禾伸堂生技股份有限公司
Holy Stone Healthcare Co., Ltd.

CLINICAL STUDY PROTOCOL

Protocol Number: IBD98-M-2002

Protocol 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

EudraCT Number:	2015-001022-42
Name of Product:	IBD98-M Delayed-release Capsules (Mesalamine and Sodium Hyaluronate)
Phase of Development:	Phase 2a
Indication:	Mild to Moderate Ulcerative Colitis
Sponsor:	Albert Wu, Chief Executive Officer Holy Stone Healthcare Co., Ltd. 4F, No. 88, Sec. 1, NeiHu Road Nei Hu District Taipei City, 11493 Taiwan Republic of China Tel: +886 2 8797 5966 Fax: +886 2 2627 9729
Protocol Version:	Final
Protocol Final Draft Date:	24 March 2015

-CONFIDENTIAL-

HOLY STONE HEALTHCARE CO., LTD., APPROVAL PAGE

Date: _____

Ivy Chen, MSc
Deputy Director, Clinical Development and Regulatory Affairs

Date: _____

Albert Wu, MBA
Chief Executive Officer

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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 Holy Stone Healthcare Co., Ltd.
- Not to implement any changes to the protocol without written agreement from Holy Stone Healthcare Co., Ltd., and prior review and written approval from the Independent Ethics Committee except where necessary to eliminate an immediate hazard to patients.
- That I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Holy Stone Healthcare Co., Ltd., including, but not limited to, the current Investigator's Brochure.
- That I am aware of, and will comply with, good clinical practices and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Holy Stone Healthcare Co., Ltd., study drug and of their study-related duties and functions as described in the protocol.

Signature: _____ Date: _____

Name (print): _____
Investigator

Site Number: _____

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Clinical Laboratory:	Local laboratories will be used

1 SYNOPSIS

Title of Study:	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
Protocol Number:	IBD98-M-2002
Investigators/Study Sites:	This study is to be conducted at 16 sites in Italy
Phase of Development:	2a
Objectives:	**Primary Objective** • To compare the percentage of patients in ulcerative colitis (UC) remission at Week 6 for each of the 2 IBD98-M dose groups versus placebo (remission defined as the Ulcerative Colitis Disease Activity Index [UCDAI] score of ≤1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and ≥1 point reduction from baseline in the sigmoidoscopy score) **Secondary Objectives** • To compare clinical improvement rates at Week 6 among treatment groups (defined as a ≥3 point reduction from baseline in the UCDAI score) • To compare endoscopic improvement at Week 6 among treatment groups (defined as a ≥1 point decrease in 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 Objectives** • To examine the effect of IBD98-M treatment on fecal calprotectin • To examine any correlation between therapeutic response to IBD98-M and baseline characteristics
Study Design and Methods:	Study IBD98-M-2002 is a Phase 2a, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in patients with active, mild to moderately active 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 4 weeks prior to baseline. During the screening period, patients will be evaluated with laboratory tests, physical examination, and sigmoidoscopy. To be eligible, patients are to have a score of ≥4 and ≤10 on the UCDAI, and a score of ≥2 on the UCDAI

	endoscopy subscore. In addition, the diagnosis of UC must be confirmed by endoscopic and histologic evidence in the past; if prior confirmation is not available, this must be done at the time of screening endoscopy. 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. Patients will be encouraged to take their medication at the same time 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 1 visit at the end of the follow-up period at Week 8 (end of study/withdrawal visit). Patients will record the dates/times of dosing (after randomization), concomitant medication, and AEs in a daily diary starting 7 days before treatment and continuing until the end of study/withdrawal visit. Rescue medication will not be permitted during the 6 weeks of the treatment period, and patients who are considered to not be benefiting from the therapy can be withdrawn and assigned an appropriate alternative UC treatment by the Investigator. Compliance will be assessed throughout the study by determining the amount of unused medication. Records will be kept of all medication dispensed, used, and returned by each patient. At the end of the study, all unused trial medication and used packaging will be returned to the Sponsor. All study medication will be accounted for and any discrepancies documented.
Selection of Patients:	<u>Inclusion Criteria</u> A patient must meet all of the following criteria to be eligible for this study. 1. Male or female, age ≥18 and <75 years, suffering from UC for at least 6 months prior to Screening 2. Female patients must be postmenopausal, sterile, or have a negative urine pregnancy test prior to entering the study and use adequate contraception during the study if of childbearing potential. 3. Diagnosis of active UC with UCDAI ≥4 and ≤10, with endoscopy score of ≥2 in the UCDAI mucosal appearance subscore 4. Patients with either newly diagnosed or relapsed UC

	(onset of current episode of relapse must be within 6 weeks of screening). Diagnosis of UC must be confirmed by endoscopic and histologic evidence in the past; if prior confirmation is not available, this must be done at the time of screening endoscopy. 5. Patients must have up-to-date surveillance colonoscopy for malignancy, per treatment guideline. 6. Willing and able to provide signed informed consent <u>Exclusion Criteria</u> A patient who meets any of the following criteria is ineligible to participate in this study. 1. Patients diagnosed with Crohn's disease, indeterminate colitis, or ischemic colitis 2. Female patients who are pregnant or breastfeeding 3. Ulcerative proctitis with <u>≤</u>15 cm of disease 4. Patients with infectious colitis as determined by assessment for *Clostridium difficile* (*C. difficile)* and fecal pathogens at screening or treatment for *C. difficile* within 30 days prior to screening 5. History of or current evidence of toxic megacolon, fulminant colitis (eg, Lichtiger score of ≥10), colonic perforation 6. Any previous colonic surgery (except appendectomy) or short bowel syndrome 7. Patients who required doses of mesalamine higher than 2.4 g/day for previous flares 8. Hypersensitivity to salicylates/aspirin 9. Use of the following medications: a) Use of oral or rectal 5-aminosalicylic (5-ASA) 4 weeks prior to randomization b) Use of systemic or rectal corticosteroid 4 weeks prior to or during screening c) Use of anti-tumor necrosis factor-alpha (anti-TNF-α) agents or other biologics such as vedolizumab within 90 days prior to or during screening d) Use of immunosuppressants (eg, azathioprine, mercaptopurine) within 6 weeks prior to or during screening e) Use of antibiotics for UC within the 7 days prior

	to or during screening 10. Clinically significantly abnormal electrocardiogram (ECG) at screening 11. Liver cirrhosis or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels >2 times the upper limit of normal (ULN) 12. Serum creatinine >2X ULN 13. Positive pre-study drug/alcohol screen 14. Participation in another clinical study involving an investigational agent within the 3 months prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device study (participation in a registry or observational study without an additional therapeutic intervention is allowed). 15. Any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety 16. Had any surgical procedure requiring general anesthesia within 30 days prior to screening or is planning to undergo major surgery during the study period 17. Any active malignancy within the last 5 years, except for basal cell carcinoma of the skin, or if female, in situ cervical carcinoma that has been surgically excised 18. Patient has a history of hepatitis (B or C) or human immunodeficiency virus (HIV). 19. In the opinion of the Investigator, the patient is unable to adhere to the requirements of the study.
Planned Sample Size:	Approximately 51 patients are to be enrolled, with 17 patients randomized to each group. <u>Sample size justification</u> Simon's randomized Phase 2 design was used. The average remission rate of placebo is approximately 0.2. With a Type I error of 0.05, 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.
Investigational Therapy:	IBD98-M (mesalamine and sodium hyaluronate) delayed-release capsules, administered orally twice a day (BID).
Reference Therapy:	Placebo capsule, administered orally BID.
Treatment Duration:	For each patient, up to 4 weeks of screening, 6 weeks of

	treatment and 2 weeks of follow-up
Criteria for Evaluation:	Efficacy: Efficacy is evaluated by assessing clinical and endoscopic changes over time. Patient-reported symptoms include stool frequency and rectal bleeding, and Investigator assessments include mucosal appearance (from sigmoidoscopy) and ratings of disease activity. The UCDAI combines these patient-reported and Investigator-reported scores. Remission as defined by UCDAI score of $\leq$1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and ≥1-point reduction from baseline in the sigmoidoscopy score. Clinical improvement is defined as a ≥3-point reduction from baseline in the UCDAI score. Endoscopic improvement was defined as a ≥1-point reduction from baseline in the UCDAI mucosal appearance subscore. Safety: Safety will be evaluated in terms of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), physical examination findings, vital signs, clinical laboratory parameters (including chemistry, hematology, coagulation, and urinalysis), and periodic ECGs.
Study Endpoints:	**Primary Endpoint** • Percentage of subjects in remission at Week 6. Remission is defined as a UCDAI score of $\leq$1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and ≥1 point reduction from baseline in the sigmoidoscopy score). **Secondary Endpoints** The secondary efficacy endpoints are as follows: • Proportion of subjects with clinical improvement at Week 6 (defined as a ≥3 point reduction from baseline in the UCDAI score) • Proportion of subjects with endoscopic improvement at Week 6 (defined as a ≥1 point decrease in UCDAI mucosal appearance subscore) • Change in symptoms (rectal bleeding and stool frequency) from baseline to each study visit The safety endpoints of this study are as follows: • Incidence and severity of all TEAEs • Incidence and severity of SAEs • Systemic tolerance (physical examination, vital signs, ECGs, and laboratory assessments of safety parameters) **Exploratory endpoints**

	• Reduction in fecal calprotectin
Statistical Methods and Planned Analyses:	Analyses will be done on the intent-to-treat (ITT) population and the per-protocol population. The primary outcome, the percentage of patients in remission at Week 6, will be calculated for each treatment group. An analysis of variance (ANOVA) approach will be used.

2 TABLE OF CONTENTS

IN-TEXT TABLES

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylic agent
6-MP	6 mercaptopurine
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANOVA	Analysis of variance
Anti-TNF-α	Anti- tumour necrosis factor alpha
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AZA	Azathioprine
BID	Twice daily
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
C. difficile	Clostridium Difficile
CPK	Creatine phosphokinase
CRP	C-reactive protein
CFR	Code of Federal Regulations
DCF	Data clarification form
DNBS	Dinitrobenzene sulfonic acid
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GAG	Glycosaminoglycan
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HA	Hyaluronic acid
Hb	Hemoglobin

HCG	Human chorionic gonadotropin
Hct	Hematocrit
HEENT	Head, Eyes, Ears, Nose, and Throat
HHA	High molecular weight hyaluronic acid
HRQoL	Health-related quality of life
IB	Investigator's Brochure
IBDQ	Inflammatory Bowel Disease Questionnaire
IBS	Irritable bowel syndrome
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
LHA	Low molecular weight HA
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCS	Mental component summary
MCV	Mean corpuscular volume
MPO	Myeloperoxidase
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect-level
PCS	Physical component summary
PT	Prothrombin time
QoL	Quality of life
RBC	Red blood cell
SAE	Serious adverse event
SF-12	12 item Short-form questionnaire

SAP	Statistical analysis plan
TEAE	Treatment emergent adverse events
Tlag	Time from administration to first quantifiable concentration
T_{max}	Time of Maximum Drug Concentration
TNBS	2,4,6-trinitrobenzenesulonic acid
UC	Ulcerative colitis
UCDAI	Ulcerative Colitis Disease Activity Index
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
WBC	White blood cell

4 INTRODUCTION

4.1 Background on Ulcerative Colitis

Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease affecting the colon. The prevalence is estimated as 70 to 150 cases per 100,000 with peak age of onset between 15 and 25 years. Ulcerative colitis affects 15% of children, and may present before school-age. The disease usually involves the rectum but may extend proximally to involve a portion of or the entire colon. About 40% to 50% of patients have disease that is limited to the rectum and the rectosigmoid colon, 30% to 40% have disease extending beyond the sigmoid flexure but not involving the whole colon, and 20% have pancolitis.[1]

The mainstay of therapy for mild to moderate UC is sulfasalazine and 5-aminosalicylic (5-ASA) agents. These agents are effective at inducing remission in UC and in maintaining remission in UC. The majority of patients with moderate to severe active UC benefit from topical, oral, or parenteral glucocorticosteroids. Remission, however, cannot be maintained with steroids. Azathioprine (AZA) or 6-mercaptopurine (6-MP) have been employed as glucocorticoid-sparing agents in patients unable to be weaned from glucocorticoids. In early 2006, the first anti-tumor necrosis factor-alpha (anti-TNF-α) agent was approved for the treatment of UC refractory to both corticosteroids and AZA/6-MP. Surgery with colectomy is curative but can be associated with significant morbidity and is thus reserved for acute severe (fulminant) colitis or resistant cases, and in some cases, as cancer prevention. Intestinal continuity can be restored by construction of an ileal pouch-anal pouch anastomosis. Pouchitis is an inflammation of the ileal pouch, occurring in up to 20% to 30% of patients with an ileal pouch-anal anastomosis. The risk of colorectal cancer is increased in patients with extensive disease, and surveillance is usually introduced after 8-10 years of disease duration with regular colonoscopies. Mortality is not increased in UC patients in general, but the disease may present as life-threatening acute severe colitis. Extra-intestinal manifestations of UC include primary sclerosing cholangitis, as well as eye, joint, and skin manifestations.[1]

4.2 Background on Investigational Products

Holy Stone Healthcare Co., Ltd., (Holy Stone Healthcare) has developed a new combination therapy IBD98-M, containing mesalamine and sodium hyaluronate, for the treatment of mild to moderate UC.

Mesalamine is an amino-salicylate non-steroidal anti-inflammatory drug. Although its mechanism of action is not fully understood, mesalamine appears to act topically rather than systemically. Mucosal production of arachidonic acid metabolites, through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic UC, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.2 Mesalamine has been approved in the US under different brand names. Currently, oral, modified-release mesalamine formulations approved for marketing in the US market include Apriso®, Asacol®, Lialda®, Pentasa®, and Delzicol®. The different formulations of mesalamine available on the market differ mainly in the location where the drug is released in the gastrointestinal tract to accomplish its therapeutic effect; thus, the indications of each product are directly related to the site of drug release.3

Sodium hyaluronate, the sodium salt of hyaluronic acid (HA), is a natural polysaccharide found in high concentrations in several soft connective tissues, including skin, umbilical cord, synovial fluid, and vitreous humor. Significant amounts of sodium hyaluronate are also found in lung, kidney, brain, and muscle tissues. Solutions of sodium hyaluronate manifest very unusual rheological properties and are exceedingly lubricious and very hydrophilic. Sodium hyaluronate may enhance the mucosal repair and restoration of the mucosal protective layer. Based on these properties, it is expected that supplementation of sodium hyaluronate may provide a protective barrier to the lining of the colon affected by UC.

IBD98-M is a delayed-release formulation, in the form of a capsule filled with enteric-coated pellets designed to allow the release of both mesalamine and sodium hyaluronate at pH 6.8 or above at the terminal ileum (ascending colon). It is

intended to be used for the treatment of mild to moderate UC. 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, then with sodium hyaluronate, and finished with an enteric coating film. The combination of mesalamine with sodium hyaluronate may allow a reduction in dose of mesalamine, to minimize side effects and enhance therapeutic efficacy.

4.3 Nonclinical Studies

IBD98E (Sodium Hyaluronate) Studies

As part of the development program for IBD98-M, nonclinical efficacy studies were performed in rat models. The concentration of HA for efficacy of 0.5% HA solution was evaluated on 2,4,6-trinitrobenzenesulonic acid (TNBS)-induced UC rat model. Thirty-six Sprague Dawley rats were divided into 2 groups (treatment group and control group, n=18 for each group). All rats were fasting at least 24 hours, then treated with 1 mL TNBS (50 mg/mL) and observed for 3 consecutive days for stool consistency. During the observation period (Day 1 to Day 3), 2 rats died. In order to confirm the colonic lesion after TNBS treatment, 5 rats with soft stools were sacrificed on Day 4. Results showed that the 2 dead rats and the 5 rats with soft stool had suffered obvious colonic injury with TNBS treatment. The remainder of the rats with soft/watery stools were treated with 0.5% HA solution (treatment group, 10 rats) or phosphate-buffered solution (control group, 7 rats) via anus for 7 consecutive days (Day 4 to Day 10). Rats with normal stool were excluded from the study on Day 4. Rats that died during the experimental period (Day 4 to Day 10) were excluded from further analyses. On Day 11, all remaining rats (treatment group, 9 rats; control group, 4 rats) were sacrificed and processed for colitis examination. The mean lengths of colitis wound in control and treatment groups were 1.875 cm and 1.25 cm, respectively. The overall results showed that the mean recovery rate of the treatment group compared to the control group was 33% (See Investigator's Brochure)4.

Treatment with 0.5% HA and 0.25% HA solutions in the TNBS-induced UC rat model was further investigated in 60 rats. Before testing, the TNF-α concentration in each rat was evaluated. Rats with TNF-α concentrations higher than the predetermined criterion of exclusion (130 pg/mL) were excluded. The remaining rats were given TNBS to induce inflammatory bowel disease (IBD) and then divided into 4 groups of 6 rats. Each group was given different test samples: (A) 0.25% HA plus 0.42% Carbomer 971, (B) 0.5% HA plus 0.08% Carbomer 971, (C) 0.25% HA, and (D) 0.5% HA. The rats were fasted for more than 24 hours before administering 1 mL of glycerol to clean out intestinal feces. The rats were then given 1 mL of TNBS via a catheter to induce IBD and observed for 4 days. On Day 1, after induction, rats were allowed normal consumption of food; feces of all rats were normal. However on Day 1, 8 rats had normal feces, 20 rats had soft stools, and 14 rats had watery stools. On Day 4, only 5 rats had watery stools continuously, 14 rats had normal stools, and 22 rats continued to have soft stools. On Day 4, rats with normal stools were excluded, and the remaining rats were divided into 4 groups and continuously given one of A, B, C, or D test samples for a period of 14 days (Day 4 to Day 17). On both Day 11 and Day 18, half of the remaining rats were sacrificed to determine the degree of lesions. The average length of colon with of inflammation colitis for Groups A and B had a range of 0-1.5 cm; Group C showed no lesions on the colon; and Group D had an average colitis length of 0-0.5 cm. On Day 4, serum TNF-α concentration was significantly higher than that on Day 0. The concentration level of TNF-α then gradually decreased, reaching its lowest point on Day 18. However, on the same day, the serum concentrations of TNF-α were not significantly different between groups. In terms of the distribution of lesion size from Day 11 to Day 18, rats in Group C had recovered, Group D showed a gradual recovery trend, but rats in Groups A and B were not significantly different. From a clinical perspective, the Group C treatment (0.25% HA) provided the greatest effect, followed by the Group D treatment (0.5% HA). However, the TNF-α concentration level of each group showed no significant difference; therefore, TNF-α could not be an evaluation indicator.

In a third efficacy study, 32 TNBS-induced UC rats were randomized to 4 groups, each with 8 rats, and were treated rectally with solutions of different molecular weights of HA: 0.25% HA with a ratio of high molecular weight HA (HHA) to low molecular weight HA (LHA) of 1:1, 0.25% HA with a ratio of 4:1, 0.125% HA with a ratio of 1:1, and 0.0625% HA with a ratio of 1:1. On Day 11 and Day 18, the rats were sacrificed, and tissue was collected for macroscopic observations and scoring. The results showed that the recovery rate was over 90% in the treatment groups of 0.25% HA with a HHA:LHA ratio of 4:1 and 0.0625% HA with a ratio of 1:1. The other groups had recovery rates of 70-80%. However, there were no statistically significant differences in wound healing between groups on Day 11 or Day 18.

IBD98-M (Mesalamine and Sodium Hyaluronate) Studies

In a nonclinical efficacy study, 2 combinations of mesalamine and HA were compared with the marketed product Colasa™ (mesalamine) and a phosphate buffer. Forty TNBS-induced UC rats randomized to 4 groups, each with 10 rats, were treated rectally with one of the following solutions: 0.0625% HA (2000 kDa HA/1000 kDa HA) plus 25% Colasa (5 mg/mL mesalamine), 0.0625% HA (2000 kDa HA/350 kDa HA) plus 25% Colasa (5 mg/mL mesalamine), Colasa (20 mg/mL mesalamine), or phosphate buffer. On Day 9 and Day 14, rats were sacrificed, and tissue was collected for macroscopic observations and scoring. Results showed that the recovery rates of rats treated with the solutions of HA plus Colasa (5 mg/mL) and Colasa alone(20 mg/mL) were superior to the phosphate buffer solution alone; and that there were no differences in recovery rates between the preparations with the 2 different molecular weights of HA.

Another efficacy study investigated the adhesion efficacy of HA on ulcer colon tissue in rats induced with colitis. The wound-healing ability of colitis rat models was also investigated. A total of 64 rats with TNBS-induced colitis were randomly divided into 4 groups to receive daily intracolonic treatment for 4 days with one of the following solutions: phosphate buffer, HA, mesalamine, and a mixture of HA and mesalamine. An additional group of 10 rats was a non-induced control group treated with

phosphate buffer. At the end of the treatment period, macroscopic and microscopic colonic injuries were scored, and myeloperoxidase (MPO) activity and cytokine gene expression were measured in colonic tissues.

The results showed that treatment of TNBS-induced colitis with HA or HA with mesalamine was superior to treatment with phosphate buffer solution and mesalamine alone in reducing inflammation and promoting colonic mucosa healing. The treatments containing HA exhibited a similar trend of reduction in MPO activity and inflammatory cytokine gene expression. The results in the rat model of inflammatory colitis support the hypothesis that HA may play an accelerating role in treating inflammatory bowel disease.

A nonclinical efficacy study evaluating the therapeutic effects and efficacy of IBD98-M was also performed in dinitrobenzene sulfonic acid (DNBS) colitis-induced pigs. Four groups, each with 3 pigs, were treated orally with capsules of IBD98-M 200 mg (2 different formulations) BID, placebo, or Pentasa® 500 mg capsules BID for 28 days. To evaluate the healing effect of test articles, endoscopy and biopsy procedures were performed. An endoscopy examination was performed on Day 0 (pre-induction) and on Days 7, 14, 35, and 49 after treatment. A biopsy was performed on Day 35 and 49 after treatment.

The results showed that IBD98-M significantly reduced erythema of the colonic epithelium induced by DNBS and enhanced healing substantially. After 28 consecutive days of oral administration, more than 80% of the IBD98-M group had colitis wound healing, compared with 62% and 50% in the Pentasa® group and placebo group, respectively.

In addition, a 28-day repeated-dose toxicity study (Study PSD14030002) and a 13-week repeated-dose toxicity study (Study PSA14030025) were conducted to evaluate the possible health hazards likely to arise from repeated exposure to the test articles mesalamine and sodium hyaluronate formulated as delayed-release pellets (same pellets used to fill the capsules in IBD98-M product), given to Sprague Dawley rats via oral gavage. As oral mesalamine formulations have been used as

treatment for the induction and maintenance of remission of UC for many years, the purpose of this toxicology study was not to define a maximum tolerated dose of mesalamine in rats. Instead, the purpose was to evaluate the safety profile of the combination of mesalamine and sodium hyaluronate in rats. Accordingly, the results show that the IBD98-M pellet formulation was well tolerated when administered either once daily for 28 days or once daily for 13 weeks at the designated dose levels of 30, 120 and 480 mg/kg of mesalamine and 4.31, 17.25, and 69 mg/kg of sodium hyaluronate. No compound-related deaths, clinical signs, or ocular abnormalities were observed. Administration of IBD98-M pellet formulation for 4 weeks had no significant effects on body weight, hematology, and clinical chemistry or urinalysis parameters. In the 28-day study, high-dose male rats displayed increased food consumption during Week 3, but no significant effects were observed at other times or in female rats. No treatment-related effects on organ weights, gross pathology, or histopathology were observed. Based on these study results, the NOAEL (no-observed-adverse-effect-level) was 480 mg/kg/day of mesalamine and 69 mg/kg/day* of sodium hyaluronate when given from the test article, IBD98-M pellet formulation.

*The NOAEL of sodium hyaluronate should be 55.2 mg/kg/day. The decrease of the amount of HA was recalculated due to the fact that the loss in the manufacturing processes should be excluded.

4.4 Clinical Studies

IBD98E (Sodium Hyaluronate) Study

In a prospective, uncontrolled, open-label 28-day Phase I pilot trial, 21 patients with active distal UC (Ulcerative Colitis Disease Activity Index [UCDAI] ≥4 and sigmoidoscopy score ≥1) received an IBD98E 50 mg/60 mL(0.083%) enema once a day. A paired student's t-test was performed to assess statistically significant differences in patients between baseline and Day 28.

No SAEs were recorded. At Day 28, 9 (42.9%) patients were clinical responders; 10 (47.6%) patients had an endoscopic response; 8 (38.1%) patients achieved clinical remission; and 10 (47.6%) achieved endoscopic remission. The mean UCDAI score decreased from 6.10 at baseline to 3.81 at Day 28 (p=0.001), and the average endoscopic score decreased from 1.57 to 1.10 (p=0.004).

In this study, IBD98E was found to be safe and has some effect in the induction of clinical and endoscopic remission.

IBD98-M (Mesalamine and Sodium Hyaluronate) Study

A Phase 1 trial (Study 110200), a single-dose, 3-way crossover study in healthy subjects, was conducted to compare IBD98-M with the US reference Delzicol® (mesalamine delayed-release capsules) and with the same IBD98-M formulation without sodium hyaluronate (mesalamine delayed-release capsules). The primary objective of this Phase 1 study was to compare the rate and extent of absorption of IBD98-M 200 mg-28.75 g* delayed-release capsule versus Delzicol 400 mg delayed-release capsule, administered as a single oral dose of 2 capsules of IBD98-M 200 mg-28.75 mg* (total dose of 400 mg-57.50* mg), or 1 capsule of Delzicol 400 mg under fasting conditions. The secondary objectives of the study evaluated whether sodium hyaluronate had an impact on the bioavailability of mesalamine from the IBD98-M delayed-release capsule, with and without sodium hyaluronate, and the safety and tolerability of IBD98-M following the administration of a single dose of 2 capsules of IBD98-M 200 mg-28.75 mg* in healthy subjects. The study also included the exploratory objective to characterize the pharmacokinetic profile of HA following administration of a single dose of 2 capsules of IBD98-M 200 mg-28.75 mg*.

The results showed an overall bioavailability of mesalamine of approximately 40% higher following IBD98-M administration under fasting conditions compared with Delzicol. The most important difference in mesalamine absorption was observed within the first 12 hours after the product administration. The lag time (T_{lag}), time from administration to first quantifiable concentration) and time of maximum drug

concentration (T_{max}) of mesalamine were 2 hours and 6 hours, respectively, for IBD98-M (with and without sodium hyaluronate), whereas they were 7.5 hours and 14 hours, respectively, for Dezicol. These values reflect the delayed release nature of the formulations. Following administration of mesalamine-sodium hyaluronate 400 mg-57.8 mg*, exogenous concentrations of HA could be differentiated from endogenous concentrations for most of the subjects. The time to reach the maximum concentration was approximately 6 hours. The elimination half-life was approximately 2.5 hours.

The overall incidence of subjects reporting treatment-emergent adverse events (TEAEs) was similar after the intake of IBD98-M versus mesalamine-only products (IBD98-M without sodium hyaluronate and Delzicol). IBD98-M was well tolerated, with no major unexpected side effects. No safety concerns with respect to the clinical biochemistry, hematology, or urinalysis tests were observed. There were no clinically relevant changes from baseline observed, and no TEAEs were laboratory abnormalities.

* The amount of HA within a capsule should be 23 mg. The total daily dose used in the Phase 1 study should be 400 mg of mesalamine with 46 mg of HA. The decrease of the amount of HA was recalculated due to the fact that the loss in the manufacturing processes should be excluded.

4.5 Rationale for Conducting the Study

Holy Stone Healthcare is developing the IBD98-M delayed-release capsule that combines mesalamine and sodium hyaluronate for the treatment of mild to moderate UC.

In UC, a damaged mucosal barrier is thought to be an initiating factor of the inflammation of the mucosa secondary to the insult by colonic bacterial flora. It has been postulated that the damaged mucosal barrier of the colon lining with insufficient essential components such as lipids and glycosaminoglycan (GAG) may be one of the potential causes of ulcerative colitis. It is therefore expected that the supplementation of some of these components might help in restoring the damaged

mucosa. This is borne out to some extent by the fact that the addition of butyrate, a short chain fatty acid, has been reported to improve the efficacy of mesalamine in refractory distal UC. The data show that the topical administration of butyrate in addition to 4 g of topical mesalamine is significantly more effective in refractory distal UC than administration of mesalamine alone in inducing remission or improvement. Further, there are also some indications that sodium hyaluronate can contribute to the hydration and maintenance of the integrity of the intestinal mucosa, thus facilitating the induction of remission of active UC.[5,6,7,8]

Based on these results, the IBD98-M delayed-release capsule may have the potential to be used for the treatment of mild to moderate UC. This combination of sodium hyaluronate and mesalamine may have additional therapeutic benefit by providing protective barriers to the lining of the colon affected by UC, in addition to the anti-inflammatory activity of mesalamine. This combination may also allow a reduction in the mesalamine daily dose, thus reducing possible mesalamine side effects.

The safety and efficacy of mesalamine is well known, and mesalamine is generally well tolerated.

The safety and efficacy of sodium hyaluronate for the proposed indication (treatment of mild to moderate UC) has not yet been fully proven in humans. However, there are some indications that it might have some therapeutic effect with acceptable safety in individual sufferers.

Mesalamine

Mesalamine is an amino-salicylate non-steroidal anti-inflammatory drug. Its oral form has been used for over 70 years to treat UC, proctitis, and proctosigmoiditis; and mesalazine enema is indicated for the treatment of UC of the distal colon and rectum. The usual dose for the delayed-release oral formulation is up to 4 g of mesalazine once daily, or in 2 or 3 divided doses.

Sodium Hyaluronate

Sodium hyaluronate functions as a tissue lubricant and is thought to play an important role in modulating the interactions between adjacent tissues. It is a polysaccharide which is distributed widely in the extracellular matrix of connective tissue and in epithelial and neural tissues, contributing significantly to cell proliferation and migration. Mechanical protection for tissues and cell layers (corneal, endothelium, and epithelium) are provided by the high viscosity of the solution. In facilitating wound healing, it is thought that sodium hyaluronate acts as a protective transport vehicle, taking peptide growth factors and other structural proteins to a site of action. It is then enzymatically degraded and active proteins are released to promote tissue repair. Among its other medical uses sodium hyaluronate is also used to coat the bladder lining in treating interstitial cystitis.

Proposed Dose for Phase 2 Clinical Studies

From the studies outlined above (Sections 4.3 and 4.4), results show that:

- In colitis rat models, the wound-healing ability of HA, with and without mesalamine, was superior to treatment with phosphate buffer solution and mesalamine alone in reducing inflammatory bowel and promoting colonic mucosa healing. This result supports the hypothesis that HA may play a beneficial role in IBD treatment.
- IBD98-M significantly reduced the erythema of colonic epithelium of pig colitis induced by DNBS and enhanced healing substantially; the healing rate following IBD98-M treatment was approximately 80%, compared to 62% and 50% following treatments with Pentasa and placebo, respectively.
- In Sprague Dawley rats, IBD98-M was well tolerated when administered once daily for 28 days to a maximum of 1075.2 mg/kg/day based on pellet weight. This is equivalent to 480 mg/kg/day of mesalamine and 69 mg*/kg/day of sodium hyaluronate.

- In a Phase I clinical trial performed in healthy males and females, the overall bioavailability of mesalamine was approximately 40% higher following IBD98-M administration compared with that of Delzicol. Further, the overall bioavailability of mesalamine was approximately 20% lower following administration of IBD98-M without the sodium hyaluronate component. The overall incidence of subjects reporting TEAEs was similar following the intake of IBD98-M and mesalamine-only products (IBD98-M without sodium hyaluronate, and Delzicol).
- Finally, in a clinical trial of safety and efficacy of an IBD98E (hyaluronate) 50 mg/60 mL enema, the clinical response was 42.9% with an endoscopic response of 47.6%. Although this was an uncontrolled, open study, this result suggests that hyaluronate may have some effect in the treatment of UC.

* The amount of HA should be 55.2 mg. The decrease in the amount of HA was recalculated due to the fact that the loss in the manufacturing processes (20% loss) should be excluded.

Overall, as shown by the nonclinical and clinical studies, mesalamine and sodium hyaluronate as a combination therapy may provide additional therapeutic benefits, compared to each individual component, such as enhanced efficacy and a reduction in mesalamine dose by up to 40%, along with lower incidence of side effects. This is further supported by the nonclinical study conducted in the TNBS-induced IBD pig model, in which the results showed that the combination formulation IBD98-M provided better efficacy on mucosal healing even though the treatment dose of mesalamine was 40% of the dose in the marketed mesalamine product.

Regarding the proposed dose of hyaluronate, the clinical trial with the hyaluronate enema offers some useful data. In this study, the dose used was 50 mg of hyaluronate. It is generally accepted that mesalamine enema is recommended for the treatment of UC of the distal colon including proctosigmoiditis, which is roughly just over one third of the large bowel. It is therefore reasonable to assume that for

the oral treatment of diffuse colitis, it may be advisable to test a daily dose of about 3 times the dose in the enema shown to have some effect in the distal colon only.

In conclusion, based on the clinical and nonclinical findings, and for the purposes of evaluating the proof-of-concept, the proposed mesalamine daily doses for this Phase 2a clinical study are 800 mg and 1.2 g, with the sodium hyaluronate daily doses of 92 mg and 138 mg per day, respectively.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

Primary Objective

- To compare the percentage of patients in UC remission at Week 6 for each of the 2 IBD98-M dose groups versus placebo (remission defined as the Ulcerative Colitis Disease Activity Index [UCDAI] score of ≤1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and ≥1 point reduction from baseline in the sigmoidoscopy score)

Secondary Objectives

- To compare clinical improvement rates at Week 6 among treatment groups (defined as a ≥3 point reduction from baseline in the UCDAI score)
- To compare endoscopic improvement at Week 6 among treatment groups (defined as a ≥1 point decrease in 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 Objectives

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

5.2 Study Endpoints

5.2.1 Primary Endpoint

- Percentage of patients in remission at Week 6

Remission as defined by UCDAI] score of ≤1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and ≥1 point reduction from baseline in the sigmoidoscopy score.

5.2.2 Secondary Endpoints

The secondary efficacy endpoints are as follows:

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

The safety endpoints are as follows:

- Incidence and severity of all TEAEs
- Incidence and severity of SAEs
- Systemic tolerance (physical examination, vital signs, electrocardiograms (ECG)s, and laboratory assessments of safety parameters)

5.2.3 Exploratory Endpoints

- Reduction in fecal calprotectin

6 INVESTIGATIONAL PLAN

6.1 Description of Overall 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 4 weeks prior to baseline. 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 UCDAI, and a score of >2 on the endoscopy subscore would be included. In addition, the diagnosis of UC must be confirmed visually by endoscopy images. 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 mg 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 voice response system (IVRS), and each patient will receive 3 capsules twice a day 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 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 will receive 3 placebo tablets BID.

Patients should be encouraged to take their medication at the same time 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 study visit. 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.

6.2 Discussion of Study Design

This Phase 2a study is being conducted as an exploratory proof of concept study to examine efficacy and tolerability of the combination of mesalamine with sodium hyaluronate. The primary objective is to determine the efficacy of IBD98-M, assessed by the ability to induce clinical and endoscopic remission after 6 weeks of treatment compared with placebo, in patients with active mild to moderate UC. The study examines 2 delayed-release doses of IBD98-M (mesalamine 0.8 g with sodium hyaluronate 92 mg, and mesalamine 1.2 g with sodium hyaluronate 138 mg) compared with placebo following 6 weeks of treatment. In addition, the study will also evaluate the safety of IBD98-M. The study design and primary/secondary objectives reflect those recommended for evaluating the efficacy, safety, and tolerability of an investigational product in patients with active mild to moderate UC.[1]

Simon's randomized Phase 2 design was used.[9] The average remission rate of placebo is approximately 0.2 With a Type I error of 0.05, 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.

7 SELECTION AND WITHDRAWAL OF PATIENTS

7.1 Inclusion Criteria

Patients must meet all of the following criteria in order to be eligible for the study:

1. Male or female, age ≥18 and <75 years, suffering from UC for at least 6 months
2. Female patients must be postmenopausal, sterile, or have a negative urine pregnancy test prior to entering the study and use adequate contraception during the study if of childbearing potential.
3. Diagnosis of active UC with UCDAI ≥4 and ≤10, with endoscopy score of ≥2 in the UCDAI mucosal appearance subscore.

4. Patients with either newly diagnosed or relapsed UC (onset of current episode of relapse must be within 6 weeks of screening). Diagnosis of UC must be confirmed by endoscopic and histologic evidence in the past; if prior confirmation is not available, this must be done at the time of screening endoscopy.
5. Patients must have up-to-date surveillance colonoscopy for malignancy, per treatment guideline.
6. Willing and able to provide signed informed consent

7.2 Exclusion Criteria

Patients meeting any of the following criteria are ineligible to participate in this study:

1. Patients diagnosed with Crohn's disease, indeterminate colitis, or ischaemic colitis
2. Female patients who are pregnant or breastfeeding
3. Ulcerative proctitis with ≤15 cm of disease
4. Patients with infectious colitis, as determined by assessment for *C. difficile* and fecal pathogens at screening, or treatment for *C. difficile* within 30 days prior to screening
5. History of or current evidence of toxic megacolon, fulminant colitis (eg Lichtiger score of ≥10), colonic perforation
6. Any previous colonic surgery (except appendectomy) or short bowel syndrome
7. Patients who required doses of mesalamine higher than 2.4 g/day for previous flares
8. Hypersensitivity to salicylates / aspirin
9. Use of the following medications:
    a. Use of oral or rectal 5-ASA 4 weeks prior to randomization

b. Use of systemic or rectal corticosteroid 4 weeks prior to or during screening

c. Use of anti-TNFα agents or other biologics such as vedolizumab within 90 days prior to or during screening

d. Use of immunosuppressants (eg, azathioprine, mercaptopurine) within 6 weeks prior to or during screening

e. Use of antibiotics for UC within the 7 days prior to or during screening

10. Clinically significantly abnormal ECG at screening
11. Liver cirrhosis or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels >2 times the upper limit of normal (ULN)
12. Serum creatinine >2X ULN
13. Positive pre-study drug/alcohol screen
14. Participation in another clinical trial involving an investigational agent within 3 months prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device trial while participating in this study (participation in a registry or observational study without an additional therapeutic intervention is allowed)
15. Any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the Investigator, would confound the study results or compromise patient safety
16. Had any surgical procedure requiring general anesthesia within 30 days prior to screening or is planning to undergo major surgery during the study period
17. Any active malignancy within the last 5 years, except for basal cell carcinoma of the skin, or if female, in situ cervical carcinoma that has been surgically excised

18. Patient has a history of hepatitis (B or C) or human immunodeficiency virus (HIV)
19. In the opinion of the Investigator, the patient is unable to adhere to the requirements of the study

7.3 Withdrawal, Removal, and Replacement of Patients

At any time, a patient's participation in the study may be terminated at his/her request or on the basis of the Investigator's clinical judgment. The reason for patient withdrawal will be noted on the electronic case report form (eCRF).

A patient may be discontinued from the study for the following medical or administrative reasons:

- Occurrence of an AE that in the judgment of the Investigator suggests an unacceptable risk to the patient
- Development of any condition on-study that, in the opinion of the Investigator or the Sponsor, places the patient at an unacceptable medical risk if he/she continues
- Pregnancy
- Patient request
- Institution of additional medical (rescue) therapy for UC. Rescue medication will not be permitted during the 6-week double-blind treatment period, and patients considered as treatment failures will be withdrawn and assigned an appropriate alternative UC treatment by the Investigator.

The Investigator may discontinue individual patients from the study at any time. Patients will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The date of and reason for study discontinuation must be recorded on the eCRF regardless of the reason for withdrawal; all patients will be asked to undergo an end-of-study/early termination evaluation. Every attempt will be made to obtain all of the end-of-study assessments, including all of the subscales

of the UCDAI (i.e., stool frequency, bleeding, physician's assessment, and sigmoidoscopy score).

This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her site for any reason, including safety or low enrollment.

In the event that a patient discontinues prematurely from the study due to a TEAE or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant.

Patients who withdraw or are withdrawn may not re-enter the study and will not be replaced under this protocol.

8 TREATMENTS

8.1 Details of Study Treatments

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 into 200-cc white, wide-mouth, round HDPE bottles sealed with an aluminum foil pad and covered with a polypropylene plastic cap. The product stability is for 12 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].

Study treatments are described in **錯誤! 找不到參照來源。**.

Table 1: Details of Study Treatments

	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	Not applicable	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

8.2 Dosage Schedule

Patients will be randomized to 1 of 3 treatment groups: IBD98-M 0.8 g/day (mesalamine 0.8 g with hyaluronate 92 mg), IBD98-M 1.2 g/day (mesalamine1.2 g with hyaluronate 138 mg), or placebo. Three blinded capsules of study medication (1 capsule from each of the 3 bottles in the medication kit) will be taken by each patient orally with water twice a day (See section 8.4). Patients will be instructed to swallow the study medication whole without breaking or chewing. Patients will be required to take the medication twice a day and will be encouraged to take their medication at the same times every day (in the morning and evening). All doses taken during the study must be recorded in the patient's diary.

8.3 Study Treatment Assignment

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

8.4 Blinding

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 IVRS-assigned kit, labeled with a unique kit ID at Visit 2, Week 0. Each kit will contain 3 bottles labeled with A, B, and C. Each patient should take **1 capsule from each bottle** twice a day. Each kit shall contain sufficient supply for 6 weeks.

The study will be double-blind. Subjects 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

8.5 Treatment Accountability and Compliance

It is the responsibility of the Sponsor to ensure that study medications provided for this study are manufactured under Good Manufacturing Practices and are suitable for human use. It is the responsibility of the Sponsor to ship a sufficient amount of dosage units to allow inVentiv to maintain an appropriate sampling for the study, and for drug retention, according to Food and Drug Administration (FDA) regulation (21 CFR 320.38, 320.63). Study medication will be stored by inVentiv as per applicable requirements.

The medications will be stored in a locked, environmentally controlled medication room with restricted access. Container(s) will bear a label containing at least the name of the study drug, lot and/or batch number, and manufacturing and/or expiry/retest date and a unique kit number. Individual patient doses will be

dispensed according to the kit number as assigned by IVRS, at Visit 3. All study drug received at the site will be inventoried and accounted for throughout the study and the result recorded in the drug accountability/retention record according to the appropriate inVentiv Standard Operating Procedure.

Compliance will be assessed by determining the amount of unused medication. Records will be kept of all medication dispensed, used, and returned by each patient. All doses taken during the study must be recorded in the patient's diary. The medication bottles (partial and empty) must be checked at the end of the study and compliance recorded on the Dosage Administration Record of the eCRF. At the end of the study, all unused trial medication and used packaging will be returned to the Sponsor. All study medication will be accounted for and any discrepancies documented.

8.6 Prior and Concomitant Illnesses, Procedures, and Medications

8.6.1 Prior and Concomitant Illnesses

Investigators should document all prior significant illnesses that the patient has experienced within 3 months prior to screening and in line with entry criteria. Additional illnesses present at the time when informed consent is given and up to the time of first dose are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as adverse events (AEs) on the eCRF.

8.6.2 Concomitant Procedures

All procedures that are performed during the study must be recorded in the patient's source documents and in the eCRF. The following should be taken into account with regard to concomitant procedures:

- Patients may not undergo major elective surgery while enrolled in this study.
- Patients may not donate blood, sperm, or oocytes during the study and for 6 months after the last dose of study drug.

8.6.3 Prior and Concomitant Medications

Patients must follow the medication restrictions outlined in the inclusion and exclusion criteria (Sections 7.1 and 7.2) during the study. The use of hormonal contraceptives will be allowed and documented. Any concomitant medication use other than the occasional use of acetaminophen will be evaluated on a case-by-case basis by the Investigator. All concomitant medication use will be documented.

The use of the following medications is prohibited during the study:

- Rectal 5-ASA, budesonide, or steroids
- Systemic (oral or intravenous [IV]) corticosteroid
- Oral or parenteral immunuosuppresants for treatment of UC
- Antibiotics for treatment of UC

9 STUDY PROCEDURES

Table 2 outlines the timing of procedures and assessments to be performed throughout the study. See Sections 錯誤! 找不到參照來源。 to 11.8 for additional details of study procedures.

Table 2: 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	**--28 to -7**	**-14 to -1**	**0**(± 1 day)	**14**(± 3 days)	**28**(± 3 days)	**42**(± 3 days)	**56**(± 3 days)
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 and Height	X					X	
12-Lead ECG	X					X	
Hepatitis Screening	X						
CBC with differential	X		X	X	X	X	X
Coagulation (aPTT, PT, INR)	X			X		X	
Serum Chemistry	X		X	X	X	X	X
Urinalysis	X		X	X	X	X	X
Pregnancy Test[b]	X		X		X	X	
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
UCDAI[c]		X	X	X	X	X	
IBDQ, SF-36			X			X	
CRP			X		X	X	
Flexible Sigmoidoscopy		X[d]				X	
Distribution of Diary / Check	X	X	X	X	X	X	
Stool for culture, C. difficile toxin, and ova & parasite	X						
Randomization			X[e]				
Treatment Distribution / accountability			X	X	X	X[f]	
Stool calprotectin			X			X	

Abbreviations: AE=adverse event; ECG= electrocardiogram; aPTT= activated partial prothrombin time; BMI= body mass index; PT= prothrombin time; INR= international normalization ratio; CRP=C-reactive protein; HRQoL= Health Related Quality of LIfe; IBDQ= Inflammatory Bowel Disease Questionnaire; *C. difficile*=Clostridium Difficile; eCRF=electronic case report form; UCDAI= Ulcerative Colitis Disease Activity Index

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

b. Pregnancy test performed at screening should be serum test, after screening should be urine pregnancy tests

c. UCDAI on Days 0 and 42 should be complete UCDAI score including the endoscopy subscore. UCDAI at Screening Visit 2, and Days14 and 28 should be partial UCDAI score including only stool frequency, rectal bleeding and physician's global assessment

d. Screening sigmoidoscopy must be performed on day -14 to -1

e. To be performed prior to dosing

f. On Day 42, there will be no study drug distribution

9.1 Patient Informed Consent

Prior to performing any study-related procedures, the Investigator (or his/her designated staff member) will obtain written informed consent from the patient.

9.2 Procedures by Study Visit

Assessments are to be performed as outlined in the following by-visit subsections.

9.2.1 Screening Period: Visit 1 (Days -28 to -7) and Visit 2 (Days -14 to -1, Baseline)

The first screening visit will occur within -28 to -7 days prior to Day 0. The following procedures will be performed:

- Informed consent
- Demographics data collection: date of birth, country, gender, and ethnicity
- Physical examination (including weight and height for body mass index [BMI])
- All current and past medical conditions and disease history
- Verification of inclusion and exclusion criteria
- Vital signs (pulse, blood pressure, and body temperature) measurements
- 12-lead ECG
- Serology for HIV, and Hepatitis B and C
- Hematology assessments: complete blood count (CBC) with differential, activated partial prothrombin time (aPTT), prothrombin time (PT), and international normalization ratio (INR)
- Serum chemistry
- Urinalysis
- Serum sample for pregnancy test
- Recording of AEs and concomitant medications
- Stool sample for C. difficile, culture, and calprotectin
- Distribution of diary

The second screening (baseline) visit will occur within -14 to -1 days prior to Day 0. The following procedures will be performed:

- Verification of inclusion and exclusion criteria

- Vital signs (pulse, blood pressure, and body temperature) measurements
- Recording of AEs and concomitant medications
- UCDAI
- Flexible sigmoidoscopy
- Distribution of diary

9.2.2 Treatment Period: Visit 3 (Day 0 [± 1 day]; Randomization)

All patients will undergo the following procedures:

- Physical examination (including weight and height for BMI calculation)
- Vital signs (pulse, blood pressure, and body temperature) measurements
- Verification of inclusion and exclusion criteria
- Hematology assessments: Complete blood count (CBC) with differential
- Serum chemistry, including C-reactive protein (CRP)
- Urinalysis
- Urine pregnancy test
- Recording of AEs and concomitant medications
- Randomization via IVRS
- Check diary
- UCDAI
- Inflammatory Bowel Disease Questionnaire (IBDQ); 36-Item Short Form Questionnaire (SF-36)
- Stool sample for calprotectin
- Reserve blood sample
- Distribution and check of diary
- Blinded study medication distribution

9.2.3 Treatment Period: Visits 4, 5, and 6 or End-of-Study Visit, or Early Termination Visit (Days 14, 28, and 42) (± 3 days)

All patients will undergo the following procedures:

- Physical examination (weight and height at Visit 6 only)
- Vital signs (pulse, blood pressure, and body temperature) measurements
- ECG (Visit 6 only)

- Hematology assessments: CBC with differential at Visits 4, 5, and 6; and aPTT, PT, and INR at Visit 4 only
- Serum chemistry (CRP at Visit 5 and 6 only)
- Urinalysis
- Urine pregnancy test (at Visit 5 and 6 only)
- Recording of AEs and concomitant medications
- UCDAI
- IBDQ; SF-36 (only at Visit 6)
- Check diary and distribution of diary (except Visit 6)
- Blinded study medication distribution (except at Visit 6)
- Stool sample for calprotectin (only at Visit 6)
- Reserve blood sample
- Flexible sigmoidoscopy (only at Visit 6)

9.2.4 Follow-up Period: Visit 7 (Day 56 [± 3 days])

Patients who prematurely withdraw from the study for any reason should complete the Early Termination Visit requirements. If the Early Termination Visit is not done, the reason(s) will be recorded in the CRF. All patients will undergo the following Visit 7 procedures:

- Vital signs (pulse, blood pressure, and body temperature) measurements
- Physical examination
- Hematology assessments: CBC with differential
- Serum chemistry
- Urinalysis
- Recording of AEs and concomitant medications

10 EFFICACY ASSESSMENTS

10.1 Ulcerative Colitis Disease Activity Index (UCDAI) Score

The modified UCDAI score will be used for assessment of efficacy during the study. Subjects are strongly encouraged to complete the symptom diary on a daily basis throughout the study.

Timing of diary entries for UCDAI

- At Baseline (Day 0), the timing of the diary entries depends on when the endoscopy is performed
    - If the endoscopy is performed within 5 days of randomization (Day 0), use the diary entries from 3 consecutive days immediately prior to the preparation day for the endoscopy.
    - If the endoscopy is performed 6 to 14 days prior to the randomization day (Day 0), the diary entries from 3 consecutive days immediately prior to Day 0 should be used.
    - The endoscopy must be performed within 14 days of randomization (Day 0).
- For visits where an endoscopy is not needed (Day 14 and 28), diary entries from the 3 days preceding the visit day will be used for the assessment of stool frequency, rectal bleeding, and physician's global assessment.
- For the Day 42 visit, diary entries from the 3 days preceding the visit day or the preparation for endoscopy, whichever comes first, will be used for the UCDAI assessment. Endoscopy must be performed within 3 days of the target visit day.

See Appendix 1 for further detail.

Endoscopy subscore of the UCDAI

Sigmoidoscopy will be conducted during the second screening visit (for baseline UCDAI) and at Day 42 ± 3 days / early termination. The cleansing preparation should be conducted per site routine. The endoscopy performed at both visits should be a sigmoidoscopy, only the segment distal to the splenic flexure should be considered for purpose of endoscopy scoring (range from 0 to 3 points) per modified UCDAI (Appendix 1). Note that the modified UCDAI designates the presence of any friability as score of 2.

10.2 Inflammatory Bowel Disease Questionnaire (IBDQ)

The Inflammatory Bowel Disease Questionnaire (IBDQ) will be used to measure disease specific quality of life (QoL). The IBDQ is a self-administered 32-item questionnaire that evaluates QoL across 4 dimensions: (1) Bowel – symptoms related to primary bowel disturbance, (2) Systemic symptoms, (3) Emotional function, and (4) Social function. The response to each question can range from 1 to 7, with 1 indicating severe problem and 7 normal health. The total IBDQ is computed as the sum of the responses to the individual IBDQ questions. The total score can range between 32 and 224, with higher scores indicating better QoL. IBDQ will be completed at Days 0 and 42. See Appendix 3.

10.3 Short Form-36

The Short Form-36 (SF-36) questionnaire will be used to measure general health-related QoL. Individual subscale scores and two summary scores will be calculated: (1) physical component summary (PCS), which includes physical functioning, role-physical, bodily pain, and general health; (2) mental component summary (MCS), which includes vitality, social functioning, role-emotional, and mental health. SF-36 form will be completed at Days 0 and 42. See Appendix 4.

11 SAFETY ASSESSMENTS

Safety assessments (vital signs, physical examinations, periodic ECG recordings, AEs, SAEs, clinical laboratory results [routine hematology and biochemistry] are to be performed as specified in the Schedule of Events, Table 2.

11.1 Vital Signs

Vital signs (body temperature, respiration rate, heart rate, and blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Events. All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Body weight (without shoes) will be recorded whenever vital signs are recorded, and height (without shoes) will be recorded at baseline only.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

11.2 Physical Examination

A complete physical examination (heart, eyes, ears, nose, and throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at Screening Visit 1, Visit 3 and Visit 6. Physical examinations will be performed by a physician. In addition, medical history will be recorded at screening, including smoking history, if applicable.

A limited physical examination to verify continued patient eligibility and to follow any change in medical history will be performed at the visits indicated in the Schedule of Assessments (Visit 4 and 5). Symptom-driven limited physical examinations will be performed as clinically indicated at any study visit. All changes not present at

baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

11.3 Electrocardiogram

A 12-lead resting ECG will be obtained at the visits indicated in the Schedule of Events.

At screening, the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the patient from the study. An assessment of normal or abnormal will be recorded, and if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs may be repeated if clinically significant abnormalities are observed or artifacts are present.

11.4 Laboratory Assessments

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the Schedule of Events.

Table 3: Laboratory Assessments

Blood Tests		
Hematology	**Serum chemistry**	**Coagulation**
Full and differential blood count Hematocrit (Hct) Hemoglobin (Hb) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential	Albumin Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Blood urea nitrogen (BUN) or urea Creatinine Creatine phosphokinase (CPK) Electrolytes (Na, K,) Gamma--glutamyl transpeptidase (GGT) Glucose Lactate dehydrogenase (LDH) Total bilirubin Total cholesterol Triglyceride C-reactive protein (CRP)	Prothrombin time (PT) Activated partial thromboplastin time (PTT) INR (international normalization ratio)
Pregnancy test: A serum pregnancy test will be performed on all female patients of childbearing potential at the screening visit		
Urinalysis (dipstick)		
Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urine human chorionic gonadotropin (HCG) (pre-menopausal females only) Urobilinogen		
Fecal calprotectin		

Blood and urine samples will be analyzed at a local laboratory facility. Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated. Stool

samples will be collected and analyzed as described in Sections 11.5 and 11.6. All laboratory reports must be reviewed, signed, and dated by the Investigator. A legible copy of all reports must be filed with both the patient's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the Investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

11.5 Stool Sample for Cultures

A stool sample will be obtained for culture, ova and parasite evaluation, and *C. difficile* assay. 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.

11.6 Fecal Calprotectin Sample Collection

A stool sample will be collected on Days 0 and 42 for the analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity.
Serum samples will be collected for CRP on Days 0, 28, and 42 for analysis of CRP, a blood biomarker for inflammation.

11.7 Diary Completion and Review

During screening, patients will be instructed on how to appropriately complete the diary. The symptoms of UC must be recorded throughout the study, including the screening period. The patient diaries will be distributed at Visit 1 to record baseline data in the 7 days prior to Day 0. Diaries will be distributed at Visits 2, 3, 4, and 5 to

collect patient data during the treatment period. Diary entries will be reviewed by site personnel at the visits indicated in the Schedule of Events.

11.8 Adverse Events

11.8.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs.

AE Reporting

Patients will be instructed to report AEs at each study visit. All AEs are to be followed until resolution or until a stable clinical endpoint is reached.

Each AE is to be documented on the CRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient gives informed consent until the follow-up visit (Visit 7). Follow-up of the AE, even after the date of therapy discontinuation, is required until the event resolves or stabilizes at a level acceptable to the Investigator.

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in Table 4 andTable 5.

Table 4: Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities

MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities

SEVERE: An event that prevents normal everyday activities

Table 5: Classification of Adverse Events by Relationship to Study Drug

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).

UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is re-administered.

POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or (3) it follows a known pattern of response to the test drug.

PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.

DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

11.8.2 Serious Adverse Events

An AE is considered “serious” if in the view of either the Investigator or Sponsor, it meets 1 or more of the following criteria:

- Is fatal
- Is life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. Since SAEs are critically important for the identification of significant safety problems, it is important to take into account both the Investigator’s and the Sponsor’s assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

<u>SAE Reporting</u>

An SAE occurring during the study or within 2 weeks of stopping the treatment must be reported to the inVentiv Health Clinical Pharmacovigilance Group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or

protocol-specific procedures. Notification can be made using the dedicated fax line or telephone line for the inVentiv Health Clinical Pharmacovigilance Group:

inVentiv Health Clinical Pharmacovigilance Fax Number: +44 1628 461184

inVentiv Health Clinical Pharmacovigilance Telephone Number: +44 1628 408408

If the Investigator contacts the inVentiv Health Clinical Pharmacovigilance Group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to the inVentiv Health Clinical Pharmacovigilance Group within 10 calendar days. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

11.8.3 Pregnancy

Female patients of childbearing potential must have a negative pregnancy test at screening. Following administration of study drug, any known cases of pregnancy in female patients will be reported until the patient completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator will follow the patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (eg, spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing a completed SAE form to the Sponsor (or designee) within 24 hours of knowledge of the event.

11.8.4 Overdose

The Investigator must immediately notify the Sponsor of any occurrence of overdose with study drug.

12 STATISTICAL ANALYSIS

A Statistical Analysis Plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP supersedes the protocol's analysis sections in case of differences.

The statistical evaluation will be performed using Statistical Analysis Software (SAS®) Version 9.2 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by treatment group. For continuous variables, data will be summarized with the number of patients,

mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and percentage of patients for each category by treatment group.

One interim analysis is planned.

12.1 Determination of Sample size

Simon's randomized Phase 2 design was used.[9] The average remission rate of placebo is approximately 0.2.[9] With a type I error of 0.05, 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

12.2 Analysis Populations

Intent-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 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.

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.

12.3 Demographic and Baseline Characteristics

All data for background and demographic variables will be listed by treatment group and patient. For these parameters, summary statistics will be provided by treatment group. For continuous data, sample size, mean, standard deviation, minimum, median, and maximum will be provided and for categorical data, sample size and frequency will be provided.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests, and any other relevant information will be listed by treatment group and patient.

12.4 Efficacy Analysis

Detailed methodology for the statistical analyses, including details of the data summary tables and figures, will be documented in the SAP.

12.4.1 Analysis of Efficacy Endpoints

The primary analysis will utilize the ITT population, with non-responder imputation. A subject is considered a non-responder if no diary data is available within Day 36 to study end or endoscopy within Day 28 to study end. Remission will be assessed, defined by a UCDAI score of ≤1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and ≥1 point reduction from baseline in the sigmoidoscopy score. Proportion rates between groups will be summarized with 95% confidence intervals included. Treatment groups will be compared using analysis of variance (ANOVA).

As a supportive analysis, the primary analysis will also be done using the per protocol population. Also, sensitivity analysis to assess the effects of missing data may be performed.

Secondary endpoints corresponding to remission or improvement will be analyzed in a manner similar to the primary endpoint. No adjustments for multiplicity will be made.

Secondary safety endpoints will be listed and summarized by treatment group.

12.5 Safety Analysis

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities, Version 18.0. The incidence of TEAEs will be summarized. Events with missing onset dates will be included as treatment-emergent. If a patient experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. SAEs and AEs causing discontinuation will be tabulated. All AEs will be listed by patient, along with information regarding onset, duration, severity, and relationship to study drug, action taken with study drug, treatment of event, and outcome.

Clinical laboratory data and vital signs will be summarized using descriptive statistics including mean values and mean change from baseline values, as well as numbers of patients with values outside limits of the normal range at each time point.

Summary tables will be provided for concomitant medications initiated during the study period.

12.6 Interim Analysis

One interim analysis for the purpose of safety and futility will be conducted after 50% of patients have completed the study. If voluntary withdrawal due to safety and/or tolerability exceeds 30% in either of the 2 active treatment groups, then no additional

patients will be enrolled into that group. No further study drug will be administered in this group, but patients will be continued to be monitored for safety. An unblinded statistician independent of the blinded study team, for whom firewalls will be established and well documented, will be assigned within inVentiv Health Biostatistics department to perform this analysis.

This unblinded statistician will also review accumulated safety data at regular intervals throughout the study. The unblinded statistician will confer with inVentiv Pharmacovigilence, as appropriate. The unblinded statistician can recommend in writing to the Sponsor whether to continue, modify, or stop the clinical study on the basis of efficacy and safety considerations. The unblinded statistician's specific duties and specific information regarding interim analyses will be fully described in the SAP.

13 STUDY MANAGEMENT

13.1 Approval and Consent

13.1.1 Regulatory Guidelines

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study protocol, Good Clinical Practices (GCPs) as defined in Title 21 of the US CFR Parts 50, 54 56, 312, and Part 11, as well as International Conference on Harmonisation (ICH) GCP consolidated guidelines (E6) and applicable regulatory requirements.

13.1.2 Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted Independent Ethics Committee (IEC). Approval is required for the study protocol, investigational drug brochure, protocol amendments, Informed Consent Forms (ICFs), and patient information sheets.

13.1.3 Informed Consent

For each study patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and ICH guidelines. The Investigator will provide the Sponsor or its representative with a copy of the IEC-approved ICF prior to the start of the study.

13.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from other source documents should be consistent with the source documents, or the discrepancies must be explained.

Clinical data will be entered on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, Internet-based electronic data capture (EDC) system maintained by inVentiv Health Clinical. Access to the EDC system is available to authorized users via the study's Internet web site, where an assigned username and password are required for access.

Any changes made to data after collection will be made through the use of Data Clarification Forms (DCFs). eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

13.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

13.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information,

13.5 Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site monitoring visits will be made at appropriate times during the study. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

The Investigator will make available to the clinical monitor source documents and medical records necessary to complete eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate

evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

13.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

13.7 Protocol Amendment and Protocol Deviation

13.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IECs for approval.

13.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and the reasons they occurred will be included in the

clinical study report. Reporting of protocol deviations to the IEC and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

13.8 Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal and local regulations.

All patients are required to give written informed consent prior to participation in the study.

13.9 Financing and Insurance

Prior to the study commencing, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

13.10 Publication Policy / Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their

Institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

14 REFERENCES

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15 APPENDICES

APPENDIX 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 Decreased vascular pattern Minimal granularity	Marked erythema Friability Granularity Absent vascular pattern Bleeding minimal trauma No ulcerations	Ulceration Spontaneous bleeding
Physician's Global Assessment	Mild	Moderate	Severe

Note: Modified from Sutherland et al. (mucosal friability moved from a score of 1 to 2)[10]

APPENDIX 2 LABORATORY ABNORMALITY CRITERIA

Criteria for assessing marked abnormalities in safety laboratory parameters are based on Grade 2 moderate intensity levels from the Division of AIDS table for grading the severity of adult and pediatric adverse events (Version 1.0, December, 2004; Clarification August 2009).

Marked Abnormality Criteria for Safety Laboratory Parameters			
Parameter	**Units**	**Direction of Change**	**Marked Abnormalities**
HEMATOLOGY			
Hemoglobin	g/dL	Low Only	≤ 7.0 g/dL
Absolute Lymphocyte Count	10^9	Low Only	<0.5 X10^9
Leukocytes	mm^3	Low Only	Absolute Value < 2,000/ mm^3
Platelets	mm^3	Low Only	<75,000/ mm^3
Absolute Neutrophil Count	mm^3	Low Only	<1000 mm^3
Prothrombin Time	%	High Only	>1.25 x ULN
CHEMISTRY			
SGPT	ULN	High Only	>3.0 x ULN
SGOT	ULN	High Only	>3.0 x ULN
Bilirubin	ULN	High Only	>2.0 x ULN

APPENDIX 3 Inflammatory Bowel Disease Questionnaire (IBDQ)

For Review Purposes Only

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

For Review Purposes Only

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

For Review Purposes Only

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

For Review Purposes Only

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

For Review Purposes Only

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

For Review Purposes Only

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

For Review Purposes Only

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

For Review Purposes Only

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

For Review Purposes Only

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

For Review Purposes Only

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

APPENDIX 4 36-Item Short-Form Questionnaire (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

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

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

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 now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c. Lifting or carrying groceries	☐1	☐2	☐3
d. Climbing several flights of stairs	☐1	☐2	☐3
e. Climbing one flight of stairs	☐1	☐2	☐3
f. Bending, kneeling, or stooping	☐1	☐2	☐3
g. Walking more than a mile	☐1	☐2	☐3
h. Walking several hundred yards	☐1	☐2	☐3
i. Walking one hundred yards	☐1	☐2	☐3
j. Bathing or dressing yourself	☐1	☐2	☐3

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4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. **During the past 4 weeks, how much of the time 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)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. **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	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

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

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

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
☐1	☐2	☐3	☐4	☐5

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9. **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 one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. **How TRUE or FALSE is each of the following statements for you?**

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

THANK YOU FOR COMPLETING THESE QUESTIONS!

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