large ulcers (∅ > 2 cm)
Ulcerated surface	None	< 10%	10-30%	> 30%
Affected surface	Unaffected segment	< 50%	50-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

SES-CD Scoring Form

	Ileum	*Right colon*	*Transverse colon*	*Left colon*	*Rectum*	*Total*	
Presence and size of ulcers (0-3)							+
Extent of ulcerated surface (0-3)							+
Extent of affected surface (0-3)							+
Presence and type of narrowings (0-3)							+
					SES-CD =		

Daperno M, D'Haens G, Van Assche G, et.al. Development and validation of a new and simple endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004; 60: 505-512.

APPENDIX 5: INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem. Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally Unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at. Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option. from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

APPENDIX 6: WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE (WPAI: CD)

Work Productivity and Activity Impairment Questionnaire: Crohn's Disease V2.0 (WPAI: CD)

The following questions ask about the effect of your CROHN'S DISEASE on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____NO____YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your CROHN'S DISEASE? *Include hours you missed on sick days, times you went in late, left early, etc., because of your CROHN'S DISEASE. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your CROHN'S DISEASE affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If CROHN'S DISEASE affected your work only a little, choose a low number. Choose a high number if CROHN'S DISEASE affected your work a great deal.

   Consider only how much CROHN'S DISEASE affected productivity while you were working.

CROHN'S DISEASE had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	CROHN'S DISEASE completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your CROHN'S DISEASE affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If CROHN'S DISEASE affected your activities only a little, choose a low number. Choose a high number if CROHN'S DISEASE affected your activities a great deal.

Consider only how much CROHN'S DISEASE affected your ability to do your regular daily activities, other than work at a job.

CROHN'S DISEASE had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	CROHN'S DISEASE completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI: CD V2.0 (US English)

Reilly MC, Zbrozek AS, Dukes E: The validity and reproducibility of a work productivity and activity impairment measure. PharmacoEconomics 1993; 4(5):353-365.

APPENDIX 7: SUBJECT DAILY DIARY RECORDING

The following will be captured daily in the electronic diary system.

Using the Bristol Stool Form Scale provided (see Appendix 3), please record the Total Number of Liquid/very soft Stools (Type 6 or 7) you had today. _____

How would you rate your Abdominal Pain today?

- ☐ 0=none
- ☐ 1= mild
- ☐ 2= moderate
- ☐ 3= severe

How would you rate your General Well Being today?

- ☐ 0= generally well
- ☐ 1= slightly under par
- ☐ 2= poor
- ☐ 3= very poor
- ☐ 4 = terrible

Did you use any Antidiarrheal Drugs today?

- ☐ 0=No
- ☐ 1=Yes

Did you experience have any elevated temperature (fever) of more than 37.8 degrees Celsius degree Celsius (100 degrees Fahrenheit) today?

- ☐ 0=No
- ☐ 1=Yes

APPENDIX 8: IDEAL BODY MASS OF NORMAL ADULTS (MEN & WOMEN)

Ideal Body Mass of Normal Adults - MEN

Actual Height		Standard Weight in Clothing	
Inches with one inch heels	Centimeters with 2.5 cm heels	Pounds in indoor clothing weighing 5 pounds	Kilograms in indoor clothing weighing 2.3 kg
62	157.5	136	61.7
62.5	158.8	137	62.1
63	160	138	62.6
63.5	161.3	139	63
64	162.6	140	63.5
64.5	163.8	141.3	64.1
65	165.1	142.5	64.6
65.5	166.4	143.8	65.2
66	167.6	145	65.8
66.5	168.9	146.5	66.4
67	170.2	148	67.1
67.5	171.5	149.5	67.8
68	172.7	151	68.5
68.5	174	152.5	69.2
69	175.3	154	69.8
69.5	176.5	155.5	70.5
70	177.8	157	71.2
70.5	179.1	158.5	71.9
71	180.3	160	72.6
71.5	181.6	161.8	73.4
72	182.9	163.5	74.1
72.5	184.2	165.3	75
73	185.4	167	75.7
73.5	186.7	169	76.6
74	188	171	77.5
74.5	189.2	172.8	78.4
75	190.5	174.5	79.1
75.5	191.8	176.8	80.2
76	193	179	81.2

Ideal Body Mass of Normal Adults – WOMEN

Actual Height		Standard Weight in Clothing	
Inches with one inch heels	Centimeters with 2.5 cm heels	Pounds in indoor clothing weighing 5 pounds	Kilograms in indoor clothing weighing 2.3 kg
58.0	147.3	115.0	52.2
58.5	148.6	116.0	52.6
59.0	149.9	117.0	53.1
59.5	151.1	118.3	53.6
60.0	152.4	119.5	54.2
60.5	153.7	120.8	54.8
61.0	154.9	122.0	55.3
61.5	156.2	123.5	56.0
62.0	157.5	125.0	56.7
62.5	158.8	126.5	57.4
63.0	160.0	128.0	58.0
63.5	161.3	129.5	58.7
64.0	162.6	131.0	59.4
64.5	163.8	132.5	60.1
65.0	165.1	134.0	60.8
65.5	166.4	135.5	61.4
66.0	167.6	137.0	62.1
66.5	168.9	138.5	62.8
67.0	170.2	140.0	63.5
67.5	171.5	141.5	64.2
68.0	172.7	143.0	64.9
68.5	174.0	144.5	65.5
69.0	175.3	146.0	66.2
69.5	176.5	147.5	66.9
70.0	177.8	149.0	67.6
70.5	179.1	150.5	68.3
71.0	180.3	152.0	68.9
71.5	181.6	153.5	69.6
72.0	182.9	155.0	70.3