STATISTICAL ANALYSIS PLAN

Phase 2a, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Trial of IBD98-M Delayed-release Capsules to Induce Remission in Patients with Active, Mild to Moderate Ulcerative Colitis.

Version Number: Final 1.0

Date: 13-DEC-2017

Study Drug: IBD98-M
Protocol No.: IBD98-M-2002
Clinical Trial Phase 2a

Statistical Analysis Plan Signature Page

Final Version 1.0, dated 13December 2017

Sponsor: Holy Stone Healthcare Co., Ltd.

Protocol: IBD98-M-2002

Study Title: A Phase 2a, Multicenter, Randomized, Double-blind, Parallel-group, Placebo controlled Trial of IBD98-M Delayed-release Capsules to Induce Remission in Patients with Active, Mild to Moderate Ulcerative Colitis.

Prepared by:

Sudheer Ravula
Statistician-II
inVentiv Health Clinical

18DEC2017
Date

Reviewed by:

Lisa R. Reeves
Principal Statistician
inVentiv Health Clinical

18DEC2017
Date

Accepted by:

Ivy Chen
C&R Director
Holy Stone Healthcare Co., Ltd.

18. Dec., 2017
Date

REVISION HISTORY

Date	Version	Description	Author
21-Aug-2015	0.1	Initial draft version	Mukesh Kumar Jha
04-Dec-2015	0.2	Sponsor comments and protocol amendment 2 incorporated	Mili Natekar
21-Nov-2017	0.2	Sponsor comments and protocol amendment 3 incorporated	Sudheer Ravula
04-Dec-2017	1.0	Medical Writer/Sponsor comments incorporated	Sudheer Ravula

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CPK	Creatine phosphokinase
CRF	Case Report Form
CRP	C-Reactive Protein
CS	Clinically Significant
ECG	Electrocardiogram
GGT	Gamma-Glutamyl Transpeptidase
Hb	Hemoglobin
Hct	Hematocrit
HDPE	High Density Polyethylene
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
INR	International Normalization Ratio
ITT	Intention-To-Treat
IWRS	Interactive Voice Web Response System
LDH	Lactate dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
PD	Pharmacodynamics
PK	Pharmacokinetics

LIST OF ABBREVIATIONS

Abbreviation	Term
PP	Per Protocol
PT	Prothrombin Time
PTT	Activated Partial Thromboplastin Time
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SF-36	36-Item Short-Form Questionnaire
TEAE	Treatment-Emergent Adverse Event
UC	Ulcerative Colitis
UCDAI	Ulcerative Colitis Disease Activity Index
USP	United States Pharmacopeia
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this document is to provide details about the statistical analysis methods specified in the study protocol IBD98-M-2002: A Phase 2a, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Trial of IBD98-M Delayed-release Capsules to Induce Remission in Patients with Active, Mild to Moderate Ulcerative Colitis, sponsored by Holy Stone Healthcare Co., Ltd. This Statistical Analysis Plan (SAP) is based on the Protocol Amendment 3 dated 09 May 2017.

2. STUDY OBJECTIVES

Primary

To compare the percentage of patients in ulcerative colitis (UC) remission at Week 6 for each of the two IBD98-M dose groups versus placebo (remission defined as the modified Ulcerative Colitis Disease Activity Index [UCDAI] score of ≤ 1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and sigmoidoscopy score not exceeding 1).

Secondary

- To compare clinical improvement rates at Week 6 among treatment groups (defined as a ≥ 3 point reduction from baseline in the modified UCDAI score)
- To compare endoscopic improvement at Week 6 among treatment groups (defined as a ≥ 1 point decrease from baseline in modified UCDAI mucosal appearance subscore)
- To determine the change in symptoms (rectal bleeding and stool frequency) from baseline to each study visit among treatment groups
- To evaluate the safety and tolerability profile of IBD98-M

Exploratory

- To examine the effect of IBD98-M treatment on fecal calprotectin
- To examine any correlation between therapeutic response to IBD98-M and baseline characteristics

3. STUDY DESIGN AND PLAN

Study IBD98-M-2002 is a Phase 2a, multicenter, randomized, double-blind, parallel group, placebo-controlled trial in patients with active, mild to moderate UC. It is being conducted as an exploratory proof-of-concept study to investigate the clinical efficacy of IBD98-M delayed-release capsules (in a fixed combination) over a 6-week treatment period and a 2-week follow-up period.

Patients will be screened for study enrollment up to 2 weeks prior to randomization (Visit 3). During the screening period, patients will be evaluated with laboratory tests, physical examinations, and sigmoidoscopy. To be eligible, patients are to have a score of ≥ 4 and ≤ 10 on the modified UCDAI, and a score of >1 on the endoscopy subscore would be included. In addition, the diagnosis of UC must be confirmed visually by endoscopy images and also by histologic evidence in the past. After the screening visits, eligible patients will be randomized to 1 of 3 study groups:

(1) IBD98-M 0.8 g/day (mesalamine 0.8 g with sodium hyaluronate 92 mg),

(2) IBD98 M 1.2 g/day (mesalamine 1.2 g with sodium hyaluronate 138 mg), or

(3) Placebo.

Up to 51 patients will be enrolled in this study (including drop-out patients), with 17 patients randomized to each treatment group. Study blind will be maintained using a double-dummy technique.

Eligible patients will be randomized centrally via an Interactive Web Response System (IWRS), and each patient will receive 3 capsules twice a day (BID) for a period of 6 weeks, administered orally in 1 of the following regimens:

- Patients in the 0.8 g/day group will receive 2 capsules of IBD98-M (200 mg of mesalamine/23 mg of sodium hyaluronate) and 1 placebo capsule BID.
- Patients in the 1.2 g/day group will receive 3 capsules of IBD98-M (200 mg of mesalamine/23 mg of sodium hyaluronate) BID.
- Patients in the placebo group will receive 3 placebo capsules BID.

Patients should be encouraged to take their medication at the same time 30-120 minutes before meals every day. During the study, patients will visit the clinic on 7 occasions: 2 visits during the screening period (the second screening visit is the baseline visit); 4 visits during the treatment period at weeks 0, 2, 4, and 6; and an end-of-study/withdrawal visit at week 8, concluding the follow-up period. Patients will record symptoms in a daily diary starting 7 days before treatment and continuing until the end-of treatment period (Visit 6). For the baseline scoring of rectal bleeding and stool frequency items, the worst score from the previous 7 days of diary data before the randomization visit will be used excluding the day of and the day after endoscopy, as well bowel preparation for endoscopy where applicable.

3.1 Study Treatments and Assessments

IBD98-M (mesalamine, United States Pharmacopeia [USP]; and sodium hyaluronate) drug product is a delayed-release capsule. Each capsule is filled with multiple-layer pellets containing 200 mg of mesalamine and 23 mg of sodium hyaluronate. Each pellet consists of a microcrystalline cellulose inner core, which is coated first with mesalamine, USP; then with sodium hyaluronate, and finished with an enteric coating film.

The enteric-coated pellets are designed to allow the release of mesalamine and sodium hyaluronate from the pellets at or above pH 6.8 at the terminal ileum (ascending colon).

The matching placebo capsule will be indistinguishable from the drug capsule. The capsules (placebo or drug) are packaged, 35 count per bottle, into 60-cc white, wide-mouth, round HDPE (High Density Polyethylene) bottles sealed with an aluminum foil pad and covered with a polypropylene plastic cap. The product stability is for 24 months when the product is stored in a stability chamber of 25° C +/- 2° C. The product should be stored at 15° to 25° C [59° to 77° F].

Details of Study Medications:

	Preparations to be Administered		
	Placebo	**Test Product (New Drug)- 0.8 g/day dose group**	**Test Product (New Drug)- 1.2 g/day dose group**
Investigational Name	Not applicable	IBD98-M	IBD98-M
Manufacturer	Holy Stone Healthcare	Holy Stone Healthcare	Holy Stone Healthcare
Total Daily Dose	Not Applicable	Mesalamine 0.8 g; sodium hyaluronate 92 mg (total 4 capsules)	Mesalamine 1.2 g; sodium hyaluronate 138 mg (total 6 capsules)
Dosage	3 placebo capsules, BID	2 test product capsules and 1 placebo capsule, BID	3 test product capsules BID
Route	Oral	Oral	Oral
Formulation	Capsule	Capsule	Capsule
Capsule Strength	Not Applicable	Mesalamine 200 mg; sodium hyaluronate 23 mg	Mesalamine 200 mg; sodium hyaluronate 23 mg

Table 1: Schedule of Events

STUDY PROCEDURE	Screening*		Treatment Period				Follow-up
	Visit 1 (Screening)	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5	Visit 6/Early termination	Visit 7
DAY	-14 to -7	-7 to -1	0 (± 3)	14 (± 3)	28 (± 3)	42 (± 3)	56 (± 3)
Informed consent	X						
Demographics/Medical History	X						
Confirm Study Eligibility	X	X	X				
Vital Signs	X	X	X	X	X	X	X
Physical Examination	X		X	X[a]	X[a]	X	X
Weight, Height, and BMI	X						
12-Lead ECG	X					X	
Hepatitis Screening [b]	X						
CBC with Differential	X		X	X	X	X	X
Coagulation (aPTT, PT, INR)	X			X		X	
Serum Chemistry[c]	X		X[c]	X	X	X[c]	X
Urinalysis	X		X	X	X	X	X
Pregnancy Test[d]	X		X		X	X	
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Modified UCDAI[e]		X	X	X	X	X	
IBDQ, SF-36			X			X	
CRP			X		X	X	
Flexible Sigmoidoscopy		X[f]				X	
Distribution of Diary/Check	X	X	X	X	X	X[g]	
Stool for culture, *C. difficile* toxin, and ova and parasite[h]	X						
Randomization			X[i]				
Treatment Distribution/accountability[j]			X	X	X	X	
Stool Calprotectin			X			X	

Abbreviations: BMI= body mass index; ECG= electrocardiogram; CBC= complete blood count; aPTT= activated partial prothrombin time; PT= prothrombin time; INR= international normalization ratio; UCDAI= Ulcerative Colitis Disease Activity Index; IBDQ= Inflammatory Bowel Disease Questionnaire; SF-36= 36-Item Short Form Questionnaire; CRP= C-reactive protein; *C. difficile*= *Clostridium difficile*; AE= adverse event; HIV= human immunodeficiency virus.

*A patient who is screened and does not meet the study entry criteria may be re-screened again only once. Please refer to Protocol Section 7.4 (Re-screening) for further details.

a. Physical examinations performed on Days 14 and 28 will be abbreviated physical examinations. New findings will be recorded as AEs.

b. Blood samples will be collected for Hepatitis B and C screening; HIV testing will not be performed in this study.

c. Cholesterol and triglycerides assessments will be done at Visits 3 and 6 only.

d. Pregnancy test performed at screening should be serum test, after screening should be urine pregnancy tests. All pregnancy test results must be available before patient dosing.

e. Modified UCDAI on Days 0 and 42 should be complete modified UCDAI score including the endoscopy subscore. Modified UCDAI at Screening Visit 2, Visit 4, and Visit 5 should be partial modified UCDAI score including only stool frequency, rectal bleeding and physician's global assessment.

f. Screening sigmoidoscopy must be performed on Day -7 to Day -1.

g. No distribution of diary at Visit 6. Only check diary from Visit 5

h. A sample will be collected and cultured during screening and at any point in the study when a patient becomes symptomatic, including worsening or return of disease activity.

i. To be performed prior to dosing.

j. Treatment distribution will be done at Visits 3, 4, and 5. Treatment accountability will be done at Visits 4, 5, and 6. All unused medication is to be returned at Visits 4, 5, and 6.

3.2 Randomization and Blinding

Patients will be assigned treatment according to a 1:1:1 randomization schedule produced by inVentiv Health Clinical. The randomization code will not be available to the bioanalytical division of inVentiv Health Clinical until the clinical and analytical phases of the study have been completed.

Blinding of study treatments to the patient, site staff, and Sponsor will be maintained during the study using a double-dummy technique. Each patient will be dispensed with an IWRS-assigned kit, labeled with a unique kit ID at Visit 3, 4 and 5. Each kit will contain 3 bottles labeled with A, B, and C with 35 capsules each, which will be necessary to cover the period between 2 visits. The kits should be returned by the patient at the next visit and a new kit will be dispensed. Each patient should take 1 capsule from each bottle twice a day. The study will be double-blind. Patients will receive 1 of 3 different treatment kits, identical in appearance, as outlined in table below.

Treatment Group	Bottle A	Bottle B	Bottle C
IBD98-M 0.8 g/day	200 mg IBD98-M	200 mg IBD98-M	Matching Placebo
IBD98-M 1.2 g/day	200 mg IBD98-M	200 mg IBD98-M	200 mg IBD98-M
Placebo	Matching Placebo	Matching Placebo	Matching Placebo

3.3 Sample Size Justification

Simon's randomized Phase 2 design was used[1, 2, 3]. The average remission rate of placebo is approximately 0.2[4]. With power of 0.8, and the difference in remission rates between the best treatment and the other treatments ≥ 0.18, each arm requires 17 patients, giving the total number of patients to be enrolled as 51. This enrollment is adequate as it will provide 28.2% precision with a 95% confidence interval for evaluation of the difference between study treatment and placebo (i.e., the primary objective), where precision is defined as 1/2 width of the confidence interval. Based on this rationale, 51 patients will be enrolled, with 17 patients randomized to each group.

4. ANALYSIS POPULATIONS

Screened Population

The screened population will include all screened patients who signed the informed consent.

Randomized Population

The randomized population will include all randomized patients irrespective of patient receiving any study drug. The treatment group assignment in this population will be defined by the treatment planned as per the initial randomization schedule.

Safety Population

The safety population will include all randomized patients who receive at least 1 dose of study drug. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety.

Intention-to-Treat Population

The intent-to-treat (ITT) population will include all randomized patients who received at least one dose of study medication irrespective of any deviation from the protocol or premature discontinuation. The treatment group assignment will be designated according to initial randomization. The ITT population will serve as the basis for the analysis of efficacy.

Per Protocol Population

The per-protocol (PP) population is a subset of the intent-to-treat population. The per-protocol population consists of all patients who do not violate the terms of the protocol in a way that would impact the study outcome significantly, as determined by the Medical Monitor who is blinded to study drug assignment. All decisions to exclude patients from the per-protocol population dataset will be made prior to the unblinding of the study.

Analyses using the per-protocol population may be provided as a sensitivity analysis.

5. DEFINITIONS AND DERIVED VARIABLES

Study Start Date, Study Stop Date, and Duration: Study start date for a given patient is defined as the date of screening and study stop date is defined as the date on which the patient end of study form was completed at the end of study. Study duration is defined as (study stop date – study start date) + 1 in days.

Baseline: Baseline for all safety and efficacy measurements will be defined as the last assessment prior to study drug administration unless stated otherwise.

Study Day: Study day will be calculated by subtracting date of first dose date i.e. day 1 from respective event date. Day 1 is the date of the first dose of study drug.

Study day= Event date – Day 1 date.

Study day= Event date – Day 1 date + 1 (For those events occurring on or after Day 1).

Modified UCDAI Score: The modified UCDAI score will be computed as combined score of stool frequency, rectal bleeding, mucosal appearance, and the physician's global assessment.

Sigmoidoscopy Score: It is the "mucosal appearance" score which is collected at visit 3 and 6 along with Rectal Bleeding, Stool Frequency and Physicians Global Assessment.

6. STATISTICAL CONSIDERATIONS

For efficacy and safety data, descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum for continuous data, and n [%] for categorical data) will be presented. Similarly, wherever applicable, changes from baseline will be summarized in the same manner.

Unless otherwise stated, the denominator for percentages will be based on the number of patients in each treatment group who provided non-missing responses to the categorical variable, all statistical tests will be two-sided and at the 5% level of significance, and all differences between treatment groups will be presented with two-sided 95% confidence intervals (CIs). All p-values will be displayed to three decimals and rounded using standard scientific notation (e.g., 0.XXX). If a p-value less than 0.001 occurs it will be shown in tables as <0.001. If a p value greater than 0.999 occurs it will be shown in the tables as >0.999.

Unless otherwise stated, percentages will be presented to one decimal place in all summaries.

Minimum and maximum values will be presented to the same number of decimal places as collected on the case report form (CRF) or within the laboratory panel; mean and median will be presented to one decimal place more than CRF data; standard deviation will be presented to two decimal places more than CRF data.

Dates will be presented in format DDMMMYYYY and numbering for tables, figures, and listings will follow ICH E3.

All statistical analyses will be performed using Statistical Analysis System (SAS®) version 9.4 or higher (SAS Institute, Cary, NC).

7. METHODS OF ANALYSES AND PRESENTATIONS

7.1 Patient Disposition

The number of patients screened and the number of screen failures at Visits 1 (screening), 2 (baseline visit), and 3 (randomization) will be summarized overall. The number of randomized patients will be presented by treatment and overall, and the number and percentage of randomized patients who were treated, completed the study, and discontinued (along with the primary reason for discontinuation) will also be presented by treatment group and overall.

The number and percentage of randomized patients in the safety, ITT, and PP populations will be summarized by treatment group and overall.

Data including screen failures, inclusion/exclusion criteria evaluation, randomization details, patients randomized but not treated, and protocol deviations or violators will be listed. Patient's analysis population will be listed.

7.2 Protocol Deviations

Protocol deviations are deviations that occurred before or during the randomized treatment period. Protocol deviations will be recorded from the screening visit. The following criteria are considered as major protocol deviations:

- Patient did not satisfy all inclusion/exclusion criteria.
- Patient was unblinded to the study treatment or if treatment code is broken by site without medical emergencies of patient.
- Treatment compliance is not in the range of 80% to 120%.
- Patient took concomitant medication during the study which was forbidden in the protocol.
- Patient is treated with any other study medication in another clinical study.

- Missing primary efficacy data at baseline and the end of treatment visit.

Protocol deviations will be identified at the study site and recorded in an Excel spreadsheet by a sponsor representative and shared with the inVentiv Health Clinical statistical programming team before database lock.

The number and percentage of ITT patients experiencing at least one major protocol deviation and the number and percentage of ITT patients with each type of major protocol deviation will be summarized by treatment group and overall.

All protocol deviations will be listed.

7.3 Demographic and Baseline Characteristics

The demographic and baseline characteristics will include age, gender, female childbearing potential status, ethnicity, race, smoking history, height, body weight, and body mass index (BMI). Demographic and baseline characteristics will be summarized using descriptive statistics for each treatment group and overall for the safety population.

BMI is derived using weight and height collected at the screening visit (Visit 1) and is computed as (weight (kg) / [height (m)]^2).

All demographic and baseline characteristics will be listed by treatment group, site number, and patient number.

7.4 Medical History

Medical history will include any significant conditions or diseases that stopped at or prior to screening (time of informed consent) or are present and stable at screening. Medical history conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system Version 17.0 or higher.

A summary table of medical history conditions by system organ class and preferred term will be presented for each treatment group and overall. The table will be sorted in alphabetical order by system organ class and in alphabetical order of preferred terms within each system organ class. The frequency and percentage of patients who present at least one occurrence of the system organ class or preferred team will be presented by treatment group and overall. The denominator

used for calculating the percentages will be the total number of patients included in the safety population for each treatment group. All medical history conditions will be listed.

7.5 Prior and Concomitant Medication

Prior medication is defined as any medication starting and ending before the first dose of study medication. Concomitant medication is defined as any medication, other than the study medication, that either started before the first dose of study medication and continued into the double-blind treatment period, or that started after the first dose of study medication. If based on available start and stop date information it cannot be determined whether a medication use is prior or concomitant, the medication use will conservatively be assumed concomitant.

Prior and concomitant medications will be classified using the World Health Organization Drug Dictionary (WHO-DD) March 2014 and will be summarized separately by treatment and overall, giving the number and percentage of patients by Anatomical Therapeutic Chemical (ATC) Level 2 and 4 code and preferred term. Patients will be counted only once at a given level if they had more than one concomitant medication use at the level. The table will be sorted in alphabetical order first by ATC Classification Level 2, then by ATC Classification Level 4, and then in decreasing frequency of preferred WHO names based on total number of patients within each combination of ATC classification levels. The denominator used for calculating the percentages will be the total number of patients included in the safety population for each treatment or overall.

All prior/concomitant medications will be listed.

7.6 Concomitant Procedures

Concomitant procedures includes all treatments taken during the effective duration of study treatment, whether or not they are recorded at baseline (i.e., have stop day greater than or equal to Day 1).

The concomitant procedures will be classified using the MedDRA coding system and will be summarized for the safety population by treatment group and overall as the number and percentage of patients by system organ class and preferred term (or higher level term, if no preferred term is available). Patients will be counted only once at each level of summarization if they are receiving more than one concomitant procedure at that level.

All concomitant procedures will be listed.

7.7 Study Drug Exposure and Compliance

Duration of exposure, in days, will be calculated for each patient as the date of the last dose of study medication minus the date of the first dose of study medication, plus 1 day. Duration of exposure will be summarized descriptively by treatment group and overall for the safety population.

In general, percent dosing compliance for an individual patient will be computed as:

(number of capsules taken) / (number of capsules expected to be taken) x 100%

Percent dosing compliance between two visits will be computed where:

number of capsules taken =
number of capsules dispensed at the earlier visit
– number of capsules returned (from those dispensed at the earlier visit)
– number of capsules reported lost/damaged (of those dispensed at the earlier visit)

and

number of capsules expected to be taken =
(date of the later visit – date of the earlier visit [+1 if the earlier visit is Visit 3]) x 6

Percent dosing compliance for the whole study will be computed where:

number of capsules taken =
number of capsules dispensed at all visits
– number of capsules returned at all visits
– number of capsules reported lost/damaged at all visits

and

number of capsules expected to be taken =
(date of the last visit – date of the first dose + 1) x 6

Percent dosing compliance will be summarized descriptively at Visits 4, 5, and 6, and for the study as a whole, by treatment group and overall for the safety population. Dosing noncompliance is defined as taking less than 80% of study medication capsules during the whole treatment period. Overall dosing compliance and by visit dosing compliance will be categorized as <80%, 80% to 100%, and >100%, and summarized descriptively by treatment group and overall for the safety population.

All study drug administration, accountability, and compliance data will be listed.

7.8 Efficacy Data Endpoints and Analyses

All efficacy endpoints will be analyzed for both the ITT population (the primary analysis population) and PP population. Comprehensive listings of all efficacy data will also be presented.

7.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of patients in remission at Week 6. A patient is considered to be in remission (a responder) at Week 6 if the patient has a modified UCDAI score of ≤1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability (a mucosal appearance score of ≤1), and sigmoidoscopy (mucosal appearance) score not exceeding 1. A patient is considered to be a non-responder if no diary data is available within the period from Day 36 to study end or endoscopy within the period from Day 28 to study end (a non-responder imputation approach).

The number and percentage of patients who are in remission at Week 6 will be presented by treatment group, along with 95% confidence intervals constructed using the Clopper-Pearson method.

The percentage of patients in remission at Week 6 will be compared between each of the IBD98-M groups and placebo using Fisher's exact test. Each test will be 2-sided and declared statistically significant at the 0.05 level. No adjustment will be made for the two comparisons.

A bar chart of the percentage of patients in remission at Week 6 for each of the two IBD98-M groups and placebo will be presented.

As a supportive analysis, the primary efficacy endpoint will also be analyzed using the per protocol population.

Also, a sensitivity analysis will be used to assess the effects of missing data. The primary efficacy endpoint will be analyzed on the ITT population without making use of the non-responder imputation approach. Similar statistical methods will be used for the sensitivity analysis as is to be used for the primary efficacy analysis on the ITT population (which will use a non-responder imputation).

7.8.2 Secondary Efficacy Endpoint and Analyses

The secondary efficacy endpoints include:

Proportion of patients with clinical improvement at Week 6 (defined as a ≥3 point reduction from baseline in the modified UCDAI score)
Proportion of patients with endoscopic improvement at Week 6 (defined as a ≥1 point decrease from baseline in modified UCDAI mucosal appearance subscore)
Change in symptoms (rectal bleeding and stool frequency) from baseline to each study visit

Proportion of Patients With Clinical Improvement at Week 6:

The modified UCDAI score system includes four variables, namely rectal bleeding, stool frequency, mucosal appearance, and the physician's global assessment of disease activity. Each variable is scored from 0 – 3 so that the total score (a summation of the 4 variable scores) ranges from 0 – 12, with higher scores indicating more severe disease[5].

A patient will have experienced clinical improvement at Week 6 if the change from baseline (the last assessment prior to the first dose of study drug) to Week 6 (Visit 6) in the modified UCDAI score is ≤ -3, where change is computed as the Week 6 modified UCDAI score minus the baseline modified UCDAI score. Only patients with a modified UCDAI score at baseline and Week 6 will have their clinical improvement status determined (no non-responder imputation).

The proportion of patients with clinical improvement at Week 6 will be summarized and analyzed using methodology similar to the primary efficacy endpoint for both the ITT and PP populations. A bar chart of the percentage of patients with clinical improvement at Week 6 by treatment group will be presented.

Proportion of Patients With Endoscopic Improvement at Week 6:

A patient will have experienced endoscopic improvement at Week 6 if the change from baseline (the last assessment prior to the first dose of study drug) to Week 6 (Visit 6) in the modified UCDAI mucosal appearance score is ≤ -1, where change is computed as the Week 6 score minus the baseline score.

Missing data will not be imputed at Week 6 if a patient has not made it to Week 6 and/or has no Week 6 mucosal appearance result.

The proportion of patients with endoscopic improvement at Week 6 will be summarized and analyzed using methodology similar to the primary efficacy endpoint for both the ITT and PP populations. A bar chart of percentage of patients with endoscopic improvement at Week 6 by treatment group will be presented.

Change in Symptoms (Rectal Bleeding and Stool Frequency) From Baseline to Each Study Visit:

Rectal bleeding is scored at each visit as normal (none), mild (streaks of blood), moderate (obvious blood), or severe (mostly blood). Stool frequency is scored at each visit as normal (none), mild (1-2 stools more than usual per day), moderate (3-4 stools more than usual per day), or severe (>4 stools more than usual per day).

The number and percentage of patients with each categorical result will be presented for each symptom (rectal bleeding and stool frequency) at baseline (the last assessment prior to the first dose of study drug) and each post baseline visit for ITT and PP populations. Each IBD98-M group will be compared to placebo at each visit using Fisher's exact test.

A shift table will be prepared for each symptom, showing the number and percentage of patients with normal, mild, moderate, and severe results at baseline versus normal, mild, moderate, and severe results at each post-baseline visit, by treatment group.

7.8.3 Exploratory Endpoint

The exploratory endpoint is the reduction in fecal calprotectin.

Fecal calprotectin will be collected at Visit 3 (Week 0) and Visit 6 (Week 6) or early termination. Change from Visit 3 to Visit 6 or early termination will be computed as the Visit 6 value minus the Visit 3 value. Descriptive statistics (n, mean, standard deviation (SD), median, minimum,

and maximum) will be presented for observed fecal calprotectin at each visit and for change from Visit 3 at Visit 6 by treatment group for the ITT and PP populations.

Change from Visit 3 to Visit 6 in the fecal calprotectin will be analyzed as the response variable in an analysis of covariance (ANCOVA) model to compare each of the IBD98-M groups versus placebo. The model will include treatment as a fixed effect and the Visit 3 fecal calprotectin value as a covariate. The treatment-by-baseline interaction will be included in the model and if the term is not significant at the 0.10 α-level, it will be excluded from the model. If the interaction is significant at the 0.10 α-level, the interaction will be investigated and appropriate interpretation made or appropriate alternative methodology identified and implemented. Least squares means and associated 95% confidence intervals will be estimated for each treatment group, and the least squares mean difference (each IBD98-M group minus placebo) and associated 95% confidence interval will be estimated for each IBD98-M treatment group. Least square means will be compared between each active treatment group and placebo using two-sided testing at the $\alpha = 0.05$ level. There will be no multiplicity adjustment.

The residuals from the above analyses will be checked for normality and homogeneity of variance. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. Any deviation from either assumption may result in further analysis using an appropriate alternative transformation (such as logarithmic or power transformation) of the data or an alternative appropriate statistical analysis.

The analysis of the above exploratory efficacy endpoint will be repeated for the PP population.

7.9 Safety Data Endpoints and Analyses

The safety endpoints include:
Treatment-Emergent Adverse Events (TEAEs)
Serious Adverse Events (SAEs)
Physical examination findings
Vital signs
Clinical laboratory parameters (including chemistry, hematology, coagulation, and urinalysis)
Electrocardiograms (ECGs).

Safety analyses will be performed on the safety population. Results will be reported by each treatment group and overall.

7.9.1 Adverse Events

All reported Adverse Event (AE) verbatim terms will be coded using the MedDRA dictionary version 17.0 or higher to provide the body system and preferred term.

A TEAE is defined as an adverse event that starts on or after the date of first dose of study medication. If the start date of an adverse event is incomplete or missing, the event will be assumed to be a TEAE, unless the incomplete start date (month and/or year) or the stop date (complete or incomplete) clearly indicates that the event started prior to dosing. Duration of the AE will be calculated in days as (AE stop date – AE start date) + 1, and will be calculated only for those events with both a complete start and stop date.

The relationship of each AE to study drug will be recorded as unrelated, unlikely, possibly, probably, and definitely. If a relation is missing for an AE, the relation of the event to study drug will conservatively be assumed to be definitely for summarization.

The severity of each AE will be classified as mild, moderate, or severe. If the severity of an AE is missing, the severity of the event will conservatively be assumed to be severe for summarization.

Number of events (e), number of patients (n) having an event, and percentage of safety patients (%) having an event will be presented by treatment group and overall for all AE and TEAE summary tables.

An overall summary of AEs and TEAEs will summarize the number of events, and the number and percentage of patients with events by treatment group and overall for the safety population.

The following categories will be included in this overall summary:

- at least one AE
- at least one related AE
- at least one SAE

- at least one related SAE
- at least one severe AE
- at least one TEAE
- at least one TEAE leading to discontinuation of study drug
- at least one related TEAE
- at least one related TEAE leading to discontinuation of study drug
- at least one serious TEAE
- at least one related serious TEAE
- at least one severe TEAE
- at least one related severe TEAE

TEAEs will be summarized by system organ class and preferred term for each treatment group and overall for the safety population. Multiple instances of an AE in each system organ class and multiple occurrences of the same preferred term will be counted only once per patient. The table will be sorted in alphabetical order by system organ class and in decreasing frequency of preferred terms based on total number of patients reporting the event within each system organ class. The denominator used for calculating the percentages will be the total number of patients included in the safety population for each treatment or overall. The following groups of events will be summarized in this manner:

- TEAEs
- Serious TEAEs
- TEAEs leading to study drug discontinuation or withdrawal from study
- Serious TEAEs leading to study drug discontinuation or withdrawal from study

- TEAEs by body system, preferred term ,and worst relationship (multiple occurrences at the body system or preferred term level will be counted only once per patient at the worst relation [related], all events will be counted at each level of relationship)
- Serious TEAEs by body system, preferred term, and worst relationship
- TEAEs by body system, preferred term, and maximum severity (multiple occurrences at the body system or preferred term level are counted only once per patient at the maximum severity, all events will be counted at each level of severity)
- Serious TEAEs by body system, preferred term, and maximum severity

All AEs will be listed.

7.9.2 Physical examinations

The number of safety population patients reporting normal, abnormal not clinically significant (NCS), abnormal clinically significant (CS), or not examined results for physical examination will be tabulated for each body system at baseline (the last assessment prior to the first dose of study drug), Visit 3, Visit 6, and Visit 7 (follow-up) using counts and percentages, by treatment group and overall.

Physical examination results will also be listed.

7.9.3 Vital Signs

Descriptive statistics will be used to summarize vital signs (body temperature, heart rate, sitting systolic blood pressure, sitting diastolic blood pressure, respiration rate, and body weight) and weight for each treatment group and overall by scheduled study visits. Values and change from baseline values for each visit (change from baseline = post baseline visit value – baseline [last value collected prior to first dose of study drug] value) will be summarized for the safety population.

The number and percentage of patients with result classified as abnormal CS and abnormal NCS will be summarized by treatment group and overall at each visit.

All vital sign data will be listed.

7.9.4 Laboratory Evaluations

The following tests will be performed throughout the study for hematology, serum chemistry, coagulation, and urinalysis:

Hematology	Serum chemistry	Coagulation	Urinalysis (dipstick)
Full and differential blood count	Albumin	Prothrombin time (PT)	Appearance
Hematocrit (Hct)	Alanine aminotransferase (ALT)	Activated partial thromboplastin time (PTT)	pH
Hemoglobin (Hb)	Alkaline phosphatase (ALP)	INR (international normalization ratio)	Protein
Mean corpuscular hemoglobin (MCH)	Aspartate aminotransferase (AST)		Glucose
Mean corpuscular hemoglobin concentration (MCHC)	Blood urea nitrogen (BUN) or Urea		Ketone bodies
Mean corpuscular volume (MCV)	Creatinine		Indicators of blood
Platelet count	Creatine phosphokinase (CPK)		Indicators of WBC
Red blood cell (RBC) count	Electrolytes (Na, K,)		Specific gravity
White blood cell (WBC) count with differential	Gamma-glutamyl transpeptidase (GGT)		Urobilinogen
	Glucose		
	Lactate dehydrogenase (LDH)		
	Total bilirubin		
	Total cholesterol		
	Triglyceride		
	C-reactive protein (CRP)		

Descriptive statistics will be presented for quantitative laboratory parameters by treatment group and time point. Baseline will be the last value collected prior to the first dose of study drug. Changes from baseline (change from baseline = post baseline visit value – baseline visit value) will also be summarized by descriptive statistics where only patients with observations at both baseline and any given visit are included. Number and percentage of patients will be presented

for categorical laboratory parameters by treatment group and time point. Shift analysis will not be performed for categorical laboratory parameters.

Shifts in laboratory test values will be presented in terms of number and percent of patients at each post-baseline visit with a result of low, normal, high, or missing (relative to the normal range for the given parameter) relative to their result at baseline classified as low, normal, high, or missing. Summarization will be by treatment group.

Patients with an incidence of clinically significant abnormalities that occur during treatment as well as those that occur prior to the start of the study treatment but worsened during the study treatment will be listed by treatment group.

All laboratory data will be listed with clinically relevant values flagged (L=Lower than normal range, H=Higher than normal range, or A=Abnormal if no reference range).

A listing of abnormal laboratory values as identified by the investigator on the case report form will be presented with clinical significance status.

Serum and urine pregnancy test results will be listed.

7.9.5 12- Lead Electrocardiogram Evaluation

12-lead electrocardiograms are performed at Visit 1 (screening) and Visit 6 or early termination; Visit 1 results (the last assessment prior to the first dose of study drug) will be used as baseline. The number and percentage of safety population patients with normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS) results will be summarized at Visit 1 (screening) and Visit 6.

Shift tables will be presented at Visit 6 showing the number and percentage of safety population patients per treatment group with normal, abnormal NCS, and abnormal CS, and missing at baseline versus Visit 6 results.

All ECG results will be listed.

7.9.6 Death

All death data will be listed.

8. PK/PD ANALYSIS

Not applicable to this SAP.

9. ANALYSIS OF OTHER ASSESSMENTS

Not applicable to this SAP.

10. HANDLING OF MISSING VALUES AND OUTLIERS

A non-responder imputation approach will be used for the primary efficacy endpoint data (see details in Section 7.8.1 of this SAP). No imputation will be done for secondary and exploratory endpoints. Missing data handling approaches for AE are in Section 7.9.1.

11. POOLING OF INVESTIGATIVE SITES

Not applicable to this SAP.

12. INTERIM ANALYSIS

No interim analysis is planned.

13. DATA MONITORING COMMITTEE

Not applicable to this SAP.

14. CHANGES FROM ANALYSIS METHODS PLANNED IN THE PROTOCOL

Any changes to planned analyses, if applicable, will be cited in the clinical study report along with the rationale for the change.

15. STATISTICAL SOFTWARE

All statistical analyses will be performed using Statistical Analysis System (SAS®) release 9.4 or higher.

16. REFERENCES

1. Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. Cancer Treat Rep. 1985; 69: 1375-1381.

2. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10:1-10.

3. Jung SH, Kim KM. On the estimation of the binomial probability in multistage clinical trials. Stat Med. 2004; 23: 881-896.

4. Su C. Outcomes of placebo therapy in inflammatory bowel disease. Inflamm Bowel Dis. 2006;12(4):328-333.

5. Antonio Tursi , Giovanni Brandimarte , Treatment of Relapsing Mild-to-Moderate Ulcerative Colitis With the Probiotic VSL # 3 as Adjunctive to a Standard Pharmaceutical Treatment: A Double-Blind, Randomized, Placebo-Controlled Study, Am J Gastroenterol advance online publication, 1 June 2010; doi: 10.1038/ajg.2010.218.

17. APPENDIX

17.1 Modified Ulcerative Colitis-Disease Activity Index Scoring System

	Mild (score = 1)	Moderate (score = 2)	Severe (score = 3)
Rectal bleeding	Streaks of blood	Obvious blood	Mostly blood
Stool frequency	1–2/day > normal	3–4/day > normal	>4/day > normal
Mucosal appearance	Erythema	Marked erythema	Ulceration
	Decreased vascular pattern	Friability	Spontaneous bleeding
	Minimal granularity	Granularity	
		Absent vascular pattern	
		Bleeding minimal trauma	
		No ulcerations	
Physician's Global Assessment	Mild	Moderate	Severe

Note: Normal = 0

Modified from Sutherland et al. (Mucosal friability moved from a score of 1 to 2).

Note: In those cases, when patients have variable values for one or more modified UCDAI items, the average must be calculated.

17.2 Inflammatory Bowel Disease Questionnaire (IBDQ)

☐ Not done

Date of completion: _____ (DD-MMM-YYYY)

✓ Please Tick only one option per question listed below

1. How frequent have your bowel movements been during the last 2 weeks?

☐ Bowel movements as or more frequent than they have ever been
☐ Extremely frequent
☐ Very frequent
☐ Moderate increase in frequency of bowel movements
☐ Some increase in frequency of bowel movements
☐ Slight increase in frequency of bowel movements
☐ Normal, no increase in frequency of bowel movements

2. How often has the feeling of fatigue or being tired and worn out been a problem for you during the last 2 weeks?

☐ All of the time

☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

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

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

5. How much of the time during the last 2 weeks have your bowel movements been loose?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

6. How much energy have you had during the last 2 weeks?

☐ No energy at all

- ☐ Very little energy
- ☐ A little energy
- ☐ Some energy
- ☐ A moderate amount of energy
- ☐ A lot of energy
- ☐ 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?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ 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?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

9. How often in the past 2 weeks have you been troubled by cramps in your abdomen?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

10. How often during the last 2 weeks have you felt generally unwell?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

11. How often during the last 2 weeks have you been troubled because of fear of not finding a bathroom?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ 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?

- ☐ A great deal of difficulty; activities made impossible
- ☐ A lot of difficulty
- ☐ A fair bit of difficulty
- ☐ Some difficulty
- ☐ A little difficulty
- ☐ Hardly any difficulty
- ☐ No difficulty; no limit sports or leisure activities

13. How often during the last 2 weeks have you been troubled by pain in the abdomen?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

14. How often during the past 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

15. How often during the past 2 weeks have you felt depressed or discouraged?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

16. How often during the past 2 weeks have you had to avoid attending events where there was no washroom close at hand?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

17. Overall, in the past 2 weeks, how much problem have you had with passing large amounts of gas?

- ☐ A major problem
- ☐ A big problem
- ☐ A significant problem
- ☐ Some trouble
- ☐ A little trouble
- ☐ Hardly any trouble

☐ 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?

☐ A major problem
☐ A big problem
☐ A significant problem
☐ Some trouble
☐ A little trouble
☐ Hardly any trouble
☐ 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 better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ 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?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

21. How often during the last 2 weeks have you felt relaxed and free of tension?

☐ None of the time
☐ A little of the time
☐ Some of the time
☐ A good bit of the time

☐ Most of the time
☐ Almost all of the time
☐ All of the time

22. How much time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

23. How much time during the last 2 weeks have you felt embarrassed as the result of your bowel problem?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

24. How much of the time during the past 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels are empty?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

25. How much of the time during the last 2 weeks have you felt tearful or upset?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time

☐ A little of the time
☐ Hardly any of the time
☐ 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?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

27. How much of the time during last 2 weeks have you felt angry as a result of your bowel problems?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks?

☐ No sex as a result of Bowel disease
☐ Major limitation as a result of Bowel disease
☐ Moderate limitation as a result of Bowel disease
☐ Some limitation as a result of Bowel disease
☐ A little limitation as a result of Bowel disease
☐ Hardly any limitation as a result of Bowel disease
☐ 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?

☐ All of the time
☐ Most of the time
☐ A good bit of the time

☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

30. How much of the time during the past 2 weeks have you felt irritable?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

31. How often during the last 2 weeks have you felt a lack of understanding from others?

☐ All of the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ Hardly any of the time
☐ None of the time

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks?

☐ Very dissatisfied, unhappy most of the time
☐ Generally dissatisfied, unhappy
☐ Somewhat dissatisfied, unhappy
☐ Generally satisfied, pleased
☐ Satisfied most of the time, happy
☐ Very satisfied most of the time, happy
☐ Extremely satisfied, could not have been more happy or pleased

17.3 36-Item Short-Form Questionnaire (SF-36)

☐ Not done

Please answer the 36 questions of the Health Survey completely, honestly, and without interruptions.

1. **In general, would you say your health is:**

   ☐ Excellent ☐ Very Good ☐ Good ☐ Fair
   ☐ Poor

2. **Compared to one year ago, how would you rate your health in general now?**

   ☐ Much better now than one year ago
   ☐ Somewhat better now than one year ago
   ☐ About the same as one year ago
   ☐ Somewhat worse now than one year ago
   ☐ Much worse than one year ago

3. **LIMITATIONS OF ACTIVITIES: The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?**

   a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

      ☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

   b) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

      ☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

   c) Lifting or carrying groceries

      ☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

   d) Climbing several flights of stairs

      ☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

e) Climbing one flight of stairs

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

f) Bending, kneeling, or stooping

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

g) Walking more than a mile

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

h) Walking several hundred yards

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

i) Walking one hundred blocks

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

j) Bathing or dressing yourself

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

4. PHYSICAL HEALTH PROBLEMS: During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a) Cut down the amount of time you spent on work or other activities

☐ Yes ☐ No

b) Accomplished less than you would like

☐ Yes ☐ No

c) Were limited in the kind of work or other activities

☐ Yes ☐ No

d) Had difficulty performing the work or other activities (for example, it took extra effort)

☐ Yes ☐ No

5. **EMOTIONAL HEALTH PROBLEMS: During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

   a) Cut down the amount of time you spent on work or other activities

   ☐ Yes ☐ No

   b) Accomplished less than you would like

   ☐ Yes ☐ No

   c) Didn't do work or other activities as carefully as usual

   ☐ Yes ☐ No

6. **SOCIAL ACTIVITIES: During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

   ☐ Not at all ☐ Slightly ☐ Moderately ☐ Severe ☐ Very Severe

7. **PAIN: How much bodily pain have you had during the past 4 weeks?**

   ☐ None ☐ Very Mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

   ☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

9. **ENERGY AND EMOTIONS: These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.**

   a) Did you feel full of life?

   ☐ All of the time
   ☐ Most of the time

☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

b) Have you been very nervous person?

☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

c) Have you felt so down in the dumps that nothing could cheer you up?

☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

d) Have you felt calm and peaceful?

☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

e) Did you have a lot of energy?

☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

f) Have you felt downhearted and depressed?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

g) Did you feel worn out?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

h) Have you been happy?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

i) Did you feel tired?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

10. SOCIAL ACTIVITIES: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little bit of the time

☐ None of the Time

11. GENERAL HEALTH: How true or false is each of the following statements for you?

a) I seem to get sick a little easier than other people

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

b) I am as healthy as anybody I know

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

c) I expect my health to get worse

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

d) My health is excellent

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false